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Preconception care: a clinical case of "think globally, act locally"

Michele G. Curtis, MD, MPH

In 1900, the life expectancy for a woman in the United States was 48.3 years; by 2004, that life expectancy had risen to 80.4 years.[1] Most of the increase is attributable to improvements in nutrition, sanitation, and other public health efforts that are focused at the population level; however, medical advances in secondary and tertiary prevention efforts that target individual patients also played a significant role. Despite evidence of the synergy between medicine and public health, the full integration of these disciplines has never been realized. This dichotomy has fostered the perception that medicine cares for individuals and that public health cares for populations. At the clinical level, health care practitioners often struggle with how to "translate" population-based risk data to the individual who is seated in front of them. To paraphrase the vernacular, "think global, act local" health care providers are grappling with the challenge to "think population, treat individual."

The concept and practice of preconception care epitomizes the difficulty, and concurrent simplicity, of translating population-based primary prevention data to individual patient care. For centuries, there have been theories and observational reports to support the idea that the health of the mother impacts directly on the health of the fetus, but it has only been in the last 60 or so years that rigorous scientific evidence and study have been able to demonstrate clearly the direct relationship between a woman's health or health risks and her current or future health and between her health and pregnancy outcomes. Most women are well aware of the long-term health risks of smoking, but many women are not aware of the adverse impacts of smoking during pregnancy or the long-term health risks that they impose on others in the household, including infants and children.

Folic acid supplementation for all women of reproductive age has achieved clear success in decreasing neural tube defects in developing fetuses, which is an accomplishment that led to fortification of the US food supply with folic acid in 1998.[2,3] Evidence is also mounting to support the idea that folate supplementation may decrease the long-term risk of cardiovascular disease, particularly in individuals with methylenetetrahydrofolate reductase mutations.[4,5] Research on the fetal origins of adult disease has demonstrated that certain adult-onset diseases (eg, hypertension, metabolic syndrome) are influenced by fetal epigenetic alterations in gene function. Gene silencing requires methyl groups, and folic acid levels impact methyl group availability. It is not unreasonable to hypothesize that folic acid supplementation will impact not only the woman's future health and the immediate health of developing fetuses but also may impact the future adult health status of that developing fetus.

There is currently an explosion of scientific research and understanding of environmental and genetic influences, which include their interactions, not only on the health of children and adults but also on that of developing fetuses and in some instances on their future progeny.[6,7] Although undernutrition had been shown previously to affect a developing fetus adversely, there is now evidence that fetal overnutrition results in adverse health outcomes in childhood and adolescence and may even contribute to intergenerational cycles of obesity.[8,9]

As obesity has increased in the United States, so too has the prevalence of diabetes mellitus. Despite medical treatment for this condition, many women of reproductive age with diabetes mellitus are not aware of the risks that this condition may impose on a developing fetus. In 1 managed care study, only 52% of the women of reproductive age with diabetes mellitus recalled any discussions with their providers about the need for glucose control before pregnancy, and only 37% of the women said that they had received any family planning advice from their providers.[10] Women who experience gestational diabetes mellitus are at increased risk for fetal macrosomia and obstetric complications during pregnancy, but the risk does not end with delivery. Women who experience gestational diabetes mellitus are at increased risk for the development of type 2 diabetes mellitus throughout their lifetime; the risk of the development of the disease is highest in the first 5 years after delivery and levels out after 10 years.[11,12] Because of this, the American Diabetes Association and the American College of Obstetricians and Gynecologists recommend either a fasting blood sugar or oral glucose tolerance test at 6-8 weeks after delivery. Evidence shows that many women with gestational diabetes mellitus are not being screened appropriately during the postpartum period, and that many women with a history of gestational diabetes mellitus were unlikely to contact their primary clinicians until they actually experienced signs of type 2 diabetes mellitus.[13-15]

In 2006, the Centers for Disease Control and Prevention Select Panel on Preconception Care defined *preconception* care as a series of ". . .interventions that aim to identify and modify biomedical, behavioral, and social risks to a woman's health or pregnancy outcome through prevention and management. . .."[16] Public reaction to this was swift and divided. Some groups took offense at the effort of the Centers for Disease

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Control and Prevention to define preconception care at the population level, perceiving it as an erosion of reproductive choices for the individual woman through an effort to maximize women's health based on a view that all women are current or potential fetal incubators. Other groups welcomed the efforts to improve the health of reproductive-age women, regardless of whether they ever became pregnant, particularly because most of a woman's life is spent not being pregnant. An overwhelming number of women will become pregnant at some point during their reproductive lives, but a significant number never will, either by choice or circumstance. So how do we exercise the global thought process that requires us to consider how a woman's current or past life circumstances may impact a possible future pregnancy without denigrating the individual woman's right locally to make her own reproductive choices? In short, how do we "think population, treat individual" to help women lead both long and healthy lives?

In its Committee Opinion on Preconception Care, the American College of Obstetricians and Gynecologists recommended that every woman of reproductive age have a reproductive life plan.[17] In clinical practice, this requires health care providers to explore whether a woman of reproductive age is either planning or at risk for a pregnancy in the next year or sooner. Because half of all pregnancies are unplanned, most women will respond "no"; but the questions also incorporate those women who may not be planning a pregnancy but who are not consistently and proactively taking steps to avoid it. For these women, the opportunity for discussion about contraception and risk factors to their own health and the health of future pregnancies and children would then be available. For women who answer "yes," that they are hoping to achieve pregnancy within the next year or so, the clinician would be able to screen and counsel the women for any risk factors that are associated with adverse health outcomes and pregnancy outcomes.

The bridge between "think population, treat individual" in the instance of preconception care may be as straightforward as asking a single question about pregnancy risk or intent. Yet this simple concept has been difficult to practice on a routine basis; the general population does not expect it to be asked, and time taken to provide the appropriate counsel to a woman on the basis of her answer is not reimbursed. In some instances, the time that is needed to do this may require a separate counseling visit and more frequent medical visits to treat any conditions that she may have. The articles in this special supplement clearly illustrate the benefits of preconception care to women and their families; however, without some significant changes in the current health care system, it will remain yet another unrealized opportunity. These changes include integrating the concept and practice of preconception care into the training of health care practitioners, restructuring the health care finance system so that prevention is rewarded commensurate with intervention, and influencing the will of the general public to demand more money for research, demonstration, and implementation projects that are related to preconception care. Without such changes, preconception care will remain another example of how, although science can prove the need to "think population," it is never translated into action at the "treat individual" level. The tragedy of this is that although local individuals suffer unnecessarily, so too do populations globally. ■

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Where is the "W"oman in MCH?

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Scientific evidence indicates that improving a woman's health before pregnancy will improve pregnancy outcomes. However, for many years, our efforts have focused primarily on prenatal care and on caring for infants after birth. The concept of preconception care has been identified repeatedly as a priority for improving maternal and infant health. Preconception care is not something new that is being added to the already overburdened healthcare provider, but it is a part of routine primary care for women of reproductive age. Many opportunities exist for preconception intervention, and much of preconception care involves merely the provider reframing his or her thinking, counseling, and decisions in light of the reproductive plans and sexual and contraceptive practices of the patient. With existing scientific evidence that improving the health of "W"omen will improve the health of mothers and children, we must focus on improving the health of "W"omen before pregnancy and put the "W" in Maternal and Child Health.

Key words: maternal and child health, preconception, woman

Leaders in the United States were alarmed in the early 1980s when it was revealed that the country's ranking in infant death among developed countries had slipped from 10th in 1960 to 19th in 1980.[1,2] Health and public policy leaders took action and initiated many national programs to help improve pregnancy outcomes (much of the efforts at the time had been towards the care of women during pregnancy and helping women enter prenatal care early). In 1981, 6 lead organizations (the American College of Obstetricians and Gynecologists [ACOG], the March of Dimes, the American Academy of Pediatrics [AAP], the American Nurses Association, the National Congress of Parents and Teachers, and the US Public Health Service [US PHS]) established an informal coalition called "Healthy Mothers Healthy Babies" to improve the quality and to reach public and professional education related to prenatal and infant care.[3] In 1987, the US PHS convened a panel of experts that produced the landmark report titled *Caring for Our Future: The Content of Prenatal Care*.[4] In 1985, concerned about the lack of progress in the reduction of maternal mortality rates worldwide and the limited attention being given to mothers in Maternal and Child Health (MCH), Rosenfield famously asked "Where is the M in MCH"?[5] From 1984-1989, the US Congress passed a series of incremental expansions of Medicaid that provided prenatal coverage for more than one million low-income women that Presidents Ronald Reagan and George H.W. Bush signed into law and state governments implemented. In 1991, the Healthy Start Initiative was launched in urban and rural communities where infant mortality rates were 1.5-2.5 times the national average to identify and develop community-based systems approaches to reducing infant deaths by 50% over the next 5 years and to improve the health and well-being of women, infants, children, and their families.[6]

During the last 30 years, the United States has succeeded in providing more focus on the "M"other; the percentage of women who had access to early prenatal care and those who received adequate prenatal care increased from 76.3% in 1980 to 83.9% in 2004.[2] The United States has succeeded in reducing infant mortality rates from 12.6 deaths per 1000 live births in 1980 to 6.8 in 2004.[2] However, other developed countries made more progress during the same period, which resulted in further deterioration of the United States ranking in infant deaths, mostly as a result of the increasing proportion of babies who are born

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preterm (from 9.4% in 1981 to 12.3% in 2003) or with low birthweight (from 6.8% in 1981 to 7.9% in 2003); in 2004, the United States ranked 29th among developed countries in infant death.[7] Efforts to reduce infant mortality rates and to improve pregnancy outcomes have focused primarily on prenatal care and the care of infants after birth. This approach reflects an emphasis on observing and monitoring a woman's health during pregnancy and intervening when and if needed (anticipation and management). However, improving the coverage, content, and use of prenatal care was a necessary, but not sufficient, step in the improvement of pregnancy outcomes in the United States.

Current scientific evidence indicates that, in many cases, the improvement of a woman's health before pregnancy (preconception health and healthcare) will improve pregnancy outcomes for both mother and infant. Many women continue to enter pregnancy in poor health and at risk for poor pregnancy outcomes because of preexisting medical conditions or exposures to teratogenic factors or because proper, scientifically based preventive action (such as folic acid supplementation) has not been taken to prevent adverse pregnancy outcomes.[8,9] Moreover, millions of women remain at risk for unintended pregnancy. They might lack the knowledge or motivation necessary to carry out their personal plans for childbearing. Today, if we want to achieve further improvements in maternal and infant outcomes, we must act before pregnancy; we must shift the focus from "anticipation and management" in prenatal care into a paradigm of "prevention and health promotion" before pregnancy and throughout a woman's lifespan. Today, it is time to expand the "Healthy Mothers Healthy Babies" model into a "Healthy Women–Healthy Mothers–Healthy Babies" model. It is time to ask the question: where is the "W"oman in MCH?"

Preconception Care is Not a New Concept

Reference to the importance of preconception health and healthcare in the improvement of pregnancy outcomes are found in documents that are hundreds of years old. For example, in 1825, Dewees[10] stated that "The physical treatment of children should begin as far as may be practicable, with the earliest formation of the embryo; it will, therefore, necessarily involve the conduct of the mother, even before her marriage, as well as during her pregnancy." In recent years, preconception care was first described by Chamberlain[11,12] as a specialty service for women who had had a previous poor reproductive outcome. It was then described in the United States by the US PHS in the landmark publication *Preventing Low Birth Weight*[1] and later by Moos and Cefalo[13] at the University of North Carolina. The concept was adopted by the US PHS Expert Panel on the Content of Prenatal Care,[3,14] which defined its components and emphasized that it is delivered most effectively as part of primary care services.,

Development of the concept was identified as a priority in the 1990s by the US PHS, whose report included, among the health promotion and disease prevention objectives for the year 2000, a recommendation to increase the proportion of primary care providers who offer age-appropriate preconception care and counseling to at least 60%.[15,16] *Healthy People 2010* includes many objectives that address preconception health. The National Committee on Perinatal Health, which was led by ACOG, AAP, and the March of Dimes, made recommendations for action and offered a prototype preconception screening tool. They encouraged all primary care providers to play an active role in promoting prevention before pregnancy.[17] The "Guidelines for Perinatal Care," which was jointly issued by AAP and ACOG, recommended that "all health encounters during a woman's reproductive years, particularly those that are a part of preconception care, should include counseling on appropriate medical care and behavior to optimize pregnancy outcomes."[18] Other ACOG publications further emphasized the importance of preconception care in the continuum of women's healthcare.[19-21] In 2002, the March of Dimes suggested that "as the key physician/primary care providers, the obstetrician/gynecologists must take advantage of every health encounter to provide preconception care and risk reduction before and between conceptions—the time when care really can make a difference."[22] The importance of preconception care as a concept was further articulated in family medicine,[17,23-25] obstetrics and gynecology,[20,21,26,27] nurse midwifery,[28] nursing,[29-31] and public health.[32] Canada's National Guidelines on Family-Centered Maternity and Newborn Care devotes an entire chapter to preconception care and describes the multitude of intrinsic and extrinsic factors that influence preconception health. Various settings that are appropriate for the administration of preconception care interventions are discussed as well as a range of social and medical issues that included stress, social support, abuse and violence, healthy lifestyle practices, and nutrition.[33] The American Diabetes Association,[34] the American Academy of Neurology,[35] and the American Heart Association/American College of Cardiologists[36] promulgated recommendations on preconception care in their specialties.

Despite this broad interest in preconception care, there has been only modest progress in the implementation of these concepts into clinical practice and the development of research studies to advance practice. Existing research indicates that most women realize the importance of optimizing their health before pregnancy, whether or not the pregnancy is planned,[37] and that most physicians think preconception care is important.[38] However, most providers do not recommend routinely or provide preconception care to their patients.[39] One randomized clinical trial found that, even when given specific training, physicians did not take action to follow up risks that were identified at the time of a negative pregnancy test.[40]

The Centers For Disease Control and Prevention (CDC) Preconception Health and Health Care Initiative

In November 2004, the CDC Workgroup on Preconception Health and Health Care, working with national ex-

perts and representatives of over 35 national, state, and local organizations, launched the Preconception Health and Health Care Initiative. The CDC workgroup includes representatives of 22 CDC programs that are concerned with the health of women and infants in areas such as infectious diseases, HIV/AIDS, injury prevention, reproductive health, nutrition, smoking, alcohol, birth defects, and genetics. The workgroup has recognized the importance of women's health in improving maternal and infant pregnancy outcomes, the immediate need to facilitate collaboration and coordinate efforts among various organizations across the country, and the need to develop consensus recommendations and to identify and address obstacles and opportunities for the promotion of preconception health and healthcare in all aspects of healthcare (clinical, public health, consumer, policy and finance, and research/surveillance/monitoring).

In June 2005, the CDC convened a group of national experts (the Select Panel on Preconception Care) to develop "Recommendations on Preconception Health and Health Care." The guiding principles, visions, and objectives of the aforementioned initiative and the recommendations for preconception health and healthcare were published in April 2006.[41] The panel's vision is that all women of childbearing age and all men have high reproductive awareness, that all pregnancies are intended and planned, and that all women of childbearing age have health coverage and are screened before pregnancy for risks that are related to adverse pregnancy outcomes. The panel's guiding principle called for improving women's health throughout the lifespan by emphasizing individual behavior and responsibility, with changes in clinical care and public policy to support such women and couples in carrying out their childbearing plans. The panel made a series of recommendations that are aimed at achieving 4 goals: (1) to improve the knowledge, attitudes, and behaviors of men and women related to preconception health; (2) to assure that all women of childbearing age in the United States receive preconception care services that will enable them to enter pregnancy in optimal health; (3) to reduce risks that are indicated by a previous adverse pregnancy outcome through interventions during the interconception period; and (4) to reduce disparities in adverse pregnancy outcomes.[41] The CDC panel further defined *preconception care* as "interventions that aim to identify and modify biomedical, behavioral, and social risks to a woman's health or pregnancy outcome through prevention and management by emphasizing those factors that must be acted on before conception or early in pregnancy to have maximal impact. Thus, it is more than a single visit and less than well-woman care. It includes care before a first pregnancy or between pregnancies (commonly known as "interconception care").

The Select Panel recognized that, to promote preconception health and healthcare, there was a need to go beyond developing and publishing recommendations. In June 2006, the CDC established 5 implementation workgroups (clinical, public health, consumer, policy and finance, and research and surveillance) to develop strategies for implementing the recommendations. These groups were to focus on core constituencies in which changes in knowledge, attitudes, and practices could lead to improvements in preconception health and healthcare. The workgroups were charged with fine-tuning and augmenting the proposed action steps, establishing priorities for follow-up action, and agreeing to take leadership for implementation of ≥ 1 action steps.

The clinical workgroup, comprising $>$ 20 physicians and nurses of various specialties, identified the definition of the content of preconception care and provider education as top priorities for the immediate future. The accompanying articles in this supplement are the result of efforts by 36 clinical care providers who worked together for $>$ 2 years to define the clinical content of preconception care.

Rationale for Preconception Care

Clinicians have counseled women regarding risk reduction in preparation for pregnancy for many years as part of routine preventive health care (eg, advising on avoiding teratogens and seeking family planning and genetic counseling), managing preexisting medical conditions (such as diabetes mellitus, hypertension, and sexually transmitted infections), and delivering preventive interventions (eg, HIV screening and vaccinations). During the past 20 years, there has been a growing realization that the development of a comprehensive program to assess and modify medical, psychosocial, and behavioral risks before pregnancy could prevent poor pregnancy outcomes for women and infants. This kind of care can help women and couples make decisions regarding the timing of conception and can improve their health in readiness for pregnancy.[1,13,18,27,28,31,32,42-45]

The goal of preconception care is to ensure that a woman and her partner are healthy and that they avoid hazardous exposures and practice healthy lifestyles before pregnancy. Many of the medical conditions, environmental exposures, personal behaviors, and psychosocial risks that are associated with negative pregnancy outcomes can be identified and modified or eliminated before conception. A comprehensive preconception care program has the potential to benefit women who desire pregnancy by reducing risks, promoting healthy lifestyles, and increasing readiness for pregnancy. For women who do not desire pregnancy, a preconception care program can reduce personal health risks and the risk of an unwanted pregnancy.

First and foremost, preconception care is important because it provides an opportunity to optimize the health of the woman independently of whether she becomes pregnant. Moreover, intervention before pregnancy is essential for the optimization of outcomes for the pregnant woman (maternal outcomes), her child, or both. In a committee opinion that was published in 2005, ACOG's Committee on Gynecologic Practice recognized the *Importance of Preconception Care in the Continuum of Women's Health Care*.[46] The CDC's *Recommendations for Preconception Health and Health Care* call for the improvement of a woman's health by managing preexisting

medical conditions (such as diabetes mellitus, obesity, epilepsy, and hypothyroidism), providing vaccines (such as rubella, hepatitis B), screening and treatment for other conditions (such as HIV/AIDS, sexually transmitted infections), and counseling for some behavioral risks (alcohol use and smoking).[41] Preconception care also provides a window of opportunity to reduce the risk of pregnancy complications that may threaten maternal health. For example, properly managing hypothyroidism before pregnancy reduces the risk of maternal hypertension, preeclampsia, placental abruption, anemia in pregnancy and postpartum hemorrhage; properly managing hypertension before pregnancy reduces the risk of preeclampsia[47]; properly managing overweight and underweight conditions reduces the risk of nutritional deficiencies, postpartum anemia, and cesarean delivery[48]; and screening for and management of chlamydia reduces the risk of pelvic inflammatory disease and ectopic pregnancy.[49] In certain conditions, however, in which it may be difficult to reduce the increased risk of serious morbidity or death that is associated with preexisting conditions (such as Eisenmenger syndrome and previous peripartum cardiomyopathy), women should be counseled about the life-threatening risks of pregnancy, provided with guidance about options for parenting, and offered avenues to secure appropriate contraception.[50-53]

There is substantial evidence that many preconception interventions reduce the risks of adverse pregnancy outcomes that include birth defects, fetal loss, low birthweight, and preterm delivery. Such interventions include the management of maternal conditions (such as diabetes, obesity, phenylketonuria, sexually transmitted infections, hypothyroidism, seizure disorders, HIV),[46] the counseling of women to avoid certain risks (such as alcohol consumption, smoking, prescription and over-the-counter teratogenic drugs, excess vitamin intake, undernutrition, household and environmental exposures to toxic substances),[54,55] the counseling of women to engage in healthy behaviors (such as reproductive life planning, folic acid consumption, proper nutrition),[47] and the counseling of women about availability of vaccines to protect the infant from the consequences of infections that affect the mother (such as rubella, varicella, hepatitis B).[56] For most of these interventions, it is very important that the interventions be delivered before pregnancy because many of the risk behaviors and exposures that can affect fetal development and subsequent outcomes have their greatest effect during organogenesis, which is from 17-56 days of pregnancy before women enter prenatal care and often before they even know they are pregnant.[57,58] This is particularly true in the case of teratogens (such as alcohol) that can cause fetal alcohol syndrome, certain prescription drugs that are known to cause birth defects, and hazardous substances in the workplace and home.

Opportunities for the Delivery of Preconception Services

Preconception health promotion and counseling implies addressing potential precursors to adverse pregnancy outcomes before becoming pregnant. This concept includes the identification of and intervention for medical and psychosocial issues, even before an individual reaches reproductive age. For example, the parent of a child with an inherited hemoglobinopathy would be counseled on the potential risk that the condition could have on their child's offspring. A sedentary teen might be counseled on her risk for obesity and its effect on future fertility and pregnancy outcomes.

Research and data regarding risks point to significant opportunities for health promotion and counseling among women of reproductive age and, in some cases, among men. Preconception guidelines should incorporate practical tools to address family planning that include contraception and birth spacing; the promotion of health education and health literacy; nutrition and weight management; alcohol, tobacco, and substance abuse; environmental and occupational exposures and hazards; risky sexual behaviors; infection risks; optimal management of medical problems; medication benefits and risks; stress reduction; domestic violence; and identification of skilled healthcare teams to address specific issues before pregnancy.

The CDC recommendations emphasize that preconception care is not limited to a single visit to a healthcare provider but that it is a process of care that is designed to meet the needs of a woman during the different stages of her reproductive life. The purpose or preconception care is to promote health throughout the lifespan for women, children, and families. Preconception care offers health services that allow women to maintain optimal health for themselves, to choose the number and spacing of their pregnancies and, when desired, to prepare for a healthy baby.

Thus, preconception care is not something new that is being added to the already overburdened healthcare provider, but it is a part of routine primary care for women of reproductive age. Just as primary care visits devote time to screening and health promotion to reduce cardiovascular disease and cancer, reproductive health promotion should become practiced more routinely during visits.

Many opportunities exist for preconception intervention. All reproductive-aged women are candidates for preconception care; however, preconception care must be tailored to meet the needs of the individual woman. For example, the provision of smoking cessation services is preconception care; choosing a medication for a patient with hypertension is preconception care. Much of preconception care merely involves the provider reframing his or her thinking, counseling, and decision-making in light of the reproductive plans and sexual and contraceptive practices of the patient. With the use of the "every woman, every time" approach, some projects across the country have encouraged primary care providers to ask women routinely about their reproductive plans and needs.[59]

Professional guidelines for those types of clinicians (obstetrician-gynecologists, family practice physicians, internists, certified nurse midwives, and nurse practitioners) who provide the bulk of primary care to women in the United

States recommend routine risk assessment and screening.[18-20,60-62] Along with risk assessment and screening, professional guidelines call for health promotion education and counseling that are related to reproductive health risks. For women with identified risks, additional counseling, testing, or brief interventions, or a combination thereof, can be carried out in the primary care setting (eg, brief evidence-based office interventions for smoking cessation or changes in prescription medications). Some women will need more intensive interventions and specialty care.

Given that preconception care should occur ideally throughout the lifespan, some recommendations will be more relevant to women at specific stages in their lives and with varying levels of risk. Health promotion, risk screening, and interventions are different for a young woman who has never experienced pregnancy than for a 35-year-old woman who has had 3 children. Women with chronic diseases, previous pregnancy complications, or behavioral risk factors might need more intensive interventions. Women who have experienced a previous adverse pregnancy outcome (eg, fetal death or premature or low birthweight birth) are another population in need of special interventions. Such variability means that the most effective and efficient means of bundling or prepackaging interventions will vary.

Who Provides Preconception Care?

National surveys indicate that 84% of women 18-44 years of age have had a healthcare visit during the past year and that most women of reproductive age obtain preventive health services during any given year,[63] all of which offer opportunities to deliver preconception care. Because approximately one-third to one-half of women have > 1 primary care provider (generally a family physician or internal medicine physician and an obstetrician/gynecologist),[64] all providers who routinely see women for well-woman examinations or other routine visits have an important role to play in improving preconception health. However, approximately only 1 in 6 obstetrician/gynecologists or family physicians provide preconception care to the majority of the women for whom they provide prenatal care.[65]

Because of the wide range of interventions that are included under the umbrella of preconception care, many such interventions can be delivered in both primary care and specialty care practices. More practice opportunities also exist in improving preconception health through wellness care, through care for women with chronic health conditions that are associated with increased preconception risk (eg, maternal diabetes mellitus), and in settings where women seek medical support for 1 specific health risk, such as smoking or obesity. Thus, all clinicians who care for women should be aware of the importance of preconception health promotion and risk assessment that are linked to intervention. This care should include consideration of the potential for pregnancy as a part of usual healthcare for men and for women of reproductive age, and healthcare providers should assess and discuss the implications of a man's or woman's present health status on a possible pregnancy. Attention to the health of prospective parents before they conceive is a natural extension of primary care practice and includes family physicians, pediatricians, general internists, obstetricians/gynecologists, nurse practitioners, and nurse midwives, among others.

Primary care clinicians should include preconception care during all recommended clinical encounters (such as postpartum visits; routine health maintenance; school, work, and family planning visits; pregnancy test visits; and well-child care for another member of the family). Primary care clinicians can also offer men information about responsible fatherhood and sexuality. Men should be engaged in preparing for fatherhood, supporting their partner in contraceptive choices, and using preventive health behaviors.

Preconception care is most effective when the woman and her partner are motivated properly. Many social and cultural influences that include attitudes and values that are projected at home and through the schools, faith communities, peer groups, and public media and contribute to decisions by men and women during their teenage and early adult years regarding sexuality and childbearing. The receptiveness of couples to preconception care is heightened at certain times, such as during a family-planning visit when a woman is considering starting or stopping a method of birth control, at the time the results of a negative pregnancy test are received, or at the time of a woman's first gynecologic examination.

Barriers to Preconception Care

The slow growth of preconception care can be attributed to the many challenges that are faced in the provision of this care. In a 1990 commentary in the *Journal of the American Medical Association*, Jack and Culpepper[42] identified the following 7 barriers to the dissemination of preconception care: (1) those women who are most in need of services are those least likely to receive them; (2) the provision of services often is fragmented badly; (3) there is a lack of available treatment services for high-risk behaviors; (4) reimbursement for risk assessment and health promotion activities is inadequate; (5) health promotion messages are not effective unless received by a motivated couple; (6) only a few conditions have data supporting intervention before conception rather than intervention early in pregnancy; and (7) many clinical training programs do not emphasize risk assessment and health promotion skills. These barriers to the delivery of preconception care as part of clinical services are as relevant today as they were at the time they were penned.

For preconception care to be fully realized, there must be fundamental changes in how care is provided to reproductive-aged women.[59,60] For preconception care to be successful, there must be a shift from the delivery of procedure-based acute care to the provision of counseling-based preventive care. In turn, for this to occur, there must be changes in the financing of medical care and in the education of trainees in the primary care specialties, which are addressed in CDC's *Select Panel on Preconception Care Recommendations*.[41]

Comment

Preconception care works; the concept is supported by science, and the logic is straightforward. Although such care has not yet been recommended universally or available, there has been substantial interest nevertheless in recent years to advance the concept.

For many years, healthcare providers, in an effort to improve maternal and infant pregnancy outcomes, have focused on the health of a woman during the latter 5 or 7 months of her pregnancy, instead of focusing on a woman's health across her lifespan to optimize the outcome of her pregnancy. If we hope to achieve better pregnancy outcomes, we must change the way we provide Maternal and Child Health services and add the "W"oman into MCH.

The time for a national discussion about how to better incorporate preconception care and women's health into our healthcare systems is overdue. The need to define the content of preconception care in the realms of clinical care, public health, and consumer awareness is clear. Equally needed is a national strategy to promote the necessary research, clinical demonstration programs, and community-based implementation that will make this care part of the fabric of health and healthcare in the United States. This supplement begins this new and exciting chapter in preconception care. ■

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The clinical content of preconception care: an overview and preparation of this supplement

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In June 2005, the Select Panel on Preconception Care established implementation workgroups in 5 areas (clinical, public health, consumer, policy and finance, and research and surveillance) to develop strategies for the implementation of the Centers for Disease Control and Prevention recommendations on preconception health and healthcare. In June 2006, members of the clinical workgroup asked the following questions: what are the clinical components of preconception care? What is the evidence for inclusion of each component in clinical activities? What health promotion package should be delivered as part of preconception care? Over the next 2 years, the 29 members of the clinical workgroup and > 30 expert consultants reviewed in depth > 80 topics that make up the content of the articles that are contained in this supplement. Topics were selected on the basis of the effect of preconception care on the health of the mother and/or infant, prevalence, and detectability. For each topic, the workgroup assigned a score for the strength of the evidence that supported its inclusion in preconception care and assigned a strength of the recommendation. This article summarizes the methods that were used to select and review each topic and provides a summary table of the recommendations.

Key words: preconception care, pregnancy care

In the introductory article to this supplement, Atrash et al[1] review the accomplishments of the first 4 years of the Centers for Disease Control and Prevention Workgroup on Preconception Health and Health Care. A key component of this initiative was the organization of the Select Panel on Preconception Care in June 2005. The panel established implementation workgroups to develop strategies for implementation of the preconception care recommendations that were published in the Morbidity and Mortality Weekly Report[2] in the following 5 areas: clinical, public health, consumer, policy and finance, and research and surveillance. Meeting over 2 days in June 2006, the members of the clinical workgroup identified 7 important questions that were considered to be critical to the advancement of the clinical preconception care agenda. These questions were: What are the clinical components of preconception care? What is the evidence for inclusion of each component in clinical activities? What health promotion package should be delivered as part of preconception care? How can preconception risks be identified? What are the best interventions for preconception risks, once identified? What are the curriculum and teaching tools to teach these concepts to clinicians? What is the research agenda for preconception care?

In 2 subsequent meetings and in a series of conference calls over the next nearly 2 years, the 29 members of the clinical workgroup and > 30 expert consultants reviewed in-depth > 80 topics in an attempt to answer the first 3 of these 7 questions. The series of articles in this supplement of the *American Journal of Obstetrics and Gynecology* are the product of this work. This article summarizes the methods that were used to select and review each topic and provides a summary table of the recommendations.

Selection of topics to be reviewed

The workgroup identified a set of specific criteria to assist in choosing among the clinical topics to be reviewed. The resulting selection criteria comprised the following items: (1) There is a good chance that the health of the mother or the infant will be improved if the condition is identified and addressed before pregnancy; (2) the burden of suffering and prevalence of the condition are sufficient to justify screening and treatment; (3) the condition is detectable in clinical care in either primary or specialty settings; (4) if screening is used, the screening methods that are available to detect the

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condition are sufficiently predictive to justify screening; or (5) clinical practice guidelines already exist that suggest that preconception interventions be implemented.

The workgroup reviewed > 700 papers that related to preconception care to create a list of potential topics; the group then applied the aforementioned criteria to determine approximately 83 topics that were reviewed. These topics, which were organized into 14 separate clinical areas, make up the accompanying articles of this supplement and together define the clinical content of preconception care.

Health promotion and risk reduction

The clinical workgroup retained the organizational structure that was promulgated by the Expert Panel on the Content of Prenatal Care,[3] which suggested that the components of preconception care include the provision of health education that is individualized to a woman's or couple's needs (health promotion), a thorough and systematic identification of risks (risk assessment), and the initiation of actions to address those risks (interventions) with women and men of reproductive age to reduce risk factors that might affect future pregnancies. The article by Moos et al[4] describes the content of the health promotion activities that are part of preconception care. The remaining articles describe the content of preconception risk assessment activities: immunizations, infectious diseases, medical conditions, psychiatric conditions, parental exposures, genetics and genomics, nutrition, environmental exposures, psychosocial stressors, medications, and reproductive history. The final 2 articles cover special populations and preconception care for fathers.

Presentation of each topic and recommendations for clinical care

The information that is provided about each topic was standardized based on the format that was developed by the United States Preventive Services Task Force.[5] Each topic is reviewed with the following structure: (1) The burden of suffering, which includes the prevalence and importance of the target condition; (2) the accuracy of the screening methods that are available to detect the condition either in primary or specialty settings; (3) the effectiveness and availability of current treatments for the condition; (4) the impact of the detection and treatment of this condition in the preconception period (to be recommended, the intervention had to be more effective if the condition was identified and addressed before pregnancy, compared with screening for and treatment during pregnancy); (5) related recommendations by other groups.

The components of preconception care were then researched by a member of the clinical committee or by a selected content expert. The first author (B.W.J.), in concert with the editors, then identified members of the clinical committee with an interest and the expertise in that content area and asked them to contribute to that article. For all articles, individual content experts outside the clinical committee were sought to contribute to a particular section or to review and comment on the article. The author who prepared each component of an article was asked to provide a summary recommendation that was based on their review of the topic. The summary recommendation was to be supported by the evidence that was presented in the article and, in the opinion of the author, to represent the current best evidence-based preconception care practice for clinicians. The information that had been provided for each topic and the recommendations were then reviewed by the first author of the article, all other authors, and the editors. In some cases, these deliberations not only resulted in modifications of the recommendation but also resulted in consensus among the group regarding the recommendation.

Strength of recommendations and quality of the evidence

The strength of the recommendation and the quality of the evidence for each of the clinical components were then rated by the authors and editors, and consensus was reached. The criteria that were used were adapted from those criteria that were used in the report of the US Preventive Services Task Force Guide of Clinical Preventive Services.[5] The following criteria were used to determine the quality of the evidence and the strength of the recommendation:

Strength of the recommendation. (A) There is good evidence to support the recommendation that the condition be considered specifically in a preconception care evaluation. (B) There is fair evidence to support the recommendation that the condition be considered specifically in a preconception care evaluation. (C) There is insufficient evidence to recommend for or against the inclusion of the condition in a preconception care evaluation, but recommendation to include or exclude may be made on other grounds. (D) There is fair evidence to support the recommendation that the condition be excluded in a preconception care evaluation. (E) There is good evidence to support the recommendation that the condition be excluded in a preconception care evaluation.

Quality of the Evidence. (I-a) Evidence was obtained from at least 1 properly conducted randomized controlled trial that was done before pregnancy. (I-b) Evidence was obtained from at least 1 properly conducted randomized controlled trial that was done not necessarily before pregnancy. (II-1) Evidence was obtained from well-designed controlled trials without randomization. (II-2) Evidence was obtained from well-designed cohort or case-control analytic studies, preferably from > 1 center or research group. (II-3) Evidence was obtained from multiple-time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence. (III) Opinions were gathered from respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

The quality of the evidence that supports the efficacy of the various components of preconception care varies greatly. Most of the evidence comes from research that was done when the focus of delivery was on a single component; interventions that address multiple pregnancy-related risk be-

TABLE

Strength of the recommendations and the quality of the evidence for preconception clinical intervention to improve maternal or the infant health

Potential component of preconception care	Strength	Quality	Recommendation
Health promotion			
Family planning and reproduction life plan	A	III	Routine health promotion activities for all women of reproductive age should begin with screening women for their intentions to become or not become pregnant in the short- and long-term and their risk of conceiving (whether intended or not). Providers should encourage patients (women, men, and couples) to consider a reproductive life plan and educate patients about how their reproductive life plan impacts contraceptive and medical decision-making. Every woman of reproductive age should receive information and counseling about all forms of contraception and the use of emergency contraception that is consistent with their reproductive life plan and risk of pregnancy.
Physical activity	C	II-2	All women should be assessed regarding weightbearing and cardiovascular exercise and be offered recommendations appropriate to their physical abilities.
Weight status	A	III	All women should have their body mass index (BMI) calculated at least annually. All women with BMIs $\geq$ 26 kg/m^2 should be counseled about the risks to their own health, the risks for exceeding the overweight category, and the risks to future pregnancies, including infertility. These women should be offered specific behavioral strategies to decrease caloric intake and increase physical activity and be encouraged to consider enrolling in structured weight loss programs. All women with a BMI $\leq$ 19.8 kg/m^2 should be counseled about the short- and long-term risks to the own health and the risks to future pregnancies, including infertility. All women with a low BMI should be assessed for eating disorders and distortions of body image. Women unwilling to consider and achieve weight gain may require referral for further evaluation of eating disorders.
Nutrient intake	A	III	All women of reproductive age should be assessed for nutritional adequacy and receive a recommendation to take a multivitamin supplement if any question of ability to meet the recommended daily allowance through food sources is uncovered. Care must be taken to counsel against ingesting supplements in excess of the recommended daily allowance.
Folate	A	I-a	All women of reproductive age should be advised to ingest 0.4 mg (400 μg) of synthetic folic acid daily from fortified foods and/or supplements and to consume a balanced, healthy diet of folate-rich food.
Immunizations	A	III	All women of reproductive age should have their immunization status for tetanus-diphtheria toxoid/diphtheria-tetanus-pertussis; measles, mumps, and rubella; and varicella reviewed annually and updated as indicated. All women should be assessed annually for health, lifestyle, and occupational risks for other infections and be offered indicated immunizations.
Substance use	A	II-2 (tobacco) III (alcohol)	All women should be assessed for use of tobacco at each encounter with the healthcare system; women who smoke should be counseled to limit exposure. All women should be assessed at least annually for alcohol use patterns and risky drinking behaviors and be provided with appropriate counseling; all women should be advised of the risks to the embryo/fetus of alcohol exposure in pregnancy and that no safe level of consumption has been established.
Sexually transmitted infections (STIs)	A	III	Healthcare providers regularly and routinely should assess STI risks, provide counseling and other strategies (including immunizations) to prevent acquisition of STIs, and to provide indicated STI testing and treatment for all women of childbearing age.
Immunization			
Human papillomavirus (HPV)	B	II-2	Women should be screened routinely for HPV-associated abnormalities of the cervix with cytologic (Papanicolaou) screening. Recommended subgroups should receive the HPV vaccine for the purpose of decreasing the incidence of cervical abnormalities and cancer. By avoiding procedures of the cervix because of abnormalities caused by HPV, the vaccine could help maintain cervical competency during pregnancy.

Continued on page S269.

TABLE

Strength of the recommendations and the quality of the evidence for preconception clinical intervention to improve maternal or the infant health

Continued from page S268.

Potential component of preconception care	Strength	Quality	Recommendation
Hepatitis B	A	III	All high-risk women who have not been vaccinated previously should receive hepatitis B vaccine before pregnancy; women who are chronic carriers should be instructed on ways to prevent transmission to close contacts and how to prevent vertical transmission to their babies.
Varicella	B	III	Because the varicella vaccine is contraindicated during pregnancy, screening for varicella immunity (by either a history of previous vaccination, previous varicella infection verified by a healthcare provider, or laboratory evidence of immunity) should be done as part of a preconception visit. All nonpregnant women of childbearing age who do not have evidence of varicella immunity should be vaccinated against varicella.
Measles, mumps, and rubella	A	II-3	All women of reproductive age should be screened for rubella immunity. Immunization should be offered to women who have not been vaccinated or who are not immune and who are not pregnant. Women should be counseled not to become pregnant for 3 months after receiving vaccination. This vaccination will provide protection against measles, mumps, and rubella.
Influenza	C	III	Influenza vaccination is recommended for women who will be pregnant during influenza season and for any woman with increased risk for influenza-related complications, such as cardiopulmonary disease or metabolic disorders, before influenza season begins.
Diphtheria-tetanus-pertussis vaccination	B	III	Women of reproductive age should be up-to-date for tetanus toxoid, because passive immunity is probably protective against neonatal tetanus. The diphtheria-tetanus-pertussis vaccine is recommended for women who might become pregnant or immediately after delivery to avoid complications of pertussis in the newborn infant.
Infectious disease			
Human immunodeficiency virus	A	I-b	All men and women should be encouraged to know their human immunodeficiency virus status before pregnancy and should be counseled about safe sexual practices. Women who test positive must be informed of the risks of vertical transmission to the infant and the associated morbidity and mortality probabilities. These women should be offered contraception. Women who choose pregnancy should be counseled about the availability of treatment to prevent vertical transmission and that treatment should begin before pregnancy.
Hepatitis C	C	III	There are no data that preconception screening for hepatitis C in low-risk women will improve perinatal outcomes. Screening for high-risk women is recommended. Women who are positive for hepatitis C and desire pregnancy should be counseled regarding the uncertain infectivity, the link between viral load and neonatal transmission, the importance of avoiding hepatotoxic drugs, and the risk of chronic liver disease. Women who are being treated for hepatitis C should have their reproductive plans reviewed and use adequate contraception while on therapy.
Tuberculosis	B	II-2	All high-risk women should be screened for tuberculosis and treated appropriately before pregnancy.
Toxoplasmosis	C	III	There is no clear evidence that preconception counseling and testing will reduce *Toxoplasma gondii* infection or improve treatment of women who are infected. However, if preconception testing is done, women who test positive can be reassured that they are not at risk of contracting toxoplasmosis during pregnancy; women who are negative can be counseled about ways to prevent infection during pregnancy. For women who convert during pregnancy, treatment should be offered.
Cytomegalovirus	C	II-2	Women who have young children or who work with infants and young children should be counseled about reducing the risk of cytomegalovirus through universal precautions (eg, the use of latex gloves and rigorous hand-washing after handling diapers or after exposure to respiratory secretions).

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TABLE
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Potential component of preconception care	Strength	Quality	Recommendation
Listerosis	C	III	Because it is not clear at what point in pregnancy women who are exposed to Listeria will become ill, preconception care should include teaching women to avoid pâté and fresh soft cheeses made from unpasteurized milk and to cook ready-to-eat foods such as hotdogs, deli meats, and left-over foods.
Parvovirus	E	III	There is not yet evidence that screening for antibody status against parvovirus or counseling about ways to avoid infection in pregnancy will improve perinatal outcomes. Good hygiene practices should be encouraged for all pregnant women.
Malaria	C	III	Women who are planning a pregnancy should be advised to avoid travel to malaria-endemic areas. If travel cannot be deferred, the traveler should be advised to defer pregnancy and use effective contraception until travel is completed and to follow preventive approaches. Antimalarial chemoprophylaxis should be provided to women who plan a pregnancy who travel to malaria-endemic areas.
Gonorrhea	B	II-2	High-risk women should be screened for gonorrhea during a preconception visit, and women who are infected should be treated. Screening should also occur early during pregnancy and be repeated in high-risk women.
Chlamydia	A	I-a	All sexually active women $\leq$ 25 years and all women at increased risk for infection with Chlamydia (including women with a history of STI infections, new or multiple sexual partners, inconsistent condom use, sex work, and drug use) should be screened at routine encounters before pregnancy.
Syphilis	A	II-1	High-risk women should be screened for syphilis during a preconception visit, and women who are infected should be treated. Because the United States Preventive Services Task Force and Centers for Disease Control and Prevention recommend screening all women during pregnancy for syphilis, screening for syphilis immediately before conception is recommended.
Herpes simplex virus	B	II-1	During a preconception visit, women with a history of genital herpes should be counseled about the risk of vertical transmission to the fetus and newborn child; women with no history should be counseled about asymptomatic disease and acquisition of infection. Although universal serologic screening is not recommended in the general population, type-specific serologic testing of asymptomatic partners of persons with genital herpes is recommended.
Asymptomatic bacteruria	E	II-1	There have been no studies to show that women with asymptomatic bacteriuria who are identified and treated in the preconception period have lower rates of low birthweight births. Further, women often have persistent or recurrent bacteriuria, despite repeated courses of antibiotics; such re-infection frequently occurs within a few months of treatment. Thus, a woman who is identified and treated for asymptomatic bacteriuria before conception must be screened again during pregnancy. For these reasons, screening for this condition as part of routine preconception care currently is not recommended.
Periodontal disease	C	I-b	There are no studies that evaluate the role of preconception or interconception screening and treatment of periodontal disease and its effect on reproductive outcomes. Routine screening and treatment of periodontal disease during preconception care, although of considerable benefit to the mother, is not recommended at this time as part of preconception care, because there is no clearly shown benefit to the fetus.
Bacterial vaginosis (BV)	D (women without preterm delivery); C (women with preterm delivery)	I-b	There are no studies that evaluate the role of preconception or interconception screening and treatment for BV and its effect on reproductive outcomes; such studies are a high priority. Routine screening and treatment of BV among asymptomatic pregnant women of average risk should not be performed because of the lack of demonstrated benefit and the possibility of adverse effects of treatment for women without BV. For pregnant women with previous preterm delivery, the inconsistent results of well-done studies prevent a clear recommendation for or against screening; however, some studies support early screening and treatment with a regimen that contains oral metronidazole. For women with symptomatic BV infection, treatment is appropriate for pregnant women and for women planning pregnancy.

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TABLE

Strength of the recommendations and the quality of the evidence for preconception clinical intervention to improve maternal or the infant health

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Potential component of preconception care	Strength	Quality	Recommendation
Group B *Streptococcus*	E	I-2	Screening for group B *Streptococcus* colonization at a preconception visit is not indicated and should not be performed.
Medical conditions			
Diabetes mellitus	A	I	All women with diabetes mellitus should be counseled about the importance of diabetes mellitus control before considering pregnancy. Important counseling topics include maintaining optimal weight control, maximizing diabetes mellitus control, self-glucose monitoring, a regular exercise program, and tobacco, alcohol, and drug cessation, along with social support to assist during the pregnancy. In the months before pregnancy, these women should demonstrate as near-normal glycosylated hemoglobin level as possible for the purpose of decreasing the rate of congenital anomalies. Women with poor control of their diabetes mellitus should be encouraged to use effective birth control. Testing to detect prediabetes and type 2 diabetes in asymptomatic women should be considered in adults who are overweight or obese (BMI $\geq$ 25 kg/m^2) and who have 1 or more additional risk factors for diabetes, including a history of gestational diabetes mellitus.
	B (overweight and obese adults)	II-2	
Thyroid disease	A	II-1	Women with hypothyroidism should be counseled about the risks of this condition to pregnancy outcomes and the importance of achieving optimal replacement therapy before conception. All women with symptoms of hypothyroidism should be screened for thyroid disease; if there is hypothyroidism, adequate therapy should be initiated.
Phenylketonuria	A	II-1	Women of reproductive age with phenylketonuria should be counseled about the importance of maintaining a low phenylalanine level during their childbearing years and should be encouraged to resume a low phenylalanine diet, particularly when they are planning to become pregnant, to avoid adverse outcomes for the offspring. Women who do not desire a pregnancy should be encouraged to use contraception.
Seizure disorders	A	II-2	Women of reproductive age with seizure disorders should be counseled about the risks of increased seizure frequency in pregnancy, the potential effects of seizures and anticonvulsant medications on pregnancy outcomes, and the need to plan their pregnancies with a healthcare provider well in advance of a planned conception. Women who take liver enzyme-inducing anticonvulsants should be counseled about the increased risk of hormonal contraceptive failure. Whenever possible, women of reproductive age should be placed on anticonvulsant monotherapy with the lowest effective dose to control seizures. Women who are planning a pregnancy should be fully evaluated for consideration of alteration or withdrawal of the anticonvulsant regimen before conception, and folic acid supplementation of 4 mg per day should be initiated for at least 1 month before conception and until the end of the first trimester to prevent neural tube defects.
Hypertension	A	II-2	Women of reproductive age with chronic hypertension should be counseled about the risks associated with hypertension during pregnancy for both the woman and her offspring and the possible need to change the antihypertensive regimen when she is planning a pregnancy. Women with hypertension for several years should be assessed for ventricular hypertrophy, retinopathy, and renal disease before pregnancy. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are contraindicated during pregnancy; women who could become pregnant while taking these medications should be counseled about their adverse fetal effects and should be offered contraception if they are not planning a pregnancy. Women who are planning a pregnancy should discontinue these medications before pregnancy.
Rheumatoid arthritis	A	III	Women with known history of rheumatoid arthritis should be advised of the natural history of the disease during pregnancy and the probability of a flare after pregnancy. The most important task is to review the patient's medication use. Nonsteroidal antiinflammatory drugs should be discontinued by 27 weeks of gestation. Methotrexate and leflunomide are extremely teratogenic and should be stopped in men and women planning a pregnancy.

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Potential component of preconception care	Strength	Quality	Recommendation
Lupus	B	II-2	Women of reproductive age with lupus should be counseled about the risks associated with lupus during pregnancy for both the woman and her offspring, the importance of optimizing disease control before pregnancy, the possible need to change the medication regimen close to conception or early in pregnancy, and the importance of specialized prenatal care once pregnant. Women whose treatment regimen involves cyclophosphamide should be advised of its teratogenic nature; whenever possible, the treatment should be changed to a safer regimen before conception, and the women should be offered contraception if they are not planning a pregnancy.
Renal disease	B	II-2	Women of reproductive age with renal disease should be counseled about the likelihood of progression of renal disease during pregnancy and irrespective of pregnancy, the increased risk of adverse pregnancy outcomes for the woman and offspring, and the importance of achievement or maintenance of normal blood pressure before conception. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are contraindicated during pregnancy; women who could become pregnant while taking these medications should be counseled about their adverse fetal effects and should be offered contraception if they are not planning a pregnancy. Women who are planning a pregnancy should discontinue these medications before pregnancy in favor of a safer regimen, whenever possible. Women who do not desire pregnancy should be offered an appropriate method of contraception.
Cardiovascular disease	B	III-3	Women of reproductive age with cardiac disease should be counseled about the risks that pregnancy presents to their health and the risks of the cardiac condition and any medications needed to treat the condition (eg, warfarin) on pregnancy-related outcomes. Women who are considering or planning a pregnancy should be counseled to achieve optimum control of the condition before conception and should be offered a suitable contraceptive method to achieve optimum timing of the pregnancy. Women whose treatment regimen involves warfarin should be counseled about its teratogenic nature; whenever possible, the treatment should be changed to a less teratogenic anticoagulant before conception. Women with a congenital cardiac condition should be offered preconception genetic counseling. Women who do not desire a pregnancy should be offered a suitable form of contraception.
Thrombophilia	C (women not using warfarin); B (women using warfarin)	III II-3	Providers may consider screening women of childbearing age for a personal or family history of venous thrombotic events or recurrent or severe adverse pregnancy outcomes. Women with a personal or family history suggestive of thrombophilia may then be offered counseling and testing for thrombophilias if they are contemplating pregnancy. Screening for thrombophilias with laboratory testing in routine care is not recommended. Women of reproductive age with a known genetic thrombophilia should be offered preconception genetic counseling to address the risk of the condition to the offspring. Women of reproductive age with a thrombophilia whose treatment regimen involves warfarin should be counseled about its teratogenic nature; whenever possible, the treatment should be changed to a less teratogenic anticoagulant before conception.
Asthma	B	II-3	All women with asthma should be counseled about the potential for their asthma control to worsen with pregnancy and the importance of achieving asthma control before a pregnancy through appropriate medical management and avoidance of triggers. Women with asthma who are planning to become pregnant or who could become pregnant should be treated with pharmacologic step therapy for their chronic asthma based on the American College of Allergy, Asthma, and Immunology–American College of Obstetricians and Gynecologists recommendations for the Pharmacologic Step Therapy of Chronic Asthma During Pregnancy. Women with poor control of their asthma should be encouraged to use effective birth control until symptom control is achieved.

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TABLE

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Potential component of preconception care	Strength	Quality	Recommendation
Psychiatric condition			
Depression/anxiety	B	III	Providers should screen and be vigilant for depression and anxiety disorders among women of reproductive age because treating or controlling these conditions before pregnancy may help prevent negative pregnancy and family outcomes. Women of reproductive age with depressive and anxiety disorders who are planning a pregnancy or who could become pregnant should be informed about the potential risks of an untreated illness during pregnancy and about the risks and benefits of various treatments during pregnancy.
Bipolar disease	B	III	Women of reproductive age with bipolar disorder should be counseled that pregnancy is a time of substantial risk of relapse, particularly after discontinuation of ongoing mood-stabilizing maintenance treatment. A relapse prevention and management strategy for bipolar disorder should be outlined before the patient attempts conception. Women of reproductive age with bipolar disorder should be counseled regarding contraceptive options, which should include options that will prevent conception during bipolar episodes.
Schizophrenia	B	III	Women of reproductive age with schizophrenia should be counseled, together with a partner or family member whenever possible, about the risks of pregnancy on their condition and the risk of their condition on pregnancy-related outcomes. They should be counseled about the importance of prenatal care, and a relapse prevention and management strategy of the illness should be outlined before the patient attempts conception. Appropriate contraception should be offered to women who do not desire a pregnancy.
Parental exposure			
Alcohol	B	I-a	All women of childbearing age should be screened for alcohol use, and brief interventions should be provided in primary care settings, which should include advice regarding the potential for adverse health outcomes. Brief interventions should include accurate information about the consequences of alcohol consumption, which should include the effects of drinking during pregnancy, information about effects beginning early during the first trimester, and warnings that no safe level of consumption has been established. Women who show signs of alcohol dependence should be educated about the risks of alcohol consumption; for women who are interested in modifying their alcohol use patterns, efforts should be made to identify programs that would assist them in achieving cessation and long-term abstinence. Contraception consultation and services should be offered and pregnancy should be delayed until it can be an alcohol-free pregnancy.
Tobacco	A	I-a	All women of childbearing age should be screened for tobacco use. Brief interventions should be provided to all tobacco users and should include brief counseling that describes the benefits of not smoking before, during, and after pregnancy; discussion of medication; and referral for more intensive services (individual, group, or telephone counseling) if the woman is willing to use these services. For pregnant women, augmented counseling interventions should be used.
Illicit substances	C	III	A careful history should be obtained to identify use of illegal substances as part of the preconception risk assessment. Men and women should be counseled about the risks of using illicit drugs before and during pregnancy and offered information on programs that support abstinence and rehabilitation. Contraception services should be offered, and pregnancy should be delayed until individuals are drug free.

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TABLE
Strength of the recommendations and the quality of the evidence for preconception clinical intervention to improve maternal or the infant health

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Potential component of preconception care	Strength	Quality	Recommendation
Family and genetic history			
All individuals	B	III	All women who are considering pregnancy should have a screening history in the preconception visit. Providers should ask about risks to pregnancy on the basis of maternal age, maternal and paternal medical conditions, obstetric history, and family history. Ideally, a 3-generation family medical history should be obtained for both members of the couple, with the goal of identifying known genetic disorders, congenital malformations, developmental delay/mental retardation, and ethnicity. If this screening history indicates the possibility of a genetic disease, specific counseling should be given, which may include referral to a genetic counselor or clinical geneticist.
Ethnicity-based	B	II-3	Couples who are at risk for any ethnicity-based conditions should be offered preconception counseling about the risks of that condition to future pregnancies. Screening and/or testing should be offered on the basis of the couples' preferences. This may require referral to a genetic counselor or clinical geneticist, especially in the instance of a positive finding.
Family history	B	II-3	Individuals identified as having a family history of developmental delay, congenital anomalies, or other genetic disorders should be offered a referral to an appropriate specialist to better quantify the risk to a potential pregnancy.
Previous pregnancies	C	III	If at least 1 member of a couple has a known chromosomal anomaly, in vitro fertilization with preimplantation genetic diagnosis should be discussed.
Known genetic conditions	B	II-3	Suspected genetic disorders may require further work-up prior to conception. Known or discovered genetic conditions should be optimally managed before and after conception.
Nutrition			
Dietary supplements	C	III	All women of reproductive age should be asked about their use of dietary supplements (vitamins, minerals, traditional/home remedies, herbal products, weight loss products, etc) as part of preconception care and should be advised about what is or is not known about their safety, impact, and efficacy.
Vitamin A	B	III	Currently the recommended dietary allowance of preformed vitamin A for women is 700 retinal activity equivalents (RAEs) per day, with a tolerable upper intake level for pregnancy of 3000 RAEs/day or 10,000 IU/day).
Folic acid	A	I-a	All women of reproductive age should be advised to ingest 0.4 mg (400 μg) of synthetic folic acid daily that is obtained from fortified foods and/or supplements. In addition, all women should be advised to consume a balanced, healthy diet that includes folate-rich foods.
Multivitamins	A	II-2	All women of reproductive age should be encouraged to take a folic acid–containing multivitamin supplement for the purpose of supporting healthy pregnancy outcomes and preventing congenital anomalies.
Vitamin D	B	II-3	There is insufficient evidence to recommend for or against routine screening or vitamin D supplementation during preconception counseling. Based on the emerging data of the importance of vitamin D for women and infants, however, clinicians should be aware of the risk factors for vitamin D deficiency. Additionally, for women with vitamin D deficiency, education on vitamin D in the diet and supplementation should be a part of preconception care. Currently, we do not have data for the optimal dose before and during pregnancy. More data are needed urgently.

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TABLE

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Potential component of preconception care	Strength	Quality	Recommendation
Calcium	A	I-b	Women of reproductive age should be counseled about the importance of achieving the recommended calcium intake level through diet or supplementation. Calcium supplements should be recommended if dietary sources are inadequate.
Iron	A	I-b	At a preconception visit, screening should be conducted for women with risk factors for iron deficiency for the purposes of identifying and treating anemia. There is evidence to recommend that all women be screened at a preconception visit for iron deficiency anemia for the purpose of improving perinatal outcome.
Essential fatty acids	B	I-b	During the preconception period, women should be encouraged to eat a diet rich in essential fatty acids, including omega-3 and omega-6 fatty acids. To achieve this, women should be advised to consume at least 12 ounces of fish and no more than 6 ounces of canned albacore tuna weekly. More research is needed critically to assess the risks and benefits of fish and fish oil consumption during the preconception period.
Iodine	A	II-2	Women of reproductive age with iodine deficiency should be counseled about the risks of this condition to pregnancy outcomes and about the importance of maintaining adequate daily dietary iodine intake of 150 μg during preconception and at least 200 μg when pregnant or lactating. Public health efforts to implement salt iodization programs should be encouraged for all women who reside in regions with endemic iodine deficiency.
Overweight	A	I-b	All women should have their BMI calculated at least annually. All women with a BMI of $\geq$ 25 kg/m^2 should be counseled about the risks to their own health, the additional risks associated with exceeding the overweight category, and the risks to future pregnancies, including infertility. All women with a BMI of $\geq$ 25 kg/m^2 should be offered specific strategies to improve the balance and quality of the diet, to decrease caloric intake, and to increase physical activity and should be encouraged to consider enrolling in structured weight loss programs.
Underweight	A	III	All women should have their BMI calculated at least annually. All women with a BMI of $\leq$ 18.5 kg/m^2 should be counseled about the short- and long-term risks to their own health and the risks to future pregnancies, including infertility. All women with a low BMI should be assessed for eating disorders and distortions of body image.
Eating disorders	A	III	All women with anorexia and bulimia should be counseled about the risks to fertility and future pregnancies. Women with these disorders should be encouraged to enter into treatment programs before pregnancy.
Environmental exposure			
Mercury	B	III	Women of childbearing age who may become pregnant should avoid consumption of shark, swordfish, King mackerel, and tile fish. Other fish consumption (such as tuna) should also be limited but is allowed in up to 2 meals of 3 oz each per week. Many state government agencies issue fish advisories and bans relating to mercury concentration in locally caught fish. In addition, the maternal diet may be supplemented with essential fatty acids from nonseafood sources.
Lead	C	II-2	There is insufficient evidence to recommend that all women should be screened for elevated levels of lead for the purpose of improving perinatal outcomes. However, women who are exposed to high levels of lead or with a history of known high lead levels, including childhood lead poisoning, should be counseled about the risk of lead to the unborn child. For women with a history of high blood lead levels, it is reasonable to test the serum lead level and, if elevated, to initiate activities to lower the levels before conception.

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TABLE

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Potential component of preconception care	Strength	Quality	Recommendation
Soil and water hazards	B	III	During a preconception visit, women should be asked if their well water has ever been tested or if there have been questions about their municipal water quality in the past. Any possible water quality problems should be investigated by the local health department; if concerns are identified, women should use bottled water for drinking and cooking. Depending on the contaminant and its concentrations, alternative locations for bathing may also be required. Although not derived from the ambient environment, dietary exposure to Bisphenol A (BPA) from canned food liners or water bottles is an emerging hazard generating conflicting recommendations from public health agencies. During the preconception visit, women should be advised about BPA avoidance in their diet.
	B (BPA avoidance)	II	
Workplace exposure	B	III	During a preconception visit, women should be asked about the work environment. If potential exposures are identified, consultation with an occupational medicine specialist may assist with a more detailed investigation regarding recommendations for work modification.
Household exposure	A	III	During a preconception visit, women should be asked about the home environment. If potential exposures are identified, consultation with an occupational medicine specialist may assist with a more detailed investigation regarding recommendations for modification of exposures.
Psychosocial risk			
Inadequate financial resources	C	III	All women should be asked about their economic status, and women who appear to be struggling financially should be referred to an agency that can check their eligibility for various types of financial assistance.
Access to care	C	III	All women should be asked about their health insurance coverage and their usual source of care. If they do not have health insurance, they should be referred to a welfare office or a private social service agency to determine their eligibility for public insurance. If they do not have a usual source of care, one should be established that will accept their insurance coverage or provide care free of charge or on a sliding fee basis.
Physical/sexual abuse	C	III	All women should be asked about their experiences of physical, sexual, or emotional violence from any source (parents, intimate partners, or strangers) currently, in the recent past, or as children. For women who are being abused or who have been abused in the recent past, the provider should express strong concern and willingness to assist in correcting the abusive situation. Appropriate evaluation, counseling, and treatment for physical injuries, sexually transmitted infections, unintended pregnancy, and psychologic trauma should be offered, which should include the provision of emergency contraception and empiric antimicrobial therapy in the case of sexual assault. Women should be offered information about community agencies that specialize in abuse for counseling, legal advice, and other services. Every clinician who sees women should have a list of such agencies easily available.
Medication			
Prescription	A	II-2	As part of preconception care, all women should be screened for the use of teratogenic medications and should receive counseling about the potential impact of chronic health conditions and medications on pregnancy outcomes for mother and child. Whenever possible, potentially teratogenic medications should be switched to safer medications before conception. For women with chronic conditions with serious morbidity (to mother and infant), the fewest number and lowest dosages of essential medications that control maternal disease should be used. For women who do not desire pregnancy, a plan for contraception should be addressed and initiated.
Over-the-counter medication	A	III	Health care providers should educate women of reproductive age about the need to discuss the use of over-the-counter medications with their provider when planning a pregnancy. Women should be advised specifically not to use aspirin if they are planning a pregnancy or become pregnant.

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TABLE

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Potential component of preconception care	Strength	Quality	Recommendation
Dietary supplements	A	II-c	Health care providers should educate women of reproductive age about the need to discuss the use of dietary supplements before pregnancy (which include herbs, weight loss products, and sport supplements) and should caution women about the unknown safety profile of many supplements. High-quality and prescription-quality dietary supplements should be encouraged.
Reproductive history			
Prior preterm birth infant	A	I-a	Pregnancy history should be obtained from all women of reproductive age. Women with a history of preterm or low-birthweight infant should be evaluated for remediable causes to be addressed before the next pregnancy and should be informed of the potential benefit of treatment with progesterone in subsequent pregnancy.
Prior cesarean delivery	A	II-2	Preconception counseling of women with previous cesarean delivery should include counseling about waiting at least 18 months before the next pregnancy and about possible modes of delivery so the patient enters the next pregnancy informed of the risks and options. Ideally, the counseling should begin immediately after the cesarean delivery and continue at postpartum visits.
Prior miscarriage	A	I-a	Women with sporadic spontaneous abortion should be reassured of a low likelihood of recurrence and offered routine preconception care. Women with $\geq$ 3 early losses should be offered a work-up to identify a cause. Therapy that is based on the identified cause may be undertaken. For women with no identified cause, the prognosis is favorable with supportive care.
Prior stillbirth	B	II-2	At the time of the stillbirth, a thorough investigation to determine the cause should be performed and communicated to the patient. At the preconception visit, women with a previous stillbirth should receive counseling about the increased risk of adverse pregnancy outcomes and may require referral for support. Any appropriate work-up to define the cause of the previous stillbirth should be performed if it was not done as part of the initial workup. Risk factors that can be modified before the next pregnancy should be addressed (eg, smoking cessation).
Uterine anomalies	B	II-3	A uterine septum in a woman with poor previous reproductive performance should be corrected hysteroscopically before the next conception. All other anomalies call for specific delineation of the anomaly and any associated vaginal and renal malformations. Although surgical correction may be advised in some cases, heightened awareness and surveillance during a subsequent pregnancy and labor should help optimize outcomes.
Special populations			
Women with disabilities	B	III	Women with disabilities should receive counseling about the risks of any medications that they use and about options to alter dosage or switch to safer medications before conception. The medical, social, and psychologic issues that are related to pregnancy and the disability should be assessed, and the woman and her family should be counseled about them. Healthcare providers should offer women with disabilities contraceptive choices that are practical and appropriate for the individual's medical and personal needs. Issues that involve informed consent and guardianship must be addressed when caring for women with developmental disabilities in relation to contraception and pregnancy. Referral for genetic counseling, if appropriate, is indicated for all women before conception; however, it may raise difficult psychosocial issues for women with disabilities; therefore, counseling referrals should be handled sensitively.

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TABLE

Strength of the recommendations and the quality of the evidence for preconception clinical intervention to improve maternal or the infant health

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Potential component of preconception care	Strength	Quality	Recommendation
Immigrant and refugee populations	B	III	Given the opportunistic fashion in which preconception care of immigrant and refugee women typically must occur, it is important to consider preconception concerns as part of all health care encounters with such women of reproductive age. Referring immigrant and refugee women to a source of ongoing primary care that is culturally and linguistically competent, and that will accept their insurance coverage or provide care free of charge or on a sliding-scale basis, is important for all such women. Seek to identify and understand the needs of immigrant women and their families; understand immigrants' potential for increased medical and social risks and previously undetected medical problems; deliver services and written materials in the preferred language of the population served; ensure that interpretation and translation services comply with all relevant federal, state, and local mandates governing language access; integrate preconception care into refugee screening; work with ethnic community-based organizations to provide preconception care messages in nonhealth care settings such as English as a Second Language classes; screen immigrants at high risk for tuberculosis and refer for them for treatment as indicated; screen immigrants born in Asia, the Pacific Islands, Africa, and other countries where hepatitis B is highly endemic, with the hepatitis B surface antigen test; assess the immunization history, including the rubella status, of immigrant women and administer any needed vaccines, or refer the women for these services; assess the mental health of immigrant women and refer them for services as needed.
Cancer	A	III	Newly diagnosed cancer survivors should be educated about fertility preservation options as soon as feasible and should be referred to reproductive specialists if these options are desired. Cancer survivors who consider pregnancy should be counseled about the potential reproductive effects of various cancer treatments on fertility and on pregnancy. Women who have received alkylating chemotherapeutic agents and/or pelvic or abdominal radiation should be counseled that they have an increased risk for premature ovarian failure. Women who have had pelvic or abdominal irradiation should be counseled that they are at risk for having a low birthweight infant. When considering pregnancy, breast cancer survivors who are candidates for selective estrogen receptor modulators should be counseled that these agents are generally avoided during pregnancy because of case reports of animal and human birth defects. A reliable nonhormonal contraceptive method should be used during treatment with a selective estrogen receptor modulator. Genetic counseling and testing should be offered to survivors of cancers that are linked to genetic mutations to inform their decisions about future reproduction. Female cancer survivors who received anthracycline chemotherapy, radiation to the heart or surrounding tissues, or both should be evaluated by a cardiologist before conception. Annual breast screening for female childhood cancer survivors who received chest radiation is recommended beginning at age 25 years.
Men	B	III	Despite the challenges and barriers, we recommend that each man who is planning with their partner to conceive a pregnancy should undergo a comprehensive medical evaluation for the purposes of disease prevention and detection and preconception education. Management should be optimized for any high-risk behaviors or poorly controlled disease states before conception is attempted.

Jack. The clinical content of preconception care: an overview and preparation of this supplement. Am J Obstet Gynecol 2008.

haviors simultaneously (eg, the "package of preconception services") have not been well-studied. There is strong evidence from multiple sources, which include randomized trials before pregnancy, for only a few conditions (eg, folic acid, diabetes mellitus). For some cases, the recommendations were based on case series that were specific to the preconception period (eg, phenylketonuria, rubella immunization); other recommendations were extrapolated from pregnancy guidelines or from data that were collected during pregnancy (eg, periodontal disease). For others (such as interventions that are related to smoking, alcohol misuse, and obesity), recommendations were based on studies of interventions that were delivered in primary care and not specifically delivered as part of preconception care. In some instances, recommendations were based on common sense. For example, most would agree that if genetic counseling is to be done, it is best done before pregnancy rather than

during pregnancy. Overall, based on the available evidence, there is a relatively short list of core interventions for which there is substantial evidence of efficacy when applied in the preconception period.

Summary of preconception recommendations

The Table provides a summary list of the topics that were reviewed, the consensus recommendation for each topic, the strength of the recommendation, and the rating of the quality of the evidence. Together, we believe that these recommendations represent the current state of the art in defining the evidence-based best practices in preconception care. These recommendations also identify the areas of preconception care in which more research is needed. We expect these recommendations to change as more information inevitably becomes available. ■

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Healthier women, healthier reproductive outcomes: recommendations for the routine care of all women of reproductive age

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By addressing the reproductive intentions and contraceptive practices and needs of every patient, providers may be able to decrease women's chances of experiencing unintended pregnancies and support women in achieving planned and well-timed pregnancies. By addressing the health promotion needs of every patient and examining and addressing her health profile for reproductive risks, irrespective of her desires for pregnancy, it is likely that more women will enter pregnancy with high levels of preconception wellness and that healthier women and healthier pregnancies and infants will result. The importance of the integration of reproductive planning and health promotion into women's routine healthcare is further emphasized when the potentially far-reaching effects of reproductive outcomes (such as unintended pregnancies, adverse pregnancy outcomes, pregnancy complications, and sexually transmitted infections) on women's health, well-being, and life circumstances are considered.

Key words: health promotion, preconception, reproductive life plan

The Select Panel on Preconception Health has set as 1 of its goals that all women of reproductive age receive preconception care services (ie, evidence-based risk screening, health promotion and interventions) that will enable them to enter pregnancy in optimal health.[1] To achieve the Select Panel's goal, the content of routine preconception care must be demystified. Although a special preconception visit is appropriate for women with complex medical and reproductive risks, it is not sufficient to recommend this strategy as a standard approach for disseminating clinical recommendations to all women.[2] Such an approach would miss many of the women who become pregnant each year, particularly those who become pregnant by chance rather than deliberate choice.

In 1990, Jack and Culpepper[3] recommended that preconception care be made available to all women and their partners as an integral part of primary care. Others have echoed this recommendation, including the American College of Obstetricians and Gynecologists (ACOG), which underscores that optimizing a woman's health before and between pregnancies must be an ongoing process.[4]

Incorporating preconception health promotion into routine care is termed *opportunistic*[2,5] because every clinical encounter before pregnancy offers an opening to explore and reinforce health promotion by addressing such topics as weight management, dietary supplementation, exercise, immunization status, benefits of deliberate decisions regarding pregnancy and contraceptive options, protection against sexually transmitted infections (STIs), and avoidance of exposures that include tobacco, alcohol, and other drugs.

By emphasizing the promotion of women's wellness at every visit, we have the potential to impact the health and well-being of women themselves and, in so doing, achieve higher levels of preconception wellness for women who become pregnant and results in a better pregnancy outcome for women and their infants. Among the recommendations of the Center for Disease Control and Prevention's (CDC) Select Panel on Preconception Health is 1 which reads: "As part of primary care visits, provide risk assessment and educational and health promotion counseling to all women of reproductive age to reduce reproductive risks and improve pregnancy outcomes."[1] Risk assessment and targeted education and counseling are based on a thorough medical history that is updated annually. The history includes all of the elements that are taught in basic medical and nursing education: medical history;

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family and genetic history; reproductive history; prescription, over-the-counter, and alternative therapies; allergies; alcohol, tobacco and illicit drug use, social history that includes personal safety; psychosocial status, diet and immunization status. Positive findings in any of these areas may be important to the woman's health in the short and long term, and/or they may be significant for the health of any pregnancy that she might conceive or for any infant that she might bear. In the succeeding articles of this supplement, the evidence is reviewed and recommendations are offered regarding whether there are benefits to addressing positive findings in each of these areas in the preconception period. The reader is encouraged to review all of these articles.

This article outlines specific recommendations for the health promotion of all women of reproductive age, irrespective of their intent to become pregnant. As described in the article, "Clinical Content of Preconception Care: An Overview,"[6] each of the recommendations has been graded for strength, and the quality of the evidence that supports the recommendation has been assessed. In other articles in this series, the burden of suffering has been defined; for this article, which is about health promotion, we have substituted the term *burden of risk*.

Family Planning Counseling and the Use of a Reproductive Life Plan

Burden of risk

Forty-nine percent of the pregnancies in the United States were identified as unintended (unwanted or mistimed) by women through the latest National Survey of Family Growth. Of these pregnancies, 44% ended in births; 42% ended in abortions, and 14% ended in fetal losses.[7] Unintended conceptions are represented in all sexually active subpopulations in the United States, with the probable exception of women who are being treated for infertility. The likelihood that a woman will experience an unintended pregnancy in her lifetime is significant. In 1994, 48% of women aged 15-44 years had experienced at least 1 unintended pregnancy sometime in their lives.[8] Forty-eight percent of unintended pregnancies occur in a month when contraception was used. In 1995, the Institute of Medicine detailed studies that examined the effects of unwanted and mistimed pregnancies on children, women, men, and families in a landmark publication, *The Best Intentions: Unintended Pregnancies and Well-being of Children and Families,* and found that such pregnancies were associated positively with elective abortions, late entry to prenatal care, low birthweight, child abuse and neglect, and behavioral problems in children.[9] Separating the impact of intendedness status from other social and environmental influences on these outcomes is, of course, difficult. The greatest impact may be additive rather than causal.[10] Unintended pregnancies, by definition, are unplanned, which means that the woman has not had an opportunity to take advantage of specific preconception health promotion and prevention activities beyond those they have undertaken for their own health, if any.

How detectable is the risk? Intendedness and unintendedness are self-reported and thus subject to reporting and recall bias. They are, by definition, only identifiable after the pregnancy has occurred.

How effective are the current treatment/prevention strategies? Contraception is highly effective; however, no method, including permanent sterilization, is perfect. Unintended pregnancies occur because of lack of contraception, imperfect use of contraception, and contraceptive failure. The latter 2 causes are significant because 49% of unintended pregnancies occur in women who used a method of contraception in the month they became pregnant.[7] Emergency contraception is available for women who determine themselves to be at risk for an unintended pregnancy. Studies indicate that women who use the levonorgestrel-only regimen for emergency contraception reduce the likelihood of pregnancy from 60%-94%.[11] Based on findings from 2 randomized controlled trials, levonorgestrel is significantly more effective that a combined estrogen and progestin approach.[12] Although the availability and quality of counseling are believed to influence decisions about the use of contraceptives, no standard definition of contraceptive counseling exists, and little research has addressed the relationship between counseling and contraceptive use, especially among adults.[13] Two recent systematic evidence reviews were unable to find research that could reliably answer whether counseling in the clinical setting can impact the successful use of hormonal contraception or successfully impact unintended pregnancies.[14,15]

Impact of preconception care. The only opportunity to prevent unintended pregnancy is before conception. The ideal reproductive planning tool would identify women who are planning to become pregnant within the next 12 months or at a later point in their lives and those women who are at risk of becoming pregnant (regardless of plans) because of lack of or inappropriate use of contraception. Existing tools or questions that facilitate women's reproductive planning include patient interview guides[16] and questions from the family planning module of the CDC's Behavioral Risk Factor Surveillance System Questionnaire. Examples of reproductive life plans have been put forth.[10] The receipt of preconception health promotion interventions that include an assessment of reproductive plans by low-income women who attend family planning clinics has been shown to increase subsequent pregnancy planning and intendedness.[17] Aside from this, reproductive planning tools have not been evaluated for feasibility or effectiveness (in terms of promoting planned pregnancies and timeliness of receipt of preconception care services) for women in the primary care or other settings. The CDC Select Panel Recommendations specify that the development, evaluation, and dissemination of reproductive life–planning tools and health education materials regarding preconception risk factors that are known to affect pregnancy outcomes is a high priority.[1]

Recommendation. Routine health promotion activities for all women of reproductive age should begin with screening women for their intentions to become or not become pregnant in the short and long term and their risk of conceiving (whether intended or not). Providers should encourage patients (women, men, and couples) to consider a reproductive life plan and educate patients about how their reproductive life plan impacts contraceptive and medical decision-making. Every woman of reproductive age should receive information and counseling about all forms of contraception from abstinence to permanent sterilization and the use of emergency contraception that are consistent with their reproductive life plan and risk of pregnancy. *Strength of recommendation:* A; *quality of evidence:* III.

Physical activity

Burden of risk. According to the CDC,[18] regular physical activity substantially reduces the risk of dying of coronary heart disease, which is the nation's leading cause of death for women and men. Exercise also decreases the risk for stroke, breast cancer, colon cancer, diabetes mellitus, and high blood pressure. It helps to control weight; contributes to healthy bones, muscles, and joints; reduces falls among older adults; helps to relieve the pain of arthritis; reduces symptoms of anxiety and depression; and is associated with fewer hospitalizations, physician visits, and medications. Moreover, physical activity need not be strenuous to be beneficial; people of all ages benefit from participating in regular, moderate-intensity physical activity, such as 30 minutes of brisk walking $\geq$ 5 times a week. Despite the proven benefits of physical activity, $>$ 50% of American adults do not get enough physical activity to provide health benefits, and 25% of adults are not active at all in their leisure time. Activity decreases with age and is less common among women than men and among those with lower income and less education.[18] Studies have found lower levels of cortisol and adrenalin in response to stressful stimuli in individuals who exercise regularly and are fit. Exercise has been associated with reduced allostatic loads and improved allostasis before pregnancy.[19]

How detectable is the risk? Detection is dependent on the provider asking and the woman honestly responding about her usual physical activity.

How effective are the current treatment/prevention strategies? There are no known direct benefits on pregnancy outcome of exercise before conception. Indirect benefits may include weight control and mood stability. Obesity is associated with numerous poor pregnancy outcomes, such as gestational diabetes mellitus, pregnancy-induced hypertension, preterm delivery, stillbirth, macrosomia, congenital anomalies.[20] Mood instability is associated with depression, which is often exacerbated in pregnancy and the postpartum period. A recent systematic review that was done under the auspices of the Agency for Health Research and Quality found several recent good- and fair-quality trials on the efficacy of counseling for physical activity in primary care; these studies found modest or no increases in physical activity, whereas previous reviews found interventions that target physical activity to be effective in the short term.[21] The National Institutes of Health recommends that all adults exercise at least 30 minutes a day on most, if not all, days of the week.[22]

Recommendation. All women should be assessed regarding weight-bearing and cardiovascular exercise and offered recommendations that are appropriate to their physical abilities. *Strength of recommendation:* C; *quality of evidence:* II-2.

Nutritional status

A woman's nutritional status has a profound impact on her own health and can impact fertility and reproductive outcomes. Considerations include diet quality and body mass index (BMI). In their article in this supplement, Gardiner et al[23] explore at length the topics of diet, supplements, and vitamins as important foundations for a healthy pregnancy. To make a difference, these topics must be addressed routinely with all women as an avenue to higher levels of nutritional health for themselves and for any pregnancies they may some day conceive.

Weight status

Burden of risk. Approximately one-third of all women in the United States are obese, and obesity is identified as the fastest growing health problem in this country. *Obesity*, defined as a BMI of $\geq$ 30 kg/m^2, is associated with elevated risks of type 2 diabetes mellitus, hypertension, infertility, heart disease, gallbladder disease, immobility, osteoarthritis, sleep apnea, respiratory impairment, social stigmatization, and a variety of cancers that include breast, uterine, and colon.[24,25] Mild-to-moderate overweight in young adults predicts subsequent obesity.[25] Weight retained from previous gestations is an important contributor to higher than optimal BMI in childbearing women.

Although most discussions of health risks that are associated with weight status focus on overweight and obesity, a 2005 analysis estimated the number of excess deaths that were associated with various BMI levels and found low BMI to be associated with excess deaths.[26] Computations revealed that 33,746 deaths were associated with BMI $<$ 18.5 kg/m^2. The prevalence of low BMI was 1.9% in women ages 25-59 years and 2.4% in women beyond age 70 years, with most of the excess deaths occurring in the older women. The study did not include women $<$ 25 years old, an age group for which there is a significant risk of female athlete syndrome (disordered eating, menstrual irregularity, and low bone mass) and disordered eating such as bulimia, anorexia nervosa, and binge-eating disorder. A recent cross-sectional study of female athletes in California found that 18.2%, 23.5%, and 21.8% met the criteria for disordered eating, menstrual irregularity, and low bone mass, respectively.[27] According to the ACOG, 7 million women and girls have eating disorders.[28] Of note, defining low BMI as $<$ 18.5 kg/m^2 also fails to capture most of the women who enter pregnancy underweight, as defined by the Institute of Medicine, whose recommendations for optimal weight gain by prepregnancy

BMI identifies the cut point for low BMI as < 19.8 kg/m^2.

Health risks of being underweight include nutrient deficiencies, heart irregularities, osteoporosis, amenorrhea, and infertility. For women who become pregnant, low pregravid weight is associated with increased risks for preterm birth, low birthweight, and intrauterine growth restrictions, all of which are major contributors to poor pregnancy outcomes in this country. A low prepregnancy BMI may also increase the risk for birth defects, such as gastroschisis. A study by Lam et al[29] found that infants who were born to underweight mothers (prepregnancy BMI, < 18.1 kg/m^2) were > 3 times more likely to have gastroschisis, compared with infants of normal weight mothers (prepregnancy BMI, 18.1-28.3 kg/m^2). In this study, every unit increase in BMI was estimated to decrease the risk for gastroschisis by approximately 11%.

How detectable is the risk? The use of a BMI chart is an easy and rapid way to assess the weight category of all patients. ACOG recommends that providers calculate each woman's BMI and review medical, social, and family risks for weight-related conditions.[24]

How effective are the current treatment/prevention strategies? Counseling to support improvements in diet and physical activity are considered first-line interventions.[24] In a systematic review, the US Preventive Services Task Force (USPSTF) concluded that counseling alone or with pharmacotherapy can promote modest sustained weight loss.[25] The most successful nonsurgical approaches to weight loss were intensive, weight-focused counseling that consists of > 1 session per month or multicomponent, intensive interventions that combine nutrition and exercise counseling with supportive, skill-building behavioral interventions. Evidence from randomized controlled trials of long-term benefits and improved health with weight loss was limited. The American Medical Association suggests that use of the stages of change model as adapted for overweight and obesity may help determine patient motivation and interest in weight loss.[30] ACOG recommends setting an initial goal of losing 5-10% of total body weight over a 6-month period as realistic and achievable.[24] Data that evaluate the effectiveness of this approach were not found. Strategies to impact low BMIs, if they are symptomatic of eating disorders, will require partnering with specialists in the field.

Recommendation. All women should have their BMI calculated at least annually. All women with BMIs ≥ 26 kg/m^2 should be counseled about the risks to their own health, the risks for exceeding the overweight category, and the risks to future pregnancies, including infertility. These women should be offered specific behavioral strategies to decrease caloric intake and increase physical activity and be encouraged to consider enrolling in structured weight loss programs. All women with a BMI ≤ 19.8 kg/m^2 should be counseled about the short- and long-term risks to the own health and the risks to future pregnancies, including infertility. All women with a low BMI should be assessed for eating disorders and distortions of body image. Women who are unwilling to consider and achieve weight gain may require referral for further evaluation of eating disorders. *Strength of recommendation:* A; *quality of evidence:* III.

Specific nutrient intake

Burden of risk. According to the National Nutrition Monitoring Survey, most women of reproductive age and older are not getting enough of the following nutrients through their diets: vitamins A, C, B6, and E; folate; calcium; iron; zinc; and magnesium. All of these nutrients are important for high levels of wellness. For instance, calcium supports and maintains optimal bone matrix; iron prevents some forms of anemia; zinc promotes healthy growth and an efficient immune system; vitamins A, C, and E are antioxidants that are important for the prevention of cardiovascular disease and cancers. In addition to being important for the health of a woman, these nutrients are important for the normal development of the embryo and the progress of a healthy pregnancy.

How detectable is the risk? Nutrient deficiencies are difficult to detect before related diseases manifest.

How effective are the current treatment/prevention strategies? The efficacy of meeting the recommended daily allowances (RDA) for all nutrients that are listed is not known relative to disease prevention. It is believed that taking a multivitamin affords a level of protection beyond that achieved through the usual food choices of most women. Willett and Stampfer,[31] who are leading researchers in the field of nutrition, have concluded that there is greater benefit than harm in recommending a daily multivitamin that does not exceed the RDA of its component vitamins for most adults. Their recommendation is based on the substantial evidence that higher intakes of folic acid and vitamins B6, B12, and D are needed and beneficial. In their review, a multivitamin is especially important for women who might become pregnant, for persons who regularly consume 1 or 2 alcoholic drinks per day, the elderly, those who tend to absorb vitamin B12 poorly, vegans, and those with limited resources to afford adequate fruits and vegetables.

Recommendation. All women of reproductive age should be assessed for nutritional adequacy and receive a recommendation to take a multivitamin supplement if any question of ability to meet the RDAs through food sources is uncovered. Care must be taken to counsel against ingesting supplements in excess of the RDAs. *Strength of recommendation:* A; *quality of evidence:* III.

Folate levels

Burden of risk. The specific nutrient, folate, has gained particular attention over the last 15 years because of the epidemiologic evidence that women who do not receive some form of folate supplementation have an increased likelihood of having a pregnancy that is complicated by neural tube defects (NTDs) and other birth defects.[32-40] Increasingly, low folate levels have been associated with the

occurrence of coronary artery disease, breast and colon cancers, and the development of some forms of dementia.[41-50] Folate levels can be altered by consuming folate-rich foods or by ingesting folic acid, a synthetic compound that is available through dietary supplements and through fortified foods. Folic acid is approximately 50% more bioavailable than folate and therefore has a greater efficiency in protecting against disease states influenced by folate levels.[51]

How detectable is the risk? Nutrient deficiencies are difficult to detect before related diseases are manifested; NTDs that are present within 28 days after conception usually are diagnosed through fetal testing, such as alpha-fetoprotein blood assays and ultrasound evaluations that are done early in the second trimester of gestation.

How effective are the current treatment/prevention strategies? Compelling evidence about the benefits of folic acid in the prevention of NTDs resulted in the 1992 US Public Health Service recommendation that "all women of reproductive age in the United States who are capable of becoming pregnant should consume 0.4 mg of folic acid (400 μg) per day for the purpose of reducing their risk of having an affected pregnancy."[52] Subsequently, the US Food and Drug Administration approved a population-based strategy to fortify all enriched grain products with folic acid, effective January 1998. The fortification levels were set relatively low but have resulted in the average woman, who eats a standard diet, ingesting an extra 190-240 μg of folic acid daily.[53,54] In 1998, the Institute of Medicine affirmed the US Public Health Service recommendation and added that women of childbearing years should take 400 μg of synthetic folic acid daily that is obtained from fortified foods and/or supplements and consume a balanced, healthy diet of folate-rich food.[55] The Institute of Medicine recommendation combines the 3 approaches that are available to individual women to increase their exposure to folic acid: supplementation, ingestion of fortified foods, and ingestion of foods that are naturally rich in folate, all of which are dependent on knowledge, behaviors, and access to the protective choices.

Supplementation is the strategy that has been promoted the longest. Two reports on trends that are related to the use of folic acid before conception indicate that, at most, daily supplementation has been adopted by $\leq$ 40% of nonpregnant women of reproductive age.[56,57]

The National Health and Nutrition Examination Surveys (NHANES) are conducted periodically by the CDC to assess the health, dietary practices, and nutritional status of noninstitutionalized civilians in the United States. In 2002, the CDC analyzed the NHANES from 2 time frames and found that the median serum and erythrocyte folate concentrations had increased significantly for women ages 15-44 years after fortification.[58] Subsequently, Dietrich et al[59] undertook further analysis of NHANES data and found that $<$ 10% of women of reproductive age reached the erythrocyte folate concentration that is associated with protection against NTDs. They excluded all survey participants in their analysis who had used any nutritional supplement in the 30 days before their laboratory testing. The researchers concluded that fortification at the presently mandated level was probably not sufficient to prevent NTDs. In the most recent analysis of NHANES data, the CDC[60] reported a 16% decline in serum folate concentrations among women aged 15-44 years from 1999-2000 to 2003-2004; red blood cell folate concentrations decreased 8% over the same time periods. Both of these findings were statistically significant.

The spina bifida rate per 100,000 live births declined 25% from 1995-2000 and 13% from 2000-2005. The anencephaly rate declined 35% from 1991-1995 and was unchanged from 1995-2005.[61] What portion of these reductions are related to the trio of prevention strategies, supplementation, fortification, and food choices and what portion is related to ascertainment biases that are related to early prenatal diagnosis and elective terminations is unknown. However, that a primary prevention opportunity exists that is inexpensive has potential health benefits beyond the prevention of congenital anomalies and which is underused suggests that more emphasis must be placed on reaching women with this simple strategy. Reinforcement of public awareness campaigns by clinicians has been demonstrated to increase the use of folic acid supplementation markedly.[62,63]

Recommendation. All women of reproductive age should be advised to ingest 0.4 mg (400 μg) of synthetic folic acid daily from fortified foods and/or supplements and to consume a balanced, healthy diet of folate-rich food.[55] *Strength of recommendation:* A; *quality of evidence:* I-a.

Immunizations

The routine care of all women should consider her risks and susceptibility to infections that are preventable through vaccination. In this supplement, Coonrod et al[6] provide a thorough review of the evidence for immunizations as part of a comprehensive preconception health and healthcare program.

By assessing every woman's immunization status routinely, irrespective of her pregnancy intentions, more women will be protected against preventable diseases and will enter pregnancy with fewer infectious disease risks. The Advisory Committee on Immunization Practices of ACOG and the American Academy of Family Physicians have identified that assessment of immunity and appropriate protection should be provided to all adults ages 19-49 years for the following diseases: tetanus, diphtheria, pertussis; varicella; and measles, mumps, and rubella. The Advisory Committee on Immunization Practices also endorses human papillomavirus vaccination for all women $\leq$ 26 years. The need for other immunizations is recommended based on specific risk factors.[64]

Recommendation. All women of reproductive age should have their immunization status for tetanus, diphtheria, pertussis; measles, mumps, and rubella; and varicella reviewed annually and updated as indicated. All women should be assessed annually for health, lifestyle, and occupational risks for other infections and offered indicated immunizations.

Strength of recommendation: A; *quality of evidence:* III.

Substance use

In their article in this supplement, Floyd et al[65] detail the importance and impact of substance exposure on pregnancy outcomes. Because the prevalence of alcohol and tobacco use by women of reproductive age is significant and has the potential to impact their own health as well as the health of any pregnancies they may conceive, these topics have been included in this article as appropriate areas for inclusion in the routine care of all women.

Tobacco

Burden of risk. According to the USPSTF, tobacco use is the leading preventable cause of death in the United States and results in 440,000 deaths annually. Over 155,000 deaths annually from neoplasms, 80,000 deaths from ischemic heart disease, and 17,000 deaths from cerebrovascular disease are attributed to smoking.[66] For women, specifically, cigarette smoking is the largest preventable cause of death and disability in this country.[67] Women who smoke have higher likelihood of dysmenorrhea, secondary amenorrhea, and menstrual irregularities. They also enter into menopause at an earlier age and are at increased risk for hip fractures. Smoking also affects health outcomes of people other than the smokers; smoking during pregnancy results in the deaths of approximately 1000 infants annually. Significant risks that are associated with smoking during pregnancy include premature births, spontaneous abortions, stillbirths, and intrauterine growth retardation. A metaanalysis found a 90% increased risk of placenta abruption in smokers[68]; smokers also have an increased risk for placenta previa.

How detectable is the risk? Screening for tobacco use usually is achieved through a verbal history that is associated with underreporting of exposure. Urinary cotinine levels can be used to screen for and monitor smoking, but this approach is not usual in clinical practices.

How effective are the current treatments/prevention strategies? Brief tobacco cessation counseling interventions that include screening, brief counseling ($\leq$ 3 minutes), and/or pharmacotherapy have proved to increase tobacco abstinence rate. The "5 As" behavioral counseling framework provides a useful strategy for engaging patients in smoking cessation discussions. The 5 As are assess, advise, agree, assist, and arrange; this approach, which has been demonstrated through clinical trials to be effective, has been endorsed by the USPSTF as an effective strategy for use in the primary care setting.[69] Clinics that implement screening systems that are designed regularly to identify and document a patient's tobacco use increase their rates of clinician intervention, although there is limited evidence for the impact of screening systems on tobacco cessation rates.[70] The USPSTF found good evidence that brief smoking cessation interventions that include screening, brief behavioral counseling ($<$ 3 minutes), and pharmacotherapy can be offered effectively in primary care settings to increase the proportion of smokers who successfully quit smoking and remain abstinent after 1 year.[71]

Recommendation. All women should be assessed for the use of tobacco at each encounter with the healthcare system, and those who smoke should be counseled, using the 5 As, to limit exposure. *Strength of recommendation:* A; *quality of evidence:* II-2.

Alcohol

Burden of risk. According to the USPSTF, alcohol misuse is associated with $>$ 100,000 deaths per year.[72] Alcohol misuse includes numerous patterns of alcohol ingestion: Risky drinkers are those who consume above the recommended daily, weekly, or per-occasion amounts; harmful drinkers experience harms that are associated with their alcohol intake but do not meet the criteria for alcohol abuse and dependence that are associated with repeated negative physical, psychological, and social effects from alcohol. Maximum recommended consumption is $\leq$ 1 standard drink per day for adult women and for anyone older than 65 years of age, and $\leq$ 2 standard drinks per day for adult men.[72] No alcohol consumption is considered safe in pregnancy. Prenatal alcohol exposure is associated with significant maternal and fetal health risks that include miscarriage, growth retardation, and fetal alcohol spectrum disorders, which includes fetal alcohol syndrome. Prenatal alcohol use is considered a leading preventable cause of birth defects and developmental disabilities in the United States.[73,74] In the *2006 National Survey on Drug Use and Health,*[75] 53% of women ages 15-44 years reported current alcohol use, and 23.6% reported binge drinking. National estimates that used the 2002 Behavioral Risk Factor Surveillance System report that more than one-half of women who do not use contraception reported alcohol use and that 12.4% of the women reported binge drinking in the 30 days preceding the survey.[76] Many women who are at risk for pregnancy will conceive and continue alcohol use during the earliest weeks of pregnancy when the greatest prenatal damage from alcohol exposure will occur. An estimated 11% of women who drink 1-2 oz of absolute alcohol a day during the first trimester have babies with features consistent with fetal alcohol syndrome,[77] which includes growth retardation, physical anomalies, neurodevelopmental abnormalities, and mental retardation. There is no established safe level of alcohol consumption during pregnancy.[78]

How detectable is the risk? Determining alcohol use patterns is dependent on the provider asking and the patient providing reliable answers. There are no known validated questionnaires for the assessment of alcohol use, but there are a number of validated screening instruments to assess alcohol abuse in childbearing-aged women (such as the TWEAK [Tolerance, Worried, Eye-opener, Amnesia, K/Cut down], T-ACE [Tolerance, Annoyed, Cut down, Eye-opener], Audit, and Audit-C).[79,80] The National Institute on Alcohol Abuse and Alcoholism produced a guidance document for clinicians (*Helping Patients Who Drink Too Much: A Clinician's Guide)*[81] that uses

quantity, frequency, and maximum amounts of alcohol consumed as a guide for advising and treating individuals who exceed recommended limits.

How effective are the current treatments/prevention strategies? A systematic evidence review that was undertaken by the USPSTF found that good quality brief multicontact behavioral counseling interventions that are delivered by primary care providers reduces risky and harmful alcohol use.[69] Very brief or brief single contact interventions were less effective or ineffective.[69] The elements in effective interventions were generally consistent with the 5 As approach to behavioral counseling interventions that have been endorsed by the USPSTF as appropriate to the primary care setting.[69] The 5 As are assess, advise, agree, assist, arrange. Evidence-based guidelines have been developed for identifying and intervening with reproductive aged women who are engaging in risky drinking. Currently, screening and brief interventions are the recommended standard of care for alcohol abuse problems in adults and pregnant women.[82] A recent randomized controlled trial found that motivational interventions that are aimed at alcohol and effective contraception in the preconception period significantly reduced the risk of alcohol-exposed pregnancies in high-risk women.[83]

Recommendation. All women should be assessed at least annually for alcohol use patterns and risky drinking behaviors and provided with appropriate counseling; all women should be advised of the risks to the embryo/fetus of alcohol exposure in pregnancy and that no safe level of consumption has been established. *Strength of recommendation:* A; *quality of evidence:* III.

STIs

Burden of risk. The CDC estimates that approximately 19 million new STIs occur annually in the United States, almost one-half of which are among young adults ages 15-24 years.[84] Although STIs are common among all ages, races, and ethnic groups, racial and ethnic minorities are affected disproportionately. In a companion article in this supplement, Coonrod et al[85] provide a detailed overview of the prevalence, screening, and treatment of STIs and review the evidence to support recommendations for women who may become pregnant. Given the prevalence of STIs and their serious health consequences, the primary care of all women, whether pregnancy is intended or not, should include assessment of STI risk, counseling, and other strategies for prevention and provision of indicated testing and treatment.

How detectable is the risk? The CDC clinical prevention guidelines for STIs (a component of the STI treatment guidelines)[86] specify that healthcare providers should routinely and regularly obtain sexual histories from their patients and address risk reduction strategies based on identified risk practices. The "5 Ps," which focus on partners, prevention of pregnancy, protection from STIs, sexual practices, and past history of STIs, is an identified approach for eliciting a complete sexual history.[86]

How effective are the current treatments/prevention strategies? The prevention of STIs is based on patient education and counseling about avoidance of STIs through changes in sexual behaviors and the preexposure vaccination of persons at risk for vaccine-preventable STIs. The CDC STI prevention guidelines advise that healthcare providers use a client-centered, interactive approach to provide counseling and education that are directed at a patient's personal risk, the situations in which risk occurs, and the use of goal-setting strategies around specific actions that can reduce the risk for STI transmission.[86] A randomized controlled trial of a client-centered approach, Project RESPECT, demonstrated that a brief counseling intervention is associated with a reduced frequency of STI risk-related behaviors and with a lowered acquisition of STIs.[87] Practice models that are based on Project RESPECT have been implemented successfully in clinical settings.[88]

Although it is known that abstaining from sexual activity or being part of a long-term, mutually monogamous relationship with an uninfected partner is the most reliable way to avoid the transmission of STIs, it is unknown whether counseling about abstinence or monogamy is effective in promoting these behaviors.

Male latex condoms, when used consistently and correctly, are effective in preventing the transmission of HIV and some other STIs, which include chlamydia, gonorrhea, and trichomoniasis. Male latex condom use is also associated with a 70% reduction in the risk for transmission of human papillomavirus. Male latex condom use might reduce the risk for transmission of herpes simplex virus-2, although data are limited. The failure of condoms to protect against STI transmission usually results from inconsistent or incorrect condom usage rather than from condom breakage. Male condoms that are made from materials other than latex have higher breakage and slippage rates when compared with latex condoms, but condoms made from polyurethane or other synthetic material should be substituted for latex condoms for those with latex allergy. Male condoms that are made from natural membrane condoms (eg, lamb cecum) have pores that do not allow the passage of sperm but that do allow the transmission of many STIs, which includes HIV and hepatitis B. Therefore, the use of natural membrane condoms for protection against STIs is not recommended.[86] Laboratory studies demonstrate that the female condom is an effective mechanical barrier to viruses, which includes HIV, and to semen. If used consistently and correctly, the female condom has been shown to reduce the risk of STIs in a limited number of clinical studies.[86] Female condoms are substantially more costly than male condoms.

The use of spermicides that contain nonoxynol-9 has been associated with disruption of the genital epithelium, which might be associated with an increased risk for HIV transmission. As such, spermicides that contain nonoxynol-9 (including condoms that are lubricated with nonoxynol-9) are not recommended for STI prevention.[86]

Preexposure vaccination is 1 of the most effective methods for the prevention of transmission of specific STIs,

which include hepatitis B, hepatitis A, and human papillomavirus. Hepatitis B vaccination is recommended for all unvaccinated, uninfected persons being evaluated for an STI. Hepatitis A vaccine is licensed and is recommended for men who have sex with men and illicit drug injecting and noninjecting drug users. A vaccine against human papillomavirus types 6, 11, 16, and 18 is available and recommended for women and girls aged 9-26 years. Vaccination strategies are discussed more fully elsewhere in this supplement.[6]

Recommendation. Healthcare providers should assess STI risks regularly and routinely, provide counseling and other strategies that include immunizations to prevent the acquisition of STIs, and provide indicated STI testing and treatment for all women of childbearing age. *Strength of recommendation:* A; *quality of evidence:* III.

Comment

By addressing the reproductive intentions and contraceptive practices and needs of every woman who seeks care, providers may be able to decrease women's chances of experiencing unintended pregnancies and support women in achieving planned and well-timed pregnancies. By addressing the health promotion needs of every woman who seeks care and examining and addressing her health profile for reproductive risks, irrespective of her desires for pregnancy, it is likely that more women will enter pregnancy with high levels of preconception wellness and that healthier women and healthier pregnancies and infants will be the result. The importance of integrating reproductive planning and health promotion into women's routine healthcare is further emphasized when the potentially far-reaching effects of reproductive outcomes (such as unintended pregnancies, adverse pregnancy outcomes, pregnancy complications, and STIs) on women's health, well-being, and life circumstances are considered. Because the reproductive capacity for most women spans nearly 4 decades, during which time her reproductive intentions and risks are likely to change, the importance of viewing women's reproductive health promotion as an on-going process is underscored. ■

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The clinical content of preconception care: immunizations as part of preconception care

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Many vaccine-preventable diseases have serious consequences for the pregnant mother, the fetus, and the neonate. This article reviews the rationale and impact of including vaccinations as part of preconception care and provides recommendations for clinical care. Vaccinations that are recommended highly in preconception care include the hepatitis B and the measles, mumps, and rubella vaccines. The role of human papillomavirus, varicella, diphtheria, tetanus, and pertussis vaccinations as part of preconception care is also discussed.

Key words: immunization, preconception care, vaccine

Many vaccine-preventable diseases may have serious consequences for both the mother and fetus during pregnancy, which makes the immunization status of women of reproductive age an important focal point for preconception care. Prevention of congenital rubella syndrome is a prototype for preconception care because it is needed before conception and is very effective in preventing a congenital disease that has significant morbidity and mortality rates. Some immunizations act by preventing congenital infection, others by preventing perinatal transmission. Some vaccines are recommended in the preconception period because they cannot be administered during pregnancy; others have maternal benefits because they avoid treatment that might have adverse consequences for the pregnancy. This article reviews the evidence for immunizations as part of a comprehensive preconception healthcare program.

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Human papillomavirus (HPV)

Burden of suffering. HPV is 1 of the most common forms of sexually transmitted infections; it appears as flat or papillary warts on the cervix, vagina, and vulva. Its prevalence in women ranges from 16-84% in study populations.[1] Several viral types have been determined as the etiologic factor that leads to cervical dysplasia and cervical cancer. There is evidence that links maternal HPV infections to juvenile-onset recurrent respiratory papillomatosis or laryngeal papillomatosis, which is an extremely rare disease that is associated with low mortality but high morbidity rates.[2] Research has documented a higher rate of exposure to HPV with vaginal delivery than cesarean section,[3] but no difference in infection rates. The risk of neonatal papillomatosis is very low, so there is no indication for a cesarean section delivery.

How detectable is the condition? Genital warts are detected by visual examination and the occasional need for biopsy to confirm the diagnosis. HPV infection is generally detected by cytologic screening, which aims to detect abnormalities in the epithelium of the cervix. Screening for high-risk types of HPV through nucleic acid tests is usually done in conjunction with cytologic screening when certain findings (atypical squamous cells) are found on cytologic examination. Direct screening for high-risk HPV is also used in the follow-up of patients with cytologic abnormalities and as a primary screening method in women ≥ 30 years.

How effective are the current treatments? Treatment of abnormal cytologic findings is highly effective in the prevention of cervical cancer.[1]

Impact of preconception care. The diagnostic evaluation of cervical cytologic

abnormalities is less complicated outside of pregnancy because certain diagnostic tests may be contraindicated during pregnancy (eg, endocervical curettage). Treatment of abnormalities that are caused by HPV is more straightforward before pregnancy; more treatment options are available before pregnancy. Because the primary screening method for HPV is cervical cytologic screening in conjunction with DNA detection, women should undergo this screening at regular intervals, which is recommended by various groups. Primary prevention for HPV has become available recently through an HPV vaccine for selected HPV types. This vaccine has the potential of reducing the incidence of HPV-related genital disease, which includes cervical, penile, vulvar, vaginal, and anal cancer and precancerous lesions.[4] The quadrivalent vaccine, by decreasing the incidence of genital warts, has the potential to reduce laryngeal papillomatosis among the children of those vaccinated.[4] Another potential benefit of the vaccine is avoidance of loop electrosurgical excision procedure and cone biopsy, which can impact cervical performance during pregnancy.[5]

Recommendations by other groups. The Advisory Committee on Immunization Practices (ACIP) currently recommends the HPV vaccine for women and girls aged 9-26 years who have not yet completed the series, with the recommendation to begin vaccination in girls who are 11-12 years old.[6] The US Preventive Services Task Force (USPSTF), American Cancer Society (ACS), and American College of Obstetricians and Gynecologists (ACOG) all recommend cytologic screening beginning at age 21 years or 3 years after the onset of sexual activity (whichever comes first).[7-9] The groups vary on the screening interval, with the USPSTF stating that most of the benefit of screening occurs with screening every 3 years; ACS recommends annual screening with conventional methods, every 2 years with liquid-based cytology; although ACOG recommends annual screening until age 30, then every 2 to 3 years if there are no previous abnormalities.[7-9]

Recommendation. Women should be screened routinely for HPV-associated abnormalities of the cervix with cytologic (Papanicolaou) screening. Recommended subgroups (ie, women and girls 9-26 years of age) should receive the HPV vaccination series for the purpose of decreasing the incidence of cervical abnormalities and cancer. By avoiding the need for procedures on the cervix because of abnormalities that are caused by HPV, the vaccine could help decrease the proportion of pregnancies that end in preterm birth that is related to cervical incompetence during pregnancy. *Strength of recommendation*: B; *quality of evidence:* II-2.

Hepatitis B

Burden of suffering. Hepatitis B is predominantly a sexually transmitted disease in the United States.[10] Causes of hepatitis B transmission include blood transfusions and transmission through semen, infected wounds or needles, and vaginal secretions. Persons at high risk for hepatitis B include men who have sex with men, intravenous drug users, and those with multiple sex partners. Almost 25% of sexual contacts of a seropositive partner will become infected. The risks of neonatal transmission range from 10% if the woman has an acute hepatitis B infection during the first trimester to 90% during the third trimester.[11] If a woman is infected chronically (demonstrated by hepatitis B surface antigen [HBsAg] seropositivity), the risk of perinatal transmission is 10-20%. If she is chronically infected and seropositive for both HBsAg and hepatitis B e antigen, the risk of transmission to a fetus is approximately 90%. Chronic infection occurs in $>$ 90% of infected infants. Chronic infection poses a risk of cirrhosis and hepatocellular carcinoma.

How detectable is the condition? Hepatitis B is detectable through clinically available serum antibody and antigen panels.

How effective are the current treatments? Vaccination is the primary method of hepatitis B prevention. Studies have not shown a decreased risk in long-term outcomes when the general population is screened, but high-risk women who were not vaccinated previously should be tested. Vertical transmission of hepatitis B is prevented by the administration of immunoprophylaxis at birth to infants with seropositive mothers. However, infants who are exposed to acute infection in utero have additional risks that include low birthweight[12] and prematurity.[13] The infants of women who are chronic carriers should receive the hepatitis B immune globulin within 12 hours of delivery and hepatitis B vaccination at birth, 1, and 6 months. This vaccination series conveys a high protective efficacy (95%) against perinatal transmission. Breastfeeding is not contraindicated for infants who have been immunized.

Impact of preconception care. There are no studies specifically of a preconception immunization program, but it makes sense to initiate this immunization before pregnancy for those who have not received it previously, rather than wait until pregnancy.

Recommendations by other groups. The USPSTF Force recommends screening pregnant women for HBsAg at the first prenatal visit (an "A" recommendation). They recommend against screening the general population for hepatitis B. In 1997, the ACIP recommended vaccination of all children ages 0-18 years. Their most recent recommendations for adults include offering vaccination to those who request the vaccine and those who are at high risk (household contacts or sex-partners of HBsAg-positive persons, sexually active persons not in a long-term monogamous relationship, men who have sex with men, those with HIV or a recent sexually transmitted infection, patients who are being treated with hemodialysis or with renal disease that may require hemodialysis, healthcare workers and public safety personnel, patients who receive certain blood products, staff and clients at institutions for the developmentally disabled, inmates of long-term correctional facilities, and persons who travel to high-risk areas).[14]

Recommendation. All high-risk women (household and sexual contacts of hepatitis B virus carriers, injection drug users,

women with sexually transmitted diseases or other high-risk behaviors that include multiple sex partners, international travelers, prisoners, and workers in healthcare, public safety, and institutions) who have not been vaccinated previously should receive hepatitis B vaccine before pregnancy; women who are chronic carriers should be instructed on ways to prevent transmission to close contacts and how to prevent vertical transmission to their babies. *Strength of recommendation:* A; *quality of evidence:* III.

Varicella

Burden of suffering. Chickenpox (varicella) is a highly contagious disease. In children, varicella is usually mild but can be severe in adults and fatal in neonates and immunocompromised persons. Infants of women with active disease during the first trimester or early second trimester are at risk for limb atrophy, scarring of the skin of the extremities, central nervous system abnormalities, and eye problems. The risk of congenital varicella from perinatal transmission during the first and second trimesters ranges from 0.4-2.0%, with a greater risk in the second trimester. Additionally, the maternal risk for severe infection, which includes varicella pneumonia, is high.[15]

How detectable is the condition? Varicella is diagnosed most commonly on the basis of its clinical presentation.

How effective are the current treatments? A 2-dose vaccination regimen has 98% efficacy against varicella infection.[16]

Impact of preconception treatment. The availability of varicella vaccine, the rare occurrence of a congenital varicella syndrome, and the severity of neonatal disease in infants of women who contract varicella late during pregnancy suggest a benefit for preconception immunization of those women who do not have a history of chickenpox.[15] A 2-dose varicella vaccine schedule is now approved for use in women of childbearing age without a history of chickenpox.[17] Because the vaccine contains live virus it should not be given to pregnant women, and women who have been vaccinated should be advised to avoid becoming pregnant for 1 month.[18,19] Breastfeeding is not contraindicated in women just vaccinated.[16]

Recommendations by other groups. The Centers for Disease Control and Prevention (CDC) ACIP recommends that all healthy children should receive their first dose of varicella vaccine routinely at 12-15 months of age and a second dose by 4-6 years of age. For those children, adolescents, and adults who received only a single dose (an earlier recommendation of ACIP), ACIP currently recommends a second catch-up vaccination to improve individual protection. The CDC ACIP recommends that all women be assessed prenatally for evidence of varicella immunity (by either a history of previous vaccination, previous varicella infection that is verified by a healthcare provider, or laboratory evidence of immunity). Those women who are not immune should be offered the vaccine (2 doses). The guideline includes specific recommendations that, if this is discovered during pregnancy, the series be initiated immediately after delivery (or termination of pregnancy) with a second vaccination in the series at the 6-week postpartum visit.[16] Because the effects of the varicella vaccine on the fetus are unknown, pregnant women should not be vaccinated. Because the varicella vaccine is a live vaccine, nonpregnant women who are vaccinated should avoid becoming pregnant for 1 month after each injection.

Recommendation. Because the varicella vaccine is contraindicated during pregnancy, screening for varicella immunity (by either a history of previous vaccination, previous varicella infection that is verified by a healthcare provider, or laboratory evidence of immunity) should be done as part of a preconception visit. All nonpregnant women of childbearing age who do not have evidence of varicella immunity should be vaccinated against varicella. *Strength of recommendation:* B; *quality of evidence:* III.

Measles, mumps, and rubella (MMR)

Burden of suffering. Measles (rubeola) is characterized by a rash and can be complicated by otitis media, pneumonia, and diarrhea; less frequent outcomes are encephalitis with long-term disability (1 in 1000 cases) and death (1-2 in 1000 cases). Measles during pregnancy has been associated with spontaneous abortion, prematurity, and low birthweight. Measles has been confirmed not to be a cause of birth defects.[20] Classic mumps causes parotitis often preceded by headache, myalgia, malaise, and anorexia. This classic presentation occurs in approximately one-third of cases; the rest are either asymptomatic (one-fifth) or cause a nonspecific respiratory illness. Serious complications such as meningitis are more likely in adults who experience the condition. There has been some association of mumps with first trimester abortion, but a specific congenital syndrome has not been described.[20] Rubella infection during pregnancy, particularly during the first 16 weeks, can result in spontaneous abortion, stillbirth, or a baby with congenital rubella syndrome. The incidence of rubella has declined by $>$ 99% since 1969, the year the rubella vaccine was licensed.[21] However, serologic surveys of various populations, which includes migrant populations in particular, found that 10-20% of women of childbearing age lack serologic evidence of immunity to rubella.

How detectable is the condition? MMR are identified by standard clinical activities.

How effective are the current treatments? The MMR vaccine has been determined to be very efficacious for all 3 viral illnesses.[20]

Impact of preconception care. Congenital rubella syndrome can be prevented by preconception screening and vaccination. Women who are not immune to rubella at a preconception visit should be vaccinated. A history of rubella during childhood is frequently inaccurate. Even with such a history, women who have not been tested previously, who have not received 2 doses of the MMR vaccine, and who are not pregnant should receive the vaccine without any testing. Women who receive the vaccination should be advised to avoid pregnancy for 3

months. Should conception occur soon after vaccination, the woman can be reassured that she is not at appreciable risk regarding the vaccination. Several large series have identified no cases of vaccination-related congenital defect.[20,22]

Recommendations by other groups. The CDC ACIP recommends that children receive a 2-dose primary series of MMR vaccination during childhood (the first at 12-15 months and the second at 4-6 years).[16] The CDC ACIP recommends that women of childbearing age who do not have acceptable evidence of rubella immunity or vaccination receive the MMR vaccine before pregnancy.[20]

Recommendation. All women of reproductive age should be screened for rubella immunity. MMR vaccination, which will provide protection against measles, mumps, and rubella, should be offered to those who have not been vaccinated or who are nonimmune and who are not pregnant. Because it is a live vaccine, women should be counseled not to become pregnant for 3 months after receiving the MMR vaccination. *Strength of recommendation:* A; *quality of evidence:* II-3.

Influenza

Burden of suffering. Epidemic influenza during fall and winter outbreaks is common and causes an annual average of 200,000 hospitalizations and 36,000 deaths. Morbidity and death is more likely in children who are < 2 years old, adults who are ≥ 65 years old, and those with medical conditions that put them at risk for complications.[23] For women with influenza during pregnancy, there is an increase in morbidity in the second and third trimesters and a possible increased abortion rate. Influenza causes increased morbidity in pregnancy that results in both serious medical complications and hospitalization.[24]

How detectable is the condition? Influenza is identified easily in standard clinical care.

How effective are the current treatments? Vaccination is approximately 70-90% effective in preventing influenza against viruses that are targeted in the preparation.[24] Vaccination of pregnant women against influenza is recommended to reduce the risk of complications and to provide passive protection to the neonate.[25-28] Inactivated influenza vaccines are generally well-tolerated, with reactions seen in $< 5\%$ of cases. Common side-effects consist of low-grade fever and mild systemic symptoms. The vaccine is prepared from viruses grown in eggs; therefore, a small amount of egg protein is present in these vaccines. Women with a history of anaphylaxis to eggs should not be vaccinated. An increased risk of Guillain-Barré syndrome is associated with the influenza vaccine, but this risk appears to be rare and significantly smaller than the overall risk that is posed by naturally occurring influenza infection. There have been no reported adverse outcomes from influenza vaccination in pregnancy. A study of influenza immunization in > 2000 pregnant women did not find adverse fetal effects that were associated with the vaccine.[24] However, the potential for adverse effects in pregnancy from influenza vaccination has been reported. Thimerosal, a mercury-based preservative that is present in most inactivated formulations of the vaccine, has been implicated in human neurodevelopment disorders, which includes autism.[29] CDC studies have not confirmed these findings.[23] Two forms of "preservative-free" vaccine are available. Fluzone (Sanofi-Pasteur, Swiftwater, PA) is manufactured without thimerosal, and Fluarix (GlaxoSmithKline, Philadelphia, PA) has the thimerosal removed at the end of the manufacturing process.[30] Serious morbidity that results from influenza infection in early pregnancy must be balanced with the rare potential for adverse effects of vaccination. Parenteral inactivated virus vaccine should be administered intramuscularly to all women who will be pregnant during influenza season from October to mid November and continues as late as May, when peak influenza activity may occur. The intranasal vaccine (LAIV, FluMist; MedImmune, Gaithersburg, MD) is a live, attenuated influenza vaccine and should not be used in pregnant women.[31]

Impact of preconception care. There are no specific data on influenza vaccination in a preconception population. Generalizations and recommendations for vaccination in the preconception period must be made on the basis of risks for women who may become pregnant or are in early gestation. Fetal exposure to influenza during the first trimester has been implicated in a nested case-control study potentially to increase the risk of schizophrenia. The biologic mechanism is not defined; however, investigators noted that it may be worth considering routine vaccination of nonpregnant women several weeks before pregnancy, given the possibility that the antibody response to influenza, rather than direct infection, may be responsible for the observed increase in risk of schizophrenia.[32]

Recommendations by other groups. The CDC currently recommends influenza vaccine in all pregnant women, regardless of gestational age during influenza season.[33]

Recommendation. Influenza vaccination is recommended for women who will be pregnant during influenza season and for any woman with increased risk for influenza-related complications, such as cardiopulmonary disease or metabolic disorders, before influenza season begins. *Strength of recommendation*: C; *quality of evidence:* III.

Diphtheria, tetanus, and pertussis (Tdap)

Burden of suffering. Pertussis, or "whooping cough," is a respiratory condition that causes long-term cough. Estimates in the United States from prospective studies suggest that from 300,000-600,000 cases of symptomatic pertussis occur each year. Complications in adults include rib fracture, pneumonia, and cough syncope. Infants who are < 12 months old are susceptible for pertussis-related death. The number of cases has dropped since the introduction of the vaccine in the United States in the 1940s until 1976; since then there has been a steady increase, especially in adolescents and adults.[34] Tetanus is a condition that is caused by the inoculation of *Clostridium tetani* spores, which are found throughout the environment, through a break in the skin. This leads to

the development of a neurotoxin in oxygen-poor wounds. Symptoms include lockjaw (trismus) followed by rigidity of skeletal muscle, including those involved in respiratory function. Five hundred fifty-four cases were reported in the time period from 1990-2001 in the United States. Neonatal infection with infection of the umbilical stump at birth is rare in the United States (3 cases in 14 years); however, it has worldwide significance, being implicated in 250,000 deaths worldwide in 1997.[35] Diphtheria causes a respiratory illness that is distinct for the development of a grayish membrane over the pharynx, palate, and nasal mucosa that can obstruct the airway. Diphtheria is rare, with only 7 cases reported in 6 years in the United States.[36]

How detectable is the condition? Pertussis may be difficult to diagnose, given its wide ranging symptoms and large differential diagnosis with other respiratory conditions. Given the rarity of tetanus and diphtheria in the postvaccine era, both may be difficult to diagnose in a timely manner.

How effective are the current treatments? One risk group of concern for pertussis is young infants (< 12 months), so household contacts of infants should be targeted for vaccination. There is no evidence that the tetanus and diphtheria toxoids (Td) vaccine is teratogenic when used extensively; the data are more limited for Tdap. Neither vaccine is believed to be contraindicated in pregnancy when given in the recommended second or third trimester.[37] The Tdap vaccine is believed to prevent some of the morbidity in adults, which includes pregnant women, given the burden of disease in this age group.

Impact of preconception care. Because passive immunity is protective against neonatal tetanus, immunization before pregnancy would be of benefit. Administration of tetanus toxoid during pregnancy is well supported and also might be preventive, especially in developing countries. Immunization before pregnancy with Tdap may protect the newborn infant with passive immunity,[38] although it is unknown whether this passive immunity might result in hindrance of the development of an immune response when infants are vaccinated.[37]

Recommendations by other groups. The CDC ACIP recommends that children receive a 4-dose primary series of Tdap to be completed by 4-6 years of age. The CDC recommends a single dose of Tdap to prevent pertussis in all adults; this may be given if a patient has not received a Td booster in the past 10 years and may be as early as 2 years after a Td immunization. To protect against pertussis in infants < 12 months, close contacts of infants should receive the Tdap vaccine. For this reason the CDC recommends Tdap for any woman who might become pregnant or for women immediately after delivery who have not been vaccinated previously.[37]

Recommendation. Women of reproductive age should be up-to-date for tetanus toxoid, because passive immunity is probably protective against neonatal tetanus. The Tdap vaccine is recommended for women who might become pregnant or immediately after delivery to avoid complications of pertussis in the newborn infant. *Strength of recommendation:* B; *quality of evidence:* III.

Comment

Adherence to the recommended immunization schedule for children (for Tdap, hepatitis B virus, HPV, MMR, and varicella vaccines); administration of catch-up, booster, and risk-appropriate immunizations to adolescents and women of reproductive age (for Tdap, hepatitis B virus, HPV, influenza, and varicella vaccines); the screening of women of reproductive age for immunity to specific infections (varicella, rubella), and provision of immunization before pregnancy for those women who are found to be nonimmune are important components of a comprehensive preconception care program. Hepatitis B and MMR vaccines are highly recommended as part of any preconception care program because there is convincing evidence that there is benefit to giving these immunizations before pregnancy and that they are highly effective at preventing maternal disease and vertical transmission (hepatitis B) and in preventing congenital rubella syndrome (MMR). Those immunizations that are recommended, but with less convincing evidence that they should be part of preconception care, are the HPV vaccine (because it may avoid treatments that can affect obstetric outcomes adversely), varicella vaccine, and Tdap vaccine, because it might prevent the severe effects of neonatal infection. Each of the immunizations are lacking strong evidence to support that intervention in the preconception period prevents the consequences that affect the pregnancy, the fetus, and newborn infant. Influenza vaccination has a "C" recommendation because vaccination to avoid the consequences of influenza infection can be administered safely either in the preconception period or in pregnancy during the flu season. ■

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The clinical content of preconception care: infectious diseases in preconception care

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A number of infectious diseases should be considered for inclusion as part of clinical preconception care. Those infections strongly recommended for health promotion messages and risk assessment or for the initiation of interventions include Chlamydia infection, syphilis, and HIV. For selected populations, the inclusion of interventions for tuberculosis, gonorrheal infection, and herpes simplex virus are recommended. No clear evidence exists for the specific inclusion in preconception care of hepatitis C, toxoplasmosis, cytomegalovirus, listeriosis, malaria, periodontal disease, and bacterial vaginosis (in those with a previous preterm birth). Some infections that have important consequences during pregnancy, such as bacterial vaginosis (in those with no history of preterm birth), asymptomatic bacteriuria, parvovirus, and group B streptococcus infection, most likely would not be improved through intervention in the preconception time frame.

Key words: infectious disease, preconception, screening

Infectious diseases can impact pregnancy-related outcomes and the reproductive health of women. Some, such as gonorrheal and chlamydial infections, may impact the ability to conceive or the site of implantation. Others, such as group B streptococcus (GBS) infection, can have important clinical consequences during pregnancy but are not preventable through preconception strategies so are not addressed through preconception care. Others, such as bacterial vaginosis (BV) and periodontal disease, are linked with adverse pregnancy outcomes in some studies; however, screening and treatment for asymptomatic disease, when initiated during pregnancy, is not associated unequivocally with improved outcomes. Because many prenatal interventions might have more impact when initiated in the preconception period, there is considerable interest in the evaluation of whether screening and treating these 2 conditions in the preconception period proves efficacious. Screening for particular infections as part of the preconception risk assessment can identify a number of potential risks to women's reproductive health and their future pregnancy outcomes and allows for those risks to be addressed before conception. This article discusses those infectious diseases that are important for consideration in preconception care.

HIV

Burden of suffering: Human immunodeficiency virus (HIV) can be transmitted

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from an infected woman to her fetus during pregnancy, labor, and delivery or through breastfeeding.[1] It has been estimated that approximately 280-370 infants in the United States were born with HIV infection in 2000.[2] Worldwide there are > 1900 infant lives lost to HIV daily and > 700,000 lost annually. Perinatal HIV transmission still accounts for > 90% of the cases of pediatric acquired immunodeficiency syndrome in the United States; 40% of these infants are born to mothers who are unaware of their HIV status.

How detectable is the condition? Primary prevention includes early education for both men and women about risky sexual behavior, such as unprotected intercourse and multiple partners, intravenous drug use, transfusions before 1985, and the benefit of the identification of HIV status before conception. Evaluation of 2 programs, the opt-in vs the opt-out approach, identifies the effect of 2 different consent designs and the impact on early detection of HIV. The opt-in approach includes informing women of their risk of HIV transmission to their newborn infant and of the ability to test for HIV and offering them the HIV test. The opt-out approach informs women that HIV testing is part of the standard battery of laboratory tests, unless they actively decline testing. Women who are given the opt-out approach tend to test more often, potentially resulting in reduced perinatal transmission.[3] Current recommendations are for a 2-stage approach to laboratory diagnosis of HIV disease in which an initial enzyme-linked immunosorbent assay (ELISA) screen (sensitivity, > 99.5%; specificity, > 99.8%) is followed by a confirmatory Western blot analysis (sensitivity, > 96%; specificity, > 99.9%).[4]

How effective are the current treatments? An important turning point occurred in 1994 when the AIDS Clinical Trial Group demonstrated that zidovudine, which was administered to a group of HIV-infected women during pregnancy and labor and to their newborn infants, reduced the risk of perinatal HIV infection by two-thirds, from 25.5-8.3%.[5] Studies confirm that treating HIV-positive mothers with antiretrovirals can reduce perinatal transmission to ≤ 2% in those women with a low viral load who do not breastfeed.[6-8]

Impact of preconception care. Knowing the HIV status of a woman before pregnancy allows for treatment and reduction of viral load, which decreases the risk of fetal transmission during pregnancy and labor. Women in the United States with HIV are advised not to breastfeed. If HIV infection is identified before conception, antiretroviral treatment can be administered, and women or couples can be given additional information to reduce the risk of mother-to-child transmission. It could also be argued that providing women with information about their HIV status before conception could alter their reproductive plans, with some women choosing not to become pregnant as a result of a positive diagnosis.

Recommendations by other groups. Because early identification and treatment initiation is the optimal method for reducing the risk of HIV infection among infants, the American College of Obstetricians and Gynecologists (ACOG), the American Academy of Pediatrics, the US Preventive Services Task Force (USPSTF), and the Centers for Disease Control and Prevention (CDC) recommend universal HIV testing in pregnancy as a routine component of the battery of prenatal blood tests, unless the test is declined. Outside of pregnancy, the CDC recommends screening all men and women from age 13-64 years for HIV.[9] Testing is to be repeated annually for those who are at high risk of acquisition. The USPSTF considers screening adults with risk factors to be an "A" recommendation and those without risk factors to be a "C" recommendation based on an updated systematic review.[10] For HIV-infected women, the USPSTF recommends the following components of preconception care: (1) effective contraception to prevent unintended pregnancy, (2) education about transmission risks and ways of decreasing them, (3) antiretrovirals with low reproductive toxicity, which can decrease vertical transmission and achieve a low viral load, with care to avoid adverse effects, (4) management of potential opportunistic infections (prophylaxis and immunization), (5) optimal nutritional status, (6) standard preconception care, (7) screening for psychologic and substance use disorders, and (8) possible consultation with a maternal fetal medicine specialist.[11] The British HIV Association makes recommendations for discordant couples who wish to achieve pregnancy: self-insemination for an infected woman with an uninfected male partner, and sperm washing for infected male and uninfected female partners.[12]

Recommendation. All men and women should be encouraged to know their HIV status before pregnancy and should be counseled about safe sexual practices. Those women who test positive must be informed of the risks of vertical transmission to the infant and the associated morbidity and mortality rates. These women should be offered contraception. Those women who choose pregnancy should be counseled about the availability of treatment to prevent vertical transmission and that treatment should begin before pregnancy. *Strength of recommendation:* A; *quality of evidence:* I-b.

Hepatitis C

Burden of suffering. Hepatitis C is becoming the silent epidemic in the United States. Nearly 4 million people in the United States are infected, and many patients are unaware that they are carriers. Hepatitis C is transmitted through contaminated blood and blood products. The most efficient modes of transmission include intravenous drug use and receipt of blood products or an organ transplant before 1992. Of intermediate risk of infection are patients on chronic hemodialysis, patients with undiagnosed liver disorders, and infants who were born to infected mothers. Less efficient modes of transmission occur in health care workers, people with multiple sexual partners, people in monogamous relationships with an infected partner, people who participate in tattooing and body piercing (with the use of common

household products like razors), and people who share straws for intranasal cocaine use. Sporadic transmission has been reported in 5% of cases of acute hepatitis and approximately 30% of cases of chronic hepatitis C. Women who test positive for anti–hepatitis C virus (HCV) antibody in pregnancy range from 0.1-4.5%.[13-15] Of note, there are settings in which the seroprevalence of hepatitis C is much higher, up to 50-90%, which include incarceration, homelessness, intravenous drug use, and migration from endemic areas.

How detectable is the condition? Screening for HCV is accomplished with tests to detect HCV antibody (anti-HCV) followed by a confirmatory test, which is usually 1 that detects HCV RNA because a low level of viremia is present in those with HCV.[16] There are no current recommendations for universal screening of women for hepatitis C, and this is not a cost-effective endeavor in low-risk women. However, screening that is based on risk factors seems to be appropriate, although long-term data that show improved outcomes are lacking.

How effective are the current treatments? Current recommended treatment for HCV consists of peginterferon and ribavirin for 24-48 weeks, with the dosages and duration dependent on HCV genotype. *Sustained virologic response*, which is defined as the absence of HCV RNA at the end of treatment and 6 months later, occurs in 40-70%, depending on HCV genotype. Currently, it is unclear whether such treatment prevents long-term sequelae of the disease.

Impact of preconception care. Women who test positive should be counseled on the risk of transmission to others and possible risk to the newborn infant. The neonatal transmission rate in pregnancy is approximately 5%. Hepatitis C may be transmitted through breastfeeding. The risk of vertical transmission increases in HIV-positive women (15%) and in the presence of maternal viremia, because vertical transmission is not known to occur in absence of detectable viral RNA. Currently, we do not have treatment for mother or infant or means to decrease perinatal transmission.[17] Because treatment is contraindicated in pregnancy and treatment duration may be up to 48 months, a woman's reproductive plans should be taken into account when considering therapy that includes a discussion of contraception while receiving treatment.

Recommendations by other groups. The USPSTF recommends not screening those women without risk factors. It states that there is insufficient evidence to screen in those women with risk factors, citing the lack of long-term data. The American Association for the Study of Liver Disease (AASLD) recommends both screening for those at high risk and treatment with evidence of liver inflammation.[16]

Recommendation. There are no data that preconception screening for hepatitis C in low-risk women will improve perinatal outcomes. Screening for high-risk women is recommended. Women who are positive for hepatitis C and desire pregnancy should be counseled regarding the uncertain infectivity, the link between viral load and neonatal transmission, the importance of avoiding hepatotoxic drugs, and the risk of chronic liver disease. Women who are being treated for HCV should have their reproductive plans reviewed and use adequate contraception while receiving therapy. *Strength of recommendation:* C; *quality of evidence:* III.

Tuberculosis

Burden of suffering. Worldwide, tuberculosis is the number 1 infectious disease killer. The CDC reported > 15,000 active cases of tuberculosis in 2001 and 10-15 million latent infections. Tuberculosis affects all parts of the body including the pulmonary, skeletal, gastrointestinal, genitourinary, and cutaneous systems. The case fatality rate approaches 50% in untreated patients, multidrug resistant infections, and infants with congenital disease. Tuberculosis during pregnancy is a risk factor for low birthweight and subsequently poor perinatal outcomes' conversion to active disease is more common in the postpartum period.

How detectable is the condition? Tuberculosis may be screened with the tuberculin skin test or with QuantiFERON-TB Gold (Cellestis Inc, Valencia, CA), an ELISA test that detects interferon-gamma in blood from sensitized persons. Both have equal sensitivity; however, the QuantiFERON-TB Gold test is believed to have greater specificity. As a result, this latter test has been found to be useful in recent immigrants who have received the bacille Calmette-Guérin vaccine, health care workers, and contact investigations.[18]

How effective are the current treatments? Based on clinical trials, treatment of latent tuberculosis infection is effective with isoniazid monotherapy (65% efficacy for 6 months and 75% efficacy for 12 months).[19] More advanced cases, which include multidrug resistant tuberculosis, require more extensive and toxic therapy.

Impact of preconception care. Screening for tuberculosis before pregnancy allows for prophylaxis completion, the opportunity to reduce the risk of poor pregnancy outcomes, and the avoidance of conversion to active disease. High-priority groups for treatment for latent tuberculosis infection include persons who converted within the past 2 years; persons with personal contact with someone who has active tuberculosis; illicit drug users; foreign-born persons from high-risk countries who have been in the United States < 5 years; the elderly; children who are <4 years old and who are exposed to high-risk adults; persons with chronic medical conditions such as HIV, diabetes mellitus, organ transplantation, end-stage renal disease, cancer, chronic steroid use, or underweight; health care workers; persons who are incarcerated; and persons who work in correction institutions.[20] Persons with a positive screening test result and who do not have evidence of active disease usually are treated with a 9-month regimen of isoniazid.[21]

Recommendations by other groups. The CDC recommends screening and treatment for latent tuberculosis in those who are at high risk for disease.[21] Pregnant

women may be treated for latent tuberculosis infection while pregnant.

Recommendation. All high-risk women should be screened for tuberculosis and treated appropriately before pregnancy. *Strength of recommendation:* B; *quality of evidence:* II-2.

Toxoplasmosis

Burden of suffering. Toxoplasmosis is a disease that is caused by infection with the protozoan *Toxoplasma gondii* that can be transmitted by an infected pregnant woman to her fetus. Raw meat and the feces of newly infected cats are the only other sources for the *Toxoplasma* protozoa infection. Approximately one-third of adult women in the United States have antibodies to toxoplasmosis, and the remainder may be at risk for a primary maternal infection during pregnancy that can result in congenital infection. Prospective studies that have been performed in the United States have established an incidence of congenital toxoplasmosis of 1.1 per 1000 live births. Of children who are born to mothers who had toxoplasmosis during pregnancy, approximately 8% are severely affected at birth. The remainder are affected with mild disease or subclinical infection but are at risk for late sequelae such as chorioretinitis, mental retardation, and sensorineural hearing loss, blindness, and epilepsy. Severe fetal effects are more likely if infection is acquired during the first or second trimester.[22,23]

How detectable is the condition? Toxoplasmosis infection is usually asymptomatic. Food and Drug Administration–approved commercial kits are available for the detection of past immunoglobulin G (IgG) and recent immunoglobulin M (IgM) infection. The tests for IgM have been noted to have limited specificity that results in high false-positive rates, especially when the incidence is low.

How effective are the current treatments? Treatment of acute toxoplasmosis during pregnancy may reduce but does not eliminate the risk of congenital infection. Should congenital infection be diagnosed, then multiple agent therapy is recommended. There is some evidence for improved outcomes when the affected infant is treated.

Impact of preconception care. Preconception testing for immunity to *T gondii* by the measurement of IgG antibody titer might provide physicians with useful information for counseling women. Women who are already immune can be reassured that they cannot become infected during pregnancy. Women who are susceptible should be counseled before pregnancy about cooking meat to a safe temperature, peeling or thoroughly washing fruits and vegetables before consumption, and properly cleansing utensils and cooking surfaces after contact with unwashed fruit or vegetables or raw meat, poultry, or seafood. If they become pregnant, they should be counseled to either avoid changing cat litter or to wear gloves and wash hands thoroughly afterwards, to keep cats inside, and to not feed raw or undercooked meat to cats.[24] Antibody testing during pregnancy that demonstrates *Toxoplasma* infection in a woman who had negative titers before pregnancy indicates that infection has occurred. In the absence of such preconception information, interpretation of titers that are obtained during pregnancy may be difficult. Thus, preconception testing might lead to a prompt diagnosis and timely treatment decisions.[25] There are no studies to suggest such testing is cost-effective or efficacious.

Recommendations by other groups. ACOG currently does not advocate testing for *Toxoplasma* infection during pregnancy, citing a low prevalence of the disease. It does advocate counseling women on modes of prevention (level C recommendation).[26] The CDC recommends education and counseling as modes to prevent infection. Testing for immunity is not mentioned.[27]

Recommendation. There is no clear evidence that preconception counseling and testing will reduce *T gondii* infection or improve treatment of those women who are infected. However, if preconception testing is done, those women who test positive can be reassured that they are not at risk of contracting toxoplasmosis during pregnancy; those women who are negative can be counseled about ways to prevent infection during pregnancy. For those women who convert during pregnancy, treatment should be offered. *Strength of recommendation:* C; *quality of evidence:* III.

Cytomegalovirus

Burden of suffering. Human cytomegalovirus is the most common viral infection in pregnancy, with an estimated birth prevalence of 0.6-2.2%. Primary maternal infection occurs in approximately 1% of pregnancies. Congenital cytomegalovirus is the leading cause of hearing loss in children; 15% of infants who are born to mothers who are infected during pregnancy will manifest hearing loss. The severity of fetal infection declines with gestational age, such that 20-30% of fetuses that are infected in the first one-half of pregnancy have serious sequelae that include intrauterine growth restriction, cerebral palsy, mental retardation, hepatosplenomegaly, petechiae, jaundice, chorioretinitis, hearing loss, thrombocytopenia, and anemia. The rate of infection increases with gestational age; therefore, fetal infection is more common later in pregnancy, but most infants are asymptomatic at birth. Cytomegalovirus infection is endemic in the community, with asymptomatic infections common during childhood.

How detectable is the condition? Cytomegalovirus is usually asymptomatic. Diagnosis is made by serologic confirmation of cytomegalovirus-specific IgM and a 4-fold rise in cytomegalovirus-IgG in paired sera. False-positive and -negative tests for cytomegalovirus-specific IgM are not rare. Fetal infection is best diagnosed by culture and/or polymerase chain reaction (PCR) of amniotic fluid after 21 weeks of pregnancy. Antenatal ultrasound scanning may identify affected fetuses but cannot exclude significant infection-related morbidity.[28]

How effective are the current treatments? There is no effective current treatment for primary cytomegalovirus infection in pregnancy. Ganciclovir crosses the pla-

centa but has not been demonstrated to improve outcomes for congenitally infected fetuses. The administration of cytomegalovirus-specific hyperimmune globulin (passive immunization) was promising in a small preliminary study by decreasing the frequency and severity of primary fetal infection.[29] Good personal hygiene, particularly hand-washing, is the most effective means of preventing infection among pregnant women.[30] There is no evidence that screening and/or treatment programs prevent infection.[31]

Impact of preconception care. There is no vaccine at present. Preconception testing of cytomegalovirus is not recommended because there is no evidence that this reduces perinatal infection. However, testing for immunity might be considered to stratify the risk of consequences of cytomegalovirus infection in pregnancy and the need for prevention efforts because primary infection poses a greater risk of sequelae of congenital infection.

Recommendations by others. The CDC and the ACOG recommend universal hand-washing precautions for pregnant women and education of reproductive-age women about hand-washing. The CDC recommends the following precautions for prevention: (1) practice good personal hygiene, especially hand-washing with soap and water (for 14-20 seconds) after contact with diapers or saliva (particularly with a child who is in daycare), (2) do not kiss children under the age of 6 years on the mouth or cheek, instead kiss them on the head or give them a hug, (3) do not share food, drinks, or utensils (spoons or forks) with young children, and (4) if pregnant and working in a daycare center, reduce the risk of getting cytomegalovirus by working with children who are > 2½ years of age, especially if you have never been infected with cytomegalovirus or are unsure if you have been infected.[32] Prenatal screening is not recommended.[32]

Recommendation. Women who have young children or who work with infants and young children should be counseled about reducing the risk of cytomegalovirus through universal precautions (eg, the use of latex gloves and rigorous hand-washing after handling diapers or after exposure to respiratory secretions). *Strength of recommendation:* C; *quality of evidence:* II-2.

Listeriosis

Burden of suffering. Listeriosis is a foodborne infection that is caused by the bacterium *Listeria monocytogenes* and typically affects pregnant women, newborn infants, and individuals with compromised immune systems. Although listeriosis is a rare disease in the United States, the case fatality rate is very high.[33] In the United States, approximately 2500 cases and 500 deaths occur each year.[34] Most cases are caused by ingestion of contaminated foods. Hispanic women in the United States are especially at risk because of ethnic preference for soft fresh cheeses, often made from raw milk. The organism can multiply at 40°F, which is the temperature of many refrigerators. It spreads hematogenously and infects the placenta in pregnancy by producing micro abscesses and fetal infection. *L monocytogenes* is associated with numerous adverse outcomes that include preterm labor, amnionitis, spontaneous abortion, stillbirth, and early-onset neonatal sepsis syndrome.[35] The common presentation in pregnancy is preterm labor, decreased fetal activity, or fetal death, with an influenza-like illness in the mother. Untreated, the fetal mortality rate approaches 50%.

How detectable is the condition? Listeria contamination of foods is detectable readily by bacteriologic culture. Listeriosis in humans is detected by culture of the products of conception in the case of spontaneous abortion, by amniocentesis with culture of the amniotic fluid in later pregnancy, or by culture from the placenta after birth.

How effective are the current treatments? If the diagnosis is made antenatally and the mother is treated with ampicillin, the maternal and neonatal outcomes are generally good.[36]

Impact of preconception care. Primary prevention efforts include improvements in food processing and consumer education.[37] The disease is not a grave problem before pregnancy in normal women; however, because exposure in early pregnancy can lead to pregnancy loss and severe maternal illness, preconceptional education is important to avoid exposure.

Recommendations by other groups. The CDC has investigated epidemics of listeriosis. Individual states have recommended education to avoid consumption of products that are implicated in such outbreaks.[38] An ACOG patient education pamphlet warns pregnant women of the disease and describes measures for food preparation to avoid it.[39]

Recommendation. Because it is not clear at what point in pregnancy women who are exposed to *Listeria* will become ill, preconception care should include teaching women to avoid pâté and fresh soft cheeses that are made from unpasteurized milk and to cook ready-to-eat foods such as hotdogs, deli meats, and left-over foods when trying to conceive or pregnant. *Strength of recommendation:* C; *quality of evidence:* III.

Parvovirus or fifth disease

Burden of suffering. Fifth disease is caused by infection with human parvovirus B-19. Infections are most common in school-aged children. The typical infection is characterized by malaise, low-grade fevers, and a facial rash (the slapped-cheek appearance of childhood).[40] Although 60% of adults have immunity,[26] in healthy adults, it can cause arthritis, arthralgias, and rarely, anemia.[41] Transmission occurs through close association, such as respiratory secretions and hand-mouth contact. Most women who are infected during pregnancy have healthy babies; however, infection during the first 20 weeks of pregnancy is associated with severe anemia, miscarriage, and fetal hydrops. Seroconversion is more likely through household than classroom exposure. The overall risk of fetal loss after maternal exposure is 6.5%. In an observational study of > 1000 women with acute parvovirus B-19 exposure, the risk of hydrops was 3.9%,[42] and fetal death occurred only with exposure at < 20 weeks of gestation.

Parvovirus has not been associated with congenital malformations.

How detectable is the condition? Both IgG and IgM antibodies can be detected with ELISA techniques as evidence of parvovirus infection. IgM can be detected after symptoms approximately 10 days after exposure; IgM antibody persists for approximately 3 months. IgG positivity provides evidence of past infection. Both are 80-90% sensitive for clinical infection. Parvovirus B-19 DNA can be detected with PCR in the amniotic fluid of affected fetuses.

How effective are the current treatments? In adults, parvovirus infection is usually mild, and there is no specific treatment for the condition unless anemia develops. There is concern for fetal effects. Frequent ultrasound surveillance is justified because parvovirus infection can lead to fetal anemia and hydrops. Cordocentesis and transfusion have proved effective in treating severe hydrops.[43,44] In fact, a survey of > 500 perinatologists with 539 cases of hydrops suggests that 89% used ultrasonography in initial management of parvovirus infection. Thirty-four percent of these cases of hydrops spontaneously resolved; 30% resulted in a fetal death, and 29% of the time there was a resolution with transfusion. Because of the possibility of spontaneous resolution, transfusion is reserved for cases of severe anemia and fetal compromise.[45] In utero exposure to parvovirus B-19 has not been associated with neurodevelopmental delay in the absence of fetal hydrops; however, a retrospective study showed that 32% of children who required in utero fetal transfusion demonstrated mild-to-severe neurodevelopmental delay.[46,47]

Impact of preconception care. No data have emerged to suggest preconception screening for immunity to parvovirus infection would prove beneficial.

Recommendations by other groups. ACOG has no preconception recommendations.

Recommendation. There is not yet evidence that screening for antibody status against parvovirus or counseling about ways to avoid infection in pregnancy will improve perinatal outcomes. Good hygiene practices should be encouraged for all pregnant women. *Strength of recommendation:* E; *quality of evidence:* III.

Malaria

Burden of suffering. Globally, malaria is 1 of the most common infections during pregnancy. Malaria is endemic in > 100 countries where > 24 million pregnant women are affected each year.[48,49] Malaria infection during pregnancy can have adverse effects on both mother and fetus and includes maternal anemia, fetal loss, premature delivery, intrauterine growth restriction, and delivery of low birthweight infants. In sub–Saharan Africa, which is the region of the world that is hardest hit by malaria, malaria infection is estimated to cause 400,000 cases of severe maternal anemia and 75,000-200,000 infant deaths annually. Maternal anemia contributes significantly to maternal death and causes an estimated 10,000 maternal deaths per year.[50] In the United States, 1324 cases of malaria were reported in 2004; all but 4 of those cases were imported. A total of 30 cases of malaria were reported among pregnant women in the United States in 2004.[51]

How detectable is the condition? In the United States, screening is not used because malaria is not endemic. Diagnosis rests on clinical criteria and confirmation of malaria through microscopy[52] or recently approved rapid diagnostic tests for malaria antigens.[53]

How effective are the current treatments? Guidelines exist for malaria infection that is diagnosed in the United States[54] that should be consulted. It is recommended that treatment be initiated only when confirmed with laboratory testing. Treatment regimens vary based on the disease severity, the species of malaria that was identified, and the region in which the disease was acquired (chloroquine resistant/sensitive). Specific regimens are recommended for pregnant women.[55]

Impact of preconception care. The traveler can reduce her risk of acquiring malaria by following several preventive approaches that include personal protection to avoid infective mosquito bites and the use of antimalarial chemoprophylaxis.[56] Women who are planning a pregnancy should be advised to (1) remain indoors between dusk and dawn, if mosquitoes are active outdoors during this time, (2) if outdoors at night, wear light-colored clothing, long sleeves, long pants, shoes, and socks, (3) stay in well-constructed housing with air-conditioning and/or screens, (4) use permethrin-impregnated bed nets, and (5) use insect repellents that contain N,N-diethyl-3-methylbenzamide (DEET) as needed. Permethrin and DEET have been shown to reduce the risk of malaria infection and are considered safe in pregnancy.[57-59]

Antimalarial chemoprophylaxis should be provided to women who are planning a pregnancy and traveling to malaria-endemic areas. For pregnant women who travel to areas with chloroquine-sensitive *Plasmodium falciparum* malaria, chloroquine has been used for malaria chemoprophylaxis for decades with no documented increase in birth defects. For pregnant women who travel to areas with chloroquine-resistant *P falciparum*, mefloquine can be used for chemoprophylaxis during the second and third trimesters. For women in their first trimester, most evidence suggests that mefloquine prophylaxis causes no significant increase in spontaneous abortions or congenital malformations, if taken during this period. Because there is no evidence that chloroquine and mefloquine are associated with congenital defects when used for prophylaxis, the CDC does not recommend that women who are planning pregnancy need to wait a specific period of time after their use before becoming pregnant.[60,61] The safety of atovaquone/proguanil use in early pregnancy has not been established, and doxycycline should be avoided in women who are planning a pregnancy. Primaquine should also be avoided because the drug may be passed transplacentally to a glucose-6-phosphate dehydrogenase–deficient fetus and cause hemolytic anemia in utero. Despite recent encouraging results, a vaccine against malaria infection in pregnancy is currently unavailable.[62]

Recommendations by other groups. The CDC publishes up-to-date information on malaria prevention for travelers for providers for adults and pregnant women.[63,64] In addition their online "Yellow Book" can be consulted.

Recommendation. Women who are planning a pregnancy should be advised to avoid travel to malaria-endemic areas. If travel cannot be deferred, the traveler should be advised to defer pregnancy and use effective contraception until travel is completed and to follow preventive approaches. Antimalarial chemoprophylaxis should be provided to women who are planning a pregnancy and traveling to malaria-endemic areas. *Strength of recommendation:* C; *quality of evidence:* III.

Gonorrhea

Burden of suffering. According to the CDC in 2005, gonorrhea occurs in about 116 per 100,000 persons;[65] infection with *Neisseria gonorrhea* is the second most common reportable disease in the United States. Some women with gonorrhea can be asymptomatic; however, gonorrhea is a major cause of cervicitis and pelvic inflammatory disease. Women with pelvic inflammatory disease are at risk for internal infections, chronic pelvic pain, and damage to fallopian tubes, which can cause infertility and increased risk of ectopic pregnancy.[66] Gonorrhea in pregnancy is associated with chorioamnionitis, premature rupture of membranes, and preterm labor. Perinatal transmission to the infant can result in severe conjunctivitis that leads to blindness if untreated and, rarely, meningitis and endocarditis.[66]

How detectable is the condition? A variety of tests are available for the detection of gonorrhea that include culture, amplified nucleic acid assays, direct immunofluorescence, and direct hybridization techniques. Sensitivity for amplification tests ranges from 66.7-100%, and specificity ranges from 96.8-100%.[66] Screening can be done in both men (from swabs of the urethra) and women (from swabs of the endocervix) or noninvasively in urine samples with amplified nucleic acid assays.[67]

How effective are the current treatments? Effective treatment for uncomplicated gonorrhea is available, is updated regularly, and can be accessed online.[68] Recently, because of resistance to quinolones, these agents are no longer recommended for treatment of gonorrhea infection.[69]

Impact of preconception care. Men and women who are being treated for sexually transmitted infections should be counseled about the risk of infertility that is imposed by having sexually transmitted diseases. Neonatal infection may result in blindness, joint infections, or blood infections. Currently, there are no data to support the greater effectiveness of screening before pregnancy over screening during pregnancy in preventing pregnancy-related complications.

Recommendations by other groups. The USPSTF recommends screening women (pregnant or not) for gonorrhea infection if risk factors exist.[70] The CDC makes similar recommendations.

Recommendation. High-risk women should be screened for gonorrhea during a preconception visit, and women who are infected should be treated. Screening should also occur early during pregnancy and be repeated in high-risk women. *Strength of recommendation:* B; *quality of evidence:* II-2.

Chlamydia

Burden of suffering. Chlamydia trachomatis is the most common bacterial sexually transmitted infection in the United States. Approximately 3 million new cases occur annually. Reported rates are higher in women than men, probably because women are more likely to receive routine health care encounters, which include testing of asymptomatic individuals.[71] Seventy to 90% of women are asymptomatic.[71] If untreated, *Chlamydia* infection can lead to pelvic inflammatory disease, infertility, and an increased risk of HIV infection. With relation to pregnancy, *Chlamydia* infection is associated with ectopic pregnancies, neonatal eye infections, and pneumonia.

How detectable is the condition? Numerous testing options exist for *Chlamydia* infection. The newer antigen detection tests may provide improved sensitivity, lower expense, and timeliness of results over culture; a sensitivity of 70-80% and a specificity of 96-100% have been reported for antigen detection tests.[67] Testing through urine specimens may improve access to and convenience of testing.

How effective are the current treatments? A well-designed randomized trial demonstrated that screening women who are at risk reduced the incidence of pelvic inflammatory disease from 28 per 1000 woman-years to 13 per 1000 woman-years and that the prevalence of chlamydial infection has declined in populations such as family planning clinics, which have been targeted by screening programs.[67] Reinfection is common; therefore, identification and treatment of all sexual partners is warranted. Effective treatments for *Chlamydia* infection are available from the CDC and are updated regularly.

Impact of preconception care. Identification and treatment before pregnancy has the potential to reduce infertility and ectopic conceptions; identification and treatment during pregnancy would be necessary to prevent neonatal eye infections and pneumonia. However, because of the risk of infertility from *Chlamydia* or gonorrhea infection, sexually active persons should be counseled to prevent transmission of sexually transmitted diseases and screened regularly for asymptomatic infections.

Recommendations by other groups. The USPSTF recommends screening nonpregnant women aged < 25 years and older women who are at high risk for *Chlamydia* infection as a strategy to prevent pelvic inflammatory disease as an "A" level recommendation.[71] Early treatment leads to decreased risk of infertility and ectopic pregnancy. They state that there is no evidence to support screening of men.[72] The CDC recommends annual screening for *Chlamydia* infection for women who are at high risk and for all pregnant women.[68] ACOG

recommends routine screening for chlamydial infection for all sexually active adolescents and other asymptomatic women who are at high risk for infection.

Recommendation. All sexually active women aged ≤ 25 and all women who are at increased risk for infection with *Chlamydia* (including women with a history of sexually transmitted infection, new or multiple sexual partners, inconsistent condom use, sex work, and drug use) should be screened annually at encounters before pregnancy. *Strength of recommendation:* A; *quality of evidence:* I-a, II-2.

Syphilis

Burden of suffering. The World Health Organization estimates that 12 million new cases of syphilis occur annually. In 2002, the CDC reported 32,000 cases of syphilis. Syphilis has declined in both women and neonates. In adults, the clinical presentation of syphilis ranges from being asymptomatic (latent syphilis) to local symptoms as in primary syphilis (genital ulcers) to more widespread symptoms such as skin rash, lymphadenopathy and mucocutaneous lesions (secondary syphilis) and finally to complications that are associated with tertiary syphilis (gummatous lesions and those that involve the neurologic, visual, and auditory systems). Congenital syphilis can come with devastating complications that include stillbirth, premature birth, neonatal death, developmental delay, blindness, deafness, bone and teeth abnormalities, and seizures.

How detectable is the condition? Identification of syphilis usually begins with a nonspecific nontreponemal test (Venereal Disease Research Laboratory or rapid plasma reagin) with sensitivity that ranges from 80-85% for primary syphilis to 90-95% for latent infection. These tests, when positive, are usually followed by a confirmatory treponemal test (fluorescent treponemal antibody-absorption treponema pallidum particle agglutination assay). This combination of tests has been used successfully in screening programs.

How effective are the current treatments? Antibiotics (usually penicillin G) can be used successfully to treat all stages of syphilis. Importantly, congenital syphilis can be treated and prevented with treatment early in pregnancy.[68]

Impact of preconception care. Preconception screening for syphilis in high-risk populations is an important step in the reduction of neonatal syphilis. Persons who are at risk for syphilis include men who have sex with men, persons in correctional facilities, commercial sex workers, persons who have sex with high-risk individuals, and persons who are diagnosed with other sexually transmitted infections. Syphilis can be cured if treated in its early stages. However, treatment does not prevent reinfection. Even if adequate treatment is established, repeat testing should occur during pregnancy in the first and third trimesters. Studies show that most stillbirths occur at about 30 weeks of gestation. Therefore, even in unplanned pregnancies, prompt and immediate treatment of syphilis might decrease the risk of stillbirth and other perinatal morbidities. Perinatal morbidity and mortality rates can be as high as 40% in women who are untreated. Preconception screening and treatment may have the additional advantage of avoiding costly and complicated penicillin desensitization in patients with penicillin allergies.

Recommendations by other groups. The US Preventive Services Task Force (USPSTF) recommends screening all pregnant women for syphilis in the first trimester ("A" level recommendation). They also recommend screening women at high risk for infection ("A" level recommendation). Many states require syphilis screening as a requirement to obtain a marriage license.[73,74] The CDC also recommends screening pregnant women, with repeat screening in the early third trimester for those at high risk (including those with a positive test earlier in pregnancy), or in areas with high morbidity from syphilis.

Recommendation. High-risk women should be screened for syphilis during a preconception visit, and women who are infected should be treated. Because the USPSTF and CDC recommend screening all women during pregnancy for syphilis, screening for syphilis immediately before conception is recommended. *Strength of recommendation:* A; *quality of evidence:* II-1.

Herpes simplex virus

Burden of suffering. At least 50 million persons in the United States have genital herpes infection. Neonatal transmission occurs in approximately 1 in 3000 deliveries. Forty percent of neonatal herpes cases result in localized skin infections. Encephalitis develops in 25% of cases, with the poorest prognosis for 25% of infected neonates who go on to have disseminated disease that can affect multiple organ systems.

How detectable is the condition? When a patient has clinical symptoms and characteristic lesions, the diagnosis is straightforward; however, clinical diagnoses should be confirmed with a culture. Although cultures have good specificity, sensitivity may be limited, as low as 50% in some cases. PCR-based tests have higher sensitivity. Evidence of past infection may be detected through serologic testing.

How effective are the current treatments? Treatment for HSV infection consists of antiviral therapy, which cannot eradicate infection. Instead, treatment is aimed at reducing symptoms, the duration of lesions, or the recurrence of lesions.

Impact of preconception care. The risk of HSV-2 sexual transmission can be reduced by the daily use of acyclovir or valacyclovir by an infected person.[75,76] Couples with an infected male partner should be encouraged to consider suppressive antiviral therapy as part of a strategy to prevent transmission, in addition to consistent condom use and avoidance of sexual activity during recurrences. Most individuals with genital herpes infection are asymptomatic, so it is important to teach couples about the signs and symptoms of genital herpes infections.[77] Women with a history of genital herpes should be counseled about the risk of vertical transmission to the fetus

and newborn child. Women who have active lesions or prodromal symptoms at the time of delivery are offered cesarean delivery to reduce perinatal transmission. To reduce the risk of recurrence at delivery and of cesarean delivery for women with a history of genital herpes, prophylactic antiviral agents may be used from 36 weeks until delivery.[78] Both HSV-1 and -2 can cause perinatal infection. Couples with a history of orolabial herpes should be counseled about good hygiene practices, because orolabial disease can also be transmitted to the newborn infant.

Recommendation by other groups. ACOG recommends cesarean delivery for women with active lesions during labor and possible suppressive therapy late in gestation. The USPSTF recommends against routine serologic screening of pregnant women or asymptomatic adults. The CDC recommends against routine serologic screening for HSV in pregnant women and states that there is not sufficient evidence to support routine suppression for women with a history of recurrent HSV.

Recommendation. During a preconception visit, women with a history of genital herpes should be counseled about the risk of vertical transmission to the fetus and newborn child; those women with no history should be counseled about asymptomatic disease and acquisition of infection. Although universal serologic screening is not recommended in the general population, type-specific serologic testing of asymptomatic partners of persons with genital herpes is recommended. *Strength of recommendation:* B; *quality of evidence:* II-1.

Asymptomatic bacteriuria

Burden of suffering. Asymptomatic bacteriuria occurs in 3-8% of pregnant women and is a risk factor for low birthweight. Between 20% and 40% of pregnant women with asymptomatic bacteriuria without adequate treatment or follow-up experience acute pyelonephritis with an attendant increased risk of fetal death and morbidity.

How detectable is the condition? Most urine tests with immediate results (urine dipstick or direct microscopy) have poor predictive values, which limits their use in screening for asymptomatic bacteriuria. Urine culture, although more expensive and time-consuming, is the test of choice for screening.

How effective are the current treatments? Appropriate antibiotic treatment of bacteriuria is 90-95% effective in the prevention of progression to pyelonephritis.

Impact of preconception care. Data are not consistent as to whether treatment has a significant positive effect on birthweight or on gestational age at birth in women with asymptomatic bacteriuria who do not go on to have acute pyelonephritis. A review of 17 studies that investigated the relationship between asymptomatic bacteriuria and low birthweight/prematurity concluded that women with asymptomatic bacteriuria have an increased rate of low birthweight/prematurity when compared with women with sterile urine. They also concluded from the 8 randomized clinical studies that were available that women with asymptomatic bacteriuria who are treated have a lower rate of low birthweight than untreated women. There are no data to suggest that screening before pregnancy is more beneficial than screening and treating during pregnancy.

Recommendations by other groups. The USPSTF concluded that early detection of asymptomatic bacteriuria is of value for pregnant women, but that screening of asymptomatic adults is not justified because of concerns that serious urinary tract disorders are relatively uncommon, the positive predictive value of screening urinalysis is low, and the effectiveness of early detection and treatment is unproved.[79]

Recommendation. There have been no studies to show that women with asymptomatic bacteriuria who are identified and treated in the preconception period have lower rates of low birthweight births. Further, women often have persistent or recurrent bacteriuria despite repeated courses of antibiotics; such reinfection frequently occurs within a few months of treatment. Thus, a woman who is identified and treated for asymptomatic bacteriuria before conception must be screened again during pregnancy. For these reasons, screening for this condition as part of routine preconception care is not recommended. *Strength of recommendation*: E; *quality of evidence*: II-1.

Periodontal disease

Burden of suffering. Periodontal disease affects up to 40% of pregnant women, with a disproportionate burden among low income women. It has been proposed that chronic infection and inflammation around the teeth might stimulate maternal or fetal responses that lead to preterm birth. Two large prospective studies have shown that maternal periodontal disease was associated with a 2- to 7-fold increase in odds for preterm delivery, with increasing risk for decreasing gestational age.[80,81] Another similar prospective study linked maternal periodontal disease to preeclampsia.[82]

How detectable is the condition? Periodontal disease is detectable by a detailed oral health examination that is performed by trained dental professionals.

How effective are the current treatments? Treatment of periodontal disease is highly effective in reducing the burden of oral disease, but treatment during pregnancy has not yet been proved clearly to improve perinatal outcomes.

Impact of preconception care. Interventional trials during pregnancy have demonstrated consistently improved maternal oral health, but findings regarding preterm birth risk reduction are conflicting. A randomized study found some reduction in premature birth for women who had scaling and root planning during pregnancy, compared with women who were treated with tooth cleaning and polishing, but the results were not statistically significant.[81] A subsequent Chilean study did find benefit in a group of women who were treated for periodontal disease compared with women who were chosen randomly for treatment after delivery.[83] However, a recent large US multicenter trial that compared 407 women who were treated at < 21

weeks of gestation to 405 women who were assigned randomly to treatment after delivery found no reduction in preterm birth at < 37 weeks of gestation, although there was a trend for reduced preterm birth at < 32 weeks of gestation.[84] The current data cannot allow for a definitive conclusion regarding cause and effect between maternal periodontal disease and preterm birth. Different studies have used different definitions of periodontal disease, and all the intervention trials have initiated treatment after the first trimester, which may be too late to reduce the risk that is associated with preterm birth. A randomized study of preconception screening and treatment of periodontal disease is needed.

Recommendations by other groups. The American Academy of Periodontology recommends that women who are pregnant or planning to become pregnant undergo a periodontal examination.[85] The Canadian Task Force of Periodic Health Examination found fair (B level) evidence for tooth brushing, good (A level) evidence for flossing to prevent gingivitis, and fair (B level) evidence to support prophylaxis and scaling, depending on periodontal status.[86]

Recommendation. There are no studies that have evaluated the role of preconception or interconception screening and treatment of periodontal disease and its effect on reproductive outcomes. Routine screening and treatment of periodontal disease during preconception care is of considerable benefit to the mother but cannot yet be recommended as having benefit for the fetus. *Strength of recommendation:* C; *quality of evidence:* I-b.

BV

Burden of suffering. BV results from a shift in the normal vaginal bacterial flora to 1 that is characterized by an increase in *Gardnerella*, *Mycoplasma* and anaerobic bacteria, and a decrease in *Lactobacilli.*[87] BV is a common cause of abnormal vaginal discharge. The true prevalence of BV in the community is not known, but studies in academic medical centers and public hospitals found that 9-23% of pregnant women had BV, with infection being more common among African American women than white women.[88] A data synthesis supports the idea that BV organisms are found in the upper reproductive tract and contribute to the risk for pelvic inflammatory disease.[89] Observational studies consistently have shown an association between BV and adverse pregnancy outcomes that include preterm delivery (relative risk, 1.4-6.9), preterm premature rupture of membranes (relative risk, 2.0-7.3), spontaneous abortion (relative risk, 1.3-2.0), and preterm labor (relative risk, 2.0-2.6).[90-93] Studies that find a higher relative risk of preterm delivery for BV are those with the earliest gestational age for BV screening. The risk of preterm delivery is > 7-fold higher for women with BV at < 16 weeks of gestation and greater than 4-fold higher for women with BV at < 20 weeks of gestation.[94]

How detectable is the condition? The most common manner in which a diagnosis of BV is made clinically is with the Amsel criteria, which were developed to evaluate symptomatic women. The Amsel criteria are (1) presence of a homogenous white discharge, (2) presence of an amine or "fishy" odor (which may be accentuated with the addition of KOH to the specimen), (3) the presence of "clue cells" on microscopy, and (4) a vaginal fluid of pH > 4.5. Three of the 4 criteria must be present to make a diagnosis of BV.[95] Gram's stain of vaginal discharge can also be used to diagnose BV and offers improved reproducibility and quality assurance, compared with the Amsel criteria. The Gram's stain method uses the Nugent criteria and scores vaginal flora from 1-10 on the basis of bacterial types and quantities: 0-3, normal flora; 4-6, intermediate abnormal flora; 7-10, BV.[96] Although these criteria are used commonly in research settings, they are not practical for clinical settings, given the need to prepare and critically read Gram's stains.

How effective are the current treatments? A short course of antibiotic therapy can alter the microflora imbalance that is associated with BV, but cure rates are variable and recurrences are common.[97] A review of the evidence has established that the benefits of therapy for BV among nonpregnant women are the relief of vaginal symptoms and signs of infection and the reduction in the risk of infectious complications after induced abortion or hysterectomy.[89] Many randomized controlled trials have investigated whether treating BV during pregnancy improves pregnancy outcomes, with conflicting results.[98-106] Results of 15 good-quality trials that involved 5888 women are summarized in a recent Cochrane review.[107] The Cochrane review concluded that there is little evidence that screening and treating all pregnant women with asymptomatic BV prevents preterm delivery, but there is some suggestion that early screening and treatment at < 20 weeks of gestation may reduce the risk of preterm delivery. The review also concluded that, among women with a previous preterm delivery, treatment does not affect the risk of a subsequent preterm delivery but is associated with a decrease in the risk of preterm premature rupture of membranes. Further support for the potential effectiveness of early screening and treatment of BV among asymptomatic pregnant women comes from a recently presented abstract from the Syracuse Healthy Start Project.[108] This project encouraged providers for pregnant women who reside in high-risk zip codes of Syracuse to screen for and treat BV at the first prenatal care visit. They report that premature delivery (11.4% vs 13.2%; $P = .2$), low birthweight (8.6% vs 11.5%; $P = .02$), delivery at < 32 weeks of gestation (2.1% vs 4.4%; $P = .001$), and very low birth rate (1.9% vs 3.8%; $P = .006$) were lower in the screened/treated group, compared with the unscreened group. First screening and treatment were at a median of 11 and 14 weeks of gestation, respectively.

Impact of preconception care. To date, no studies have evaluated the role of preconception or interconception screening and treatment of BV on subsequent pregnancy outcomes; this has been identified as an important area for future research, given its established association with preterm delivery. BV is a particularly appealing risk factor to target, be-

cause it is potentially preventable and treatable. Furthermore, because of its higher prevalence among black women, the prevention and treatment of BV may help reduce at least part of the racial disparity in preterm delivery.[89] However, the frequency of recurrence of BV and the variable cure rate may be factors that limit the value of preconception detection and treatment in terms of the eradication of BV before a subsequent pregnancy. Because BV is common, screening and treatment could subject a substantial number of women to the inconvenience and minor side-effects of antibiotics. Although the regimens that are used to treat BV generally are considered safe in pregnancy, several studies do raise the possibility of harm to some women or their infants. In 2 studies, a subgroup of women who did not have BV, but who received treatment with metronidazole or clindamycin, experienced trends toward higher incidence of preterm delivery at < 34 weeks of gestation (12-13% vs 4-5%).[109] In addition, neonatal sepsis was increased significantly among women who received vaginal clindamycin therapy.[110]

Recommendations by other groups. Presently, the USPSTF,[111] the CDC,[68] and the ACOG[112] do not recommend screening and treatment for BV among pregnant women of any risk category. The USPSTF states that "there is good evidence that screening and treatment of BV in asymptomatic women of average risk does not improve outcomes such as preterm labor or preterm birth" and recommends against routinely screening average-risk asymptomatic pregnant women for BV. The USPSTF goes on to state that there are "good-quality studies with conflicting results that screening and treatment of asymptomatic BV in high-risk pregnant women reduces the incidence of preterm delivery." The magnitude of benefit exceeded the risk in several studies,[113,114] but the single largest study reported no benefit among high-risk pregnant women.[115] Thus, the USPSTF concludes that the evidence is insufficient to recommend for or against routinely screening high-risk pregnant women for BV. The USPSTF does provide clinical considerations when making decisions to screen and treat or not and states that, for women with a history of preterm delivery, screening for BV is an option, noting that the optimal screening test for BV is not certain nor is the optimal time to screen and the optimal treatment regimen. The 3 trials that demonstrated a reduction in preterm delivery screened in the second trimester (13-24 weeks of gestation) and used oral metronidazole or oral metronidazole and erythromycin. Reasons for the conflicting results are not clear but may involve differences in other risk factors for preterm delivery among enrolled women, which include variations in immunologic response to BV, or differences in drug regimens or timing of therapy.[116]

Recommendation. There are no studies that evaluate the role of preconception or interconception screening and treatment for asymptomatic BV and its effect on reproductive outcomes; such studies are a high priority. Routine screening and treatment of BV among asymptomatic pregnant women of average risk should not be performed because of the lack of demonstrated benefit and the possibility of adverse effects of treatment for women without BV. For pregnant women with previous preterm delivery, the inconsistent results of well-done studies prevent a clear recommendation for or against screening; however, some studies support early screening and treatment with a regimen containing oral metronidazole. For women with symptomatic BV infection, treatment is appropriate for pregnant women and for women planning pregnancy. *Strength of recommendation*: D (for women without previous preterm delivery), C (for women with previous preterm delivery); *quality of evidence*: I-b.

GBS

Burden of suffering. The gastrointestinal tract serves as the natural reservoir for GBS and is the likely source of vaginal colonization. Genital tract colonization is found in approximately 10-30% of women and can be transient, chronic, or intermittent. GBS is a common cause of early-onset neonatal sepsis (1700 cases in the United States in 2001[117]) and meningitis and can be transmitted to the newborn infant by passage through a colonized genital tract (0.4 cases per 1000 live births in 2006).[118]

How detectable is the condition? Culture of the lower vagina/rectum is done with traditional laboratory methods and detects lower tract colonization. Rapid tests have been produced but may not detect light colonization such that they have not been incorporated into screening programs.[119] PCR techniques appear to have adequate sensitivity, but questions arise regarding availability on a 24/7 basis.

How effective are the current treatments? Intrapartum antibiotics are 90% effective at the prevention of early-onset neonatal sepsis.[119]

Impact of preconception care. Pregnant women should be screened for vaginal/rectal GBS colonization at 35-37 weeks of gestation. Women who are colonized should receive antibiotics in labor to reduce the risk of vertical transmission to the newborn infant. There is no evidence that identification of genital tract colonization in the nonpregnant patient provides clinical benefit. In fact, even genital tract colonization in early pregnancy is not predictive of neonatal GBS sepsis.[120]

Recommendations by other groups. The CDC has recommended a strategy of universal screening for genital colonization by GBS at 35-37 weeks of gestation, with antibiotics in labor for those with positive cultures. This strategy has been endorsed by ACOG and other groups. There are no recommendations for screening nonpregnant adults.

Recommendation. Screening for GBS colonization at a preconception visit is not indicated and should not be performed. *Strength of recommendation:* E; *quality of evidence:* II-2.

Comment

As discussed in this article, there is ample evidence that clinicians should address many infectious conditions in their preconception care activities. Risk assessment,

screening, and treatment for specific infections should be a component of preconception care (strength of recommendation of "A") because there is convincing evidence that treatment of these infections before pregnancy prevents infertility, ectopic implantation, and neonatal infections (*Chlamydia*); consequences to the developing fetus (syphilis); or transmission of an infectious agent with potential for chronic infection of the offspring (HIV). Infections with less strong recommendation ("B") for consideration in preconception care include the detection and treatment of tuberculosis, gonorrheal infection, and HSV in selected individuals. Those infections that lack clear evidence for inclusion in preconception care (strength of recommendation of "C") include hepatitis C, toxoplasmosis, cytomegalovirus, listeriosis, malaria, BV in women with previous preterm birth, and periodontal disease. In some cases, such as for toxoplasmosis, the interventions are primarily patient education; it is unclear whether the recommendation by a provider (to avoid certain foods and changing cat litter boxes) impacts patient behavior or, ultimately, the pregnancy outcome. In the case of periodontal disease and BV, randomized trials that have been conducted during pregnancy have had mixed results for the prevention of preterm birth, although data that have evaluated the potential impact of intervention in the preconception period are altogether lacking. Given the association of periodontal disease and BV with preterm birth in observational studies, trials to evaluate specifically the effect of preconception treatment interventions for these conditions are warranted. A number of infections have important consequences during pregnancy yet should be excluded from preconception care, for example with a "D" level recommendation for BV in those with no history of preterm birth and "E" level recommendations that include parvovirus, asymptomatic bacteriuria, and GBS infection. ■

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The clinical content of preconception care: women with chronic medical conditions

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This article reviews the medical conditions that are associated with adverse pregnancy outcomes for women and their offspring. We also present the degree to which specific preconception interventions and treatments can impact the effects of the condition on birth outcomes. Because avoiding, delaying, or achieving optimal timing of a pregnancy is often an important component of the preconception care of women with medical conditions, contraceptive considerations particular to the medical conditions are also presented.

Key words: chronic, medical condition, preconception

Preconception care includes the detection and optimal control of specific medical conditions to optimize pregnancy-related outcomes for the woman and her offspring. The increased rate of pregnancy by women age 35 years and older has led to an increase in the proportion of women with chronic diseases upon conception.[1] To inform reproductive decision making, women with medical conditions should be presented with information with regard to the risk of pregnancy complications and maternal morbidity and mortality given pregnancy, disease prognosis irrespective of pregnancy, whether there are conflicts between maternal treatment and fetal well-being, the extent of risk the condition or medications used to treat the condition place on the fetus, optimal timing of pregnancy (if desired), and the woman's ability to conceive at present and in the future. Possible preconception care strategies for women with medical conditions might include optimizing disease control in preparation for pregnancy, changing a potentially teratogenic treatment regimen to one that is safer for the fetus, and provision of family planning services to delay or avoid pregnancy.[2]

Experts consider that preconception care should be provided in the context of well-woman and/or chronic disease care[3-5] rather than as an isolated preconception care visit by women who are planning a pregnancy because most components can be embedded in the process of primary and preventive care.[6,7] Furthermore, the integrated approach recognizes that a large proportion of women would be missed by pre-

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Conflict of Interest: Anne L. Dunlop, MD, MPH; Brian W. Jack, MD; Michael C. Lu, MD, MS, MPH; Andra James, MD, MPH; Cynthia S. Shellhaas, MD, MPH; Lynne Haygood-Kane Hallstrom, DO, CNM, MS; Benjamin D. Solomon, MD; W. Gregory Feero, MD, PhD; and M. Kathryn Menard, MD, MPH have no conflict of interest including grants, honoraria, advisory board membership, or share holdings. Joseph N. Bottalico, DO, is a member of the CDC Select Panel on Preconception Care, a voluntary unpaid position in which he represents the American College of Osteopathic Ob-Gyn and the American Osteopathic Assn (no known conflict). He is also an (appointed, unpaid) volunteer member of the NJ DHSS Diabetes Advisory Council, also without conflict. With the New Jersey Chapter of the March of Dimes, he is a member of the annual conference planning committee (no known conflict) and has received one honorarium from the March of Dimes jointly with the Johnson and Johnson foundation (New Brunswick, NJ) for a grand rounds presentation on preconception care presented to the OB-Gyn Dept at UMDNJ-SOM in December 2007. He sits on the regional MCH consortium's BOD (Southern NJ Perinatal Cooperative) and chairs their Clinical/QA committee which also presents no known conflicts. Mona R. Prasad, DO, MPH is the recipient of a $25,000 service grant from the March of Dimes for the year 2008.

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conception care strategies if such strategies were not systematically delivered as part of women's health care because approximately half of pregnancies are unintended, and even those who plan their pregnancies might not do so in conjunction with their health care providers.

There are several medical conditions for which there is a link to adverse pregnancy outcomes for women and their offspring as well as evidence that the effect of the condition can have an impact by preconception care. These conditions will be reviewed in this manuscript. Because avoiding, delaying, or achieving optimal timing of a pregnancy is often an important component of the preconception care of women with medical conditions, contraceptive considerations particular to the medical conditions are also presented

Diabetes mellitus

Burden of suffering

The National Ambulatory Medical Care Survey[8] demonstrated that diabetes affects approximately 1.85 million (21 per 1000) women in the United States aged 18-44 years. In 2002, 9.3% of women of reproductive age had known diabetes.[1] Whereas approximately 1% of pregnancies in the United States are complicated by pregestational diabetes (predominately type 2),[9] gestational diabetes (GDM) occurs in approximately 7% of pregnancies, with rates varying from 1% to 14%.[10] Given the high recurrence rate of GDM (30-84%) in subsequent pregnancies,[11,12] as well as the increased rate of subsequent type 2 diabetes and metabolic syndrome with a past history of GDM,[13,14,15,16] attention to prediabetic risk factors between pregnancies is reasonable, especially in those women who are also obese.

The prevalence of risk factors for diabetes mellitus is increasing in the United States. Based on 2005-2006 US data from the National Health and Nutrition Examination Survey (NHANES),[17] 30.5% of women aged 20-39 years were obese (body mass index [BMI] $\geq$ 30 kg/m^2). The Healthy People 2010 objective of an obesity prevalence of less than 15% has not been met for women (or men) of any age. An increased prevalence of obesity in US adolescents has also been documented and is associated with declining levels of physical activity.[18]

The links between obesity, insulin resistance, and type 2 diabetes mellitus are well known. An association between obesity and elevated risk of GDM is also probable. Data are not readily available for US reproductive-age females with regard to the prevalence of prediabetes; however, increasing overweight, obesity, and ethnicity trends suggest that a rise in prevalence may be occurring. These population trends may also be contributing to a rising prevalence of GDM. Obesity alone increases the risk of pregnancy complications such as hypertension, large babies, birth trauma, and cesarean section. More recently, it has also been found that the offspring of obese and overweight women, independent of diabetes, have an increased risk of congenital malformations and that obesity and diabetes contribute to birth defects synergistically.[19]

Major congenital malformations are among the leading causes of perinatal mortality in pregnancies complicated by pregestational (type 1 or type 2) diabetes. Whereas the risk of malformations in the general population is 2-3%, reported rates of malformations in pregnancies complicated by pregestational diabetes vary from 3% to 8% to 6-12%, and risk varies directly with preconception and first-trimester glycemic control.[20,21] The risk of spontaneous abortion is also related to glycemic control in the first trimester.[22] Although virtually any organ system can be affected, the most characteristic congenital anomalies include sacral agenesis, complex cardiac defects, spina bifida, and anencephaly. These malformations occur during the critical period of fetal organogenesis, approximately 5-8 weeks after the last menstrual period.[23,24]

How detectable is the condition?

Screening tests for diabetes have been well validated and are widely utilized. Although recommended by the American Diabetes Association and the American College of Obstetricians and Gynecologists, the rate of post partum rescreening after GDM is suboptimal and reported to be less than 50% in 1 study.[25] Testing to detect prediabetes and type 2 diabetes in asymptomatic women should be considered in adults who are overweight (BMI $\geq$ 25 kg/m^2) or obese (BMI $\geq$ 30 kg/m^2) and who have 1 or more additional risk factors for diabetes, including a history of GDM.[26]

How effective are the current treatments?

Preconception control of diabetes reduces the risk of congenital malformations.[27] Lifestyle modification with weight reduction and exercise has been shown to reduce the risk of progression from prediabetes to diabetes.[28-30] Although oral antidiabetic agents are widely prescribed for women with type 2 diabetes and polycystic ovary syndrome, insulin is the preferred treatment for women who are planning a pregnancy. Because angiotensin-converting enzyme inhibitors, statins, and angiotensin receptor blockers are also commonly prescribed for women with pregestational diabetes and because these drugs present risks in pregnancy, modification of drug therapy in the preconception period is important.

Impact of preconception care

The National Ambulatory Medical Care Survey[8] demonstrated that preconception diabetes control has the potential to reduce the risk of pregnancy loss and congenital malformation for approximately 113,000 births each year. Improved control of maternal glucose and antepartum fetal surveillance has led to a significant reduction in the perinatal mortality rate in pregnancies complicated by diabetes.[9,20,31] The increased rate of congenital malformations in infants born to mothers with pregestational diabetes is significantly reduced when women maintain good blood glucose control during the critical period of organogenesis. Several clinical studies have demonstrated that diabetic women who seek medical care before pregnancy and who have good glycemic control at the time of conception reduce their risk of having a fetus with major malformations to nearly that of the nondiabetic population.[27,32] Glycosylated hemoglo-

bin levels correlate directly with the frequency of congenital anomalies. Hemoglobin A1C levels should be as close to normal as possible (< 7%) before conception is attempted.[20,26,33]

Contraception is important for women who chose not to have a pregnancy and for helping women achieve optimal timing of pregnancy in relation to the optimal control of their condition. There is a theoretical concern that hormonal contraceptives may increase insulin resistance in women who are diabetic. In its Medical Eligibility Criteria for Contraceptive Use, the World Health Organization (WHO) asserts that the advantages of contraception—including low-dose combination contraceptives (oral, injectable, vaginal ring, or skin patch formulations) and all forms of progesterone-only contraceptives (oral, injectable, implantable formulations outweigh the risks of insulin resistance in diabetic women, except for those with vascular disease or diabetes for more than 20 years.[34] FDA labeling on the Cooper T380A intrauterine device (FEI Products, Tonawanda, NY) lists diabetes as a contraindication for use due to compromised immunity;[35] however, the WHO lists the Copper T380A as a recommended method for women with diabetes, with a caution that a woman with diabetes on insulin may be at higher risk of method failure.[34]

Recommendations by other groups

The American Diabetes Association and the American College of Obstetricians and Gynecologists have developed clinical practice guidelines for care before pregnancy for women with diabetes.[9,26,33]

Recommendation. All women of reproductive age with diabetes should be counseled about the importance of diabetes control before pregnancy. Important preconception counseling topics include maximizing glucose control; self-monitoring of blood glucose; maintaining optimal weight; evaluation for vascular complications; modification of drug treatment if conception is planned or likely; a regular exercise program; tobacco, alcohol, and substance abuse cessation; and social support to assist during the pregnancy. In the months before pregnancy, these women should demonstrate as near-normal glycosylated hemoglobin as possible for the purpose of decreasing the rate of congenital anomalies and spontaneous abortion. Those with suboptimal control of their diabetes should be encouraged to use effective birth control. *Strength of recommendation:* A; *quality of evidence:* I.

Testing to detect prediabetes and type 2 diabetes in asymptomatic women should be considered in adults who are overweight or obese (BMI $\geq$ 25 kg/m^2) and who have 1 or more additional risk factors for diabetes including a history of GDM. *Strength of recommendation:* B.

Women with GDM should be rescreened 6-12 weeks postpartum. *Strength of recommendation*: E.

Thyroid disease

Burden of suffering

Thyroid disease is the second most common endocrine disease that affects women of reproductive age.[36] Hyperthyroidism occurs in approximately 0.2% of all pregnancies, with the most common cause being Graves' disease (95%).[37] The incidence of maternal and neonatal morbidity is significantly higher in patients whose hyperthyroidism is not medically controlled.

The causes of maternal morbidity include a higher incidence of preeclampsia, congestive heart failure, thyroid crisis, and placental abruption. The causes of neonatal morbidity include fetal growth restriction, low birthweight, preterm birth, and stillbirth, as well as neonatal immune-mediated hypo- or hyperthyroidism. Maternal and fetal outcome is directly related to the control of hyperthyroidism.[37] Women whose thyroid glands have been ablated for Graves' disease might have circulating thyroid-stimulating antibodies that can induce thyrotoxicosis in their fetuses.[38]

Overt hypothyroidism, a low free thyroxine level, and an elevated thyroid stimulating hormone (TSH) occurs in approximately 2.5% of all pregnancies in the United States.[39,40] Subclinical hypothyroidism, a normal free thyroxine with an elevated TSH, may be somewhat more common, with a prevalence of 2-5% in pregnant women.[39,41,42] Furthermore, a large cross-sectional study found that, among patients with hypothyroidism taking thyroid medication, only 60% were within the normal range of TSH.[42]

It is well established that overt hypothyroidism, particularly during the first trimester, is associated with intellectual impairment of the offspring as well as pregnancy complications including hypertension and preeclampsia, placental abruption, anemia, postpartum hemorrhage, preterm birth, low birthweight, and fetal death.[44,45] More recently studies have shown that subclinical hypothyroidism during pregnancy is also associated with impaired psychomotor development of offspring as well as an increased risk of poor pregnancy outcomes such as placental abruption, preterm birth, low birthweight, and stillbirth.[40,43-48]

How effective are the current treatments?

Both hyper- and hypothyroidism are highly treatable conditions, with the specific treatment varying according to the diagnosis. Clinical practice guidelines for treating patients with hyper- and hypothyroidism exist.[49]

Impact of preconception care

There is strong evidence that treatment of thyroid conditions improves pregnancy outcomes. Among women with hyperthyroidism in whom the diagnosis is made early in pregnancy and for whom treatment is started promptly or who become pregnant while the thyrotoxicosis is under control, the prognoses for mother and offspring are excellent in the majority of studies.[37] Similarly, studies have shown that women with hypothyroidism in whom the diagnosis is made early in pregnancy and for whom replacement is initiated or who have adequate replacement prior to pregnancy do not have an increased risk for perinatal morbidity.[50] No well-designed studies have specifically evaluated the treatment of thyroid disease before pregnancy, compared with that during pregnancy.

There are no special considerations about contraceptive methods among women with thyroid disease unless the

thyroid disease is complicated by hypertension.[51] However, the most common gynecoendocrine anomaly in women with untreated hypothyroidism is anovulation;[52] therefore, conception may be less frequent among women with hypothyroidism.[53]

Recommendations by other groups

Both the American College of Obstetricians and Gynecologists and the American Association of Clinical Endocrinologists have developed preconception clinical practice guidelines for pregnant women with thyroid disease.[36,38] For women with hyperthyroidism who are pregnant, the medication of choice is typically propylthiouracil. Regarding preconception issues, the guidelines specify that it is advisable to achieve euthyroidism before conception. The ideal form of treatment of hyperthyroidism for women who wish to become pregnant has not been defined but depends on patient understanding of the advantages and disadvantages of each and patient and physician preference. Specifically, there is no evidence that radioactive treatment given to the mother before pregnancy has any adverse effect on the fetus or children later in life; however, it is customary to avoid pregnancy for the first 6 months after radioactive iodine treatment.

The guidelines recommend the testing of thyroid function for women with a personal history of thyroid disease or symptoms of thyroid disease. Routine assessment for the presence of subclinical hypothyroidism is not recommended. The guidelines further specify that women being treated for hypothyroidism will require increased doses of thyroxine early and throughout pregnancy to maintain adequate levels; this is especially important during the first trimester.[36,38]

Recommendation. Women of reproductive age with thyroid disease should be counseled about the risks of these conditions on pregnancy-related outcomes for the woman and offspring, and the importance of achieving optimal replacement therapy prior to conception. All women with symptoms of hypothyroidism should be screened for thyroid disease, and if hypothyroid, they should be adequately replaced. *Strength of recommendation:* A; *quality of evidence:* II-1.

Phenylketonuria

Burden of suffering

Phenylketonuria (PKU) is a metabolic disorder that results from an inherited deficiency of a liver enzyme known as phenylalanine hydroxylase. This enzyme deficiency leads to elevated levels of the amino acid phenylalanine in the blood and other tissues. Elevated phenylalanine levels result in mental retardation, microcephaly, delayed speech, seizures, eczema, behavior abnormalities, and other symptoms, if left untreated. Approximately 1 of every 15,000 infants in the United States is born with PKU.[54] The offspring of mothers with PKU are at risk for a number of adverse outcomes associated with high maternal phenylalanine concentrations.

There is a strong relationship between increasing levels of phenylalanine and fetal abnormalities. Fetuses exposed to maternal phenylalanine levels of 3-10 mg/dL had a 24% chance of microcephaly and congenital heart disease was not seen; in contrast, fetuses exposed to maternal phenylalanine levels greater than 20 mg/dL had a 73% chance of microcephaly and a 12% chance of congenital heart disease.[54,55] Facial dysmorphisms, microcephaly, low birthweight, fetal growth restriction, developmental delay, and learning difficulties are also associated with maternal phenylalanine levels.[56,57] Unfortunately, few women with PKU achieve metabolic control prior to conception and maintain it during pregnancy,[54] and the difficulty of controlling blood phenylalanine levels as patients get older is widely recognized.[58]

How detectable is the condition?

All states perform newborn screening for PKU.[54]

How effective are the current treatments?

Effective treatment for PKU involves strict metabolic control using a low-phenylalanine diet. The newborn screening program for PKU has been remarkably successful in that infants, when diagnosed early in the newborn period and treated to achieve good metabolic control, have normal health and development and can likely expect a normal life span. However, metabolic control of PKU can be difficult to achieve, and poor control can result in significant decline of mental and behavioral performance.[54]

Impact of preconception care

It has been demonstrated that the adverse outcomes associated with maternal PKU can be prevented when mothers adhere to a low phenylalanine diet before conception and continue it throughout their pregnancy.[54,59-61]

Recommendations by other groups

The American College of Obstetricians and Gynecologists and the National Institutes of Health have issued recommendations with regard to the screening and management of PKU.[54,59] They recommend that phenylalanine levels below 6 mg/dL be achieved at least 3 months before conception and that levels of 2-6 mg/dL be maintained throughout the pregnancy.

Recommendation. Women of reproductive age with phenylketonuria should be counseled about the importance of maintaining low phenylalanine during their child-bearing years and should be encouraged to resume a low phenylalanine diet, particularly when they are planning to become pregnant, to avoid adverse outcomes for the offspring. Women who do not desire a pregnancy should be encouraged to use contraception. *Strength of recommendation:* A; *quality of evidence:* II-1.

Seizure disorders

Burden of suffering

Seizure disorders affect approximately 1% of the general population.[62] It has been estimated that 3-5 per 1000 births are to women with seizure disorders, making them the most common serious neurological complications during pregnancy.[63] Both the seizure disorder itself and the medications used to treat the disorder can have serious impacts on pregnancy outcomes. Women with seizure disorders are at increased risk for an increase in the frequency of seizures during

pregnancy. During pregnancy, seizure frequency increases in approximately one third of women with seizure disorders.[64]

There is an increased incidence of congenital anomalies among offspring born to women who experience seizures during pregnancy, whether they are on treatment or not, and to those who take anticonvulsant medications. The risk of major malformations, minor anomalies, and dysmorphic features is 2- to 3-fold higher for infants of mothers with epilepsy who receive treatment with antiepileptic drugs, compared with the risk for infants of mothers without epilepsy.[65]

Other adverse pregnancy-related outcomes associated with seizure disorders include spontaneous abortion, low birthweight, diminished head circumference, developmental disabilities, neonatal hemorrhagic disorder (caused by anticonvulsant-induced vitamin K deficiency), and perinatal death.[66]

Many anticonvulsants commonly used to treat seizure disorders, including phenytoin, carbamazepine, barbiturates, and valproate have known teratogenicity in humans,[66] which can cause neural tube defects, cleft lip and palate, cardiac anomalies, facial abnormalities, and skeletal abnormalities. The risk of anomalies increases significantly with higher-dose therapy[67] and polytherapy, compared with monotherapy.[68] One mechanism of teratogenicity may be anticonvulsant-related reductions in folic acid, disturbances in folic acid-mediated biochemical processes, or both.[66]

How effective are the current treatments?

Currently available anticonvulsant medications are effective in controlling seizures among those with seizure disorders.[69]

Impact of preconception care

To date, no well-designed studies have specifically addressed the role of specific preconception strategies for the management of seizures on pregnancy-related outcomes for women with seizure disorders and their offspring. However, existing randomized controlled trials and cohort studies clearly document the teratogenicity of phenytoin, carbamazepine, barbiturates, and valproate and the increased risk of teratogenicity at higher doses and with polytherapy.[66-68]

Preconception counseling and family planning are important in the care of women of reproductive age who have seizure disorders. Preconception counseling can appropriately inform women of the risks to their own health from pregnancy and the risks of their condition on pregnancy-related outcomes. A thorough assessment by a neurologist prior to pregnancy could address whether the woman is an appropriate candidate for a withdrawal of anticonvulsant therapy or for adjustment of her medication regimen (with the goal of achieving monotherapy, if possible, and the lowest possible dosages to control seizures). The principles that govern withdrawal in women considering pregnancy are the same as the principles for withdrawal for the general population of patients with seizures.[70] In general, withdrawal can be considered in any woman who has been seizure free for at least 2 years.[70]

Contraception is important for women who choose not to have a pregnancy and for helping women achieve optimal timing of pregnancy in relation to the optimal control of their condition. There are considerations in choosing a contraceptive method for women with seizure disorders. Combined oral contraceptives do not exacerbate seizures; however, the efficacy of oral contraceptives is impaired by concomitant use of anticonvulsants that induce liver enzymes (eg, phenytoin, carbamazepine, barbiturates, topiramate, and tiagabine). Specifically among women without seizures, the failure rate of combined oral contraceptives with high estrogen dose ($\geq 50\ \mu m$) is 0.7 per 100 woman-years, whereas the rate increases to 3.1 per 100 woman-years in those receiving liver enzyme-inducing anticonvulsants. Failure rates are higher for combined oral contraceptives with lower doses of estrogen ($\leq 35\ \mu m$). Progestin-only methods also have a higher failure rate.[66,71]

Recommendations by other groups

The American Academy of Neurology has a published practice guideline for the management of women with seizure disorders,[63] which specifies that women of reproductive age with seizure disorders should be placed on monotherapy at the lowest dose whenever possible, and folic acid supplementation should be instituted at 0.4 mg per day. If hormonal contraception is chosen by women taking an enzyme-inducing anticonvulsant, the risks of failure should be discussed and a formulation that includes at least 50 μm of ethinyl estradiol should be used.

Women planning to become pregnant should be evaluated for the possibility of adjustment (or withdrawal) of their anticonvulsant medication and prepregnancy counseling. If withdrawal is planned, this should be completed at least 6 months prior to conception.[63] The American College of Obstetricians and Gynecologists has an educational bulletin addressing seizure disorders in pregnancy, which specifies that to optimize the neonatal outcome in a patient requiring anticonvulsant therapy, using a single drug at the lowest possible dose to control seizures is preferable.[65]

Recommendation. Women of reproductive age with seizure disorders should be counseled about the risks of increased seizure frequency in pregnancy, the potential effects of seizures and anticonvulsant medications on pregnancy outcomes, and the need to plan their pregnancies with a health care provider well in advance of a planned conception. Those taking liver enzyme-inducing anticonvulsants should be counseled about the increased risk of hormonal contraceptive failure. Whenever possible, women of reproductive age should be placed on anticonvulsant monotherapy with the lowest effective dose to control seizures.

Those who are planning a pregnancy should be fully evaluated for consideration of alteration or withdrawal of the anticonvulsant regimen prior to conception and should initiate folic acid supplementation of 4 mg per day for at least 1 month prior to conception and until the

end of the first trimester to prevent neural tube defects. *Strength of recommendation:* A; *quality of evidence:* II-2.

Hypertension

Burden of suffering

In 2002, a national survey estimated that 3% of women of reproductive age had chronic hypertension (HTN).[1] In 2002, the hospital estimate for HTN prior to pregnancy among 15-54 year old women was 28.9 per 1000 deliveries, a 2-fold increase from 12.3 in 1993.[72]

Pregnancies complicated by chronic HTN, especially if severe, may be associated with worsening hypertension, preeclampsia and eclampsia, central nervous system hemorrhage, cardiac decompensation, and renal deterioration.[73,74] HTN during pregnancy also poses substantial fetal risks that include preterm birth, intrauterine growth restriction, placental abruption, and fetal demise.[75] Superimposed preeclampsia in women with hypertension is associated with significant adverse perinatal outcomes.[76] Pregnancy outcome is related to the degree of hypertension and the presence or absence of preeclampsia.[77-79]

How effective are the current treatments?

The medical treatment of high blood pressure is very effective in reducing long-term, adverse cardiovascular outcomes and stroke as demonstrated in many studies of the past 40 years.[80] However, the data supporting improved pregnancy-related outcomes among women with HTN treated with antihypertensive medications are less compelling. A systematic review of management of chronic hypertension during pregnancy concluded that "the evidence base regarding pharmacologic management of chronic hypertension during pregnancy is too small to either prove or disprove moderate to large benefits of antihypertensive therapy."[74]

There is, to date, no scientific evidence that antihypertensive therapy will improve perinatal outcomes for women with mild hypertension in pregnancy (140-179 mm Hg systolic or 90-109 mm Hg diastolic blood pressure).[81-83] Specifically, multiple metaanalyses of randomized controlled trials show that the major maternal outcomes improved by treating mild to moderate hypertension include decreased progression to severe hypertension and decreased need for additional antihypertensive therapy.[84,85] There are, however, demonstrable benefits for pregnancy-related outcomes from antihypertensive therapy among women with severe chronic hypertension (systolic blood pressure $\geq$ 180 mm Hg or diastolic blood pressure $\geq$ 110 mm Hg).[79]

Methyldopa has been the most commonly tested therapy, with 14 randomized controlled trials demonstrating its efficacy at reducing blood pressure and safety during pregnancy.[84] Metaanalyses of beta-blocker trials show a borderline increase in small-for-gestational-age infants, with no related increase in perinatal mortality as well as a decrease in the incidence of respiratory distress syndrome.[86] Among the beta-blockers, atenolol, especially when started early in pregnancy, has been associated with fetal growth restriction in several uncontrolled studies and 1 small trial. From these studies, however, the causal nature of the association remains unclear because of multiple agents being simultaneously administered and the inability to separate effects of the mother's underlying pathophysiology from effects of the drug. Labetalol has been associated with fetal growth restriction in 3 randomized trials of hypertensive disorders other than chronic hypertension. Other beta-blockers, such as metoprolol, pindolol, and oxprenolol, have not been associated with fetal growth retardation, but available data concerning these agents are scarce.[87]

Calcium channel blockers have mostly been evaluated for use late in pregnancy so their benefit-to-risk ratio remains unclear, although they are generally regarded as safe and effective.[88] Diuretics are known to decrease the circulating plasma volume, but a metaanalysis of 9 randomized trials evaluating diuretics during pregnancy did not find an increased risk of adverse fetal events nor did a large cohort study.[87] Angiotensin II receptor blockers are contraindicated in pregnancy, having been linked to miscarriage, fetal death, fetal renal failure, and malformations.[89-92]

Impact of preconception care

To date, no well-designed studies have addressed the effects of specific preconception strategies for the management of HTN on pregnancy-related outcomes for the woman and her offspring. However, 3 trials synthesized in a recent review had evidence relevant to the preconception management of chronic hypertension because they included women 30-54 years of age. The data, involving 8565 women aged 30-54 years with mild to moderate HTN, show approximately 250 (95% confidence interval, 158-1606) such women need to be treated for 5 years to prevent a fatal or nonfatal cardiovascular event such as stroke. Women who are either younger than those involved in the trials or who are treated for intervals shorter than 5 years can expect less clinical benefit from antihypertensive therapy.[87]

Contraception is important for women who choose not to have a pregnancy and for helping women achieve optimal timing of pregnancy in relation to the optimal control of their condition. Patients with mild or well-controlled HTN (140-159/90-99) may be considered for low-dose combination oral contraceptives or progestin-only methods, particularly in the absence of other risk factors such as smoking, diabetes, hyperlipidemia, or obesity. Combination pills are not recommended in moderate to severe HTN ($>$ 160/100) or if blood pressure cannot be monitored.[93] The WHO lists the Copper T380A as a recommended method of contraception for women with mild or moderate to severe hypertension or if blood pressure can not be monitored.

Recommendations by other groups

Both the American College of Obstetricians and Gynecologists (ACOG) and the National High Blood Pressure Education Program (NHBPEP) recommend that the preconception care of women with hypertension should include counseling about the sizable (25%) risk of superimposed preeclampsia and its associated complications and that those with

hypertension of several years' duration should undergo a preconception assessment for ventricular hypertrophy, retinopathy, and renal disease because target organ damage can progress during pregnancy.

Both ACOG and the NHBPEP have statements to address the treatment of high blood pressure during pregnancy. The ACOG practice bulletin states there is no evidence that antihypertensive treatment for mild to moderate hypertension improves maternal or fetal outcomes, even for women who are already receiving hypertension treatment. ACOG suggests treatment may be stopped during pregnancy or not initiated until blood pressures reach 150-160 mm Hg systolic or 100-110 mm Hg diastolic, unless the mother has underlying renal or cardiovascular disease. Continuing previous antihypertensive medication is another option, although angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are contraindicated during pregnancy.[90] The NHBPEP recommends the same guidelines as ACOG.[91]

Recommendation. Women of reproductive age with chronic hypertension should be counseled about the risks associated with hypertension during pregnancy for both the woman and her offspring and the possible need to change the antihypertensive regimen when she is planning a pregnancy. Those with hypertension for several years should be assessed for ventricular hypertrophy, retinopathy, and renal disease prior to pregnancy. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are contraindicated during pregnancy; women who could become pregnant while taking these medications should be counseled about their adverse fetal effects and should be offered contraception if they are not planning a pregnancy. Women who are planning a pregnancy should discontinue these medications prior to pregnancy. *Strength of recommendation:* A (because of medications); *quality of evidence:* II-2.

Rheumatoid arthritis

Burden of suffering

Rheumatoid arthritis (RA) is the most common rheumatic disease that complicates pregnancies. It affects 1-2% of the adult population with a female predominance.[94] Fortunately, the disease remits in approximately 70-80% of patients during pregnancy,[95] probably because of the normal shift to a less inflammatory state and human leukocyte antigen mismatch between the mother and fetus.[96-98] However, 20-30% of patients will continue to have active or worsening disease during pregnancy.[99]

RA does not decrease fertility but may prolong time to conception.[100,101] Most reports do not show any increase in fetal morbidity or losses among pregnant women with RA.[102,103] However, active RA may increase the risk of low birthweight, and corticosteroid use may increase the risk of fetal growth restriction and preterm premature rupture of membranes.[104] Approximately 90% of patients flare in the postpartum period, usually within the first 3 months.[105] The flare may be caused by decreased progesterone and cortisol, increased prolactin, and a return to Th1 predominance.[106] Presently it is unclear whether breast-feeding might exacerbate postpartum flare.[107]

How effective are the current treatments?

No treatment is curative for RA; however, several therapies modify the disease or result in the control of symptoms associated with RA. The safety of agents used to treat RA during pregnancy was recently reviewed by Chamber et al.[108] Based on available data, the teratogenic risk of corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs) following first-trimester exposure is minimal. NSAIDs should be discontinued by 27 weeks' gestation to avoid premature closure of the ductus arteriosus. The active metabolite of leflunomide undergoes extensive enterohepatic circulation and has a prolonged and unpredictable half-life; cholestyramine administration may enhance elimination of leflunomide metabolite before pregnancy.

Safety data on other disease-modifying antirheumatic drugs are limited. NSAIDs are compatible with breast-feeding, although there is potential risk of jaundice and kernicterus. Corticosteroids may be used, but breast-feeding should occur 4 hours after the last dosing. Hydroxychloroquine and sulfasalazine should be used cautiously, and azathioprine, cyclosporine, cyclophosphamide, methotrexate, and chlorambucil should be avoided. There are insufficient data regarding tumor necrosis factor antagonists, anakinra, and rituximab in relation to pregnancy or lactation.[109]

Impact of preconception care

No studies have investigated the effect of preconception strategies on pregnancy-related outcomes for women of reproductive age with RA. Preconception counseling and family planning are important in the care of the woman of reproductive age with RA. Patients should be advised of the natural history of the disease during pregnancy and the likelihood of flare during pregnancy. Also, patients should be counseled about the extremely teratogenic effects of methotrexate and leflunomide and the need to discontinue these medications prior to pregnancy. Decisions regarding the continued use of other disease-modifying antirheumatic drugs in patients planning a pregnancy should be made by weighing potential benefits against known fetal risks. Women with RA who are using these medications should be offered suitable contraception. Male patients should be made aware of the effects methotrexate, leflunomide, sulfasalazine, and cyclophosphamide may have on their fertility.

Contraception is important for women with RA who do not desire to have a pregnancy. Hormonal contraception including oral contraceptive pills may be used but their long-term effects on RA remain unclear.[110] Intrauterine devices should not be used by women with RA if they are on corticosteroids or other immunosuppressive therapy. [93]

Recommendations by other groups

No practice recommendations or treatment guidelines related to the treatment of rheumatoid arthritis in pregnant women or women planning a pregnancy are identified.

Recommendation. Women of reproductive age with RA should be advised of the natural history of the disease during pregnancy and the probability of a flare after pregnancy. The most important task is to review the patient's medication use. NSAIDs should be discontinued by 27 weeks' gestation. Methotrexate and leflunomide are extremely teratogenic and should be discontinued in women planning a pregnancy. Men with RA should be informed of the possible effects of leflunomide, sulfasalazine, and cyclophosphamide on fertility. *Strength of recommendation:* A; *quality of evidence:* III.

Systemic lupus erythematosus (SLE)

Burden of suffering

SLE is 1 of the most common autoimmune disorders that affect women of reproductive age. In the United States, the prevalence of SLE is 14.6 to 50.8 cases per 100,000 in the general population. The incidence of SLE is much more common among females than males and among African Americans than whites, with a prevalence of SLE in female African Americans from 17.9 to 283 cases per 100,000.[111]

Whether exacerbations of SLE are more common during pregnancy remains controversial. However, it is generally agreed that exacerbations during pregnancy are common (57% of those with SLE).[112] SLE increases the risk of spontaneous abortion, intrauterine fetal death, preeclampsia, and fetal growth restriction, with the greatest risk being of preterm birth (25%). In addition, approximately 10% of women with SLE and anti-Ro antibodies will have a baby with neonatal lupus. Perinatal outcomes among women with SLE depend on the stability of the disease. Prognoses for both mother and child are best when SLE is quiescent for at least 6 months before the pregnancy and when the mother's underlying renal function is stable and normal or near normal.[112]

How detectable is the condition?

SLE is diagnosed according to diagnostic criteria defined by the American College of Rheumatology, which involve the assessment of physical examination features as well as laboratory parameters and should be considered among women with recurrent spontaneous abortions.[113]

How effective are the current treatments?

No treatment is curative for SLE; however, several therapies are disease modifying or result in the control of symptoms associated with SLE.

Randomized controlled trials demonstrate that maternal treatment with low-dose aspirin and subcutaneous heparin is as effective as low-dose aspirin and prednisone or low-dose aspirin alone in avoiding adverse fetal consequences with less frequent preeclampsia, premature rupture of membranes, and preterm delivery.[114,115]

Azathioprine and cyclophosphamide are the 2 most commonly used cytotoxic agents used in treating SLE. Cyclophosphamide is teratogenic in humans and should therefore be avoided during pregnancy, and appropriate contraception should be advised during the periods of cyclophosphamide therapy.[112,116] Azathioprine has not been associated with congenital defects in humans; however, the number of reported cases with adequate follow-up may not be sufficient to detect a small increase in these rates.[117-119] For patients in whom immunosuppression is necessary to control disease, azathioprine may be continued throughout pregnancy. Cyclosporin A does not seem to be associated with teratogenicity in human studies[120,121] and may be considered as an alternative to other cytotoxic agents for severe disease in patients with SLE.

Hydroxychloroquine is the most common antimalarial drug used to treat SLE. Cohort studies reveal that it is safe to use during pregnancy.[122-125] Because withdrawal of hydroxychloroquine is associated with flares of SLE, it should not be stopped unnecessarily during pregnancy in patients with SLE.[112]

Impact of preconception care

A number of studies demonstrate that active SLE at the time of conception is associated with a higher risk of disease exacerbation during pregnancy and a higher rate of adverse pregnancy-related outcomes.[126-129] Rates of exacerbation range from 7% to 33% in women who have been in remission for at least 6 months to 61-67% in women who have active disease at the time of conception. Flares and adverse pregnancy outcomes are particularly elevated among those with lupus nephritis upon conception.[127,129,130] The longer the patient is in remission at the time of conception, the greater the chance the pregnancy will be carried to term without complications.[112]

Contraception is important for women who choose not to have a pregnancy and for helping women achieve optimal timing of pregnancy in relation to the optimal control of their condition. There are numerous considerations in choosing a contraceptive method for women with SLE. Case reports associate estrogen-containing contraceptives with exacerbation of SLE,[131-134] but retrospective studies have failed to find such an association.[135-137] However, there is some evidence that the risk of thromboembolism related to combined oral contraceptives may be higher in SLE patients, especially those with positive antiphospholipid antibodies.[138,139] Progestin-only contraceptives may be a good choice for patients with antiphospholipid antibodies or with risk factors for thromboembolic disease (age $\geq$ 35 years old, obese, smoking, hypertension). Intrauterine contraceptive devices are associated with an increased risk of infection among SLE patients, especially those who are on immunosuppressive therapy.[112]

Recommendations by other groups

Experts advise that in patients with SLE pregnancy is best undertaken during periods of disease quiescence. In particular, nephritis, if present, should be in remission for at least 6 months before conception. Because of its teratogenicity, cyclophosphamide should be avoided in pregnancy. Furthermore, it is advised that all pregnancies complicated by SLE should be considered high risk and managed with involvement of a high-risk perinatal team.[112]

Recommendation. Women of reproductive age with SLE should be coun-

seled about the risks associated with SLE during pregnancy for both the woman and her offspring, the importance of optimizing disease control prior to pregnancy, the possible need to change the medication regimen close to conception or early in pregnancy, and the importance of specialized prenatal care once pregnant. Those whose treatment regimen involves cyclophosphamide should be advised of its teratogenic nature and, whenever possible, should be changed to a safer regimen prior to conception and offered contraception if they are not planning a pregnancy. *Strength of recommendation:* B; *quality of evidence:* II-2.

Chronic renal disease

Burden of suffering

The incidence of moderate chronic renal disease is estimated to be between 6 and 12 per 10,000, respectively.[140] The diagnosis of renal disease before pregnancy is approximately 0.03% in a population-based study of pregnant women with kidney disease.[141] The potential impact of chronic renal disease is dependent on the degree of serum creatinine elevation, defined as mild (0.9-1.4 mg/dL), moderate (1.4-2.5 mg/dL), or severe (> 2.5 mg/dL), and the level of hypertension.[142]

Pregnant women with mild renal disease and normal blood pressure have a greater than 90% chance of a successful outcome and are unlikely to be affected by the progression of renal disease.[143] On the other hand, women with moderate or severe renal disease before pregnancy are at risk for developing worsening renal function during pregnancy. In 1 study, for women with serum creatinine levels above 2.0 mg/dL at the beginning of pregnancy, the progression to end-stage renal disease was 23% within 6 months after delivery.[144]

Maternal morbidity associated with moderate to severe chronic renal disease commonly includes the development of preeclampsia, anemia, chronic hypertension, and cesarean delivery. Adverse pregnancy outcomes associated with maternal renal disease include preterm delivery, fetal growth restriction, and increased fetal loss and stillbirth.[141,144-149] In fact, most pregnancies with moderate to severe renal insufficiency will result in a preterm birth.[150]

When hypertension is present at conception (defined as mean arterial pressure > 105 mm Hg), there is a 10-fold increase in fetal loss at comparable serum creatinine levels, compared with women who are spontaneously or therapeutically normotensive.[151] Additionally, proteinuria is associated with poor pregnancy outcomes and long-term progression of renal disease.[152]

A separate issue from the effect of renal disease on pregnancy is the possible effect on the fetus of drugs used to treat renal disease. Angiotensin-converting enzyme inhibitors and/or angiotensin II receptor blockers, which are commonly used among renal patients, are known teratogens (discussed more fully in *Hypertension* section).

How effective are the current treatments?

The impact of current treatment varies, depending on specific diagnosis. Management guidelines for pregnant women with chronic renal disease are based solely on retrospective and observational series and opinions.[142]

Impact of preconception care

To date, no well-designed studies have specifically addressed the role of specific preconception strategies for the management of patients with renal disease. However, cohort studies document that the higher the serum creatinine, proteinuria, and blood pressure prior to conception, the greater the risk of disease progression during pregnancy and adverse pregnancy outcomes.[143,144,151,152]

Preconception counseling and family planning are important in the care of women of reproductive age with renal disease. Preconception counseling can appropriately inform women of the risks to their own health from pregnancy and the risks of their condition and medications that may be used to treat the condition on pregnancy-related outcomes as well as the need for blood pressure control prior to and throughout the pregnancy to lessen risks.

Contraception is important for women who choose not to have a pregnancy or in helping women achieve optimal timing of pregnancy in relation to control of their condition. Absolute contraindications to oral contraceptive pills relevant to women with chronic kidney disease include significant cardiovascular disease, history of venous thromboembolism, smokers older than 35 years, and impaired liver function. Systemic lupus erythematosus, hypertriglyceridemia, hypertension, and diabetes mellitus are relative contraindications, and lower-dose oral contraceptive pills may be reasonable. Progestin-only pills can be considered for patients who cannot take estrogen. [93]

Recommendations by other groups

There were none identified.

Recommendation. Women of reproductive age with renal disease should be counseled about the likelihood of progression of renal disease during pregnancy and irrespective of pregnancy; the increased risk of adverse pregnancy outcomes for the woman and offspring; and the importance of achievement or maintenance of normal blood pressure prior to conception. Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers are contraindicated during pregnancy; women who could become pregnant while taking these medications should be counseled about their adverse fetal effects and should be offered contraception if they are not planning a pregnancy. Women who are planning a pregnancy should discontinue these medications prior to pregnancy in favor of a safer regimen whenever possible. Women who do not desire pregnancy should be offered an appropriate method of contraception. *Strength of recommendation:* B; *quality of evidence:* II-2.

Cardiovascular disease

Burden of suffering

Approximately 3% of women 18-44 years of age have cardiac disease, and approximately 1% of pregnancies are complicated by cardiac disease.[1] Congenital heart disease in pregnancy is increasingly common as more affected women are surviving into reproductive age.[153] For women with cardiac disease, however,

the physiologic alterations of pregnancy can result in decomposition of the cardiac condition with increased symptoms, morbidity, and mortality.[154] In fact, cardiac conditions account for 10-25% of maternal mortality in the United States and are almost exclusively seen in patients with pulmonary hypertension, endocarditis, coronary artery disease, cardiomyopathy, and sudden arrhythmias.[155]

The prediction of maternal and neonatal outcomes is based on classification of the severity of heart disease.[156,157] A large prospective Canadian cohort of pregnant women with heart disease revealed that those at greatest risk for a cardiac event in pregnancy had at least 1 of the following: a prior cardiac event or arrhythmia, New York Heart Association functional class greater than II or cyanosis, left heart obstruction, or systematic ventricular dysfunction. The estimated risks of a cardiac event in pregnancy with 0, 1, and more than 1 of these predictors were 5%, 27%, and 75%, respectively.

In the same cohort, the risk of fetal or neonatal death was doubled from the baseline of 2-4% if any of the following were present: New York Heart Association class greater than II or cyanosis at the baseline prenatal visit, maternal left heart obstruction, smoking during pregnancy, multiple gestations, and use of anticoagulants throughout pregnancy.[154] The risk of heart disease is increased in the offspring of patients with almost all forms of congenital heart disease and is higher if the affected parent is the mother.[154,158]

A sizable proportion of those with cardiac diseases (eg, valvular heart disease, prosthetic heart valves, and dilated cardiomyopathy) may be treated with warfarin. Warfarin, a coumadin derivative that is used for the control of blood clotting, can produce a characteristic embryopathy with first-trimester exposure and, less commonly, central nervous system abnormalities and fetal bleeding with exposure after the first trimester.[159] In contrast, heparin does not cross the placenta and is not known to be teratogenic. However, several reports of heparin failure that resulted in serious consequences for pregnant women with mechanical heart valves have caused some to recommend that warfarin be used preferentially in women with mechanical prosthetic valves during the second and third trimesters of pregnancy. The Centers for Disease Control and Prevention recommendations specify that to avoid exposure to warfarin during early pregnancy, heparin should be substituted for warfarin before the onset of pregnancy whenever possible.[160-162]

How effective are the current treatments?

There are effective medical and surgical treatments for a variety of congenital and acquired cardiac conditions. A complete discussion of treatment of cardiac conditions is beyond the scope of this manuscript. A thorough discussion of the treatment of congenital and acquired cardiac conditions during pregnancy has been published.[163]

Impact of preconception care

Cohort studies demonstrate improved maternal and fetal outcomes when cyanotic heart disease[164,165] and symptomatic obstructive lesions (eg, aortic stenosis and pulmonary stenosis)[166] are corrected prior to pregnancy. During pregnancy, cardiovascular surgery is more dangerous, involving a 6% risk of maternal mortality and a 30% risk of fetal mortality.[167] Otherwise, there are no published studies addressing the effect of preconception intervention strategies or pregnancy-related outcomes for women with cardiac disease. However, cohort studies document adverse pregnancy-related outcomes (for the woman and her offspring) associated with various cardiac diseases. Maternal and neonatal mortalities are high (30% and 12%, respectively) among patients with pulmonary hypertension.[168] Patient knowledge of these risks prior to conception may affect their desire to have children.

Preconception counseling is important in the care of women of reproductive age with cardiac disease. Preconception counseling can appropriately inform women of the risks to their own health from pregnancy and the risks of their condition on pregnancy-related outcomes. For patients with congenital heart disease, genetic counseling prior to pregnancy may help identify the risk to the offspring. Finally, a thorough assessment by a cardiologist prior to pregnancy to define the cardiac lesion and assess the presence of ventricular function, pulmonary pressure, severity of obstructive lesions, persistence of shunts, and presence of hypoxemia can inform whether the problem can be corrected or palliated before pregnancy.[163]

Contraception is important for women who choose not to have a pregnancy, for which pregnancy may be contraindicated, or in helping women achieve optimal timing of pregnancy in relation to the optimal control of their condition. There are numerous considerations in choosing a contraceptive method for women with cardiac disease. Sterilization of the male partner carries the least risk for the woman with cardiac disease who is in a monogamous relationship and who does not desire children. Barrier methods and the Copper T380A are also safe and effective when used consistently. Those patients who have right to left shunts, ischemic heart disease, a history of stroke, or who have multiple risk factors for cardiovascular disease (eg, age $>$ 35 years, smoker, diabetes, uncontrolled hypertension) should not use oral contraceptives.[169,170] Progestin-only contraceptives, including the progestin-releasing intrauterine device, may be used by women with cardiac disease.[169,171]

Recommendations by other groups

The American Heart Association and the American College of Cardiology have a joint guideline for the management of valvular heart disease in pregnancy.[172] Additionally, they have a joint guideline for warfarin therapy for pregnant patients that recognizes 3 options: (1) use heparin or low-molecular weight heparin (LMWH) throughout pregnancy; (2) use warfarin throughout pregnancy, changing to heparin or LMWH at 38 weeks' gestation with planned labor induction at approximately 40 weeks; or (3) use heparin or LMWH in the first trimester, switching to warfarin in the second trimester and continuing it until approximately 38 weeks' gestation and then changing to heparin or LMWH at 38 weeks with planned labor induction at approximately 40 weeks.[162]

Recommendation. Women of reproductive age with cardiac disease should be counseled about the risks pregnancy presents to their health, as well as the risks of the cardiac condition and any medications needed to treat the condition (eg, warfarin), on pregnancy-related outcomes. Those who are considering or planning a pregnancy should be counseled to achieve optimum control of the condition prior to conception and should be offered a suitable contraceptive method to achieve optimum timing of the pregnancy. Those whose treatment regimen involves warfarin should be counseled about its teratogenic nature and, whenever possible, should be changed to a less teratogenic anticoagulant prior to conception. Those with a congenital cardiac condition should be offered preconception genetic counseling. Those who do not desire a pregnancy should be offered a suitable form of contraception. *Strength of recommendation:* B; *quality of evidence:* II-3.

Thrombophilia

Burden of suffering

Thrombophilias (disorders that predispose to spontaneous, inappropriate venous clotting events) can be inherited or acquired. The prevalence of the various thrombophilias vary substantially with ethnicity, and numerous studies have yielded varying estimates of the prevalence of thrombophilias in pregnancy. The most common inherited disorders during pregnancy are mutations in factor V Leiden, prothrombin gene, and methylenetetrahydrofolate reductase. Whites have a higher rate of genetic thrombophilias than other racial groups.[173] The factor V Leiden mutation may be present in as many as 1 in 20 Caucasian individuals, but it is very uncommon in Asian populations. Antiphospholipid antibody syndrome is the most commonly acquired thrombophilia of pregnancy and is more common in blacks.[174]

Several studies demonstrate an association between thrombophilias and adverse pregnancy outcomes. Maternal effects of thrombophilias include an increased risk of venous thromboembolism (including deep vein thrombosis, pulmonary embolism, and cerebral vein thrombosis), arterial thrombosis (peripheral and cerebral), and severe preeclampsia. Placental and fetal effects include thrombosis and infarcts, placental abruption, recurrent miscarriage, fetal growth restriction, fetal stroke, and death.[175-179]

How detectable is the condition?

The presence of a thrombophilia in an individual may be suspected in the presence of a personal or family history of venous thrombotic events, a history of recurrent early or late pregnancy loss, severe preeclampsia, severe intrauterine growth restriction, or placental abruption/insufficiency. The sensitivity and specificity of family history as a tool for detecting the thrombophilias in the prenatal setting is largely unknown and very likely varies among populations. Laboratory testing for specific thrombophilias is widely available and both sensitive and specific if properly ordered and interpreted.

A thrombophilia work-up may include testing for the following conditions: factor V Leiden, prothrombin G20210A mutation, antithrombin III deficiency, hyperhomocystinemia, protein C deficiency, protein S deficiency, and the presence of lupus anticoagulants.[175-186] Although genetic testing for factor V Leiden and prothrombin G20210A can be offered and interpreted at any time, antithrombin III assays are affected by anticoagulation and acute thrombosis, and protein C and protein S assays are affected by acute thrombosis, pregnancy, oral contraceptives, and warfarin.[176] Because of the complexity and variety of tests available for thrombophilia, primary care providers may wish to work with a genetics health professional and/or a hematologist when confronted with this clinical scenario.

How effective are the current treatments?

There are no randomized trials evaluating thromboprophylaxis for prevention of recurrent adverse pregnancy outcomes in women with previous severe preeclampsia, fetal growth restriction, or abruptio placenta in association with thrombophilias. Therefore, any recommendation to treat such women with low-molecular-weight heparin with or without low-dose aspirin in subsequent pregnancies should remain empiric and/or prescribed after appropriate counseling of the patients regarding risks and benefits.[173]

Although treatment is controversial, current American College of Obstetricians and Gynecologists guidelines (level C: based primarily on consensus and expert opinion) recommend offering treatment in pregnancy for women with homozygotic factor V Leiden and prothrombin G20210A mutations, antithrombin III deficiency, and compound heterozygous factor V Leiden/prothrombin G20210A mutations.[175] Additionally, treatment is recommended for women with protein C or protein S deficiency as well as for women who are factor V Leiden or prothrombin G20210A mutation heterozygotes. Treatment of women with hyperhomocystinemia or methylenetetrahydrofolate reductase mutations is not well established; whereas folic acid supplementation in women with hyperhomocystinemia is safe, treatment is not necessarily efficacious.[176,177,180-184]

Impact of preconception care

No studies have specifically evaluated the effect of treatment of thrombophilias prior to conception. However, because untreated thrombophilias are associated with adverse maternal and fetal consequences and it is well established that warfarin, commonly used to control blood clotting, is teratogenic, preconception counseling and family planning are important considerations for women with thrombophilias.

Preconception counseling can appropriately inform women of the risks to their own health from pregnancy and the risks of their condition, and any medications used to treat their condition, on pregnancy-related outcomes. Preconception care may allow women to optimize control of their condition prior to pregnancy and allow women to transition to a medication regimen that is safer for the fetus. For patients with heritable disorders, genetic counseling prior to

pregnancy may help identify the risk to the offspring.

Contraception is important for women who choose not to have a pregnancy and for helping women achieve optimal timing of pregnancy in relation to control of their condition. Because estrogens promote hypercoagulable states, combination oral contraceptive pills are contraindicated among women with thrombophilias. There are no contraindications to progestin-only methods, intrauterine devices, or barrier methods.[93]

Recommendations by other groups

The American College of Obstetricians and Gynecologists has a practice bulletin addressing thrombophilias in pregnancy,[187] although this bulletin does not specifically address preconception concerns related to thrombophilia. The American Heart Association and the American College of Cardiology have a joint guideline for warfarin therapy for pregnant patients that recognizes 3 options:[162] (1) use heparin or LMWH throughout pregnancy; (2) use warfarin throughout pregnancy and change to heparin or LMWH at 38 weeks' gestation with planned labor induction at approximately 40 weeks; or (3) use heparin or LMWH in the first trimester, switching to warfarin in the second trimester, continuing it until approximately 38 weeks' gestation and then changing to heparin or LMWH at 38 weeks with planned labor induction at approximately 40 weeks.

Recommendation. Providers may consider screening women of reproductive age for a personal or family history of venous thrombotic events or recurrent or severe adverse pregnancy outcomes. Women with a personal or family history suggestive of thrombophilia may then be offered counseling and testing for thrombophilias. Screening for thrombophilias with laboratory testing in routine care is not recommended. Women of reproductive age with a known genetic thrombophilia should be offered preconception genetic counseling to address the risk of the condition to the offspring. *Strength of recommendation:* C; *quality of evidence:* III.

Women of reproductive age with a thrombophilia whose treatment regimen involves warfarin should be counseled about its teratogenic nature and, whenever possible, should be changed to a less teratogenic anticoagulant prior to conception. *Strength of recommendation:* B; *quality of evidence:* II-3.

Asthma

Burden of suffering

Asthma affects up to 8.2% of pregnant women and 9.4% of women of reproductive age in the United States.[188] For approximately 30% of women with asthma, the severity of the disease worsens during pregnancy. Women who are most likely to experience worsening of their asthma during pregnancy are those with severe or poorly controlled asthma prior to pregnancy.[189] Subsequent pregnancies tend to follow a course similar to the first pregnancy with respect to status of asthma severity.[190]

Asthma that is not adequately controlled during pregnancy can result in serious complications for both the mother and the fetus. Maternal complications include preeclampsia, hypertension, and hyperemesis gravidarum.[191] Fetal complications include increased stillbirth and infant death, neonatal hypoxia, intrauterine growth retardation, premature birth, and low birthweight.[191,192] Women whose asthma is adequately controlled during pregnancy have perinatal outcomes similar to those of nonasthmatic women.[193-195] Studies and observations of pregnant women with asthma demonstrate that the risks of uncontrolled asthma appear to be greater than the risks of necessary asthma medications.

Studies of pregnant women demonstrate that most inhaled asthma medications are safe for patients to use while pregnant. In fact, inhaled corticosteroids are the prophylactic treatment of choice for pregnant women with mild, moderate, or severe persistent asthma, according to the National Asthma Education and Prevention Program Expert Panel (NAEPP).[196] Specifically, existing observational cohort data do not associate an increased risk of preeclampsia, total congenital malformations, preterm birth, or low-birthweight infants with maternal exposure to inhaled beta agonists, cromolyn, inhaled corticosteroids, or oral theophylline. Maternal use of oral corticosteroids, however, has been associated with reduced birthweight, an increased risk of preeclampsia, and an increased risk of oral clefts (first-trimester use).[197] Nevertheless, although some increased risks may be associated with the gestational use of oral corticosteroids, these risks are probably still less than the potential risks to the mother and the fetus of severe uncontrolled asthma.

How effective are the current treatments?

There is general agreement that it is safer for pregnant women with asthma to be treated with asthma medications than to have asthma symptoms or exacerbations and reduced lung function that may potentially impair oxygenation of the fetus.[198] Short-acting beta agonists induce bronchodilation and are the initial rescue therapy in pregnant and nonpregnant asthmatics. Although this class of medications has a pregnancy category C rating, the human data for albuterol, metaproterenol, and terbutaline are reassuring. Anticholinergics (category B), in addition to bronchodilators, are usually added to short-acting beta agonists for additional rescue therapy.

Oral corticosteroids (category C) are used for asthma exacerbations that do not respond to initial rescue therapies. Unfortunately, the use of oral corticosteroids during the first trimester of pregnancy is associated with a 3- to 6-fold increased risk of oral clefts and low birthweight in infants[199] as well as an increased risk of maternal preeclampsia.[200] However, when indicated for management of severe asthma, these risks of therapy are much less than the risks of uncontrolled severe asthma that can include maternal and/or fetal death.

To both avoid uncontrolled asthma in the mother and minimize the possible need for oral corticosteroids, preventive therapy with controller medications is paramount. The choice of controller therapy may differ in the pregnant vs nonpregnant asthmatic. The first therapy currently recommended by the

American College of Allergy, Asthma, and Immunology (ACAAI)-American College of Obstetricians and Gynecologists 2000 position paper is still cromolyn or nedocromil (category B) because of reassuring animal and human data for use during pregnancy. Unfortunately, these are most efficacious in mild asthmatics, and further therapy is usually warranted.

Inhaled corticosteroids are the most effective prophylactic therapy for asthma, and both beclomethasone and budesonide have reassuring human data during pregnancy. In fact, the Food and Drug Administration changed budesonide from pregnancy category C to B (all other inhaled corticosteroids are C). The ACAAI-ACOG 2000 position paper recommends the addition of salmeterol (a long-acting beta agonist) only in patients not controlled by a maximum dose of inhaled corticosteroids. Leukotriene modifiers (montelukast and zafirlukast, both category B) have been used in asthma therapy. However, no human data are available, and as a systemic medication, it should be used in pregnancy only if it was effective for the patient prior to pregnancy. Animal data for the leukotriene modifiers are reassuring. Theophylline (category C) has reassuring human data and may be considered in patients not controlled by inhaled corticosteroids.

Impact of preconception care

There are no published studies that specifically evaluate the impact of preconception asthma care on pregnancy-related outcomes for the woman and fetus. However, research demonstrates that women with severe asthma prior to pregnancy are more likely to worsen during pregnancy, reinforcing the importance of adequate asthma control prior to conception.[189] Subsequent pregnancies tend to follow a course similar to the first pregnancy in any given patient,[190] suggesting the potential for interconception care focused on achieving asthma control between pregnancies.

A single published study has evaluated health care outcomes for pregnant women with asthma who were and were not using an inhaled corticosteroid medication prior to the pregnancy. This study found that patients using an inhaled corticosteroid before pregnancy experienced a decrease in the rate of asthma-related physician and emergency department visits during the pregnancy, whereas the patients not using an inhaled corticosteroid before pregnancy experienced no change in these measures. Those patients using an inhaled corticosteroid before pregnancy did not have an increase in adverse pregnancy outcomes relative to the group that was not using them.[201] Inhaled corticosteroids are recommended in the 2004 NAEPP asthma and pregnancy guidelines as the prophylactic treatment of choice for pregnant women with persistent asthma.[196] The preferred agent in these guidelines is budesonide because this is the only inhaled corticosteroid with Food and Drug Administration category rating B, based on accumulated evidence from the Swedish Medical Birth Registry indicating that budesonide treatment is not associated with an increased risk of congenital malformations[202] or with an increased risk of preterm delivery, stillbirth, or low birthweight.[203]

Morbidity during pregnancy because of smoking may be independent of and additive to morbidity because of asthma. Furthermore, maternal smoking may be associated with increased risk for wheezing and development of asthma in her child.

Recommendations by other groups

No organizations or professional associations have published guidelines or recommendations for the delivery of specific preconception care to women with asthma. However, the National Asthma Education and Prevention Program (NAEPP) has developed a clinical practice guideline for management of asthma during pregnancy, which recommends that asthma be treated aggressively in women who are pregnant.[196] Inhaled corticosteroids are recommended in the 2004 NAEPP asthma and pregnancy guidelines as the prophylactic treatment of choice for pregnant women with persistent asthma.[196] The preferred agent in these guidelines is budesonide because this is the only inhaled corticosteroid with Food and Drug Administration category rating B, based on accumulated evidence from the Swedish Medical Birth Registry indicating that budesonide treatment is not associated with an increased risk of congenital malformations[202] or with an increased risk of preterm delivery, stillbirth, or low birthweight.[203]

Recommendation. Women of reproductive age with asthma should be counseled about the potential for their asthma control to worsen with pregnancy and the importance of achieving asthma control prior to a pregnancy through appropriate medical management and avoidance of triggers. Women with asthma who are planning to become pregnant or who could become pregnant should be treated with pharmacologic step therapy for their chronic asthma based on the ACAAI-ACOG recommendations for the Pharmacologic Step Therapy of Chronic Asthma During Pregnancy. Those with poor control of their asthma should be encouraged to use effective birth control until symptom control is achieved. *Strength of recommendation:* B; *quality of evidence:* II-3.

Conclusion

All women of reproductive age presenting to the primary care setting are considered candidates for preconception care.[3,5] In addition to general preconception health promotion, health care providers for women of reproductive age with chronic medical conditions should also address with the woman her risk of pregnancy complications and maternal morbidity and mortality given: pregnancy, disease prognosis irrespective of pregnancy, whether there are conflicts between maternal treatment and fetal well-being, the extent of risk the condition or medications used to treat the condition place on the fetus, optimal timing of pregnancy (if desired), and the woman's ability to conceive at present and in the future. Because avoiding, delaying, or achieving optimal timing of a pregnancy is often an important component of the preconception care of women with medical conditions, health care providers should explicitly address re-

productive planning and contraceptive considerations for women of reproductive age with chronic medical conditions.

Because a high proportion of pregnancies is unintended, and even women with intended pregnancies do not typically plan their pregnancies with a health care provider, providers must be proactive in systematically addressing reproductive planning and preconception health care interventions with their patients to ensure that those with chronic medical conditions have the necessary knowledge to inform their decisions and actions around family planning and reproduction. ■

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The clinical content of preconception care: women with psychiatric conditions

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For a substantial proportion of women, pregnancy can be complicated by the occurrence or reoccurrence of a psychiatric condition. Psychiatric disorders during pregnancy are associated with poor obstetric outcomes, higher risk of postpartum psychiatric illness, increased rates of substance abuse, lower participation in prenatal care, and adverse infant and family outcomes. As part of preconception care, providers should be vigilant and screen for psychiatric disorders among women of reproductive age, as the detection and appropriate management of these conditions can reduce the occurrence of adverse pregnancy and family outcomes. This manuscript reviews the treatment options and the risks and benefits of discontinuing, changing, or continuing psychotropic medications for women of reproductive age with common psychiatric disorders (depression and anxiety disorders, bipolar disorder, and schizophrenia) and offers recommendations for preconception care.

Key words: anxiety, bipolar, depression, preconception, schizophrenia

For a substantial proportion of women of reproductive age, the antenatal and postpartum periods can be complicated by the onset of a psychiatric condition or the occurrence or reoccurrence of a preexisting psychiatric condition. Psychiatric disorders during pregnancy have been associated with poor obstetric outcomes, higher risk of postpartum psychiatric illness, increased rates of substance abuse, lower participation in prenatal care, and adverse infant and family outcomes.[1] The detection and appropriate management of psychiatric conditions among women of reproductive age before or early in pregnancy is critical for preventing morbidity during and after the pregnancy for the woman and her offspring. In managing psychiatric conditions during pregnancy and among women who could become pregnant, the clinician must consider and weigh the risks and benefits of discontinuing, changing, or continuing psychotropic medications. Preconception considerations for common psychiatric disorders are discussed in this manuscript.

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Depression and anxiety disorders

Burden of suffering

Mood and anxiety disorders are highly prevalent among women of reproductive age and are comorbid in over 50% of those diagnosed with either. There is evidence that the emergence of a new psychiatric illness or the relapse of a preexisting one during pregnancy is highly prevalent (10-20%).[2] Of note, while anxiety disorders tend to persist chronically following their onset, depressive disorders are usually episodic, with very high rates of recurrence (85% at 15 years). There is much evidence suggesting that depression and anxiety during pregnancy and postpartum have a severe impact on family life, the mother-infant relationship, and the future mental health of the child.[1-7] These may be mediated by environmental, neurohormonal, and genetic influences.[8,9] Depression increases the risk of tobacco, alcohol, and illicit drug use, and may contribute to inadequate prenatal care. In addition, it increases the risk of self-injurious and suicidal behavior. Several studies have found an association between depression during pregnancy and preterm delivery, lower birthweight, smaller head circumference, low Apgar scores, and postpartum depression.[2,10,11] Moreover, perinatal depression can have short- and long-term developmental, cognitive, and behavioral effects on the child.[1,2,9,12,13] Depression can lead to reduced interaction and irritability towards the child.[6]

Although little is known about the prevalence of anxiety disorders (social anxiety disorder, panic disorder, obsessive compulsive disorder, posttraumatic stress disorder, and generalized anxiety disorder) during and after pregnancy, anxiety disorders may be more common than depression during pregnancy.[5] Anxiety disorders during pregnancy and postpartum have been associated with poor neonatal outcome, obstetric com-

plications, childhood behavioral problems, and avoidance of the child by the mother.[2] In women with preexisting obsessive compulsive disorder (OCD), pregnancy may precipitate a worsening of symptoms. Of note, obsessions of infanticide or child harm are a common feature of postpartum OCD. Their content can include child sexual abuse.[14] Posttraumatic stress disorder (PTSD) has been described in pregnancies in women who had a previous complicated delivery. PTSD may also present in the postpartum period following a traumatic childbirth.[5,14] Postpartum PTSD may affect a woman's future childbearing decisions, her ability to breastfeed, and the relationship between mother and infant.[5,14] PTSD also frequently follows abuse and is frequently comorbid with depression and generalized anxiety disorder.[15]

How detectable is the condition?

Diagnostic and Statistical Manual of Mental Disorders-IV-TR criteria are currently used to diagnose Depressive and Anxiety disorders.[16] Available screening tools are the PHQ-9, QIDS, GAD-7, Beck Depression Inventory, and the Hamilton Rating Scale, among others. Risk factors for depression and anxiety during and after pregnancy include a history of mood or anxiety disorder, marital problems, inadequate support system, recent stressors, lower socioeconomic status, and unwanted pregnancy.[2,17]

How effective are the current treatments?

Depression and anxiety disorders can be treated effectively during pregnancy with psychotherapy, cognitive behavioral therapy, interpersonal psychotherapy, and/or medications. A review of 12 psychotherapy trials involving nonpregnant subjects in primary care settings found that psychotherapy resulted in similar outcomes to those obtained using antidepressants and better outcomes than a primary care physician's usual care.[18] In addition, electroconvulsive therapy is an effective treatment for depression, and is safe during pregnancy.[19,20]

In recent years, antidepressant use during pregnancy has increased significantly. In 1 large study, selective serotonin reuptake inhibitor use increased from 1.5% in 1996 to 6.2% in 2005.[21] All psychotropic medications diffuse across the placenta and none have yet been approved by the US Food and Drug Administration (FDA) for use during pregnancy.[2] Data accumulated over the last 30 years suggest the limited teratogenic effects of most antidepressants (including selective serotonin reuptake inhibitors [SSRIs], tricyclic antidepressants [TCAs], and venlafaxine).[2-4,22,23] However, paroxetine's FDA classification has recently been changed from C to D based upon a retrospective study that found a 1.5-2 times increased risk of congenital cardiac malformations associated with exposure to paroxetine in the first trimester. Moreover, 2 large case-control studies that found an association between SSRI use during early pregnancy—particularly paroxetine—and anencephaly, craniosynostosis, and omphalocoele[24] and right ventricular outflow abnormalities.[25] Even still, the absolute risk associated with exposure was very small. Furthermore, recent studies have linked exposure to antidepressant therapy during pregnancy with preterm delivery and/or lower birthweight. A retrospective study of depressed women treated with SSRIs or untreated found in utero exposure to SSRIs linked with earlier gestational age and lower birth rate; the exposed group also had higher rates of neonatal respiratory distress syndrome, jaundice, and feeding problems.[26,27] A particular concern was the potential adverse effect of late trimester exposure to SSRIs with 1 small study reporting pulmonary hypertension of the newborn.[28] A naturalistic study of depressed women and healthy controls found an association between preterm delivery and exposure to antidepressant therapy, while maternal depression itself was not linked with preterm delivery.[27] All of these newer studies have added an extra level of complexity in the decision-making process of the treatment of depression during pregnancy. Treatment should be the result of an individualized risk-benefit assessment.[29] Thus, in women with less severe symptoms, it may be appropriate to consider nonpharmacologic interventions such as psychotherapy.[29] However, if the symptoms are moderate to severe, if there is a history of previous postpartum depression or recurrent major depressive disorder, a combination of psychotherapy and medications is advised.[29,30]

Impact of preconception care

Identification of depression and anxiety disorders prior to pregnancy allows time to discuss treatment options and, if necessary, to change to a treatment regimen that is safer during pregnancy. The goal should be for the woman to be euthymic during pregnancy to prevent negative outcomes. Women with a history of mood or anxiety disorder should be informed about the high risk of relapse (50-75%) when discontinuing maintenance medication.[2,31] Any necessary changes in medications should be made prior to conception to decrease the exposure of the fetus to multiple medications. Such preconception medication adjustment also allows for gradual tapering of the antidepressant to minimize the risk of withdrawal symptoms. It also allows opportunity to monitor for relapse, which is most likely in the initial months following withdrawal.

Recommendations by other groups

The American College of Obstetrics and Gynecology (ACOG), in a November 2007 Practice Bulletin, recommended that paroxetine use in pregnant women and women planning a pregnancy should be avoided if possible, and that fetal echocardiography be considered for women who are exposed to paroxetine in early pregnancy. They further recommend that treatment with all SSRIs during pregnancy should be individualized, and that use of a single medication at a higher dose should be favored over the use of multiple medications.[2,4]

Recommendation. Providers should screen and be vigilant for depression and anxiety disorders among women of reproductive age, as treating or controlling these conditions prior to pregnancy may help prevent negative pregnancy and family outcomes. Women of reproductive age with depressive and anxiety disorders who are planning a pregnancy or

who could become pregnant should be informed about the potential risks of an untreated illness during pregnancy and about the risks and benefits of various treatments during pregnancy. Identifying healthy women at risk along with appropriate referral for social and psychological interventions during the preconception visit might prevent the emergence of anxiety and depressive disorders during pregnancy and postpartum. *Strength of recommendation*: B; *quality of evidence*: II-2.

Bipolar disorder

Burden of suffering

Bipolar disorder (BD) is particularly challenging during the reproductive years, as associated outcomes may include lower fertility rates, strong genetic loading, potential fetal teratogenic risk from medications to control the condition, and high risk of recurrence if treatment is discontinued abruptly.[32] There is a strong familial pattern in bipolar disorder, with about 10% of first-degree relatives, including offspring, also affected.[33] Women with BD are also at higher risk for other psychiatric disorders and medical illnesses including obesity, migraines, and thyroid dysfunction. Hypomanic and manic episodes often include high-risk sexual activity with significant risk of unintended pregnancy. Moreover, women with BD might exhibit poor insight into their condition that interferes with appropriate treatment. Some studies suggest a protective effect of BD during pregnancy.[2] More recent studies show a high risk of relapse, especially if medications are discontinued.[34] In a recent prospective study that estimated the risk of recurrence of BD during pregnancy in women who either discontinued or continued the use of a mood stabilizer, 70.8% of the overall population of women was found to experience at least 1 episode of illness during their pregnancy. Recurrence risk was 2.3 times greater after discontinuing mood stabilizer treatment. Women who discontinued the mood stabilizer spent over 40% of their pregnancy in a mood episode, compared to 8.8% of the women who continued their medication. Furthermore, women who discontinued the mood stabilizer abruptly had a 50% risk of recurrence within 2 weeks versus 22 weeks in women who gradually tapered their mood stabilizer treatment.[35] Moreover, women with BD are at high risk of relapse during the postpartum period (20-80%) and have a 10-20% prevalence of postpartum psychosis.[1,36] Postpartum psychosis is associated with high rates of suicide and infanticide.[1,4,34]

How detectable is the condition?

DSM-IV-TR criteria are currently used to diagnose BD.[16] Women should be assessed for BD at the preconception visit, at least to identify those with a history of BD but who may be functioning well, and who may not be in contact with psychiatric services. Women should be screened by asking about family history of mood disorders as well as personal history of depression, psychosis, and mania. Women at risk should receive a formal psychiatric assessment.

How effective are the current treatments?

BD is a severe recurrent illness that is associated with high rates of morbidity and mortality in the absence of adequate treatment. Identifying and treating women prior to pregnancy might prevent negative outcomes. Medications used to treat BD (including lithium and anticonvulsants) are associated with increased risk of fetal anomalies. First-trimester exposure to lithium increases the risk of cardiac malformations to levels that range 10-20 times greater than in the general population. Still the absolute risk remains low, 1:1000-1:2000. Compared with lithium, anticonvulsants such as carbamazepine and valproic acid may confer even greater risks of malformations (1-7%), including neural tube defects, craniofacial anomalies, and microcephaly. Moreover, valproic acid was found to have long term neurobehavioral effects in children exposed in utero across all the trimesters.[37] Of note, most of the data regarding use of lamotrigine as monotherapy have not shown an increase in risk of major malformations. However, a recent report of the North American Antiepiletic Drug Registry has suggested an increase risk of oral clefts associated to first-trimester exposure to lamotrigine monotherapy. More data are still necessary to corroborate these findings.[34,38,39] Atypical antipsychotics are widely used in the treatment of BD; however, there are limited data about their use during pregnancy. It is highly recommended that required changes in medications be done prior to conception to decrease the exposure of the fetus to multiple medications. Illness history and reproductive safety of medications are the most important factors to consider when planning treatment. A risk assessment should include the patient's: 1) prior response to medications; 2) illness severity; 3) duration of euthymia; 4) time to relapse after discontinuing medications; and 5) time to recover with reintroduction of medications.[34] Thus, in women with low risk of relapse, medication should be tapered slowly over the course of 6 weeks. High potency antipsychotics could be used if needed. Women with more severe risk of relapse are recommended to continue medications.[40] Despite the dearth of data, folic acid supplementation (4 mg daily) is recommended to prevent neural tube defects for patients being treated with anticonvulsants.[34] It is also important to address the consumption of caffeine, nicotine, illicit drugs, and alcohol, as well as poor nutrition and the general level of stress and sleep deprivation.

Impact of preconception care

Identification of bipolar disorder prior to pregnancy allows time to discuss treatment options and, if necessary, to switch to a medication that is safer during pregnancy. The goal should be for the woman to be euthymic during pregnancy to prevent negative outcomes. Women with a history of BD should be informed about the high risk of relapse when discontinuing maintenance medication.[2] Any necessary changes in medications should be made prior to conception to decrease the exposure of the fetus to multiple medications.[41] Women with BD often have limited social supports, and preconception assessment can provide an opportunity to help such women mobilize these. When possible, the partner or family should be involved in the

advance planning of relapse prevention and management strategies. This can be particularly helpful to improve outcome in women with poor insight, poor impulse control, and cognitive impairment. The preconception visit also provides for the opportunity to educate women regarding the importance of planning for pregnancy and of available long-acting contraceptive methods that can provide protection during bipolar relapses.

Recommendations by other groups

The ACOG, in an April 2008 Practice Bulletin, recommend that the use of valproate and carbamazepine during pregnancy should be avoided, when possible, particularly during the first trimester. They further recommend that a fetal echocardiogram should be considered in women exposed to lithium during the first trimester.

Recommendation. Women of reproductive age with BD should be counseled that pregnancy is a time of substantial risk of relapse, particularly following discontinuation of ongoing mood stabilizing maintenance treatment. A relapse prevention and management strategy for bipolar disorder should be outlined before the patient attempts conception.[42] When possible, the partner or family member should be involved in the advance planning. Women of reproductive age with BD should be counseled regarding contraceptive options, including those that will prevent conception during bipolar episodes. *Strength of recommendation*: B; *quality of evidence*: II-2.

Schizophrenia

Burden of suffering

Women with schizophrenia are probably among the most vulnerable to psychiatric complications of pregnancy. They have a high risk of malformations and fetal demise. They are at high risk for relapse while not taking their medications, placing prenatal care and their own well-being in jeopardy. Psychosis during pregnancy can lead to fetal abuse, neonaticide, and inability to recognize signs or symptoms of labor. In addition, they have a higher risk of unwanted and unplanned pregnancies, and are more likely to be unmarried and have limited social support.[2,43] Women with schizophrenia are more prone to exhibit poor insight into their condition and cognitive impairment that might interfere with their ability to participate in treatment.

How detectable is the condition?

DSM-IV-TR criteria are currently used to diagnose schizophrenia.[16,43] Women should be screened by asking about family history of psychotic and affective disorders, as well as personal history of psychosis. Women at risk should receive a formal psychiatric assessment.

How effective are the current treatments?

Schizophrenia is a chronic and debilitating illness. Treatment of schizophrenia with antipsychotics has been shown to decrease psychotic symptoms and improve functioning. When possible, antipsychotics should be avoided during the first trimester.[1] However, women with severe symptoms, including the inability to care for oneself or cooperate in prenatal care; impairment of reality testing, with potential danger to self or others; and disorganized thought, perception, and behavior, should receive pharmacotherapy.[4] There are more data about the use of typical than atypical antipsychotics. High-potency typical antipsychotics (haloperidol, perphenazine, trifluoperazine) were shown to be less teratogenic than low-potency typical antipsychotics (chlorpromazine).[4,44] Currently, many women with schizophrenia are using atypical antipsychotics; however, there are limited data about their use during pregnancy. Recommendations call for their use during pregnancy if the woman has a history of nonresponse to the better-studied antipsychotics, or is at significant risk of relapse should the medication be discontinued.[43,44] Atypical antipsychotics increase the risk for obesity, diabetes, and hypertension. It is advisable to closely monitor weight gain, blood pressure, and blood glucose. It is also recommended to address avoidable factors such as the use of caffeine, nicotine, illicit drugs, and alcohol, as well as poor nutrition, general level of stress, and sleep deprivation.

Impact of preconception care

Although the course of schizophrenia during pregnancy is not well defined, these pregnancies should be considered high risk. Psychosis itself poses a substantial risk for both mother and fetus. Women with schizophrenia tend to have poor nutrition and a high prevalence of tobacco, alcohol, and illicit drug use. Identification and treatment of women prior to pregnancy might improve outcomes for both mother and baby. Any necessary changes in medications should be done prior to conception to decrease the exposure of the fetus to multiple medications.[4] Preconception care also provides the opportunity to offer contraceptive methods to prevent unintended pregnancy.

Recommendations by other groups

None identified.

Recommendation. Women of reproductive age with schizophrenia should be counseled, together with a partner or family member whenever possible, about the risks of pregnancy on their condition and the risk of their condition on pregnancy-related outcomes. They should be counseled about the importance of prenatal care, and a relapse prevention and management strategy of the illness should be outlined before the patient attempts conception. When possible, the partner or family member should be involved in the advance planning. Appropriate contraception should be offered to women who do not desire a pregnancy. *Strength of recommendation*: B; *quality of evidence*: II-2.

Conclusion

As part of preconception care, providers should be vigilant and screen for psychiatric disorders among women of reproductive age, particularly those who are planning a pregnancy or who could become pregnant, as treating and controlling these conditions prior to pregnancy may reduce the occurrence of adverse pregnancy and family outcomes. In making treatment decisions for women of reproductive age with psychiatric disorders, the clinician, together with the

patient, must consider both the risks of the condition during pregnancy and postpartum as well as the risk and benefits of the medications used to control these disorders. ■

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The clinical content of preconception care: alcohol, tobacco, and illicit drug exposures

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Substance abuse poses significant health risks to childbearing-aged women in the United States and, for those who become pregnant, to their children. Alcohol is the most prevalent substance consumed by childbearing-aged women, followed by tobacco, and a variety of illicit drugs. Substance use in the preconception period predicts substance use during the prenatal period. Evidence-based methods for screening and intervening on harmful consumption patterns of these substances have been developed and are recommended for use in primary care settings for women who are pregnant, planning a pregnancy, or at risk for becoming pregnant. This report describes the scope of substance abuse in the target population and provides recommendations from the Clinical Working Group of the Select Panel on Preconception Care, Centers for Disease Control and Prevention, for addressing alcohol, tobacco, and illicit drug use among childbearing-aged women.

Key words: alcohol, preconception, substance abuse, women

Alcohol, tobacco, and illicit drug use are among the leading causes of morbidity and mortality in the United States.[1,2] These exposures are modifiable by public health interventions[3] with tobacco use and substance abuse (alcohol and/or illicit drugs) being listed among the 10 leading health indicators for the US population in *Healthy People 2010*.[4] A substantial proportion of childbearing-aged women consume 1 or more of these substances, thereby increasing their risks for adverse health outcomes, and if pregnant, adverse pregnancy outcomes. Prenatal alcohol use is a leading preventable cause of birth defects and developmental disabilities. Smoking during pregnancy causes placenta previa, abruption, premature rupture of membranes, preterm delivery, fetal growth restriction, and low birthweight.[5,6] Prenatal smoking can also cause sudden infant death syndrome (SIDS),[5,7] and infants born to mothers who smoke are more likely to have orofacial clefts.[8] Illicit substance abuse increases risk for stillbirth, prematurity, low birth weight, and intrauterine growth retardation.[9] This report is one in a series of articles on preconception care and describes the prevalence of use of the above substances in childbearing-aged women along with current evidence and recommendations for best practices in detection and intervention in clinical practice settings serving women in the preconception period. Members of the Clinical Working Group of the Select Panel on Preconception Care, Centers for Disease Control and Prevention (CDC), developed the recommendations presented herein after their review of relevant literature, including previously published evidence-based recommendations. The methods used to judge the strength of the evidence for the recommendations were adapted from those used in the US Preventive Services Task Force (USPSTF) *Guide to Clinical Preventive Services* and are described in an earlier article by Jack et al.[10]

Alcohol–Burden of Risk and Disease

The *2006 National Survey on Drug Use and Health* (NSDUH)[11] found that 11.8% of pregnant women reported current alcohol use and 2.9% reported binge drinking (≥ 5 drinks on the same occasion). Alcohol use rates for nonpregnant childbearing-aged women (15-44 years) in the survey were 53% for current use and 23.6% for binge drinking. National estimates using the 2002 Behavioral Risk Factor Surveillance System found that among the 7.6% of childbearing-aged women (18-44 years) who were sexually active and not using birth control, more than half reported alcohol use, and approximately 1 in 8 reported binge drinking.[12] Many of these women will become pregnant without realizing it and continue alcohol use during the early first trimester when fetal organ systems are being formed. Alcohol is a known teratogen that poses serious risk to the development of the central nervous system throughout gestation.[13] Prenatal alcohol

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exposure is associated with significant maternal and fetal health risks including spontaneous abortion,[14,15] prenatal and postnatal growth restriction birth defects, and neurodevelopmental deficits including mental retardation,[16-19] with fetal alcohol syndrome being the most commonly known condition along a spectrum of effects known as fetal alcohol spectrum disorders (FASD). Prenatal alcohol use is considered a leading preventable cause of birth defects and developmental disabilities in the United States[20] and there is no established safe level of alcohol consumption during pregnancy.[21,22] Using abstraction of existing records as a means of identifying cases of FASD (growth retardation, physical anomalies, and neurodevelopmental abnormalities including mental retardation) in Alaska, Arizona, Colorado, and New York, the CDC reported that prevalence rates among those states ranged from 0.3 to 1.5 cases per 1000 live-born infants.[23] Another study evaluated a variety of FASD estimates drawn from studies using a variety of methodologies and concluded that the prevalence of FASD in the United States is likely to be between 0.5 to 2 cases per 1000 live births.[24] The lifetime cost burden for FASD is estimated to be $2 million per case.[25] Alcohol use levels prior to pregnancy are the strongest predictor of alcohol use during pregnancy.

Detection and Intervention

Evidence-based guidelines have been developed for identifying and intervening with childbearing-aged women who are engaging in excessive drinking (ie, > 7 drinks/week or > 3 drinks on 1 occasion). A number of validated screening instruments are available for use in pregnant and nonpregnant, preconception childbearing-aged women including the TWEAK (Tolerance or number of drinks needed to feel high; Worry or concerns by family or friends about drinking behavior; Eye-opener in the morning; blackouts or Amnesia while drinking; self-perception of the need to [K] cut-down on alcohol use), T-ACE (Tolerance [how many drinks does it take to make you feel high?]; Annoyed [have people annoyed you by criticizing your drinking?]; Cut down [have you ever felt you ought to cut down on your drinking?]; Eye-opener [have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover?]), AUDIT (Alcohol Use Disorders Identification Test; a 10-item screening tool for identifying risky drinkers), and AUDIT-C (3-item version of the Alcohol Use Disorders Identification Test).[26-28] A recent systematic review of the evidence on the effectiveness of behavioral interventions in reducing risky/harmful alcohol use[1] in adults was conducted by the USPSTF. Twelve clinical trials of adults, most of which included childbearing-aged, nonpregnant women, were reviewed. The clinical outcomes of interest were drinks per day, drinks per week, and not binge drinking. The systematic review found good evidence overall for the effectiveness of screening and behavioral interventions in reducing these outcomes among adults in primary care settings at 6 and 12 months, but found limited evidence for their effectiveness in reducing alcohol-related morbidities.[29,30] A second systematic review and meta-analysis based on 8 trials focused on patients in primary care also concluded that brief alcohol interventions are effective in reducing alcohol consumption at 6 and 12 months.[31] Currently, the USPSTF recommends screening and brief counseling interventions for adults with alcohol use problems in primary care settings including nonpregnant and pregnant childbearing-aged women, concluding that the benefits of behavioral counseling interventions in reducing risky drinking outweighs any potential harm.

Two additional alcohol studies have appeared that target nonpregnant, childbearing-aged women in specific with counseling interventions aimed at reducing risky drinking. One study, appearing after the USPSTF report, confirms the efficacy of a brief motivational intervention in combination with effective contraception use in reducing risk for alcohol-exposed pregnancies (AEP) in women at high risk in the preconception period.[32] The study provided women at high risk in diverse settings with a 4-session counseling intervention and a contraception counseling and services visit during a 14-week window of time. Outcome measures were assessed at 3, 6, and 9 months postintervention. Women could reduce their risk for an AEP by reducing risky drinking, initiating effective contraception use, or both. The study found that the odds of reducing risk for an AEP were 2-fold higher for women in the intervention group as compared with women in the control group at all 3 follow-up visits, and that significantly more women in the intervention group changed both risk behaviors as compared with the control group. Another study targeting childbearing-aged women attending physicians' offices in community health practice settings found that alcohol use screening and brief advice from a physician significantly decreased alcohol use among women who received the intervention compared with those who did not receive the intervention.[33]

The National Institute on Alcohol Abuse and Alcoholism produced a guidance document for clinicians (*Helping Patients Who Drink Too Much: A Clinician's Guide*)[34] that uses quantity, frequency, and maximum amounts of alcohol consumed as a guide for advising and treating individuals who exceed recommended alcohol consumption limits (www.niaaa.nih.gov). In 2005, in collaboration with the CDC, the American College of Obstetricians and Gynecologists (ACOG) produced and distributed a tool kit (*Drinking and Reproductive Health: A Fetal Alcohol Spectrum Disorders Prevention Tool Kit)* that is available free at www.acog.org and describes techniques for screening and counseling prenatal and preconception women who consume alcohol. In addition to the recommendation of the USPSTF to screen and intervene with adults with alcohol use disorders in primary care settings, the American Academy of Pediatrics and ACOG have identified alcohol, tobacco, and illicit drug use as areas that should be assessed at all health encounters during a woman's reproductive years and particularly visits that are part of preconception care.[35] They further recommend that patients should be counseled about the benefits of abstaining from alcohol,

tobacco, and illicit drug use before and during pregnancy. The Department of Health and Human Services, Office of the Surgeon General, released an updated *Advisory on Drinking and Pregnancy* in 2005 advising women who are pregnant, planning to become pregnant, or at risk of becoming pregnant to abstain from alcohol use.

Recommendation. All childbearing-aged women should be screened for alcohol use and brief interventions should be provided in primary care settings including advice regarding the potential for adverse health outcomes. Brief interventions should include accurate information about the consequences of alcohol consumption including the effects of drinking during pregnancy, that effects begin early during the first trimester, and that no safe level of consumption has been established. Those women who show signs of alcohol dependence should be educated as to the risks of alcohol consumption, and for women interested in modifying their alcohol use patterns, efforts should be made to identify programs that would assist them to achieve cessation and long-term abstinence. Contraception consultation and services should be offered and pregnancy delayed until it can be an alcohol-free pregnancy. *Strength of recommendation*: B; *quality of evidence*: I-a.

Tobacco–Burden of Risk and Disease

Smoking during pregnancy can be harmful to the mother and the fetus. National data drawn from birth certificates filed from 1990-2002 documented a decline in smoking during pregnancy with 18.4% reporting prenatal smoking in 1990 as compared with 11.4% in 2002.[36] A population-based study in 10 states that looked at quit rates during pregnancy found that between 1993 and 1999, rates of smoking cessation in pregnancy increased from 37-46%.[37] The 2006 NSDUH found tobacco use was reported by 16.5% of pregnant women and 29.5% of nonpregnant childbearing-aged women.[11] Regardless of pregnancy status, women who smoke are at increased risk for a wide range of cancers (ie, lung, cervical, pancreatic, bladder, and kidney), cardiovascular disease, and pulmonary disease.[38]

Fetal effects of exposure to maternal smoking include intrauterine growth retardation, prematurity, low birthweight, and sudden infant death syndrome (SIDS). Maternal complications include premature rupture of membranes, placenta previa, and placental abruption with suggestive evidence for an association between smoking and ectopic pregnancy and spontaneous abortion.[5] Estimates indicate that eliminating smoking during pregnancy would reduce infant deaths by 5% and reduce the proportion of low birthweight singleton births by 10%.[39,40] Secondhand smoke exposure of an infant causes respiratory illnesses such as asthma and bronchitis, ear infections, and SIDS.[41,42]

Detection and Intervention

Screening for tobacco use in clinical settings usually consists of the patient's self-report of smoking when queried by the health provider. Nondisclosure of smoking does not appear to be a significant problem among nonpregnant women of childbearing age (nondisclosure rate about 1.2%),[43] but it may be a problem for pregnant women. One randomized controlled study used cotinine-verified quit rates to test the efficacy of an intervention to reduce smoking during pregnancy.[44] The study found a 35% nondisclosure rate for smoking at the endpoint measure of the study (eighth month) through comparison of self-reported smoking and urinary cotinine levels that were indicative of smoking. Another study on smoking during pregnancy found 73% of self-reported nonsmokers had elevated cotinine levels.[45] Researchers have found that the use of a multiple-choice format question when assessing smoking status that consists of asking the patient to describe her smoking using 1 of 3 options (I smoke regularly now, about the same as before finding out I was pregnant; I smoke regularly now, but I've cut down since I found out I was pregnant; or I smoke every once in a while) can improve disclosure. In a randomized controlled study this approach resulted in a 40% increase in disclosure over the standard question "do you smoke?"[46]

Although substantial research literature exists for interventions to increase smoking cessation among adults, women in general, and pregnant women, clinical studies focusing specifically on nonpregnant women of childbearing age are not available. Because the efficacy of cessation interventions are robust across population groups, the recommendations for women in the preconception period are the same as those for adults overall. Studies find that spontaneous smoking cessation rates among women who become pregnant range from 11-28% among publicly funded pregnant smokers and from 40-65% among privately insured pregnant smokers.[47] Such results have led some to suggest that even higher cessation rates could occur among women in the preconception period if evidence-based tobacco-dependence treatments were provided uniformly to this group.[48] Clinical trials demonstrating that preconception smoking cessation improves pregnancy outcomes have not been a research focus. However, if a woman achieves smoking cessation in the preconception period and maintains it throughout the prenatal period, pregnancy outcomes should be comparable with, if not better than, those reported in prenatal smoking cessation programs.

An authoritative clinical practice guideline for clinicians in identifying and treating childbearing-aged women who use tobacco products is *Treating Tobacco Use and Dependence*,[49] which contains comprehensive, evidence-based guidelines that have been developed for the treatment of tobacco dependence and have been shown to be safe and effective. A total of 6000 articles were reviewed for the guideline and 180 randomized controlled studies were identified for potential inclusion in the systematic review. Evidenced-based recommendations resulting from the summaries of the reviews and meta-analyses addressed screening and intervention. The guideline concluded that screening for tobacco use significantly increases rates of physician intervention (strength of evidence = A). Further, the findings

support the conclusion that tobacco dependence treatment is effective (strength of evidence = A). This dependence treatment includes brief advice and intervention using the 5 A's (ask, advise, assess, assist, arrange) and pharmacotherapies. Food and Drug Administration-approved medications for nonpregnant women include bupropion, nicotine replacement therapy (gum, inhaler, lozenge, nasal spray, and patch), and verenacline. Face-to-face individual and group counseling as well as telephone counseling have also been shown to be effective treatments.[48] For women who do not wish to attempt tobacco cessation, use of effective motivational enhancement strategies can increase future quit attempts. A concise summary of the guideline recommendations can be found online at http://jama.ama-assn.org/cgi/content/abstract/283/24/3244.

In May 2008, a new updated version of the guideline was released that further confirms the efficacy of smoking cessation interventions. It finds that although both psychosocial and medication interventions are efficacious, a combination of the 2 can bring about even higher rates of smoking cessation. The guideline recommends psychosocial interventions for pregnant women, but notes that the safety and efficacy of medications has not been established for this population.[50] The new report can be accessed at www.surgeongeneral.gov/tobacco/. A useful guide for clinicians (*Helping Smokers Quit: A Guide for Clinicians)* is available at www.ahrq.gov/clinic/tobacco/clinhlpsmksqt.htm.

Currently, there are tobacco prevention and control programs in all states and the District of Columbia, funded from various sources (eg, tobacco taxes, master settlement agreements, general state budget, and CDC). All states provide free telephone cessation counseling accessible through a single portal number (1-800 QUIT NOW), although the level of support available (number of counseling calls, availability of free medication) varies between states. These programs can be of much assistance to clinicians in referring women for more intensive counseling services.

Recommendation. All childbearing-aged women should be screened for tobacco use. A brief intervention should be provided to all tobacco users that includes: counseling describing the benefits of not smoking before, during, and after pregnancy; a discussion of medications; and referral to more intensive services (individual, group, or telephone counseling) if the woman is willing to use these services. *Strength of recommendation*: A; *quality of evidence*: I-a.

Illicit Substances–Burden of Risk and Disease

The 2006 NSDUH reported that 8.3% of respondents 12 years and older stated they had used illicit drugs during the past month. Commonly used illicit drugs used included marijuana (6%), cocaine (1%), inhalants (1.3%), hallucinogens (0.7%), and heroin (0.14%). Among nonpregnant women aged 15-44 years, 10% reported illicit drug use during the past month and 4% of pregnant women reported using illicit drugs during this same time period. These rates are similar to a report in 2001 that found the proportion of nonpregnant and pregnant women who reported using illicit drugs to be 8.3% and 3.7%, respectively.[51] Women who use illicit drugs often experience higher rates of sexually transmitted diseases, human immunodeficiency virus, hepatitis, domestic violence, and depression as compared with women who do not use illicit drugs.[52] Use of illicit drugs during pregnancy is associated with an increased risk of maternal complications and adverse outcomes for infants and children. The effects of cocaine and marijuana have been the focus of a number of studies but difficulties arise in sorting out the independent effects of these and other drugs given the high prevalence of polydrug use (including alcohol and tobacco). Cocaine use has been linked to increased risks for low birth weight, prematurity, perinatal death, abruptio placenta, and small for gestational age births.[53,54] A meta-analysis found increased risk for these outcomes in children exposed to cocaine vs those not exposed, but among those only exposed to cocaine, significant associations were found only for placental abruption and premature rupture of membranes.[55] Evidence of increased risk for maternal and postneonatal mortality associated with perinatal cocaine use has also been reported for substance abuse disorders in general use.[56,57] Marijuana use has been less implicated in adverse pregnancy outcomes,[58] but effects on intellectual development have been reported in young children tested using the Stanford-Binet Intelligence Scale.[59,60]

Effects of prenatal cocaine exposure on development and behavior in the children have been extensively studied. A systematic review reported in 2001 concluded there was no convincing evidence of cocaine-specific effects on development in that the effects observed could be the sequelae of multiple other risk factors including tobacco, marijuana, alcohol, and environment.[61]

Detection and Intervention

Although a number of well-validated, brief instruments are available for use in primary care setting for screening childbearing-aged women for alcohol abuse, fewer such instruments are available for use in screening women for illicit drug use. A recent systematic review of screening instruments for illicit drug use found fair evidence for the use of the CRAFFT[2] (C, have you ever ridden in a Car driven by someone [including yourself] who was high or had been using alcohol or drugs?; R, have you ever used alcohol or drugs to Relax, feel better about yourself, or fit in?; A, have you ever used alcohol or drugs while you are by yourself, Alone?; F, do you ever Forget things you did while using alcohol or drugs?; F, does your Family or do your Friends ever tell you that you should cut down on your drinking or drug use?; T, have you ever gotten in Trouble while you were using alcohol or drugs?) in adolescents. For adult populations, the Alcohol Substance Involvement Screening Test and Drug Abuse Screening Test have acceptable accuracy and reliability for use in practice settings.[62] However, the USPSTF stopped short of endorsing routine use of these screening tools in primary care settings because of the unavailability of evidence sufficient to weigh the potential benefits and potential harm associ-

ated with their use. Nevertheless, in a Committee Opinion in 2004 addressing at-risk drinking and illicit drug use, the Committee on Ethics of the ACOG endorsed the use of universal screening questions, brief intervention, and referral to treatment for both obstetric and gynecologic patients.[48] The Substance Abuse Mental Health Services Administration, Center for Substance Abuse Treatment has produced 3 best practices guidelines addressing treatment of substance abuse, all of which recommend screening by either clinician questioning or use of a validated screening tool with follow-up assessment of those screening positive; brief interventions for mild to moderate substance-related problems; and referral to specialized treatment for dependence disorders.[63-65] Toxicologic drug testing is available from a number of commercial laboratories but is generally not recommended for use in universal screening in primary care settings.

Effective interventions for treating illicit drug abuse and dependence are both behavioral and pharmacologic. There is substantial literature around effective treatments for illicit drug abuse. One recent metaanalysis assessed the efficacy of psychosocial treatments for cannabis, cocaine, opiate, and polysubstance abuse in 34 controlled trials.[66] Types of psychosocial treatments included contingency management, relapse prevention, general cognitive behavior, and cognitive behavior therapy and contingency management combined. The researchers found a moderate effect size across all conditions and all substances ($d = 0.45$; confidence interval: 0.27-0.63), which they noted was comparable with other effective treatments in psychiatry. Psychosocial therapies worked best for cannabis abuse and least well for polysubstance abuse. Medications were also used in 16 of the studies. Medications used in the polysubstance use studies included methadone and buprenorphine; methadone in the opiate studies; and naltrexone, buprenorphine, and methadone in the cocaine studies. Antidepressants are also used in treating cocaine abuse.[67] Research continues in evaluating pharmacotherapeutics for substance abuse with one recent study finding both methadone maintenance therapy and buprenorphine maintenance therapy more effective and more cost-effective than no drug therapy, but also tempered these findings with a word of caution about monitoring patients for safety concerns previously identified in the use of these medications.[68]

Manualized guides for behavioral treatment of substance abuse have also been investigated. One multisite study looked at 4 psychosocial treatments for cocaine-dependent patients and found that a manual-guided treatment consisting of intensive drug counseling and group drug counseling produced better outcomes on the Addiction Severity Index-Drug Use Composite score than cognitive therapy or supportive-expressive therapy and group drug counseling or group counseling alone.[69] Another 9-session efficacious intervention for treating marijuana dependence that combined motivational enhancement therapy and cognitive behavioral therapy was recently adapted into a manualized version for clinicians.[70]

Some evidence exists for reducing drug-exposed pregnancies by improving contraception use among women who are sexually active and engaging in alcohol and illicit drug abuse. In one intervention study using an advocacy model, participants increased participation in alcohol and drug treatment programs and increased contraception use from 5% prior to enrollment to 61% at 12 months, thereby effectively reducing their risk for a drug-exposed pregnancy.[71] A clinical trial that focused on reducing risks for an AEP among polysubstance users also found success in reducing risk for an AEP by providing a motivational intervention in conjunction with contraceptive consultation and services. At the 9-month follow-up, significantly more women in the treatment group had reduced risky drinking and instituted effective contraception use.[32]

Recommendation. A careful history should be obtained to identify use of illegal substances as part of the preconception risk assessment. Childbearing-aged women should be counseled on the risks of illicit drug use before and during pregnancy and offered information on counseling and treatment programs that support abstinence and rehabilitation. Contraception services should be offered and pregnancy should be delayed until individuals are drug free. *Strength of recommendation*: C; *quality of evidence*: III.

Conclusions

Alcohol, tobacco, and illicit drug use pose significant health risks to the health of childbearing-aged women and their children. Early identification of patterns of use of these substances in the preconception period provides the opportunity to assist women in reducing major health risks. Studies have shown the feasibility and efficacy of interventions designed to reduce substance use in childbearing-aged women. Implementation of these recommendations in clinical practice settings can play an important role in improving the health of women and their families. ■

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The clinical content of preconception care: genetics and genomics

Benjamin D. Solomon, MD; Brian W. Jack, MD; W. Gregory Feero, MD, PhD

The prevalence of paternal and maternal genetic conditions that affect pregnancy varies according to many factors that include parental age, medical history, and family history. Although some genetic conditions that affect pregnancy are identified easily early in life, other conditions are not and may require additional diagnostic testing. A complete 3-generation family medical history that includes ethnicity information about both sides of the family is arguably the single best genetic "test" that is applicable to preconception care. Assessment of genetic risk by an experienced professional has been shown to improve the detection rate of identifiable risk factors. Learning about possible genetic issues in the preconception period is ideal, because knowledge permits patients to make informed reproductive decisions. Options that are available to couples before conception include adoption, surrogacy, use of donor sperm, in vitro fertilization after preimplantation genetic diagnosis, and avoidance of pregnancy. Future technologic advances will increase the choices that are available to couples.

Key words: family history, genetics, preconception

Applications of genetics (the scientific study of heredity) and genomics (the study of an organism's complete genetic makeup) are expanding into virtually every sphere of healthcare; preconception care is no exception. However, the evidence-based application of genetics and genomics to preconception care is a work in progress for several reasons. First, less research attention has been given to genetic and genomic interventions in the preconception setting than to those in the prenatal period. Second, conducting prospective randomized trials in either the prenatal or preconception period is problematic ethically and legally. Finally, genetic technologies are emerging at a mind-numbing pace, and time will be required to develop evidence to support their utility.

Despite the rapid evolution of this field, individuals who provide medical care to any person who is considering pregnancy should be aware of recommendations for genetic care in the preconception and prenatal period.[1,2] Some recommendations apply to all individuals. Other recommendations are more important for patients with specific risk factors. In many cases, these recommendations draw heavily on consensus and expert opinion. Additionally, most prenatal care guidelines have been extrapolated to the preconception period. Logically, this makes sense; however, formal studies that demonstrate the validity of this extrapolation are lacking and likely will never be completed. One final caveat is that the diversity and rarity of many genetic disorders that affect pregnancy ensure that any document that contains recommendations, including this one, will be incomplete.

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All individuals

Obtaining a complete 3-generation family medical history that includes ethnicity information about both sides of the family is arguably the single best genetic "test" that is applicable to preconception care. Additionally, a discussion of obstetric and medical history and parental age at anticipated delivery are critical aspects of a preconception healthcare visit. Family history and other historic data provide an inexpensive and noninvasive assessment of conditions that might affect pregnancy. Learning about these risks in the preconception period is ideal. Improved knowledge about the heritability of a disorder can allow individuals to make informed reproductive decisions and can improve prenatal care during pregnancy. Options that are available to couples before conception include adoption, surrogacy, use of donor sperm, preimplantation genetic diagnosis after in vitro fertilization with transfer of unaffected embryos, and avoidance of pregnancy. Future technologic advances likely will broaden further the choices that will be available to couples.[3-7]

Providers of preconception care should also urge women to take a multivitamin, with at least 400 μg of folate, daily beginning at least 1 month before conception. Folate has been shown to reduce the incidence of neural tube defects and may also reduce the incidence of other malformations such as orofacial clefting, limb deficiencies, cardiac defects, urinary tract defects, and omphalocele. Women with a history of medical conditions such as epilepsy or diabetes mellitus or a previous gestation with a neural tube defect may require increased folate intake.[8-10]

Finally, in addition to the testing discussed in Table 1, all couples, regardless

TABLE 1
Recommended counseling/testing by race/ethnicity

Ethnicity (of at least 1 member of the couple)	Disorders with recommended counseling/testing	Type of test
White	Cystic fibrosis[a]	DNA testing of *CFTR* gene[11]
European	Cystic fibrosis[a]	DNA testing of *CFTR* gene[11]
Ashkenazi Jewish	Canavan disease, cystic fibrosis,[a] familial dysautonomia, Tay-Sachs disease, Gaucher's disease, Niemann-Pick disease *Type A*, Bloom syndrome, mucolipidosis IV, Fanconi anemia Group C	Canavan disease: DNA testing of *ASPA* gene[13,15,19]
		Cystic fibrosis: DNA testing of *CFTR* gene[11,13,15,19,20]
		Familial dysautonomia: DNA testing of *IKBKAP* gene[13,15,19]
		Tay-Sachs disease: enzyme assay for hexosaminidase-A level or DNA testing of *HEXA* gene[13,15,19]
		Gaucher's disease: DNA testing of *GBA* gene[13,15,19]
		Niemann-Pick disease *Type A*: DNA testing of *SMPD1* gene[13,15,19]
		Bloom syndrome: DNA testing of *BLM* gene[13,15,19]
		Mucolipidosis IV: DNA testing of *MCOLN1* gene[13,15,19]
		Fanconi anemia Group C: DNA testing of *FANCC* gene[13,15,19]
French-Canadian	Tay-Sachs disease	Enzyme assay for hexosaminidase-A level or DNA testing of *HEXA* gene[12,14,19]
Cajun	Tay-Sachs disease	Enzyme assay for hexosaminidase-A level or DNA testing of *HEXA* gene[12,14,19]
African	Sickle cell disease/trait, thalassemia	Complete blood count with red blood cell indices (RBC), iron indices, hemoglobin electrophoresis[16,17,18]
Mediterranean	Thalassemia	Complete blood count with red blood cell indices and iron indices; hemoglobin electrophoresis if anemia and normal iron indices[16,17,18]
Asian	Thalassemia	Complete blood count with red blood cell indices and iron indices; hemoglobin electrophoresis if anemia and normal iron indices; DNA testing of alpha-globin genes for alpha thalassemia if Southeast Asian with low mean corpuscular volume anemia but normal iron studies[16,17,18]

[a] Cystic fibrosis should be discussed with patients of all races/ethnicities.

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of ethnicity, should be made aware of the availability of cystic fibrosis–carrier screening.[11]

Recommendation. All women who are considering pregnancy should have a screening history in the preconception visit. Providers should ask about risks to pregnancy that are based on maternal age, maternal and paternal medical conditions, obstetric history, and family history. Ideally, a 3-generation family medical history should be obtained for both members of the couple with the goal of identifying known genetic disorders, congenital malformations, developmental delay/mental retardation, and ethnicity. If this screening history indicates the possibility of a genetic disease, specific counseling should be given that may include referral to a genetic counselor or clinical geneticist. *Strength of recommendation:* B; *quality of evidence:* III.

All women should take a multivitamin with at least 400 μg of folate daily, starting at least 1 month before conception. Women with specific risk factors may require higher daily dosages of folate. *Strength of recommendation:* A; *quality of evidence:* II-2.

All couples should be made aware of the availability of cystic fibrosis–carrier screening. *Strength of recommendation:* B; *quality of evidence:* III.

Couples with ethnicity-based genetic risk factors

Ancestry influences the probability of being a carrier of many disorders that affect pregnancy. Typically, carriers themselves will not show any signs of a genetic disorder, and there is often no known family history of the condition. The guidelines for testing by ethnicity include conditions for which there is evi-

TABLE 2
Details from personal or family history that should prompt further counseling

Chromosomal disorders (eg, Trisomy 21)
Clotting disorders
Deafness
Developmental delay/mental retardation (eg, Fragile X syndrome)
Early infant death
Heart defects
Other known genetic disorders (eg, phenylketonuria, Marfan syndrome)
Neural tube defects
Familial cancer syndromes (known or suspected)
Family history of other congenital malformations
Neural tube defects
Orofacial clefts
Recurrent miscarriages
Sickle cell disease or trait
Sudden infant death syndrome
Thalassemia
Thrombophilia

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dence that testing is effective or for which there is strong expert opinion that testing should be performed. However, this is not meant to imply that these conditions do not occur or should be ignored in populations of other ethnicities. Individuals of mixed ancestry or ethnicity should consider carrier testing that is recommended for any component ethnicity. A formal referral could be considered if practitioners are unsure which disorders should be tested. Table 1 contains a summary of counseling/testing by ethnicity.[11-20]

Carrier testing can have important psychologic consequences for an individual and should only occur after informed consent is obtained. Choosing the appropriate test and interpreting results of testing can be complex and may vary between different ethnic groups. For example, with the current recommended mutation panel, negative carrier testing for cystic fibrosis in an Ashkenazi Jewish couple would result in a different chance of having an affected child than negative testing in an African American couple. Depending on the provider's proficiency in genetics, carrier testing may necessitate referral to genetic services.[11,13,15,19,20]

Recommendation. Couples who are at risk for any ethnicity-based conditions should be offered preconception counseling about the risks of that condition to future pregnancies. Screening and/or testing should be offered based on the couple's preferences. This may require referral to a genetic counselor or clinical geneticist. *Strength of recommendation:* B; *quality of evidence:* II-3.

Couples with genetic risk factors that are based on specific family history

If at least 1 member of a couple has a family history of developmental delay, congenital anomalies, or other known or suspected genetic conditions, the couple should be referred to a qualified healthcare provider for appropriate counseling and potential testing.[2,4] If a disorder in the individual's family has been identified as having a genetic cause, it may be possible to test an individual to determine whether the couple is at risk for having an affected child. For example, a family history of known genetic conditions such as cystic fibrosis or Tay-Sachs disease should prompt the offer of testing for at least the person with affected relatives. If the person is found to have inherited a gene that could cause the disorder in their children, the partner could be tested to quantify the overall risk. In the case of an X-linked disorder such as hemophilia, sex selection should be discussed.[2,21-26] Table 2 gives information about examples of family history findings that should prompt further counseling/testing.

Recommendation. Individuals who are identified as having a family history of developmental delay, congenital anomalies, or other genetic disorders should be offered a referral to an appropriate specialist to better quantify the risk to a potential pregnancy. *Strength of recommendation:* B; *quality of evidence:* II-3.

Couples with genetic risk factors that are based on previous pregnancies

A history of recurrent pregnancy loss (classically defined as > 2 spontaneous abortions) should prompt testing of both parents for genetic conditions such as chromosomal anomalies and hereditary thrombophilia.[17,27,28] Testing for chromosomal anomalies can be performed by a test of peripheral blood for chromosome analysis (karyotyping).[2] If a chromosomal anomaly such as a balanced translocation is found, providers should discuss the use of in vitro fertilization with preimplantation genetic diagnosis to increase the chance of an unaffected pregnancy.[29-31]

Recommendation. If at least 1 member of a couple is found to have a chromosomal anomaly, in vitro fertilization with preimplantation genetic diagnosis should be discussed. *Strength of recommendation:* C; *quality of evidence:* III.

Individuals with risk factors caused by known genetic conditions

Individuals with known genetic conditions should be counseled regarding optimal control of their condition and the chances of having affected offspring; these individuals should be aware of how the presence of a genetic disorder could affect both their health and the health of the fetus. For example, women with sickle cell disease have an increased risk of preterm labor and premature rupture of membranes; women with Marfan syndrome have an increased risk of aortic dissection during pregnancy.[32,33]

In certain genetic disorders, there are specific recommendations for management in the preconception period. For example, women with sickle cell disease require increased amounts of folate; women with phenylketonuria should maintain low phenylalanine diets before conception, because infants who are born to women with phenylketonuria with phenylalanine levels of > 20 mg/dL are more likely to have microcephaly, developmental delay, growth restriction, and heart defects.[17,34,35]

Recommendation. Suspected genetic disorders may require further work-up

TABLE 3
Further resources

Resources	Comments
American College of Medical Genetics (www.acmg.net)	Includes links to the latest standards and guidelines for clinical genetics laboratories, with disease/phenotype-specific standards and guidelines
CDC National Office of Public Health Genomics (cdc.gov/genomics)	Resources on how human genomic discoveries can be used to improve health and prevent disease
Gene tests (genetests.org)	Reviews about specific conditions, laboratory and clinical directories, handouts for patients
Genetic Alliance (geneticalliance.org)	Information about specific disorders and advocacy, support, and discussion groups
Genetic and Rare Diseases Information Center (rarediseases.info.nih.gov/html/resources/info_cntr.html)	Information about specific disorders, explanations for patients, financial assistance information, and access to specialists
National Society of Genetic Counselors (nsgc.org)	Directory of genetic counselors, guidelines for counseling specific conditions
Online Mendelian Inheritance in Man (ncbi.nlm.nih.gov/sites/entrez?db=omim)	Searchable database of genes and genetic disorders that targets healthcare professionals
PubMed (ncbi.nlm.nih.gov/PubMed)	Medical literature database
US Surgeon General's Family History Initiative (hhs.gov/familyhistory)	Education about family health history through tools such as My Family Health Portrait

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before conception. Known or discovered genetic conditions should be managed optimally before and after conception. *Strength of recommendation:* B; *quality of evidence:* II-3.

Comment

No provider is expected to be aware of every genetic condition that possibly could affect a pregnancy; however, it is important that all providers be able to do 2 things. First, providers should be able to ask the right questions to determine who might be at risk. This includes the ability to take a 3-generation family history. Second, providers should know when to refer a patient and to whom a patient should be referred. There is a wide array of excellent educational resources regarding genetic disorders and family history that are available on the web. Table 3 contains a list of resources. Finally, providers should keep in mind that this is a very rapidly expanding field. Researchers are unraveling the genetic causes of many conditions for which screening and testing may soon become available.[36] ■

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The clinical content of preconception care: nutrition and dietary supplements

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Women of child-bearing age should achieve and maintain good nutritional status prior to conception to help minimize health risks to both mothers and infants. Many women may not be aware of the importance of preconception nutrition and supplementation or have access to nutrition information. Health care providers should be knowledgeable about preconception/pregnancy-related nutrition and take the initiative to discuss this information during preconception counseling. Women of reproductive age should be counseled to consume a well-balanced diet including fruits and vegetables, iron and calcium-rich foods, and protein-containing foods as well as 400 μg of folic acid daily. More research is critically needed on the efficacy and safety of dietary supplements and the role of obesity in birth outcomes. Preconception counseling is the perfect opportunity for the health care provider to discuss a healthy eating guideline, dietary supplement intake, and maintaining a healthy weight status.

Key words: folic acid, health risks, pregnancy-related nutrition, reproductive-age women

At the time of conception, maternal nutritional status is an important determinant of embryonic and fetal growth.[1] Placental and fetal growth is most vulnerable to maternal nutrition status during the preimplantation period and the period of rapid placental development, which occurs during the first few weeks of development typically before pregnancy has been confirmed.[2] Most organs form 3-7 weeks after the last menstrual period and any teratogenic effects may occur by this time.[3] Evidence is emerging that a mother's diet and lifestyle influence the long-term health of her children.[2,4] Recent research suggests that inadequate levels of maternal nutrients during the crucial period of fetal development may lead to reprogramming within the fetal tissues that predisposes the infant to chronic illnesses in adulthood.[5] A woman's nutritional status is influenced by numerous variables including genetics, environment, lifestyle habits, the presence of disease or physiological stressors, and drug-toxicant exposures.[6]

Nutritional assessment and recommendations are important components of preconception counseling. The key components of the nutrition care process include:

- A nutrition assessment, including analysis and interpretation of anthropometric data and adequacy and quality of dietary habits (including dietary supplements).
- A nutrition diagnosis, which will identify and label any nutrition-related problems or risk factors such as obesity or eating disorders.
- The nutrition intervention, at which time the individual's dietary goals and plan of action are established and care is delivered with the emphasis on appropriate weight gain, consumption of a variety of foods according to the Dietary Guidelines 2005, appropriate dietary supplement use, and physical activity.
- Nutrition monitoring, evaluation, and referrals to dietitians occur as needed, depending on the individual's needs.[7,8]

In this manuscript, we review the evidence for safety and efficacy of nutrition, dietary supplements, and maternal weight during the preconception period.

Dietary intake prior to conception

Background: The quality of a woman's diet during pregnancy has an influence on positive fetal and maternal outcomes; therefore, a healthy, balanced diet is important before as well as during pregnancy.[1,9] Many women of child-bearing age in the United States do not maintain a healthy diet prior to, during, and after pregnancy. Not all women have financial or logistical access to a high-quality diet.[10] Furthermore, several studies have shown that most women of reproductive age are not getting enough vitamins A, C, B6, and E, folic acid, calcium, iron, zinc, and magnesium in their diet.[11-13] This underscores the importance of encouraging healthy eating behaviors early in a woman's child-bearing years because improving dietary habits requires long-term effort.

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Clinical studies have shown a positive association between a healthy diet during the preconception period and pregnancy and improved birth outcomes.[14,15] For example, a case-control study on the risk of orofacial clefts by Krapels et al[16] concluded that the preconception energy-adjusted intake of vegetable protein, fiber, beta-carotene, vitamin C, vitamin E, iron, and magnesium were all significantly lower in cases compared with controls. Additionally, there have been a number of reviews written on the importance of a healthy diet prior to and during pregnancy.[7,10,17-19] In 1992, the Institute of Medicine (IOM) published Nutrition during Pregnancy and Lactation: An Implementation Guide.[20] The IOM has also published a series of reports establishing the dietary reference intakes (DRIs).[21] Throughout this review, we will state the DRI for each supplement we discuss.

Finally, the US Department of Agriculture's (USDA) Food Guide Pyramid and Dietary Guidelines for Americans have resources for patients to consume foods that meet the nutritional requirements of pregnancy.[22] USDA has released the MyPyramid food guidance system, which includes MyPyramid Plan for Moms, which helps women identify the appropriate food plan according to pregnancy status, age, weight and height, and physical activity level (www.mypyramid.gov/mypyramidmoms).

MyPyramid identifies an appropriate food plan that covers the individual's energy needs and dietary reference intakes in the perinatal period.[1,7]

Dietary supplements

Background: Although many of our required vitamins, minerals, amino acids, essential fatty acids, and other constituents are found in food, the physiologic demands of the woman during preconception and pregnancy may require additional dietary supplementation. Requirements for folic acid, calcium, iron, zinc, vitamin D, vitamin C, and vitamin B increase substantially during pregnancy.[22] In the United States, dietary supplements are regulated differently than prescription medications by the Food and Drug Administration (FDA). This difference in regulation may influence the quality of products on the market, and our knowledge of dietary supplement safety and efficacy prior to conception and during perinatal period. There exist serious concerns about dietary supplement safety and efficacy, quality control, misidentification, adulteration, contamination, adverse events, and interactions with medications.[23]

Various national surveys estimate that 18-52% of the US population use dietary supplements and women use more supplements then men.[24-26] Many women use multivitamins, single vitamins, herbal products, traditional medicines, folk remedies, weight loss or sport supplements, and other dietary supplements prior to and during pregnancy.[27-29] Unfortunately, many women do not discuss their dietary supplement use with their health care professionals.[30,31] It is critical that all health care professionals ask their patients which vitamins, minerals, herbs, traditional remedies, and other dietary supplements they are using. Women should be encouraged to bring in the labels or bottles of all dietary supplements (pills, powders, teas, etc) to determine whether excessive levels of specific nutrients (or other bioactive compounds) are being consumed on a daily basis.[8,32]

Evidence for efficacy: Although many health care professionals do recommend certain dietary supplements prior to, during, and after pregnancy (eg, folate, iron, and calcium), the safety and efficacy of many dietary supplements (eg, sport supplements and weight loss products) have not been well established. For example, there are few clinical trials evaluating the safety and efficacy prior to and during pregnancy on herbal products.[33-35] Today much data available on herbal products are based on case reports, animal studies, and retrospective studies.[36,37] Because of the high prevalence of dietary supplement use among women, more research on the safety and efficacy of dietary supplements prior to and during pregnancy is urgently needed. Future studies should focus on subject characteristics that may influence our ability to meet maternal and infant demands (genetic and environmental), sensitivity, and selectivity of measured outcomes and proper use of proxy measures.[38]

Recommendation. All women of reproductive age should be asked about their use of dietary supplements (vitamins, minerals, traditional/home remedies, herbal products, weight loss products, etc) as part of preconception care plan and should be advised about what is or is not known about their impact, safety, and efficacy. *Strength of recommendation:* C; *quality of evidence:* III.

Vitamin A

Background: Vitamin A is a fat-soluble vitamin found in several forms. Vitamin A found in foods that come from animals (liver, whole milk) is called preformed vitamin A. It is absorbed in the form of retinol, which is made into retinal and retinoic acid (other active forms of vitamin A) in the body. Vitamin A that is found in fruits and vegetables is called provitamin A carotenoid, which is made into retinol in the body. There is also a synthetic analog (13-cis retinoic acid) isotretinoin (Accutane; Roche Pharmaceuticals, Nutley, NJ), a medication used to treat severe, cystic acne, and related dermatoses. Adequate vitamin A is essential for proper visual functioning, fetal growth, reproduction, immunity, and epithelial tissue integrity.[39] Because vitamin A is lipid soluble, it crosses the placenta easily and has a long half-life. Although normal fetal development requires sufficient vitamin A intake, very high levels of preformed vitamin A (retinoic acid) supplementation has been associated with miscarriage and birth defects that affect the central nervous system and craniofacial, cardiovascular, and thymus development.[39]

Currently the recommended dietary allowance of preformed vitamin A for women is 700 retinol activity equivalents (RAEs) per day, with a tolerable upper intake level of 3000 RAEs/day or 10,000 IU/day.[40] Dietary sources of vitamin A and beta-carotene (leafy vegetables, carrots, eggs, and diary products) do not pose a risk of excessive intakes and should be included in a healthy diet. Vitamin A from beta-carotene is not

known to increase the risk of birth defects.[41]

Evidence of efficacy: During pregnancy, evidence in humans suggests that more than 10,000 IU of vitamin A per day may be teratogenic, resulting in cranial/neural crest defects.[42] However, other studies have shown that periconceptional vitamin A exposures greater than 10,000 IU/day were not associated with increased risk for cranial neural crest defects or neural tube defects.[43] Although animal data clearly show that high dose vitamin A is teratogenic, such data are difficult to obtain in humans as human clinical trails are not ethically possible.[41]

Vitamin A also appears to be protective in pregnant women with human immunodeficiency virus/acquired immunodeficiency syndrome.[44-47] There is growing evidence from clinical trials in developing countries that vitamin A may protect against maternal morbidity, although more research is needed.[44,48-50]

Current recommendations: A World Health Organization expert group consultation concluded that daily doses of up to 10,000 IU (equivalent to 3000 μg retinol) or weekly 25,000 IU (7500 RAEs) are probably safe, especially in areas in which vitamin A deficiency is thought to be common[51] The half-life of the main metabolite of retinoic acid is 50 hours, so most of the drug and biotransformation products are gone within 10 days of the last dose. Etretinate and isotretinoin (Accutane), synthetic derivatives of retinol, are known to cause serious birth defects and should not be taken during pregnancy or if there is a possibility of becoming pregnant. The current recommendation is to discontinue such medications such as at least 1 month prior to attempting pregnancy.

Recommendation. Currently the recommended dietary allowance of preformed vitamin A for women is 700 RAEs per day, with a tolerable upper intake level for pregnancy is 3000 RAEs/day or 10,000 IU/day; *Strength of recommendation:* B; *quality of evidence for toxicity:* III.

Folic acid

Background: Folic acid, a water-soluble B-complex vitamin required for deoxyribonucleic acid synthesis and cell division, is a nutrient currently recognized as important prior to and during pregnancy because of its proven preventive properties against neural tube defects (NTDs).[52] Neural tube defects are serious birth defects of the spine (spina bifida) and brain (anencephaly). NTDs affect approximately 3000 pregnancies each year in the United States and are the second most common major congenital anomaly worldwide.[53] Populations at increased risk for NTDs or folic acid deficiency include Hispanic women, obese women, diabetic women with poor glycemic control, women with prior NTDs, and women with seizure disorder taking antiepileptic medications.[12,54,55]

Folate levels can be increased by consuming folate-rich foods or ingesting folic acid, a synthetic compound available through dietary supplements and through fortified foods. The major dietary sources of naturally occurring folate are legumes, green leafy vegetables, citrus fruits and juices, and breads and cereals that contained folic enriched flour. Folic acid is approximately 1.7 times more bioavailable than folate and therefore has a greater efficiency in impacting folate levels.[56] Supplementing dietary intake with folic acid has been recommended by many professional organizations because of the difficulty for woman to obtain the extra folate required periconceptionally through the diet alone. The current recommended daily intake (RDI) for folic acid is 400 μg for women of preconception age and 600 μg during pregnancy.[57] The recommended dose is higher (4000 μg) for women who have had a infant with an NTD.[58] Numerous studies have reported that women in the United States do not consume the recommended 400 μg of folic acid.[59-61] Furthermore, inadequate folate levels have been linked to increased risks of stroke, cancer, and dementia.[62,63]

Evidence of efficacy: There is clear scientific evidence that folic acid protects against neural tube defects. Numerous observational and randomized controlled studies culminate in an estimate that at least 70% of NTDs could be prevented if the embryo were exposed to protective amounts of folic acid during the critical window of organogenesis.[52,64-66]

Current recommendations: The US Public Health Service, American Academy of Pediatrics, American Dietetic Association, American College of Obstetricians and Gynecologists (ACOG), and American Academy of Family Medicine recommend that women consume 400 μg of folic acid daily.[7,67-69] The USDA recommends women of child-bearing age who may become pregnant and those in the first trimester of pregnancy consume adequate synthetic folic acid daily (from fortified foods or supplements) in addition to food forms of folate from a varied diet.[70]

Recommendation. All women of reproductive age should be advised to ingest 0.4 mg (400 μg) of synthetic folic acid daily, obtained from fortified foods and/or supplements. In addition, all women should be advised to consume a balanced, healthy diet, which includes folate-rich foods. *Strength of recommendation:* A; *quality of evidence:* I-a.

Multivitamins

Background: Multivitamins are typically the most commonly used dietary supplements reported in surveys in the United States.[71,72] Willett and Stamfer[73] concluded that there is greater benefit than harm in recommending a daily multivitamin that does not exceed the daily recommended intake of its component vitamins for most adults. In their review, Willett and Stamfer[73] noted that a multivitamin is especially important for women who might become pregnant, persons who regularly consume 1 or 2 alcoholic drinks per day, those who tend to absorb vitamin B12 poorly, vegans, and those with limited resources to afford adequate fruits and vegetables.

Evidence of efficacy: There is substantial evidence showing that taking multivitamins with at least 400 μg of folic acid daily may also reduce the incidence of other malformations such as orofacial cleft, limb deficiencies, cardiac defects,

urinary tract defects, and omphalocele.[74-80] A recent metaanalysis of 41 trials reported that multivitamin supplements provide consistent protection against neural tube defects, cardiovascular defects, limb defects, and other birth defects.[74] In this metaanalysis, both case control studies (odds ratio [OR], 0.76; 95% confidence interval [CI], 0.62-0.93) and cohort and randomized controlled studies (OR, 0.42; 95% CI, 0.06-2.84) showed lower incidence of cleft palate when women took mulitvitamins.

For oral cleft with or without cleft palate, case control studies (OR, 0.63; 95% CI, 0.54-0.73) and cohort and randomized controlled studies (OR, 0.58; 95% CI, 0.28-1.19) followed the same pattern. For urinary tract anomalies and congenital hydrocephalus, only the case controls studies showed a statistically significant decrease in anomalies. Finally, for congenital hydrocephalus there was an OR of 0.37 (95% CI, 0.24-0.56) in case control studies and 1.54 (95% CI, 0.53-4.50) for cohort studies, and randomized controlled studies.[74] Although multiple micronutrient supplementation is theoretically preferable to supplementation with iron and folic acid alone, especially in developing countries in which multiple deficiencies are prevalent, more data need to be collected to determine the advantages of different multiple micronutrient formulations for pregnant and lactating women.[81]

Recommendation. All women of reproductive age should be encouraged to take a folic acid–containing multivitamin supplement for the purpose of supporting healthy pregnancy outcomes and preventing congenital anomalies. *Strength of recommendation:* A; *quality of evidence:* II2.

Vitamin D

Background: Vitamin D is a lipid-soluble vitamin important in the metabolism of calcium and phosphorus. It promotes calcium absorption and bone mineralization. It may be obtained from either endogenous production from sun exposure or dietary sources. The major dietary sources are fortified items, particularly milk, orange juice, and some breakfast cereals. Other dietary sources include fatty fish (salmon, mackerel, tuna, sardine), egg yolks, beef liver, and cheese.

Vitamin D is essential for the health of pregnant women and their infants. Currently there is an increasing prevalence of vitamin D insufficiency and deficiency in pregnant women and infants in the United States and internationally.[82-87] Vitamin D deficiency is common among pregnant women in ethic minority groups.[88] Vitamin D deficiency during pregnancy is reflected in lower maternal weight gain; biochemical evidence of disturbed skeletal homeostasis in the infant; and in extreme situations, reduced bone mineralization, radiologically evident rickets, and fractures.[89,90] Additionally, vitamin D insufficiency has also been associated in some studies with other health outcomes that affect women, including asthma, diabetes, autoimmune diseases, and certain cancers.[83,91-93]

Women at risk for vitamin D deficiency include women who are not exposed to enough sunlight; whose dietary vitamin D intake is low (no dairy or lactose intolerant); who wear head coverings.

Evidence of efficacy: The optimal dose of vitamin D for the preconception period and during pregnancy is unknown. Observational studies and vitamin D supplementation trials among pregnant women at high risk of vitamin D deficiency showed improved neonatal handling of calcium with improved maternal vitamin D status. Results concerning the effects of vitamin D on maternal weight gain and fetal growth in these high-risk populations are conflicting and inconclusive.[94,95] Despite taking prenatal vitamins, vitamin D deficiency has been demonstrated in pregnant women.[83] Most experts agree that the current DRI of 200-400 IU is too low and that based on current evidence, daily requirements may be closer to 1000 IU or higher and that more research is needed on the optimal vitamin D dose and blood concentrations for several health outcomes.[83]

Current recommendations: The American College of Obstetricians and Gynecologists recommend daily consumption of 400-800 IU.[96] In the United States, the current DRI is 200 IU/day with 200 IU/day in pregnancy. The USDA guidelines note that people with dark skin and people exposed to insufficient ultraviolet band radiation (ie, sunlight) consume extra vitamin D from vitamin D-fortified foods and/or supplements.[22]

Recommendation. The evidence is insufficient to recommend for or against routine screening or vitamin D supplementation during preconception counseling. Based on the emerging data of the importance of vitamin D for women and infants; however, clinicians should be aware of the risk factors for vitamin D deficiency. Additionally, for women with vitamin D deficiency, education on vitamin D in the diet and supplementation should be a part of preconception care. Currently we do not have data for the optimal dose prior to and during pregnancy. More data are urgently needed. *Strength of recommendation:* B; *quality of evidence:* I b.

Calcium

Background: Calcium is essential for bone development and health and maintenance throughout life and in pregnancy, yet many women in the United States do not consume the recommended amount of calcium prior to and during pregnancy.[97-99] During pregnancy, the growing fetus receives its total nourishment from maternal sources. The dynamic balance between skeletal calcium storage and fetal nutritional needs can affect the maternal calcium equilibrium adversely. Therefore, if adequate bone has not been built before pregnancy and adequate calcium is not part of the maternal diet, bone can be degraded as calcium is taken from the maternal skeleton.[100] When completing a diet history during preconception counseling, it is important to ask about dietary calcium consumption (milk, fortified orange juice, etc), calcium supplementation, and use of antacids to assess the woman's overall calcium intake. Vitamin D intake is necessary to facilitate calcium absorption.

Evidence of Efficacy: Studies indicate that increases in calcium intake during pregnancy improve maternal bone health of mother and neonate. Higher birthweight babies, a reduced risk of preterm delivery, and lower infant blood pressure have all been linked with a high calcium intake during pregnancy.[100,101] More research is needed to assess the optimal does of calcium prior to and during pregnancy.[100,102-106] A 2008 metaanalysis of 12 good-quality clinical trials reported that the risk of high blood pressure was reduced with calcium supplementation rather than placebo (11 trials, 14,946 women: relative risk (RR), 0.70; 95% CI, 0.57-0.86). There was also a reduction in the risk of preeclampsia associated with calcium supplementation (12 trials, 15,206 women: RR, 0.48; 95% CI, 0.33-0.69). There was no overall effect on the risk of preterm birth or stillbirth or death before discharge from the hospital.[107] Many reviews have concluded that the lack of available evidence restricts the ability to form strong conclusions, especially with respect to supplementation's effect on maternal bone health during pregnancy. More research is needed to assess the optimal does of calcium prior to and during pregnancy.[100,102-106]

Current recommendations: The Institute of Medicine currently recommends 1000 mg/day of calcium for pregnant and lactating women who are 19-50 years old and 1300 mg/day for pregnant and lactating women who are younger than 19 years old.[108]

Recommendation. Women of reproductive age should be counseled about the importance of achieving the recommended calcium intake level through diet or supplementation. Calcium supplements should be recommended if dietary sources are inadequate. *Strength of recommendation:* A; *quality of evidence:* I b.

Iron

Background: Iron deficiency is the most common nutritional deficiency worldwide and is the most common cause of anemia in pregnancy. The prevalence of iron deficiency and iron deficiency anemia in the United States is significant among vulnerable populations. For example, the National Health and Nutrition Examination Survey 1999-2000 reported iron deficiency prevalence among women aged 12-49 years was 9-16%. Among minority females in the same age group, the prevalence of iron deficiency was approximately 3 times higher than the Healthy People 2010 objective of 5%.[109]

Reproductive-aged women are at risk of iron deficiency because of blood loss from menstruation, poor diet, and frequent pregnancies.[110] In a study of fertile women, only 20% had iron reserves of greater than 500 mg, 40% had iron stores of 100-500 mg, and 40% had virtually no iron stores.[111] Potential fetal complications secondary to anemia include spontaneous prematurity and intrauterine growth restriction.[112] The mechanism(s) by which this occurs are not clear. Prior to conception and during pregnancy, women should eat iron-rich foods (lean meat, poultry, and iron fortified cereals). Foods that inhibit iron absorption, such as whole-grain cereals, unleavened whole-grain breads, legumes, tea, and coffee, should be consumed separately from iron-fortified foods. The Centers for Disease Control and Prevention (CDC) recommends 18 mg/day for women and 27 mg/day for all pregnant women[113]

Evidence of efficacy: There are several systematic reviews reporting the benefits of iron combined with folate prior to and during pregnancy. The Cochrane collaboration completed a systematic review on 20 randomized controlled trials of iron supplementation in pregnancy with normal hemoglobin levels ($>$ 10 dL) at less than 28 weeks of gestation.[114] Iron supplementation raised or maintained the serum ferritin level above 10 mg/L and reduced the number of women with low hemoglobin levels late in pregnancy. The reviewers concluded that iron supplementation had no detectable effect on any substantive measures of either maternal or fetal outcomes.[114] One review looked at 8 trials involving 5449 women.[115] Routine supplementation with iron or folate raised or maintained serum iron and ferritin levels and serum and red cell folate levels. Supplementation resulted in a substantial reduction of women with a hemoglobin level below 10 or 10.5 g in late pregnancy.

A more recent prospective study done by Ronnenberg et al[116] in 2004 examined the relation between preconception hemoglobin concentration and pregnancy outcomes in 405 healthy Chinese women who were planning pregnancy. This study showed an association between preconception maternal anemia status and adverse pregnancy outcomes. The odds of low birthweight and fetal growth restriction were 6.5 and 4.6 times higher, respectively, in women with moderate anemia (hemoglobin $<$ 95 g/L) compared with nonanemic controls. Anemia attributed to iron deficiency was significantly associated with decreased birthweight.

A recent randomized controlled trial of 867 pregnant women (less than 20 weeks) was assigned randomly to receive prenatal supplements with 30 mg of iron as ferrous sulfate or placebo until 26-29 weeks of gestation. The mean birthweight was higher by 108 g ($P = .03$), and the incidence of preterm delivery was lower (8% vs 14%; $P = .05$) in the 30 mg group compared with the control group. Iron supplementation did not affect the prevalence of small-for-gestational-age infants or third-trimester iron status.[117]

In another recent clinical trial, 513 low-income pregnant women were randomly assigned to receive a monthly supply of ferrous sulfate or placebo until 28 weeks of gestation. Compared with placebo, iron supplementation from enrollment to 28 weeks of gestation did not significantly affect the overall prevalence of anemia or the incidence of preterm births but led to a significantly higher mean birthweight ($P = .010$), a significantly lower incidence of low-birthweight infants ($P = .003$), and a significantly lower incidence of preterm low-birthweight infants ($P = .017$).[118] Additional studies on the effectiveness of preconception iron supplementation on preventing prenatal iron depletion are needed.[119]

Current recommendations: The CDC issued guidelines in 1998 for preventing

iron deficiency based on age and sex. They state that for girls aged 12-18 years and nonpregnant women of child-bearing age, iron status screening should occur every 5-10 years during a routine examination. Annual iron screening should be conducted for women with existing risk factors for iron deficiency. If anemia is confirmed with a second test, a trial of oral iron is warranted. Other sources recommend confirmation of iron deficiency as a cause of the anemia prior to initiation of therapy.[120] The American College of Obstetricians and Gynecologists recommend all pregnant women should be screened for anemia and those with iron deficiency anemia should be treated with supplemental iron, in addition to prenatal vitamins.[110] The USDA food guidelines recommend that women of child-bearing age who may become pregnant eat foods high in hemeiron and/or consume iron-rich plant foods or iron-fortified foods with an enhancer of iron absorption, such as vitamin C–rich foods[22]

Recommendation. At a preconception visit, screening should be conducted for women with risk factors for iron deficiency for the purposes of identifying and treating anemia. There is evidence to recommend that all women should be screened at a preconception visit for iron deficiency anemia for the purpose of improving perinatal outcomes. *Strength of recommendation:* A; *quality of evidence:* IB.

Essential fatty acids

Background: The essential fatty acids (EFA) linoleic and alpha-linolenic acid, and their long-chain derivatives arachidonic acid and docosahexaenoic acid (DHA) are important structural components of cell membranes, the central nervous system, and retinal cell membrane structure.[121,122] EFAs cannot be synthesized in the body and must be ingested by food. Essential fatty acids are found in such foods as oily fish, flax seeds, walnuts, and vegetables oils.

In 2005, the FDA and Environmental Protection Agency, because of high mercury levels detected in fish, issued warnings that advise young children, pregnant women, nursing women, and women of child-bearing age to avoid consuming swordfish, king mackerel, shark, and tilefish. The warnings also recommend that those groups eat no more than 12 ounces of fish weekly and no more than 6 ounces of canned albacore tuna weekly.[123] Concerns have been raised that eating oil-rich fish exposes the fetus to dioxins and polychlorinated biphenyls, which are environmental pollutants.

Several studies have shown an association between maternal dietary intake of oily fish or oils providing n-3 EFA during pregnancy and visual and cognitive development, maturity of sleep patterns, and motor activity in infants.[124-127] Whether all woman should be supplemented and at what dose of EFAs (eg, fish or fish oil supplements during preconception and pregnancy) has been the subject of much debate and recent research[3]

Evidence of efficacy: There is mixed evidence for the efficacy of essential fatty acids such as fish oil against adverse pregnancy outcomes for mother and child during preconception and pregnancy.[128,129] For example, epidemiological evidence suggests an association between fish intake and birthweight. Another study showed a positive correlation with low fish consumption in early pregnancy and increased risk for preterm delivery and low birthweight.[130] A metaanalysis of 6 randomized controlled trials demonstrated that supplementation with omega-3 fatty acids was associated with a significantly greater length of pregnancy than in control subjects; however, there was no evidence that supplementation influenced the percentage of preterm deliveries, the rate of low-birthweight infants, or the rate of preeclampsia.[131]

In a review, the results of several randomized clinical studies have indicated that supplementation with fish oils may lead to modest increases in gestation length, birthweight, or both.[132] The Cochrane collaboration review of 6 clinical trials found women randomized to a fish oil supplement had a mean gestation that was 2.6 days longer than women allocated to placebo or no treatment. Birthweight was slightly greater in infants born to women in the fish oil group compared with controls. However, there were no overall differences between the groups in the proportion of low birthweight or small-for-gestational-age babies.[133]

Current recommendations: There are several recommendations and guidelines about omega fatty acid consumption for women. The Institute of Medicine set adequate intake for linoleic acid (N-6) 3 g/day for pregnant women and 12 g/day for women 18-50 years old. The adequate intake for α-N-3 is 1.4 g/day for pregnant women and 1.1 g/day for women 18-50 years old, respectively.[134] The USDA recommends to keep total fat intake between 20-35% of calories, with most fats coming from sources of polyunsaturated and monounsaturated fatty acids, such as fish, nuts, and vegetable oils.[70]

The International Society for the Study of Fatty Acids and Lipids recommends adequate intakes of 4.44 g of linoleic acid and 2.22 g of α-N-6, with 0.22 g or more of DHA and 0.22 g of EFA for adults and 0.3 g or more of DHA daily for pregnant women.[135] The Perinatal Lipid Intake Working Group recently released guidelines for maternal dietary fat intake in Europe. After reviewing the literature, they report that intakes of up to 1 g/d DHA or 2 · 7 g/day n-3 long-chain polyunsaturated fatty acids have been used in randomized clinical trials without significant adverse effects. These guidelines recommend that pregnant and lactating women should aim to achieve an average dietary intake of at least 200 mg of DHA per day. The guidelines note that women of child-bearing age should aim to consume 1-2 portions of sea fish per week, including oily fish.[136]

Recommendation. During the preconception period, women should be encouraged to eat a diet rich in EFAs including omega 3 and omega 6 fatty acids. To achieve this, women should be advised to consume at least 12 ounces of fish weekly and no more than 6 ounces of canned albacore tuna weekly. More research is critically needed to asses the risks and benefits of fish and fish oil con-

sumption during the preconception period. *Strength of recommendation:* B; *quality of evidence:* I-b.

Iodine

Background: Worldwide iodine deficiency is the single most important preventable cause of brain damage. In 2005 the World Health Organization estimated 2 billion people, 35% of the world population were iodine deficient.[137] Iodine is necessary for the production of thyroid hormones, thyroxine, and triiodothyronine, and it must be provided in the diet. Inadequate iodine intake leads to inadequate thyroid hormone production and to a spectrum of disorders, iodine deficiency disorders, including abortion, stillbirth, mental retardation, cretinism, increased neonatal and infant mortality, goiter, and hypothyroidism. Iodine is readily transferred to the fetus, and the fetal thyroid concentrates iodine and synthesizes thyroid hormones by 10-12 weeks' gestation. Iodine deficiency in pregnancy negatively affects the normal maturation of the developing fetal central nervous system, particularly myelination, and is responsible for cognitive impairment, permanent mental retardation, and in its most severe form, cretinism.[138]

Iodine deficiency disorders are among the easiest and least costly of all disorders to prevent. Adding a small amount of iodine in the form of potassium iodate or potassium iodide to dietary salt is effective for prevention. Salt iodization is the recommended, preferred strategy to control and eliminate iodine deficiency. Sufficient dietary iodine throughout the life cycle, especially during the preconception period, can minimize the risk of iodine deficiency during critical, early fetal development. Studies of the impact of iodine supplementation specifically before pregnancy have not been done. Identification and treatment of iodine deficiency disorders before pregnancy is an effective preventive public health strategy.

Current recommendations: The Institute of Medicine's Food and Nutrition Board recommend minimum daily intake of iodine in the United States of 150 μg for nonpregnant adults, 220 μg for pregnant women, and 290 μg for lactating women.[139] The World Health Organization, United Nations Children's Fund, and the International Council for Control of Iodine Deficiency Disorders recommend daily iodine intake of 150 μg for adults (≥ 12 years of age) and 200 μg for pregnant and lactating women.[140]

Recommendation. Women of reproductive age with iodine deficiency should be counseled on the risks of this condition to pregnancy outcomes and the importance of maintaining adequate daily dietary iodine intake of 150 μg during preconception and at least 200 μg when pregnant or lactating. Public health efforts to implement salt iodization programs should be encouraged for all women residing in regions with endemic iodine deficiency. *Strength of recommendation: A; quality of evidence: II-2.*

Preconception weight and body mass index

Overweight

Background: Approximately one third of all women in the United States are obese, and obesity is identified as the fastest-growing health problem in the country.[141] Obesity, defined as a body mass index (BMI) of 30 kg/m^2 or greater, is associated with elevated risks of type 2 diabetes; hypertension; infertility; heart disease; gallbladder disease; immobility; osteoarthritis; sleep apnea; respiratory impairment; social stigmatization; and a variety of cancers, including breast, uterine, and colon.[142-145] Adverse perinatal outcomes associated with maternal obesity include neural tube defects, preterm delivery, stillbirth, gestational diabetes, hypertensive and thromboembolic disorders, macrosomia, low Apgar scores, postpartum anemia, cesarean delivery, and shoulder dystocia.[142,143] Furthermore, women who are obese before conception tend to gain and retain more weight during pregnancy.[146]

The risks associated with high BMIs are best addressed before conception because weight loss during pregnancy is not recommended. Health risks are better established for obese persons than for overweight individuals (BMI 25-29.9 kg/m^2). However, even mild to moderate overweight in young adults predicts subsequent obesity.[144,147] Weight retained from previous gestations is an important contributor to higher-than-optimal BMIs in child-bearing women.

Evidence of efficacy: Counseling to support improvements in diet and physical activity are considered first-line interventions.[147] In a systematic evidence review, the US Preventive Services Task Force concluded that counseling alone or with pharmacotherapy can promote modest sustained weight loss.[144,147] The most successful nonsurgical approaches to weight loss were intensive, weight-focused counseling consisting of more than 1 session per month or multicomponent, intensive interventions that combine nutrition and exercise counseling with supportive, skill-building behavior interventions. Evidence from randomized controlled trials of long-term improved health with weight loss is limited.

Interventions about gestational weight from randomized controlled trials in pregnant obese women have mixed results. In a review by Guelinckx et al[148], only 2 of 7 trials, using nutrition and physical activity as an intervention, reached a significant decrease in gestational weight gain. There is a growing literature of clinical trials on the safety and perinatal outcomes for women who have undergone gastric bypass surgery.[149-155]

ACOG suggests that utilizing the stages of change model as adapted for overweight and obesity may help determine patient motivation and interest in weight loss. ACOG recommends setting an initial goal of losing 5-10% of total body weight over a 6 month period as realistic and achievable.[147] Weight loss is not recommended during any pregnancy, irrespective of pregravid weight. Therefore, to minimize the risks of obesity on reproductive outcomes, interventions must occur before pregnancy.

Current recommendations: In an ACOG Committee Opinion on obesity issued in October 2005, the following recommendations were made: (1) BMI should be calculated for all women and (2) appro-

priate interventions or referrals to promote a healthy weight and lifestyle should be offered.[147] Relative to nonpregnant populations, the US Preventive Services Task Force found that counseling and pharmacotherapy can promote modest sustained weight loss and that pharmacoptherapy appears to be safe in the short term; however, long-term safety has not been established. The task force also noted that, in selected patients, surgery promotes large amounts of weight loss with rare but potentially severe complications.[144]

In 1990, the IOM published a report that reevaluated the evidence regarding optimal weight gain during pregnancy. The report concluded that prepregnancy body weight should be taken into account when advising on optimal weight gain. For women with a normal prepregnancy BMI, a weight gain of around 0.4 kg/week during the second and third trimesters is recommended. For underweight women, a weight gain of 0.5 kg/week is the target, whereas for overweight women, 0.3 kg/week is recommended[156]

Recommendation. All women should have their BMI calculated at least annually. All women of reproductive age with a BMI of 25 kg/m^2 or greater should be counseled about the risks to their own health, the additional risk associated with exceeding the overweight category, and the risks to future pregnancies, including infertility. All women with a BMI of 25 kg/m^2 or greater should be offered specific strategies improve the balance and quality of the diet, decrease caloric intake, and increase physical activity, and be encouraged to consider enrolling in structured weight-loss programs. *Strength of recommendation:* A; *quality of evidence:* I-b.

Underweight

Background: Although most discussions of health risks associated with weight status focus on overweight and obesity, a 2005 analysis estimating the number of excess deaths in adults are associated with various BMI levels revealed that 33,746 deaths were associated with BMIs less than 18.5 kg/m.[157] Health risks of being underweight include nutrient deficiencies, heart irregularities, osteoporosis, amenorrhea, and infertility. For women who become pregnant, low pregravid weight is associated with increased risks for preterm birth and low birthweight, which are all major contributors to poor pregnancy outcomes.[157-160]

Evidence of efficacy: A low prepregnancy BMI may also increase the risk of birth defects such as gastroschisis. A study by Lam et al[161] found that infants born to underweight mothers (prepregnancy BMI $<$ 18.1 kg/m^2) were more than 3 times as likely to have gastroschisis compared with infants of normal-weight mothers (prepregnancy BMI 18.1-28.3 kg/m^2). In this study, every unit increase in BMI was estimated to decrease the risk for gastroschisis by about 11%.

Weight gain in pregnancy cannot overcome the risks associated with a low pregravid weight. Therefore, women should be counseled during the preconceptional period on the potential risks of their weight on fertility and on pregnancy outcome.

Recommendation. All women should have their BMI calculated at least annually. All women of reproductive age with a BMI 18.5 kg/m^2 or less should be counseled about the short- and long-term risks to their own health and the risks to future pregnancies, including infertility. All women with a low BMI should be assessed for eating disorders and distortions of body image. *Strength of recommendation:* A; *quality of evidence:* III.

Eating disorders

Background: Women with eating disorders such as anorexia nervosa and bulimia nervosa may have higher rates of miscarriage, low birthweight, obstetric complications, and postpartum depression. Eating disorders are associated with nutritional, metabolic, endocrine, and psychological changes that have potentially negative effects on fetal development. Pregnancy was thought to be a rare occurrence among women with anorexia nervosa; however, women who are below threshold for clinical symptoms or are in remission may not have compromised fertility. Women with bulimia nervosa may have less difficulty conceiving, but they may experience significant difficulty during the pregnancy related to binge eating, purging, and laxative or diuretic use.[162]

Women with eating disorders may be reluctant to disclose symptoms, and there are no reliable laboratory indicators for eating disorders, so clinicians need to be aware of warning signs and use effective assessment techniques.[163] Assessment should be done for conditions such as bulimia and anorexia; once identified, nutritional counseling and in some cases treatment of an underlying emotional condition should be initiated. A multidisciplinary approach is most effective in treating a woman with an eating disorder in pregnancy.[163,164]

Recommendation. All women of reproductive age with anorexia and bulimia should be counseled about the risks to fertility and future pregnancies and should be encouraged to enter into treatment programs before pregnancy. *Strength of recommendation:* A; *quality of evidence:* III.

Conclusion

Good nutrition is an essential component of attaining a healthy pregnancy and birth outcome. Women of reproductive age should be advised that the quality of a woman's diet may influence her pregnancy outcomes. Women of reproductive age, especially those who are planning a pregnancy, should be counseled to consume a well-balanced diet including fruits and vegetables, calcium-rich foods, and protein-containing foods daily and increase their consumption of iron-rich or iron-fortified foods in conjunction with vitamin C–rich foods to enhance iron absorption. Women should consume folate-rich foods daily including 400 μg of folic acid daily. More research is critically needed in the area of the safety and efficacy of fish consumption and dietary supplements. Health care professionals should address optimal weight gain, healthy diet, and the use of dietary supplements as a part of preconception care. ■

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The clinical content of preconception care: care of psychosocial stressors

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In the period before conceiving, many women are under considerable psychosocial stress, which may affect their ability to conceive and to carry a pregnancy successfully to term. Thus, health care providers who interact with women in the preconception and interconception period should ask their patients about possible psychosocial risks. It is no longer sufficient to wait until the woman mentions a problem or seeks advice; the provider must be proactive, because many women do not realize the potential impact of stressors on their pregnancy outcomes nor are they always aware that their provider is interested in their psychosocial as well as their physical health.

An income that puts women below or near the federal poverty level is one such stress. If a woman's economic situation can be improved before the pregnancy, she is more likely to be healthy after conception, because increased income can reduce financial stress, improve food security, and improve well-being in other ways. Therefore, all women should be asked about their economic status and those who appear to be struggling financially should be referred to an agency that can check their eligibility for various types of financial assistance.

Many women of childbearing age have difficulty accessing the primary care services needed for preconception care. Usually this is due to lack of insurance, but it may also be caused by living in an area with an insufficient number of providers. Certainly all women who are uninsured, and possible many who are on Medicaid and have difficulty finding providers who will accept Medicaid, have access problems. All women should be asked about their health insurance coverage and their usual source of care. If they do not have health insurance, they should be referred to an agency that can determine their eligibility. If they do not have a usual source of care, one should be established that will accept their insurance coverage or provide care free of charge or on a sliding fee basis.

Intimate partner violence, sexual violence outside of an intimate relationship (usually rape), and maltreatment (abuse or neglect) as a child or adolescent place a woman at elevated risk during a pregnancy, as well as having possible adverse impacts on the fetus, the infant, and the child. Studies show that women believe it is appropriate for health care providers to ask about interpersonal violence, but that they will not report it spontaneously. Therefore, screening for ongoing and historical interpersonal violence, sexual violence, and child maltreatment should be incorporated into routine care by all health care providers.

Key words: access to care, intimate partner violence, preconception care, psychosocial stress

A growing body of evidence suggests that chronic psychosocial stress may disturb the body's capacity to maintain *allostasis*, or stability through change. Examples of allostasis include feedback inhibition on the hypothalamic-pituitary-adrenal (HPA) axis to keep the body's stress response in check,[1] and modulation of the body's inflammatory response by the HPA axis.[2] In the face of chronic and repeated stress, however, these systems may deteriorate. If a woman enters pregnancy with her allostatic system in a less than optimal state, she may be more susceptible to a number of pregnancy complications, including preterm birth. An important objective of preconception care is to restore allostasis by reducing chronic, unremitting psychosocial stress before pregnancy.

Thus, health care providers who interact with women in the preconception and interconception period should ask the women for whom they care about possible psychosocial risks. It is no longer sufficient to wait until the woman mentions a problem or seeks advice; the provider must be gently and sensitively proactive, because many women do not realize the potential impact of stressors on their pregnancy outcomes, nor are they aware that their pro-

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vider is interested in their psychosocial as well as their physical health.

Intimate partner violence, sexual violence outside of an intimate relationship (usually rape), and maltreatment (abuse or neglect) as a child or adolescent, all place a woman at elevated risk during a pregnancy; they also have possible adverse impacts on the fetus, the infant, and the child. This article will consider 3 types of psychosocial risks: inadequate financial resources, inability to easily access healthcare, and intimate partner and other types of violence. (Discrimination on the basis of race, ethnicity, sexual preference, and similar factors are also major psychosocial stressors, but this article is limited to those risks that can be affected by the healthcare provider.)

Inadequate financial resources

Burden of suffering

Approximately 13% of women ages 18-64 years have incomes that put them below the federal poverty level. Women in the prime childbearing years are even more likely to be poor: 21% of women ages 18-24 years and 15% of women ages 25-44 years are below the poverty level.[3] In 2006, 29% of women ages 18-64 years were in the "low income" category (below 200% of the federal poverty level), including 42% of women ages 18-24 years and 34% of women ages 25-24 years.[3] In 2006, 4 million (3/10) female-headed households with children were living in poverty.[4] Poverty or low income status makes it difficult to obtain the food, shelter, and other necessities of life that make it possible to experience a healthy pregnancy.[5,6] For example, in 2003-2004, 38% of poor women were food insecure (worried about food supplies, skipped meals, or did not eat during a day because there was not enough money for food), despite the fact that one third of food stamp recipients are women ages 18-35 years.[7]

How detectable is the condition?

A few simple questions allow a healthcare provider to ascertain a woman's economic status: is she receiving Medicaid, Temporary Assistance to Needy Families (TANF or "welfare"), food stamps, or housing assistance? Are her children receiving free school lunches or breakfasts? However, not all women who could use economic assistance are receiving any or all of the benefits to which they are entitled. Moreover, undocumented women and those who have been in the country legally for less than 2 years are ineligible for some benefits. When providers suspect that a woman is not receiving the economic assistance that she needs, they need to probe gently. For example, they could ask whether she has problems paying her regular household expenses, or refer her to a social service agency that can make such a determination. Certain facilities, such as community health centers and WIC and food stamp offices, may also offer on-site assistance with applications for various benefits, including Medicaid.

How effective are the current treatments?

Federal, state, and local governments have programs to assist women with no earnings or very low earnings. Women who fall below 200% of the federal poverty level should be referred to the local welfare agency or a private social service agency to ensure that they are receiving all the benefits for which they are eligible. Unfortunately, benefit programs are seldom able to lift women out of poverty.

Impact of preconception care

It seems reasonable to assume that if a woman's economic situation can be improved before the pregnancy, she is more likely to be healthy after conception, because increased income can reduce financial stress, improve food security, and improve well-being in other ways. However, there are no data to prove this assumption.

Recommendation. All women should be asked about their economic status and those who appear to be struggling financially should be referred to an agency that can check their eligibility for various types of financial assistance. *Strength of recommendation:* C; *quality of evidence:* III.

Inability to easily access healthcare

Burden of suffering

An unknown percentage of women of childbearing age have difficulty accessing the primary care services needed for preconception care. Usually this is due to lack of insurance: national surveys indicate that uninsured women (67%) are less likely than women with either private (90%) or public insurance (Medicaid: 88%) to have had a provider visit in the past year.[8] Difficulty in access, however, may also be due to living in an area with an insufficient number of providers. Certainly all women who are uninsured, and possible many who are on Medicaid and have difficulty finding providers who will accept Medicaid, have access problems. In 2004-2005, 19% of women ages 18-64 years were uninsured and 10% were on Medicaid.[9]

How detectable is the condition?

If asked, women are usually willing to admit difficulties in accessing care.

How effective are the current treatments?

Although most pregnant women are eligible for Medicaid (states differ in eligibility based on poverty status and on coverage of undocumented women and those who have been in the country legally for less than 2 years), in most states they lose their pregnancy-related eligibility by 60 days postpartum, unless the state has a federal waiver to expand family planning and sometimes other services. Some women remain Medicaid-eligible because they qualify for TANF or Supplemental Security Income benefits, or are so poor that they meet income eligibility guidelines. Because Medicaid covers a wide range of benefits, those who have Medicaid should be able to access preventive and primary care in community health centers, hospital outpatient departments, or health departments, if private providers refuse to accept them as patients. The problems of geographic access are not easily solved. Undocumented women and those who have been in the country legally for less than 2 years are not eligible for Medicaid and will have problems accessing care,

although many health departments, community health centers, and hospital outpatient departments will serve them.

Impact of preconception care

For a woman to receive preconception care or to obtain prenatal care early in her pregnancy, she must have access to a source of primary care. Thus, it is urgent that access be ensured before pregnancy occurs.

Recommendation. All women should be asked about their health insurance coverage and their usual source of care. If they do not have health insurance, they should be referred to a welfare office, Medicaid outstation site, or a private social service agency to determine their eligibility for public insurance. If they do not have a usual source of care, one should be established that will accept their insurance coverage or provide care free of charge or on a sliding fee basis. *Strength of recommendation:* C; *quality of evidence:* III.

Intimate partner violence, sexual violence, and childhood maltreatment

Burden of suffering

Intimate partner violence, sexual violence outside of an intimate relationship (usually rape), and maltreatment (abuse or neglect) as a child or adolescent all place a woman at elevated risk during a pregnancy, and also have possible adverse impacts on the fetus, the infant, and the child.

The Centers for Disease Control (CDC) and Prevention define interpersonal violence as physical abuse, sexual abuse, threats of physical or sexual abuse, and/or emotional abuse that occurs between 2 people in a close relationship, including current and former spouses and dating partners.[10] The National Violence against Women Survey conducted in the late 1990s reported that 25% of surveyed women said that they were raped and/or physically assaulted by a current or former spouse, cohabitating partner, or date at some time in their lifetime, and 1.5% said that such an event had occurred in the previous 12 months. The survey estimated that approximately 4.8 million intimate partner rapes and physical assaults are experienced annually by women in the United States.[11] The 2005 Behavioral Risk Factor Surveillance System found that more than 10,000 women 18 years or older (23.6%) had a lifetime history of interpersonal violence. Those who experienced interpersonal violence were more likely to report current adverse health conditions and health risk behaviors.[12]

Interpersonal violence is a critical reproductive health problem for women. If a physical assault occurs during pregnancy—as in an estimated 4% to 8% of pregnancies[13]—there is the possibility of harm to the fetus, as well as to the woman. Physical, sexual, and emotional abuse *before* a pregnancy can also take a significant toll. Abuse before a pregnancy puts a woman at risk for abuse during the pregnancy. A North Carolina study found that the prevalence of physical abuse before pregnancy was 6.9%; during pregnancy, 6.1%; and after a mean of 3.6 months postpartum, 3.2%. Almost three-fifths (59%) of those abused in the year before their pregnancy were abused during the pregnancy.[14] Moreover, several literature reviews have found strong associations between interpersonal violence and a wide range of behaviors and conditions that could adversely affect a pregnancy, including inconsistent contraception use, unplanned pregnancies, sexually transmitted diseases, depression, and posttraumatic stress disorder.[15,16] Although the literature linking interpersonal violence to poor pregnancy outcomes is less conclusive, it is likely that it is associated with low birthweight and preterm birth.[17,18] If emotional abuse occurs before a pregnancy, there is the possibility of its continuing during the pregnancy and of psychological damage to the woman that may interfere with a healthy pregnancy and with positive parenting practices.

Sexual violence, which may occur within or outside a domestic situation, has also been associated with adverse effects on women's physical and mental health. According to 1 review, 27% of women in national surveys report a history of childhood sexual abuse and 15% report having experienced a rape at some time in their life. Pregnant women who have experienced sexual violence are more likely to be severely depressed, as well as to use cigarettes, alcohol, or drugs during pregnancy. The risk of poor reproductive health outcomes may increase with the severity of the sexual violence.[19]

In 2005, an estimated 899,000 children in the United States were victims of abuse or neglect—51% of whom were girls.[20] Maltreatment as a child or an adolescent may have psychological consequences that reach into the reproductive years. A study of abuse found abuse in adolescent dating relationships to be associated with depression, substance abuse, and antisocial behavior among females.[21]

How detectable is the condition?

Screening for ongoing interpersonal violence and for a history of interpersonal violence, sexual violence, and child maltreatment should be incorporated into routine care by all healthcare providers.

Studies show that women believe it is appropriate for healthcare providers to ask about interpersonal violence but that they will not report it spontaneously.[22,23] Thus, informal and formal screening tools are advised. The American College of Obstetricians and Gynecologists (ACOG) and the CDC and Prevention have developed a slide lecture on "Intimate Partner Violence during Pregnancy, A Guide for Clinicians," which can be downloaded from the CDC website.[24] ACOG recommends the following statement and questions:

Violence is a problem for many women. Because it affects health and well-being, I ask all my patients about it.

1. In the last year (since I saw you last), have you been hit, slapped, kicked, or otherwise physically hurt by someone? (If yes, by whom? Number of times? Nature of injury?)
2. Since you've been pregnant, have you been hit, slapped, kicked, or otherwise physically hurt by someone? (If yes, by whom? Number of times? Nature of injury?)
3. Within the last year, has anyone made you do something sexual that you didn't want to do? (If yes, who?)

4. Are you afraid of your partner or anyone else?

A randomized trial of screening instruments and procedures for interpersonal violence found that women preferred self-completed approaches, using either paper and pencil or a computer, to face-to-face questioning.[25] Despite the recommendations of several groups, and the availability of screening instruments, only a small percentage of providers actually screen routinely.[26,27]

How effective are the current treatments?

Women who are currently being abused should be referred to appropriate agencies. Interventions to modify the behavior of batterers have not proven effective; however, healthcare providers can assist women who are currently being abused both by encouraging them to be safer, ie, have safety plans, and by suggesting separation of the woman from a current abuser by legal and other means. Psychological treatment should be sought for women who have experienced interpersonal violence, sexual violence, or child maltreatment in the past because of the possibility of sequelae that could impact a pregnancy.

Impact of preconception care

Identification and separation of a woman from a current abuser should take place before pregnancy to prevent the possibility of violence during pregnancy. Identification of a woman who has experienced interpersonal violence, sexual violence, or child maltreatment in the past should also occur before pregnancy so that any psychological trauma can be treated and possible adverse effects minimized. One study found that abuse assessment, providing information about sources of assistance and about safety plans, and a nurse case management protocol reduced the level of interpersonal violence and helped women to adopt safety behaviors.[28]

Recommendation. All women should be asked about their experiences of physical, sexual, or emotional violence from any source (parents, intimate partners, or strangers) currently, in the recent past, or as children. For those who are being abused, or have been abused in the recent past, the provider should express strong concern and willingness to assist in correcting the abusive situation. Appropriate evaluation, counseling and treatment for physical injuries, sexually transmitted infections, unintended pregnancy, and psychological trauma should be offered, including the provision of emergency contraception and empiric antimicrobial therapy in the case of sexual assault. Women should be offered information about community agencies that specialize in abuse for counseling, legal advice, and other services. Every clinician who sees women should have a list of such agencies easily available. Surprisingly, in 2004, the United States Preventive Services Task Force stated that it "found insufficient evidence to recommend for or against routine screening . . . of women for intimate partner violence . . ."[29] Clearly, additional research is needed to provide the evidence needed for a recommendation that would be in agreement with professional groups. Women should also be asked about abuse or sexual violence in their past and referred for appropriate counseling. *Strength of recommendation:* C; *quality of evidence:* III.

Conclusion

Most of the attention currently being paid to preconception care has focused on physical health and health behaviors, but in the absence of adequate financial resources and access to care, it is unlikely that women can obtain preconception care or achieve optimal preconception health. Thus, obtaining information about these factors during the preconception period is essential. In addition, physical or sexual abuse before pregnancy or a history of such abuse in the past has the potential to cause significant harm to the mother, the fetus, and the newborn infant. Thus, primary care providers should empathetically inquire about these psychosocial risks if they are present, and be prepared to provide or refer for assistance. ■

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The clinical content of preconception care: the use of medications and supplements among women of reproductive age

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The use of prescription and over-the-counter medications and dietary supplements are common among women of reproductive age. For medications, little information about the teratogenic risks or safety is available, as pregnant women are traditionally excluded from clinical trials, and premarketing animal studies do not necessarily predict the effects of treatment in human pregnancy. Even less is typically known about the effects of dietary supplements on pregnancy outcomes, as they are not held to the same rigorous safety and efficacy standards as prescription medications. Congenital anomalies associated with medication use are potentially preventable, because they are linked with modifiable maternal exposures during the period of organogenesis. However, as women of reproductive age experience acute and chronic conditions that can result in adverse outcomes for the woman and her offspring, the benefits of use of a particular medication before or early in pregnancy may outweigh the risks. Resources and principles outlined in this article will aid healthcare providers in selecting appropriate medication regimens for women of reproductive age, particularly those with chronic health conditions, those who are planning a pregnancy, and those who may become pregnant.

Key words: medication, preconception, prescription, teratogen

Medication usage among pregnant women and women of reproductive age is common. A survey of women giving birth in Oklahoma[1] reports that the average number of medications taken during pregnancy ranged from 1.6-2.9 (excluding vitamin and mineral supplements), depending on the trimester. The same survey reported that 54% of all products consumed in pregnancy were over-the-counter (OTC) medications. Another source estimates that more than 80% of pregnant women take OTC or prescription drugs during pregnancy.[2] National surveys among women of reproductive age document that chronic conditions often requiring the ongoing administration of medications for maintenance are not uncommon among women of reproductive age.[3] As maternal age and body mass index increase, it is likely that an even greater proportion of women who are planning a pregnancy or who could become pregnant will have chronic diseases that necessitate prescription medications.

Presently, congenital anomalies are among the leading causes of infant mortality in the United States.[4] It is estimated that approximately 10-15% of congenital anomalies are due to teratogenic maternal exposures. Congenital anomalies caused by teratogenic exposures, such as certain medications, are considered preventable, as they are linked with modifiable maternal exposures during the period of organogenesis.[5] It follows that maternal avoidance of teratogenic exposures would minimize congenital anomalies. However, as women of reproductive age and those who are pregnant experience acute and chronic health conditions that must be medically managed, in many instances avoidance of medications is neither possible nor advisable.

The benefits of medication use during pregnancy are not restricted to the recovery of maternal health, but extend to the protection of the fetus in many instances. Poorly controlled diabetes mellitus is teratogenic, whereas the appropriate management of diabetic pregnant women can prevent diabetic embryopathy.[6] Uncontrolled asthma can decrease oxygen in the fetal blood, possibly impairing fetal growth and survival.[7] Uncontrolled high blood pressure increases the risks of placental problems and fetal growth retardation.[8] The treatment of infectious diseases of the reproductive tract can significantly reduce the prevalence of preterm birth and its effects.[1,9] For all pregnant women infected with HIV, the Center for Disease Control (CDC) recommends the drug zidovudine (AZT) to minimize perinatal transmission.[10] The periconceptional use of folic acid can prevent most neural tube defects[11] and a considerable number of congenital anomalies of the cardiovascu-

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TABLE 1
FDA classification of medication safety during pregnancy

Category	Description
A	Adequate, well-controlled studies in pregnant women have not shown an increased risk of fetal abnormalities.
B	Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women; or animal studies have shown an adverse effect, but adequate and well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women; or no animal studies have been conducted and there are no adequate and well-controlled studies in pregnant women.
D	Studies, adequate well-controlled or observational, in pregnant women have demonstrated a risk to the fetus. However, the benefits of therapy may outweigh the potential risk.
X	Studies, adequate well-controlled or observational, in animals or pregnant women have demonstrated positive evidence of fetal abnormalities. The use of the product is contraindicated in women who are or may become pregnant.

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lar system, urinary tract, and limb deficiencies.[12,13]

Teratogenicity is a complex process and is dependent on the timing of the exposure in relation to the gestational age, the dose, and route of administration. The developmental stage of the conceptus is particularly critical in determining teratogencity. For example, after 24 weeks' gestation, the antibiotic tetracycline can cause permanent staining of the offspring's teeth. During the second and third trimesters, angiotensin-converting enzyme (ACE) inhibitors can damage the fetal kidneys. The period of greatest sensitivity to most teratogenic exposures is the period of organogenesis, from 18-60 days postconception (approximately 4.5-11 weeks after the last menstrual period).[14] Exposures after the period of organogenesis usually do not result in structural anomalies, although there are exceptions. Rather, teratogenic exposures during the fetal period (after 60 days postconception) typically result in growth restriction or functional disorders of the central nervous system, kidneys, or other organs.

The dose and route of administration of the agent are other important features of potential teratogenicity. Teratogenic effects occur only when the dose of an agent exceeds a threshold.[15] Higher doses and chronic exposures are of more concern than lower doses and single exposures. A teratogenic effect is less likely with the use of dermal agents with minimal systemic absorption. Finally, the way in which the woman or offspring metabolize an agent is influenced by genotype, which ultimately determines the effective "dose" of the exposure. Processes relevant to medication processing that are influenced by genotype include metabolism, receptor binding, drug distribution, placental transport, and cellular sensitivity. In addition, physiologic changes that occur during pregnancy and affect the pharmacokinetics and/or pharmacodynamics include: changes in body weight and body composition; delayed gastric emptying and gastrointestinal transit time; expanded plasma volume; increased cardiac output and blood flow to the uterus, kidneys, skin, and mammary glands; decreased plasma albumin; increased glomerular filtration rate; and changes in the activity of hepatic enzymes.[16] It may be necessary to adjust the dosage and/or frequency of medication used during pregnancy.

For most medications, little information about teratogenic risk or safety is available at the time of marketing, as pregnant women are traditionally excluded from clinical trials. Premarketing animal studies do not necessarily predict the effects of treatment in human pregnancy. Medications for which there were false-negative animal teratology studies include captopril, enalapril, carbimazole, methimazole, and misoprostol. Although comparably more research has been performed on hypertension, depression, and other conditions that commonly occur in women of reproductive age, no areas can be considered well-studied in pregnancy. A review conducted in 2001 concluded that there was not enough information to assess the teratogenic risk or safety during pregnancy of more than 90% of prescription medications approved by the US Food and Drug Administration (FDA) in the previous 20 years.[17] Gaps in information are even more substantial for OTC and dietary supplements.

Given the above, it can be difficult for health care providers and women to decide whether to use a given medication during pregnancy as well as for women who are planning to or who could become pregnant. The decision must be individualized according to the woman and her unique circumstances, considering the balance of risks, benefits, and efficacy of treatment for mother and fetus. There are resources available to aid health care providers and women in their medical decision-making. The US FDA uses a risk classification system for medications based on data from human and animal studies to help interpret the risks associated with use of medications during pregnancy.[18] The current FDA classification system uses the letters A, B, C, D, and X for the 5 categories (Table 1). Drugs for which there is evidence of fetal risk but "the potential benefits from the use of the drug in pregnant women may be acceptable despite its potential risks" are classified as class D. Drugs that are "contraindicated in women who are or may become pregnant" are classified as class X. Critics of the FDA classification system argue that the risk categories are limited in that they do not indicate the

risk based on time during gestation in which the medication is used and that the letters imply a gradation of risk that does not necessarily exist. In actuality, category X reflects a benefit-risk judgment, but drugs in this category may be no more toxic than those in categories C or D. An understanding of both the value and limitations of the FDA categories of risk is necessary for counseling women of reproductive age who have taken or may need to take a given medication. In response to criticism of the current system of classification, the FDA has proposed to amend its regulations concerning the format and content of the "Pregnancy," "Labor and delivery," and "Nursing mothers" subsections of the "Use in Specific Populations" section of the labeling for human prescription drug and biological products. Specifically, the FDA is proposing to require that labeling includes a summary of the risks of using a drug during pregnancy and lactation, a discussion of the data supporting that summary, and relevant clinical information to help health care providers make prescribing decisions and counsel women about the use of drugs during pregnancy and/or lactation. The proposal would eliminate the current pregnancy categories A, B, C, D, and X.[19]

There are several additional resources that healthcare providers may utilize. The textbook *Drugs in Pregnancy and Lactation*[20] includes a fetal risk summary containing a review of literature about a particular drug to provide more data for decision making by the prescribing health care provider. Complete and up-to-date information regarding medication teratogenic risks can be found on the online REPRORISK system (www.reprotox.org), available from Micromedex, which contains periodically updated, scientifically reviewed resources. In addition, the Organization of Teratology Information Specialists has compiled "fact sheets" on various prescription and OTC medications and supplements (available at http://otispregnancy.org/otis_fact_sheets.asp).

More details about preconception considerations for various prescription and OTC medications and supplements are found below.

Prescription medications

A recent study finds that 1 of every 13 visits made to ambulatory practices by women of reproductive age results in the prescription of a potentially teratogenic (class D or X) medication. The same survey found that contraceptive counseling was provided on less than 20% of visits that documented use of a potential teratogen by a woman of reproductive age, and that women using low-risk drugs (class A or B) received contraceptive counseling as frequently as women using potential teratogens. A table of medications generally accepted to be contraindicated in the preconception period and pregnancy is found in Table 2. A more complete listing of potential teratogens (class D or X) is found as an appendix in the article by Schwarz et al.[21]

Recommendations by other groups

Several professional organizations have issued recommendations regarding the use of drugs related to their specialty in pregnancy. Specifically, there are established practice guidelines for use of medications to manage diabetes,[22] hypertension,[23] seizure disorders,[24] thyroid disorders,[25] disorders requiring anticoagulation,[26] asthma,[27] gastrointestinal disorders,[28] tuberculosis,[29] sexually transmitted infections including HIV,[9,10] migraine headaches,[30] the management of acne using isotretinoin, and psychiatric and psychologic disorders (including depression and bipolar disorders).[31,32] Recently, the FDA has changed the labeling of paroxetine (Paxil) from class C to D based on the results of recent studies suggesting that the drug increases the risk of birth defects, particularly heart defects, when women take it during the first 3 months of pregnancy.[33]

Recommendation. All women of reproductive age should be screened for the use of teratogenic medications and should receive counseling about the potential impact of chronic health conditions and medications on pregnancy outcomes for mother and child. Whenever possible, potentially teratogenic medications should be switched to safer medications before conception. For women with chronic conditions with serious morbidity (to mother and infant), the fewest number and lowest dosages of essential medications that control maternal disease should be used. For women not desiring pregnancy, a plan for contraception should be addressed and initiated. *Strength of recommendation*: A; *quality of evidence*: II-2.

OTC medications

Commonly used OTC medications among women of reproductive age include analgesics; cough, cold, and allergy remedies; and remedies for gastrointestinal upset.[34,35] The safety of commonly used examples of these OTC medications are given in Table 3.

Related recommendations by other groups

As part of a preconception care visit, the American College of Obstetricians and Gynecologists (ACOG) recommends that women inform their health care provider of their use of OTC medications. The ACOG also recommends that women who are pregnant talk to their doctor before using any OTC medication during pregnancy.

Recommendation. Health care providers should educate women of reproductive age about the need to discuss the use of OTC medications with their provider when planning a pregnancy. Women should be specifically advised not to use aspirin if they are planning a pregnancy or become pregnant. *Strength of recommendation*: A; *quality of evidence*: III.

Dietary Supplements

The 1994 Dietary Supplement Health and Education Act (DSHEA) defined dietary supplements (DSs) as vitamin, mineral, herb/botanical, amino acid, enzyme, protein, probiotic, glandular, or hormone-like substances. Various national surveys have estimated that 18-52% of the US population uses dietary supplements and many women use dietary supplements before and during pregnancy.[36-38] In the United States, dietary supplements are not regulated in the same way as prescription medications and do not necessarily undergo clinical trials for safety and efficacy, especially in pregnancy. However, concerns about safety, effectiveness, quality control, contamination, adverse events, and

TABLE 2
Medications contraindicated (class X) in pregnancy

Agent	Comments
Angiotensin-converting enzyme inhibitors (antihypertensive), and angiotension II receptor blockers	May cause kidney abnormalities in fetus when used in 2nd or 3rd trimesters.
HMG-CoA reductase inhibitors (statins)	A range of abnormalities has been reported for exposures during the 4th-9th week of gestation.
Androgens and testosterone derivatives	Cause masculinization of female fetus.
Carbamazapine (anticonvulsant)	Risk of fetal death, mental retardation, and malformed hearts, genitals, cleft palates, and arteries. Should be switched to another, less teratogenic agent before conception whenever possible. Use should be reserved only for cases where benefit outweighs risk.
Coumadin derivatives	Risk of bone and cartilage deformities, mental retardation, and vision problems. Should be switched to heparin before conception whenever possible.
Folic acid antagonists	Risk of spontaneous abortion and malformations.
Leflunomide, thalidomide	Risk of limb deformities. Use only with strict pregnancy prevention protocols.
Lithium (antidepressant)	Associated with increased risk of cardiovascular anomalies.
Phenytoin (anticonvulsant)	Risk of fetal hydantoin syndrome, including intrauterine growth restriction with small head circumference, dysmorphic facies, orofacial clefts, cardiac defects, and distal digital hypoplasia. Use should be reserved only for when benefit outweighs risk.
Streptomycin and kanamycin (antiinfective)	Risk of ototoxicity.
Tetracycline (antiinfective)	Risk to developing bones and teeth causing discoloration of teeth and skeletal abnormalities.
Valproic acid (anticonvulsive)	Risk of central nervous system dysfunction, spina bifida, development delay, intrauterine growth retardation, and cardiac anomalies. Should be switched to another, less teratogenic agent before conception whenever possible. If benefit of use outweighs risk, should be administered in 3-4 divided doses and should not be combined with carbamazapine and phenobarbitol.
Isotretinoin, known as Accutane (antiacne)	Elevated risk of spontaneous abortion and many anomalies.

Information from Briggs et al.[19]

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interactions with medications have been raised in the literature about dietary supplements.[39] Although many health care professionals will recommend certain dietary supplements before and during pregnancy (eg, folate, iron, and calcium), the safety and efficacy of many dietary supplements (eg, botanicals and weight loss products) has not been well established before or during pregnancy.[40] Most of the data available have been based on case reports, animal studies, and retrospective studies. Clinical trials evaluating the safety and efficacy of dietary supplements before and during pregnancy are needed especially for vitamin D, fish oil, and botanical products. It is critical that all health care professionals ask their patients what vitamins, minerals, herbs, traditional remedies, and other dietary supplements they are using.

Recommendations by other groups

Health Canada has reported that at this time there is not enough scientific information about the safety of various herbs and herbal products to recommend their general use during pregnancy and lactation. Women should use these products cautiously, and critically examine any information about their proposed benefits.[41]

Recommendation. Health care providers should educate women of reproductive age about the need to discuss the use of dietary supplements before pregnancy, including herbs, weight loss products, and sport supplements, and should caution women about the unknown safety profile of many supplements. High-quality and prescription-quality dietary supplements should be encouraged. *Strength of recommendation:* A; *quality of evidence:* II-C.

Conclusion

Given the widespread use of prescription and OTC medications and dietary supplements—including herbs, weight loss products, and sport supplements—among women of reproductive age, the growing prevalence of women with chronic conditions during their reproductive years, and the unknown safety profile or known risk of teratogenicity of many medications and supplements, health care providers should educate women of reproductive age about the

TABLE 3
FDA classification of common over-the-counter medications

Drug name	FDA Class by Trimester	Drug Class	Use in Pregnancy
Analgesics			
Acetominophen	B/B/B	Nonnarcotic	Pain reliever of choice.
Aspirin	D/D/D	Salicylate	Not recommended except for specific indications; associated with increased perinatal mortality, neonatal hemorrhage, decreased birth weight, prolonged gestation and labor, and possible teratogenicity.
Ibuprofen Ketoprofen Naproxen	B/B/D B/B/D B/B/D	NSAID NSAID NSAID	Avoid in 3rd trimester; associated with oligohydramnios, premature closure of the fetal ductus arteriosus with subsequent persistent pulmonary hypertension of the newborn infant, fetal nephrotoxicity, and periventricular hemorrhage.
Cough and cold remedies			
Chlorpheniramine	B	Antihistamine	Antihistamine of choice.
Pseudoephedrine	B	Decongestant	Oral decongestant of choice; possible association with gastroschisis.[33]
Guaifenesin	C	Expectorant	Possible increased risk of neural tube defects.
Dextromethorphan	C	Antitussive	Appears to be safe in pregnancy.
Diphenhydramine	B	Antihistamine	Possible oxytocin-like effects at high dosages.
Clemastine	B	Antihistamine	Unknown safety profile.
Gastrointestinal remedies			
Aluminum hydroxide/ Magnesium hydroxide	B	Antacid	Appears to be safe in pregnancy.
Calcium carbonate	C	Antacid	Appears to be safe in pregnancy.
Simethicone	C	Antiflatulant	Appears to be safe in pregnancy.
Cimetadine	B	Antihistamine	Preferred after antacids; generally regarded as safe.
Ranitidine	B	Antihistamine	Preferred after antacids; generally regarded as safe.
Nizatidine	C	Antihistamine	Not recommended because of adverse animal studies.
Famotidine	B	Antihistamine	Probably safe; data needed.

FDA, Food and Drug Administration.
Adapted with permission from "Over the Counter Medications in Pregnancy," June 15, 2003, American Family Physician.[43]

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need to discuss the use of all medications and supplements with their health care provider, particularly if they are planning a pregnancy or could become pregnant. Numerous resources exist to aid health care providers in selecting appropriate medications that balance the risk and benefit (for both the woman and any offspring she may conceive) of using particular medications while planning a pregnancy or during pregnancy.

In medically managing the chronic and acute health conditions women may face while planning a pregnancy, it is useful to classify medications as either "essential" or "nonessential." Essential medications are those necessary to treat diseases with serious morbidity for the women and/or her fetus. Nonessential medications are those used to treat conditions without serious morbidity. In general, the goals of preconception medical management include the following[42]:

1. Identify the pattern of medication and supplement use before conception.
2. Counsel women with chronic conditions about the potential impact of the condition and its various treatments on the health of the woman and the fetus. Provide preconception counseling of women for whom drugs are essential to allow them to make informed decisions regarding the avoidance or timing of pregnancy.
3. Establish effective treatment for chronic conditions before conception.
4. Manage all chronic conditions and acute illnesses throughout pregnancy.
5. Counsel women to avoid the use of nonessential medications, including prescription (eg, isotretinoin for acne) and OTC medications and dietary or herbal supplements.
6. Avoid the use of medications with high teratogenic risk when equally effective treatments with lower risks are available, for example, warfarin (an

anticoagulant), and valproic acid (an anticonvulsant).
7. Limit the use of essential medications to the smallest number of drugs possible that will effectively treat maternal disease without compromising the health of the woman or her fetus.
8. Limit each essential medication to the smallest dose that can be used to effectively treat maternal disease without compromising the health of the woman or her fetus. ■

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The clinical content of preconception care: reproductive history

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A history of previous birth of a low birthweight infant, previous cesarean sections, multiple previous spontaneous abortions, prior stillbirth, or uterine anomaly identifies women at increased risk for recurrent abortion, preterm birth, or stillbirth. We review the evidence for the potential benefit of reproductive history in identifying strategies for evaluation and treatment to prevent recurrent adverse pregnancy outcome. We offer evidence-based recommendations for management of women with these histories.

Key words: low birthweight, preconception, preterm birth, reproductive history

Preconception risk assessment includes a comprehensive evaluation of a woman's reproductive history to identify factors related to previous poor pregnancy outcomes that may be amenable to intervention before any future pregnancies occur.[1,2] Because an adverse outcome in an earlier pregnancy is associated with an increased risk for adverse outcomes in subsequent pregnancies, information such as previous spontaneous abortion, preterm birth, fetal growth restriction, stillbirth, surgical delivery, diabetes, and pregnancy-induced hypertension should be collected.[3] Preconception diagnosis and treatment of certain conditions, including maternal autoimmune disease and uterine malformations, may reduce the risk of recurrent pregnancy losses.

Prior low birthweight infant

Burden of suffering: A birthweight of less than 2500 g includes infants that were born preterm (< 37 weeks) and infants that suffer from fetal growth restriction (FGR), whether born before or after 37 weeks. About 30% of preterm infants are growth restricted as well.

Preterm birth

Preterm birth is now the leading cause of neonatal death in the United States and is the leading cause of infant mortality for nonwhite babies.[4] Women who have had a preterm birth have increased risk for subsequent preterm birth.[5-8] The earlier in gestation the first preterm birth, the greater the risk for another. Women with 1 preterm birth before 35 weeks have a 16% risk of a second preterm birth. Risk increases to 41% after 2 preterm births and to 67% after 3 preterm births.[9] Other than multiple gestations, previous preterm birth is often found as the single most important risk factor for another preterm birth among multiparous women. Multivariate analysis in a large Alabama study of a primarily low income population reported that women with previous preterm delivery had an odds ratio of 2.8 for preterm birth in subsequent pregnancy.

The only other risk factor of similar magnitude was prepregnancy maternal weight of less than 50 kg.[7] Early preterm delivery (23-27 weeks' gestation) was closely associated with subsequent early preterm delivery (< 28 weeks).[10] A population-based study from Texas concluded that prior preterm birth accounted for 10% of subsequent preterm births.[9] A number of conditions are associated with recurrent preterm birth: African American ethnicity, inflammatory changes in the placenta, low maternal prepregnant weight (< 50 kg) or body mass index less than 19.8 kg/m^2, a large interpregnancy weight loss (> 5 kg/m^2), cigarette smoking, short interpregnancy interval (< 12 months), history of cervical insufficiency, or short cervix on transvaginal ultrasound during subsequent pregnancy.[8] All but the first 2 could potentially be influenced before the next pregnancy. Maternal periodontal disease is associated with increased risk for preterm delivery. However, treatment during pregnancy has not been consistently beneficial. This prob-

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lem is considered in detail elsewhere in this supplement.[11]

Fetal growth restriction

Growth-restricted fetuses account for almost half of all stillbirths.[12] They are also at high risk for fetal asphyxia during labor, meconium aspiration, serious neonatal morbidity, and death. Risk continues into childhood and adulthood. A growing literature associates FGR birth with hypertension, coronary artery disease, diabetes, obesity, and other chronic health problems among adult survivors.[13]

The etiology of FGR is complex but can be described in 3 broad categories: maternal, fetal, and placental.[13,14] Maternal risk factors include low prepregnancy weight, malnutrition, poor weight gain during pregnancy, maternal age younger than 16 years or older than 35 years, a short interpregnancy interval, and smoking and substance abuse as well as number of chronic maternal illnesses that are detailed in other papers in this supplement.

Chronic maternal vascular disease, hypertension, renal insufficiency, diabetes mellitus, and the collagen vascular diseases (especially when complicated by preeclampsia) account for nearly one-third of FGR cases.[15] Fetal risk factors include chromosomal abnormalities, a number of genetic syndromes, fetal viral and protozoal infections, and multiple gestations. Placental factors include chronic placental abruption, placenta previa, placental infarctions, and chronic placental villitis. Placental mosaicism accounts for up to 25% of unexplained FGR. Malaria accounts for a high proportion of FGR births and stillbirths in areas in which transmission is high.[13,15] The recurrence risk of FGR is about 20%.

How detectable is the condition? In the United States, virtually all infants are weighed at birth, and women generally know the birthweight of their infants. Maternal illness can be identified by a careful history and obtaining the patients' medical records from the previous delivery. Transvaginal measurement of cervical length during a subsequent pregnancy identifies women with a short cervix ($<$ 25 mm at 20-24 weeks, $<$ 30 mm at 16-20 weeks) who have markedly increased risk for preterm birth.[8,16] However, there are no validated, standardized ways to confirm a diagnosis of cervical insufficiency prior to pregnancy.[17] Determining the presence of placental inflammation requires obtaining a pathology report from the previous low birthweight pregnancy. Pathological examination of the placenta is not routine, although this is increasingly performed in the case of an abnormal birth outcome.

FGR is diagnosed in utero by ultrasound measurement of fetal biparietal diameter, abdominal circumference, femur length, and calculated estimates of fetal weight in comparison with standardized curves of these parameters versus gestational age. FGR is diagnosed in the neonate by birthweight corrected for gestational age. The usual criterion for defining FGR is birthweight below the 10th percentile of births at that gestational age.

How effective are the current treatments? Low maternal prepregnancy weight and large interpregnancy weight losses are important risks for both preterm birth and low birthweight, and weight gain prior to pregnancy might reduce risk for these women, but this has not been tested. The complex associations of body mass index with pregnancy outcomes are described elsewhere in this supplement.[18]

Smoking cessation programs are effective in reducing pregnancy loss.[19] Interpregnancy interval can be extended by contraception; however, no interventional studies exist at present.

Incompetent cervix is identifiable in some cases by a history of painless dilatation in the previous labor. Cervical cerclage procedures prior to pregnancy have been used for many years for women with a history of multiple late midtrimester losses and appear effective when compared with the same patient's past history, but there are no randomized prospective trials.[17] A very large international trial compared cerclage during pregnancy plus bed rest with bed rest alone and found a small but statistically significant reduction in delivery prior to 33 weeks and very low birthweight deliveries.[20] With the recognition that a short cervix found by transvaginal ultrasound during pregnancy identifies women at risk for recurrent preterm delivery, there is great interest in how to treat this group. Most evidence to date is that cervical cerclage during pregnancy is not beneficial.[21] However, in 1 metaanalysis, risk of preterm birth was reduced by cerclage for the subgroup of women with a singleton pregnancy, prior preterm delivery, and a short cervix by ultrasound in the current pregnancy.[22]

Recent studies found highly significant reductions in subsequent preterm birth if women with a previous preterm infant are treated with injections of 17-hydroxyprogesterone caproate from 16 to 36 weeks of gestation.[23] Additional benefits include reductions in neonatal death, respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, and necrotizing enterocolitis in the progesterone-treated group. Similar benefits have been reported with daily use of vaginal suppositories of natural progesterone.[24] A 2005 metaanalysis of 10 trials confirmed these findings.[25] Use of progestational agents once labor has started is not effective. Recent evidence suggests that progesterone is of benefit to women with a shortened cervix.[26] 17-Hydroxyprogesterone caproate is presently available only through compounding pharmacies. It has been granted orphan drug status by the US Food and Drug Administration (FDA). An FDA panel has recommended approval for the indication of preventing preterm birth.[27] Progesterone suppositories are also available only through compounding pharmacists.

Dietary long-chain polyunsaturated fatty acid supplementation is discussed in the nutrition section of this supplement.[18] Supplementation has been found to slightly increase the mean gestational length but not with any reduction in low birthweight, preterm birth, or rate of preeclampsia.

Management of women with a history of an FGR infant includes obtaining the records of the previous pregnancy and

the infant if it survived and searching for specific neonatal and maternal conditions that may have been associated. Chronic illnesses, especially those that produce vascular disease, should be managed to optimize the mother's health before pregnancy. Maternal exposure to tobacco, alcohol, and cocaine should be eliminated if possible. Programs that reduce maternal cigarette smoking have been proven to reduce FGR births.[13,15] Risk for FGR decreases when women with low body mass index increase their weight between pregnancies.[15] Because short interpregnancy interval is associated with both preterm birth and FGR, delaying conception to allow for an interpregnancy interval of 18-24 months may be beneficial.

A portion of preterm births and FGR result from multiple births occurring after in vitro fertilization (IVF). The frequency of multiple births can be reduced by reducing the number of embryos transferred. Where FGR is associated with specific genetic syndromes, gamete donation, or IVF and preimplantation genetics may offer a solution.[15] Maternal periodontal disease is associated with both preterm birth and FGR, although intervention programs during pregnancy have not been consistently effective, suggesting that dental care prior to pregnancy may be necessary.

Impact of preconception care: Preconception care provides the opportunity to identify women at risk by determining their pregnancy history. Women with previous preterm or FGR infants should be evaluated for remediable conditions such as cervical insufficiency, cigarette smoking, and low maternal weight and chronic illness (for example, hypertension that may predispose them to another preterm or FGR delivery). Planning of pregnancies is advised to avoid short birth intervals and optimize management of maternal illness. Women with a history of preterm birth should be counseled about risk of recurrent preterm labor, the possible use of a progestational agent in the next pregnancy, and the need for early enrollment in prenatal care to make treatment possible.

Recommendations by other groups: The American College of Obstetricians and Gynecologists (ACOG) notes both the apparent benefits of progesterone for high-risk women and the problem of no commercial availability of 17-hydroxyprogesterone caproate. The ACOG does not make a clear recommendation to use progesterone but states that its use should be restricted to women with a documented history of spontaneous birth at < 37 weeks.[28]

The ACOG does not recommend preconception measures for previous FGR birth but makes detailed suggestions for screening during pregnancy and pregnancy management. Early ultrasound is advised for all women with previous FGR birth, as are subsequent ultrasounds to evaluate growth. Once FGR is diagnosed, approximately weekly fetal assessment with Doppler velocimetry, contraction stress test, biophysical profile, and nonstress testing with amniotic fluid volume assessment are recommended to reduce perinatal mortality. When tests are abnormal, daily monitoring is recommended with early delivery, despite prematurity if fetal heart rate testing and Doppler velocimetry become abnormal.[29]

Recommendation. Pregnancy history should be obtained from all reproductive-age women. Those with a history of a preterm or FGR infant should be evaluated for remediable causes to be addressed before the next pregnancy. *Strength of recommendation:* A; *quality of the evidence:* II-2.

Women with a previous spontaneous preterm birth should be informed of the potential benefit of treatment with progesterone in subsequent pregnancy. *Strength of recommendation:* A; *quality of the evidence:* I-b.

Prior cesarean delivery

Burden of suffering: In the United States, cesarean delivery is the most commonly performed obstetrical procedure. Thirty percent of women undergo cesarean delivery, which is a 46% increase since 1996.[30] A woman considering pregnancy after a previous cesarean will be faced with deciding the mode of delivery for the next pregnancy: whether to have an elective repeat cesarean or attempt a trial of labor (TOL). If TOL is successful, the patient can expect a faster recuperation period, shorter hospital stay, lower risk for postoperative complications (eg, bowel injury, infection, blood loss), lower risk of respiratory complications in the newborn (eg, transient tachypnea of the newborn), and higher likelihood of having a successful trial of labor in future pregnancies than a woman who undergoes elective cesarean before labor.[31] However, women who start a TOL may still need a cesarean during labor for failure to progress or nonreassuring fetal heart rate and are at risk for dehiscence or complete uterine rupture (incidence 1 per 200 deliveries) during labor, with expulsion of the fetus into the mother's abdomen, which may lead to death (4%) or severe disability for the infant.[32,33] Maternal complications of uterine rupture might include severe hemorrhage requiring blood transfusion (1 per 90 deliveries) or hysterectomy (1 per 500 deliveries).[34,35]

An elective repeat cesarean section prior to labor has fewer complications than the same procedure performed during labor but more than with a successful TOL.[23] However, multiple cesareans increase risk for later pregnancies. Rates of placenta previa have been reported to range from 0.24% in patients undergoing a first cesarean delivery to 6.74% in patients with 6 prior cesarean deliveries.[36] Among patients with a placenta previa, the rate of accreta can range between 3% in women with 1 prior cesarean and 61%-67% among women with 4 or more cesarean deliveries.[37] Placenta accreta and its more severe variations, placenta increta and percreta, can produce massive bleeding requiring emergency hysterectomy and possibly leading to death.

The decision to have a TOL or elective repeat cesarean can best be made after careful consultation with an obstetrician or other expert health care provider and is based on information about the previous cesarean, most especially the type of uterine incision (whether low transverse, low vertical, T incision, or classical) and type of repair (whether single layer or 2 layer). Every effort should be made to

obtain the official operative report for the first cesarean.

The outcome of TOL is influenced by a variety of factors:

- The type of incision. Transverse uterine incision and lower segment vertical incisions have the least risk for rupture, whereas classical vertical incisions and T incisions increase risk for rupture and are contraindications to TOL.[38] Rates of uterine rupture range between 4% and 9% in women with prior classical or T-shaped incisions. Lower rates have been reported in women with prior low vertical (1-7%) or low transverse incisions (0.2-1.5%).[30,39,40] Most studies present prior cesarean delivery as a composite variable, essentially grouping all nontransverse incisions into 1 category. Therefore, it is difficult to provide relative risks for each type of incision.
- Type of repair. Whether the incision was repaired with a single vs double-layer uterine closure may be another determinant of risk. Single-layer closures have been reported to confer a 4- to 8-fold adjusted increase in risk for uterine rupture during TOL over the risk with a conventional 2-layer uterine closure.[33,41] However, 4 retrospective studies and 1 case-control study with a total of 1372 patients reported no substantial differences in uterine rupture with single- vs double-layer closure.[42-46]
- Maternal characteristics. Maternal obesity increases risk[35] as does maternal age over 30 years.[47]
- Time since last cesarean. A short interdelivery interval (defined as months from the previous delivery to the index delivery) increases risk. One study found this effect for interdelivery intervals of less than 24 months,[48] another for interdelivery intervals of less than 18 months,[49] and a third for interpregnancy intervals (defined as months from delivery to the subsequent conception) of less than 6 months.[50] These data suggest a reasonable minimal interval from delivery to the next conception to be approximately 15 months.[50]
- Labor initiation. Induction of labor, especially with prostaglandin E2, is associated with a substantial increase in the risk of uterine rupture.[51-53] Induction with misoprostol appears associated with even more risk.[46]
- Number of prior cesarean sections. Previous preterm cesarean delivery appears to increase risk for rupture, even when the incision was transverse.[52] Multiple cesarean deliveries, all with lower-segment transverse incisions, do not appear to significantly increase rate of uterine rupture during TOL compared with those with a single prior operation.[53]

Shipp et al[54] combined many of these risk factors in a simple formula to predict risk for uterine rupture during a TOL. They assigned numerical scores to the various factors: adding 2 points for 2 or more prior cesareans, 1 point for interdelivery interval 18 months or less, 1 point for maternal age 30-39 years, and 2 points for maternal age 40 years or greater, and subtracting 1 point for a prior vaginal delivery and 1 prior cesarean. Women with the lowest score (–1) had a 0.26% risk of rupture during TOL, whereas women with scores of 0, 1, 2, 3, and 4 had uterine rupture risks of 0.25, 1.11, 2.43, 3.70, and 14.29, respectively. This work, if validated by others, may simplify discussion of risk with patients.

How detectable is the condition? Women are aware of whether they have undergone prior cesarean delivery but may not know the type of scar or details of the repair.

Impact of preconception care: A preconception visit prior to a subsequent pregnancy would allow discussion of the potential maternal and newborn risks and benefits of a TOL vs elective repeat cesarean delivery. Ideally this discussion should begin prior to discharge after the cesarean and continue at the postpartum visit and should include a description of the type of uterine incision and repair the patient just experienced.

Because uterine rupture with TOL is reduced by a delay of 18 months or more from previous cesarean, a discussion of family-planning methods is strongly indicated. A review of potential operative morbidity with multiple cesarean deliveries and an appraisal of long-term risks of placental previa or placental accreta with multiple cesarean deliveries should also be discussed along with interventions for management and potential maternal complications.[55]

Recommendations by other groups: The ACOG issued a 2006 committee opinion on the evaluation and management of women with prior cesarean delivery, recommending that when labor induction is needed, the patient be informed of increased risk of uterine rupture and that use of misoprostol or other prostaglandins and oxytocin in sequence be avoided.[51]

Recommendation. Preconception counseling of women with prior cesarean delivery should include counseling about waiting at least 18 months before the next pregnancy and about possible modes of delivery so the patient enters the next pregnancy informed of the risks and options. Ideally the counseling should begin immediately after the cesarean and continued at postpartum visits. *Strength of recommendation:* A; *quality of evidence:* II-2.

Prior miscarriage

Burden of suffering: There are 2 forms of spontaneous abortion to consider in the preconception period. One is sporadic pregnancy loss, which occurs at random throughout reproduction in 10-15% of clinically recognized pregnancies.[56] Another is recurrent abortion, which is defined as 3 or more consecutive spontaneous abortions and occurs in about 1% of fertile couples.

How detectable is the condition? A careful obstetric history can determine the number and gestational age of the spontaneous abortion(s). Recurrent abortion is defined as 3 or more consecutive spontaneous abortions; some recommend not including biochemical pregnancies (pregnancies with a pregnancy test and missed menses as the only manifestation) in this count.[57]

How effective are the current treatments? Patients with sporadic abortion should be reassured that the prognosis is good for future pregnancies and offered routine preconception care. Those with a loss at a gestational age greater than 14 weeks may benefit from consideration that their loss was due to preterm birth or fetal loss. Women with recurrent early pregnancy loss (RPL; < 15 weeks' gestation) should be offered a work-up including measurement of antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibody), parental karyotyping, and imaging of the uterus with pelvic ultrasound (sonohysterography or 3-dimensional ultrasound) or hysterosalpingogram. No recommendation can be made about thyroid testing, glucose tolerance, or luteal phase defects because data are not conclusive about their association with RPL.

No randomized controlled studies have shown any benefit from measuring infectious agents, antinuclear antibody, paternal leukocyte antigens/antipaternal antibodies, or their associated treatments and thus cannot be recommended. Those with elevated antiphospholipid antibodies may benefit from treatment with heparin and low-dose aspirin; 2 small trials found rates of spontaneous abortion reduced by 54% for treatment with both vs aspirin alone.[57] There is also evidence of improved blood flow on histopathologic data with these treatments.

Couples with an identified chromosomal anomaly should be offered genetic counseling and prenatal testing of the fetus in subsequent pregnancies. Preimplantation embryo testing can identify specific chromosomal abnormalities (such as translocations or specific gene defects) and may be an option for those couples with access to assisted reproductive technology. This therapy is not recommended for screening of aneuploidy or without a known genetic defect.

Those diagnosed with a uterine septum on imaging can undergo resection of the septum via hysteroscopy with reported rates of live births of 70-85% based on case series data. Similarly, removal of uterine fibroids is an option when they are identified and felt to be contributing to RPL, such as a large submucous fibroid, which deforms the cavity. All surgical treatments are largely based on case series, so the actual treatment effect is unclear. When no cause is identified, the prognosis is still favorable.

Couples can be reassured that a successful pregnancy occurs in a next pregnancy in 50-75% of women. Although no randomized controlled studies exist, psychological support and tender loving care have been shown to improve outcomes in RPL patients.[58] One study demonstrated an 86% rate of successful pregnancy with specific counseling and support vs 33% with no specific care.[59] Another study found miscarriage rates of 26% vs 51% for those with and without supportive therapy, respectively.[60] Because of the noninvasive nature of this therapy, it should be offered to these patients to help them through this difficult time.

Impact of preconception care: Work-up for recurrent spontaneous abortion is done in the preconception period. Surgical correction of uterine anomalies such as a septum must be corrected in the preconception period. Some treatments such as heparin therapy are initiated early in pregnancy, so identification of antiphospholipid antibodies must be accomplished prior to pregnancy. Those with a loss at a gestational age greater than 14 weeks may benefit from consideration that their loss was due to preterm birth or fetal death and receive a comprehensive workup for these etiologies as discussed below.

Recommendations by other groups: ACOG recommends the work-up cited in previous text and treatment with heparin and aspirin in those with repeated (2 abnormal results 6-8 weeks apart) antiphospholipid antibodies. The European Society for Human Reproduction and Embryology states that treatment of antiphospholipid antibodies with aspirin or heparin requires further randomized trials, citing design issues of existing studies.[60] They recommend testing thyroid function and glucose intolerance based on benefits for overall fetal development and low cost. Neither group recommends routine karyotyping of abortus tissue in future pregnancies,[60] nor does either recommend therapy with progestational agents. Both, in addition to the American Society for Reproductive Medicine, recommend against treatment with intravenous immunoglobulin.[58,61]

Recommendation. Women with sporadic spontaneous abortion should be reassured of a low likelihood of recurrence and offered routine preconception care. Those with 3 or more early losses should be offered a work-up to identify a cause. Therapy based on the identified cause may be undertaken. For those with no identified cause, the prognosis is favorable with supportive care. *Strength of recommendation:* A; *quality of evidence:* I-a.

Prior stillbirth

Burden of suffering: The definition of stillbirth includes the following: "death prior to the complete expulsion or extraction from its mother of a product of human conception, irrespective of the duration of pregnancy and which is not an induced termination of pregnancy, and that the fetus does not breathe or show other evidence of life such as beating of the heart, pulsation of the umbilical cord, or definite movement of voluntary muscles."[62] Reporting of fetal deaths is required in most states if it involves "a fetal death of 350 g or more, or if weight is unknown, of 20 completed weeks' gestation or more."[62,63] The US stillbirth rate in 2003 was 6.2 stillbirths per 1000 live births and fetal deaths, equaling the number of infant deaths in the United States.[62] Stillbirths constitute half of all perinatal mortality and 50% have an undetermined cause of death. There is significant racial disparity in the stillbirth rate; the rate for non-Hispanic black women is more than double that of non-Hispanic white women.[63]

How detectable is the condition? Stillbirth is readily recognized at birth by the absence of any signs of life. Women generally know if they have had one. The risk of recurrent stillbirth is increased 2- to 10-fold for women with a history of prior stillbirth(s) over the risk for women with no such history.[64-66] The risk depends on maternal race and characteristics of the prior still-

TABLE
Estimates of maternal risk factors and risk of stillbirth

Condition	Prevalence (%)	Estimate rate of stillbirth per 1000	Odds ratio[a]
All pregnancies		6.4	1.0
Low-risk pregnancies	80	4-5.5	0.86
Hypertensive disorder			
Chronic hypertension	6-10	6-25	1.5-2.7
Pregnancy-induced hypertension			
Mild	5.8-7.7	9-51	1.2-4.0
Severe	1.3-3.3	12-29	1.8-4.4
Diabetes			
Treated with diet	2.5-5	6-10	1.2-2.2
Treated with insulin	2.4	6-35	1.8-4.4
Systemic lupus erythematosus	< 1	40-150	6-20
Renal disease	< 1	15-200	2.2-30
Thyroid disorders	0.2-2	12-20	2.2-3.0
Thrombophilia	1-5	18-40	2.8-5.0
Cholestasis of pregnancy	< 0.1	12-30	1.8-4.0
Smoking > 10 cigarettes	10-20	10-15	1.7-3.0
Obesity (before pregnancy)			
BMI 25-29.9 kg/m^2	21	12-15	1.9-2.7
BMI ≥ 30 kg/m^2	20	13-18	2.1-2.8
Low educational attainment (< 12 y vs ≥ 12 y)	30	10-13	1.6-2.0
Previous growth-restricted infant ($< 10\%$)	6.7	12-30	2.-4.6
Previous stillbirth	0.5-1	9-20	1.4-3.2
Multiple gestations (current pregnancy)			
Twins	2.7	12	1.0-2.8
Triplets	0.14	34	2.8-3.7
Advanced maternal age (reference < 35 y)			
35-39 y	15-18	11-14	1.8-2.2
≥ 40 y	2	11-21	1.8-3.3
Black women compared with white women	15	12-14	2.0-2.2

BMI, body mass index.
Source: Fretts RC. Etiology and prevention of stillbirth. Am J Obstet Gynecol 2005;193:1923-35.[68] Used by permission.
[a] Odds ratio with the factor compared with the risk factor absent.

Stubblefield. The clinical content of preconception care: reproductive history. Am J Obstet Gynecol 2008.

birth, including etiology, gestational age, and the presence of fetal growth restriction. In addition, a history of stillbirth increases the risk of a range of adverse pregnancy outcomes in the subsequent pregnancy.

How effective are the current treatments? Present management is based on a search for risk factors during the subsequent pregnancy, with intensive prenatal care based as much as possible on what is known of the causes of the previous stillbirth. During the preconception or initial visit, the obstetric provider obtains a detailed medical and obstetrical history; reviews the evaluation of the prior stillbirth; determines recurrence risk based on available information; and discusses the risk of other obstetrical complications, such as placental abruption, preterm delivery, and cesarean delivery.[67] The Table lists common maternal factors associated with stillbirth from a recent systematic review of the medical literature.[68]

There is little evidence to form recommendations for the management of sub-

sequent pregnancy after stillbirth. Counseling is individualized to the patient's particular circumstances or risk factor. For example, if a couple experienced a previous second-trimester stillbirth as a result of a cystic hygroma and nonimmune hydrops caused by Turner's syndrome, they can be reassured that Turner's syndrome is a sporadic condition and is not associated with advanced maternal age. However, in the subsequent pregnancy, one can offer nuchal translucency ultrasound to provide reassurance to the couple.

First-trimester sonograms are advised for accurate dating. Although the predictive value for maternal serum screening in the first trimester is low, performing maternal serum pregnancy-associated plasma protein-A may provide some reassurance regarding the recurrent risk of stillbirth from placental causes.[69] If not previously performed as part of the work-up for the initial stillbirth, early diabetes screen, anticardiolipin antibodies, and thrombophilia work-up may be performed. For example, a woman with a previous stillbirth associated with fetal growth restriction or placental pathology significant for thromboses may benefit from thrombophilia testing and treatment with aspirin and heparin if thrombophilia testing is positive.[70,71]

In the second trimester, a fetal anatomic survey may be performed at 18-20 weeks. Similar to the first-trimester screen, the predictive value of second-trimester analytes for stillbirth (maternal serum alpha-fetoprotein [MSAFP], human chorionic gonadotropin [hCG], estriol, and inhibin-A) is poor but may provide additional information. MSAFP testing may be associated with the presence of a placental abnormality if it is elevated in a structurally normal fetus.[72] Likewise, an abnormally elevated B-hCG may be associated with an increased risk of stillbirth but has poor predictive value.[73]

Because nearly half of all stillbirths are associated with FGR, serial sonograms for fetal growth are customary, starting at 28 weeks. If there is evidence of fetal growth restriction, then the frequency of ultrasound to monitor fetal growth is increased, usually to every 2-4 weeks, and Doppler studies and antepartum fetal testing are recommended. The ACOG technical bulletin on intrauterine growth restriction outlines management strategies.[74]

In all women with a previous stillbirth, maternal assessment of fetal movement or fetal kick counts may be started at 28 weeks' gestation. Antepartum fetal testing, such as twice-weekly nonstress tests and amniotic fluid index or biophysical profiles, may be initiated at 32 weeks or 1-2 weeks before the gestational age of the previous stillbirth.[75] Caution must be used when interpreting the antepartum fetal surveillance of a fetus of less than 32 weeks' gestation.

The delivery plan should be discussed with the couple well in advance of the third trimester. The timing of the delivery depends on maternal anxiety, cervical ripeness, and the cause of the previous stillbirth. In most cases, elective induction at 39 weeks' gestation or earlier delivery with documented fetal lung maturity may be appropriate.[76]

Impact of preconception care: Many women do not receive comprehensive counseling with regard to the cause of the stillbirth because either an incomplete evaluation was performed or because in 50% of cases with complete evaluation, the cause remains unknown. The most important preconception intervention begins with a comprehensive assessment at the time of the stillbirth and this should be undertaken in all cases. This recommendation is based on stillbirths defined as fetal deaths occurring at or after 20 weeks of gestation or more than 350 g birthweight. However, early second-trimester intrauterine fetal demise may not differ in etiology from stillbirths occurring after 20 weeks and a comprehensive evaluation as described in this section may be useful.

The single most important tests are an autopsy and pathologic examination of the placenta. If the parents refuse autopsy, they may accept a limited physical examination of the neonate by a perinatal pathologist. Postmortem magnetic resonance imaging may be useful. Cytogenetic studies are essential. The highest yield of viable cells is from an amniocentesis taken after recognition of the fetal death and prior to birth.[77] Additional useful laboratory tests may include maternal fasting glucose, a Kleihauer-Betke test to detect fetal-maternal hemorrhage, urine toxicology, hemoglobin A_{1c}, and a thrombophilia work-up in normally formed infants.[68,78]

A preconception visit to review the circumstances and work-up of the previous stillbirth is important. Review of available reports of the fetal autopsy, placental pathology, and appropriate testing is important to guide management of the subsequent pregnancy and in some cases may suggest interventions that should be undertaken prior to the next pregnancy. Because many stillborn infants have had fetal growth restriction, the interventions to prevent FGR discussed in previous text may be appropriate. Examples of possible interventions include maternal dietary supplementation with folic acid to prevent recurrence of neural tube defects, tight control of blood glucose for diabetic women to prevent other major fetal malformations, and management of other genetic conditions by preimplantation genetics and embryo selection. Because cigarette smoking is related to growth restriction and stillbirth, smoking cessation is an important preconception intervention.[79] Couples often experience feelings of anxiety, personal guilt, and apprehension when contemplating pregnancy after having a stillborn infant and may require additional psychosocial support.

Recommendations by other groups: The ACOG issued a 2007 committee opinion providing detailed suggestions for the evaluation of stillbirth at the time that it occurs. These include a detailed review of the mother's medical history; obstetric history; history of the prenatal course; physical examination of the fetus with weight, head circumference, and length; multiple photographs of the infant and placenta; placental pathology; fetal karyotype; whole-body X-ray and autopsy if possible; and documentation of findings. The findings should be communicated to the family.[78]

Recommendation. At the time of the stillbirth, a thorough investigation to de-

termine causation should be performed and communicated to the patient. At the preconception visit, women with a previous stillbirth should receive counseling about the increased risk of adverse pregnancy outcomes and may require referral for support. Any appropriate work-up to define the etiology of the previous stillbirth should be performed if not done as part of the initial work-up. Risk factors that can be modified prior to the next pregnancy should be addressed, for example, smoking cessation. *Strength of recommendation:* B; *quality of evidence:* II-2.

Uterine anomalies

Burden of suffering: Two to four percent of fertile women with normal reproductive outcomes are believed to have congenital mullerian anomalies.[80,81] The prevalence of such anomalies in women with history of poor reproductive performance (recurrent first- and second-trimester losses) is estimated at 13%.[82] Prevalence rates as high as 7-8% in the general population and 25% in the recurrent pregnancy loss population have been reported in series in which minor anomalies were included (eg, minor arcuations and "hypoplastic" uteri).[83] It has also been estimated that a congenital uterine malformation complicates 1 in 594 pregnancies.[84] The most common uterine anomalies are septate (35%), bicornuate (26%), and arcuate or subseptate (18%), but these proportions may vary, depending on the specific population studied and the methodology used to ascertain the diagnosis.[81] The overall live birth rates in patients with mullerian anomalies are lower than average and are estimated around 60% for the bicornuate and septate uterus and 40% for the unicornuate and didelphic uterus. It is generally agreed that the rates of prematurity, growth restriction, postpartum hemorrhage, cervical incompetence, malpresentation, pregnancy-associated hypertension, dystocia, uterine rupture in labor, and cesarean deliveries are higher in patients with mullerian anomalies.

How detectable is the condition? Because of increased use of ultrasound and magnetic resonance imaging (MRI) for miscellaneous gynecological complaints, mullerian anomalies are being increasingly detected in women whose reproductive performance has not been previously tested. In women with recurrent pregnancy loss, however, the gold standard for the diagnosis and accurate classification of uterine anomalies is a hysterogram (HSG) followed by a laparoscopy and hysteroscopy if the HSG is abnormal. More recently the use of MRI and 3-dimensional ultrasound have emerged as noninvasive alternatives for the diagnosis and classification of anomalies with a good degree of specificity and sensitivity.[85,86] It should also be noted that approximately 20% of women with mullerian anomalies harbor a coexistent renal or ureteral anomaly that should be ruled out with either a renal scan or intravenous pyelogram.

How effective are the current treatments? The literature concerning the effectiveness of treatments on reproductive outcomes in women with Mullerian anomalies is mostly observational and retrospective. In women with anomalies whose reproductive performance has not been previously tested, the course of action should be individualized and depends on the nature and complexity of the anomaly and associated gynecologic symptoms. Although there is no evidence that proactive interventions improve outcomes, most authorities favor hysteroscopic incision of a uterine septum when identified.

The best results appear to occur in women with history of recurrent pregnancy loss who have a uterine septum greater than 1 cm long. In those patients, hysteroscopic resection/incision of the septum restores a normal live birth rate of about 80-90% and reduces miscarriage rates to background levels of 15-20%.[82,87,88] There is anecdotal evidence that excision of coexisting vaginal septum may be beneficial in reducing risk of dystocia and cesarean delivery in subsequent pregnancies. There is no credible evidence that surgical correction of a unicornuate, bicornuate, didelphic, or T-shaped uterus improves pregnancy and live birth rates. Some individual patients, however, with bicornuate or didelphic uteri who have had repeatedly poor outcomes despite intensive obstetric management may benefit from a Strassman reunification metroplasty.[89]

Impact of preconception care: Preconceptional identification of a uterine septum usually calls for hysteroscopic resection to improve subsequent pregnancy outcomes, particularly in the recurrent loss population. Identification of a coexistent renal or ureteral anomaly should also call for heightened awareness during the next pregnancy because of an increased risk of hypertension, recurrent urinary tract infections, and urinary tract injury during cesarean. Although there is no strong evidence of overall benefit,[90] intensive obstetrical and sonographic surveillance of subsequent pregnancies could theoretically allow early identification of risk markers for preterm labor and incompetent cervix and deployment of interventions that may optimize fetal outcomes (eg, bed rest, progesterone use, cerclage placement, tocolysis, and steroid use). Because of a reported increase in the risks of ectopic pregnancy in women with mullerian anomalies, early pregnancy tracking by hCG levels and sonography is also warranted for early detection and noninvasive management of ectopics.[91]

In patients with anomalies who require assisted reproductive technologies to conceive, the overall pregnancy rates after IVF appear to be lower than in the general population, although the series are small.[91]

Occasional difficulties may arise during egg retrievals (because of unusual ovarian position in the pelvis) and embryo replacement (because of cervical stenosis or deformity) that require special skills to overcome. Extra care should also be taken by the IVF team to minimize the risk of multiple pregnancies because of the increased baseline risk of preterm labor.

Recommendation. A uterine septum in a woman with poor prior reproductive performance should be hysteroscopically corrected before the next conception. All other anomalies call for specific delineation of the anomaly and any asso-

ciated vaginal and renal malformations. Although surgical correction may be advised in some, heightened awareness and surveillance during a subsequent pregnancy and labor should help optimize outcomes. *Strength of recommendation:* B; *quality of evidence:* II-3.

Conclusion

A large number of specific conditions that increase risk of preterm birth or adverse pregnancy outcome can be diagnosed based on reproductive history. Many of these can be successfully treated prior to pregnancy or early in a subsequent pregnancy to reduce risk. There is good evidence for some treatments, for example, smoking cessation and use of 17-hydroxyprogesterone caproate after previous preterm birth. Case series show the often dramatic benefit of hysteroscopic resection of uterine septa after recurrent miscarriage, and we recommend this, but there have been no randomized trials.

Placental inflammation exists in most extremely preterm deliveries and is a central problem, but intrauterine growth restriction and stillbirth are major problems that can result from many different etiologies. Reduction of risk requires a program of searching for possible causes, managing those causes, and closely monitoring the subsequent pregnancy with ultrasound and antepartum fetal heart rate monitoring. However, truly proving that such management leads to the improved outcome would require withholding care from some. This poses a very difficult ethical dilemma for investigators. Concerted application of our present knowledge should help reduce adverse pregnancy outcomes, but much more remains to be done to understand causes and develop effective therapies. ■

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The clinical content of preconception care: preconception care for special populations

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Women with disabilities, immigrant and refugee women, and cancer survivors may have medical, psychosocial, and/or cultural issues. Appropriate preconception guidance and management of reproductive planning and preconception issues is essential to ensure that women in these groups can make informed reproductive decisions and achieve optimal reproductive outcomes.

Key words: cancer, disability, immigrant, preconception, refugee

Ongoing preconception risk assessment, guidance, and intervention, when integrated into primary and specialty care, can accomplish 3 goals. The first is to minimize risks for a woman, if she becomes pregnant, and risks to her offspring. The second is to optimize a woman's health in her reproductive years and beyond. The third is to assist a woman to proactively plan for her reproductive future. These goals are important to achieve for all women of reproductive age, but may be of particular importance among women who are at risk for poor reproductive health outcomes or who have special reproductive health needs.

Women with disabilities and immigrant and refugee women may experience physical, social, and/or cultural barriers to accessing and obtaining health care, including preconception care. They may have also have to face and overcome a variety of personal obstacles, and these strengths should be acknowledged by care providers as they creatively strategize with these women so they may secure ongoing, viable health care and plan their reproductive futures to their best advantage.

There are increasing numbers of cancer survivors of reproductive age. Cancer survivors benefit from guidance about risks of treatment to their fertility and about fertility preservation options. They should be counseled about risks of past or current treatment to their current and future health and how these risks may impact pregnancy or the health of potential offspring. Ongoing screening is indicated for some survivors, and may uncover medical issues, such as impaired cardiac function, that are important to diagnose preconceptionally so that a woman can make fully informed reproductive decisions.

This article summarizes the value of preconception counseling and interventions specific to each of these groups of women and identifies clinical guidelines, where applicable.

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Women with disabilities

Burden of suffering

There are an estimated 54-60 million people with disabilities in the United States and more than half are women, many of reproductive age.[1] Individuals may be born with disabilities or may acquire them during the course of a lifetime. The impairment may be stable or progressive. Disabilities include those affecting motor or sensory abilities, as well as developmental disabilities and mental illness. People with disabilities may experience a variety of barriers to care. Besides physical and administrative barriers, women with disabilities have identified attitudinal barriers to gynecologic care. They report that providers may assume that they are not sexually active or that they do not desire pregnancy.[2-4] Preexisting medical issues can affect a woman's health in pregnancy and the pregnancy outcome.[5] In a large sample of women with disabilities, those with functional limitations, of all ages, were more likely to report fair or poor health, current smoking, hypertension, overweight, and mental health problems than women without functional limitations.[6] Studies report that women with physical disabilities experience the same rates of abuse as other women but experience a longer duration of abuse.[7,8] Some disabilities, such as systemic lupus erythematosus (SLE), can worsen in pregnancy and some may be exacerbated postpartum, such as rheumatoid arthritis or multiple sclerosis. SLE is associated with an increased risk of fetal loss, fetal growth restriction, and preeclampsia.[9] Conditions that are common in pregnancy may be more severe in women with disabilities. Examples are fatigue, fluid retention, bladder dysfunction, and problems with weight gain. There are certain complications that may develop or worsen during pregnancy because of a woman's disability.[2] Women with spinal cord injuries are at risk for autonomic dysreflexia, which can be precipitated by pelvic examinations or labor.

Those with limited mobility and those who use wheelchairs are at an increased risk for deep vein thrombosis. Among women with neurologic conditions, urinary tract infections, respiratory dysfunction, urinary incontinence, spasticity, constipation, or pressure ulcers may be issues in pregnancy. Women who

have impaired balance, muscle weakness, or paralysis are at increased risk for falls during pregnancy.[2-4]

How detectable is the condition?

Disabilities are identified through history and physical examination and through indicated diagnostic tests and evaluation by specialists.

How effective are the current treatments?

Women with disabilities will have greater access to care and willingness to participate in care if physical, administrative, and attitudinal barriers are minimized. Preconception consultation with medical specialists, nursing, social services, and occupational and physical therapists can assist in planning and can potentially maximize pregnancy outcomes, although supporting data are lacking.

Genetic counseling is valuable for women with or at risk for genetic conditions, and their families, to give them the opportunity to make informed decisions about whether they will elect genetic testing, the risk of having an offspring given a particular heritable or genetic condition, and the options they will have based on the results.[5]

Impact of preconception care

Planning preconceptionally to maximize social and environmental supports for women with disabilities would seem advantageous considering the demands of parenting, and research has shown that disabled persons who have intact social support report a better quality of life than those who lack social support.[10] Avoidance of teratogenic effects can only be successful if women taking teratogenic medications are counseled preconceptionally about the use of these medications and plan with their providers the best way to balance their medical treatment with a desire for a healthy pregnancy and infant. Women who discover they are at risk for a genetic condition preconceptionally, as opposed to during pregnancy, may use this information in weighing whether or not they desire to become pregnant and–depending on the condition–have more options to choose from to avoid passing the condition to their offspring.

Recommendations by other groups

The American College of Obstetricians and Gynecologists,[11,12] along with other groups,[13] have made recommendations.

Recommendation. Providers should understand that women with disabilities can have healthy pregnancies and that disabilities can coexist with wellness. Providers should work to remove physical, administrative, and attitudinal barriers to the care of disabled women.

All women of reproductive age, including those with disabilities, should receive counseling about the potential effects of any medications they use on pregnancy-related outcomes and about options to alter dosage or switch to safer medications prior to conception. The medical, social, and psychological issues related to pregnancy and the disability should be assessed, and the woman and her family should be counseled on them. Health care providers should offer women with disabilities contraceptive choices that are practical and appropriate for the individual's medical and personal needs. Issues involving informed consent and guardianship need to be addressed when caring for women with developmental disabilities, in relation to contraception and pregnancy. Referral for genetic counseling, if appropriate, is indicated for all women preconceptionally; however, it may raise difficult psychosocial issues for women with disabilities and, therefore, counseling referrals should be handled sensitively. *Strength of recommendation:* B; *quality of evidence:* III.

Immigrant and refugee populations

Burden of suffering

There is ample research on the epidemiologic paradox showing that foreign-born women have better birth outcomes despite late access to prenatal care and probably less access to preconception care (healthy migrant effect) than US-born women. However, refugee women–who have often lived under extremely stressful conditions in their home country (war, persecution) and spent time in refugee camps–are a group of immigrants who have worse birth outcomes when compared with US-born women. Immigrant women face social, language, and cultural barriers that may affect their preconception health. Immigrants from developing countries may have a lower level of overall health, if they have had limited or no access to health care in their countries of origin. However, foreign-born women may also display healthy behaviors that should be maintained after immigration to the United States and that are at risk of getting lost as a result of acculturation (eg, less likely to use tobacco and alcohol or drugs, less sedentary lifestyle). Preexisting medical issues can affect a woman's health in pregnancy and the pregnancy outcome.[14] Immigrants from regions of the world where tuberculosis and hepatitis B are common may suffer from the effects of these untreated conditions.[15] Immigrant women may experience psychological stresses related to the events that motivated their immigration, events occurring while immigrating, and events occurring in the United States. Separation from family, uncertain immigration status, social isolation, and occupational stresses may negatively impact their mental and physical health. Immigrant women face unique challenges in accessing health care. Of the estimated 16.6 million foreign-born women in the United States in 2003, more than half (59.2%) were noncitizens–a figure that includes documented and undocumented immigrants.[16] Women who are noncitizens are far more likely than citizens to have no usual source of health care (26.1%) and no health insurance (45.5%), and almost 3 times more likely to have not seen a health professional in the past year compared with those born in the United States, according to the Health Resources and Services Administration.[17] Immigrants who do not speak English may have difficulty finding health care. Immigrants' perceptions and beliefs surrounding health and illness and their attitudes toward health care providers vary widely depending on their cultures and the extent of their interactions with health care in the United States.[18-20]

How detectable is the condition?
Pregnancy is the time at which immigrant women of reproductive age are most likely to receive health care services. Therefore, identification in the preconception or interconception period is difficult, especially identification of those who are undocumented and may be reluctant to seek care or to be able to afford it if they are ineligible for health coverage benefits.

How effective are the current treatments?
The effectiveness of preconception care for immigrant women is limited by the barriers described in this section. It seems reasonable that the preconception health of immigrant women could be improved by increasing culturally competent outreach efforts and improving access to care.[21,22] It is difficult to support this assertion because there is a lack of published studies about outreach and approaches to the care of immigrant women.

Impact of preconception care
Preconception care can help reduce the incidence of perinatal complications through identification and management of clinical issues. For a woman to receive preconception care, she must have access to a source of primary care. Thus, access to primary care must be ensured before pregnancy occurs.

Recommendations by other groups
None identified.

Recommendation. Given the opportunistic fashion in which preconception care of immigrant and refugee women typically must occur, it is important to consider preconception concerns as part of all health care encounters with immigrant and refugee women of reproductive age. Referring such women to a source of ongoing primary care that is culturally and linguistically competent, and that will accept their insurance coverage or provide care free of charge or on a sliding fee basis, is important for immigrant and refugee women. Seek to identify and understand the needs of immigrant women and their families. Understand immigrants' potential for increased medical and social risks and previously undetected medical problems. Deliver services and written materials in the preferred language of the population served. Ensure that interpretation and translation services comply with all relevant federal, state, and local mandates governing language access.

Integrate preconception care into refugee screening. Work with ethnic community-based organizations to provide preconception care messages in nonhealth care settings such as English as a second language classes. Screen immigrants at high risk for tuberculosis and refer for treatment as indicated. Screen immigrants born in Asia, the Pacific Islands, Africa, and other countries where hepatitis B is highly endemic, with the hepatitis B surface Antigen (HBsAg) test. Highly endemic means that $>$ 8% of the population in that country has hepatitis B virus infection. Assess the immunization history, including the rubella status, of immigrant women and administer any needed vaccines, or refer for these services. Assess the mental health of immigrant women and refer for services as needed. *Strength of recommendation:* B; *quality of evidence:* III.

Cancer survivors

Burden of suffering
For many types of cancers, survival has increased in the past decades. In 1996, it was projected that the prevalence of cancer survivors 16-44 years of age would be 1 in every 900 persons in the United States by the year 2000.[23] Cancer survivors of reproductive age face the challenge of integrating the experience of cancer and its treatment into their future plans, including their plans for reproduction.

There are potential negative physical and psychological impacts of the cancer experience on pregnancy and child rearing, but positive psychosocial effects have been identified as well.[24,25] Cancer survivors are at risk for permanent infertility or compromised fertility. Factors affecting male infertility include the type of cancer (eg, testicular) and effects of chemotherapy or radiation on sperm number, motility, morphology, and DNA integrity. In girls and women, fertility may be compromised by surgical, medical, or radiation treatments, which may decrease the quantity of primordial follicles, affect hormonal balance, or interfere with reproductive organ function.[23,26] Depression, chronic fatigue, cognitive changes, and neuropathies–all of which can make pregnancy and parenting more difficult–are not uncommon treatment side effects experienced by cancer survivors. A cancer survivor with a history of abdominal/pelvic radiation who becomes pregnant has an increased risk of having a low birth-weight infant, with an inverse association observed between higher doses of radiation and infant birth weight.

Studies of cancer survivors have not found them to have an increased risk for miscarriage or birth defects, and most types of chemotherapy are not linked to adverse pregnancy outcomes.[27,28] Furthermore, there is no documented increase in risk of childhood cancer among the offspring of childhood cancer survivors, but longer follow-up is needed.[29] However, survivors of hereditary cancers, such as certain types of breast, ovarian, and colorectal cancers, who test positive for the genetic mutations associated with these cancers, risk passing on these mutations to their offspring.

Genetic testing for the BRCA1 and BRCA2 genetic mutations has been shown to be highly sensitive but the specificity is not well studied.[30] Women who have received anthracycline-based chemotherapy regimens or radiation in the area of the heart or surrounding tissues are at an increased risk for heart damage.[31] This damage may manifest months or years later and, although rare, could worsen in pregnancy or the postpartum period.[32] Childhood cancer survivors who received doxorubicin and who had resultant left ventricular dysfunction before pregnancy have been documented to have further declines in cardiovascular function after pregnancy.[33]

How detectable is the condition?
Cancer survivors planning their reproductive futures may have had cancer as a child or as an adult. Their risk for infertility can be assessed, in part, by the history of their cancer and treatment. Records of cancer treatment can be very helpful. Permanent infertility or com-

promised fertility in survivors depends on their age, sex, and pretreatment fertility; the type of cancer; treatment type, dose, and intensity; size and location of radiation fields; and method of administration of chemotherapy. The older a woman is at the time of the cancer diagnosis, the higher her risk of premature ovarian failure (POF). The chemotherapeutic agents most likely to cause POF are the alkylating agents. Examples of commonly used alkylating agents are cyclophosphamide, nitrogen mustard, and procarbazine. The woman's age at the time of radiation treatment, the total dose, and the number of exposures affects the degree of damage to ovarian tissue. Women who receive pelvic or abdominal radiation, plus chemotherapy, have a higher risk for POF than those receiving only chemotherapy.[34]

How effective are the current treatments?

Fertility preservation is very important to many cancer survivors. The 2 most successful methods are sperm cryopreservation for men and embryo freezing for women. Limited data show that fertility preservation techniques do not decrease the success of cancer therapy.[23] No clear guidelines exist regarding timing of conception postcancer diagnosis. Generally the advice is to wait until treatment is concluded. Breast cancer survivors comprise a large group of reproductive-aged women who may be planning or contemplating pregnancy. These women have typically been counseled to wait 2 years before conception to pass the period of highest risk for recurrence. However, for women with localized disease, survival has not been shown to be adversely affected when conception occurred within the 2 years after diagnosis.[35] Genetic counseling is valuable for women with a personal or family history of a cancer with a known associated genetic mutation so that the woman may explore her risk and the implications of testing herself and future offspring for the mutation.

Impact of preconception care

Cancer survivors have an increased risk of having a low birth-weight baby. Control of other risk factors for low birth weight, such as smoking cessation, has been shown to reduce the risk of having a low birth-weight infant.

Diagnosis of cardiac dysfunction prior to pregnancy permits the initiation of medication, if indicated, that may delay the progression of the dysfunction,[36] and makes it possible to counsel the woman about her risks for a further decline in function during or after pregnancy. If she elects to become pregnant, appropriate monitoring can be planned during pregnancy and delivery including anesthesia management for labor and birth.[30]

Preconceptional genetic counseling is valuable for women with a known personal history of hereditary cancer, to give them the opportunity to make informed decisions about whether they will explore the option of preimplantation genetic testing.[25]

Recommendations by other groups

The American Society of Clinical Oncologists[24] and the American Society for Reproductive Medicine[26] have published recommendations about fertility preservation in cancer patients. The Children's Oncology Group has published risk-based pediatric cancer survivor guidelines.[30]

Recommendation. Newly diagnosed cancer survivors should be educated about fertility preservation options as soon as feasible and should be referred to reproductive specialists if these options are desired.[24] Cancer survivors considering pregnancy should be counseled about the potential reproductive effects of various cancer treatments on fertility and on pregnancy. Women who have received alkylating chemotherapeutic agents and/or pelvic or abdominal radiation should be counseled that they have an increased risk for POF. Women who have had pelvic or abdominal irradiation should be counseled that they are at risk for having a low birth-weight infant. When considering pregnancy, breast cancer survivors who are candidates for selective estrogen receptor modulators (SERMs) should be counseled that these agents are generally avoided during pregnancy because of case reports of animal and human birth defects.[37] A reliable nonhormonal contraceptive method should be used during treatment with a SERM. Genetic counseling and testing should be offered to survivors of cancers linked to genetic mutations to inform their decisions about future reproduction. Female cancer survivors who received anthracycline chemotherapy, radiation to the heart or surrounding tissues, or both should be evaluated by a cardiologist prior to conception. Annual breast screening for female childhood cancer survivors who received chest radiation is recommended beginning at age 25 years. *Strength of recommendation:* A; *quality of evidence:* III.

Conclusion

Women with disabilities, immigrant and refugee women, and cancer survivors all face the challenge of integrating their experiences into their reproductive decision making.

Providers who seek to understand both their challenges and their strengths can team with these women to help them achieve better health, including reproductive health.

Women in all 3 of these groups will benefit from discussion of their reproductive life plans. Providers who make no assumptions about what a given woman's reproductive plan might be and who initiate the discussion will aid women in making informed reproductive decisions. Preconception guidance and interventions that address physical, psychosocial, and/or cultural issues can produce better health for these groups of women and for their potential offspring. ■

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The clinical content of preconception care: preconception care for men

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Little attention has been given to men's preconception health and health care. This paper reviews the key elements of an approach to optimizing the preconception health status of men. Preconception care for men is important for improving family planning and pregnancy outcomes, enhancing the reproductive health and health behaviors of their female partners, and preparing men for fatherhood. Most importantly, preconception care offers an opportunity, similar to the opportunity it presents for women, for disease prevention and health promotion in men. Currently, no consensus exists on service delivery of preconception care for men—who should provide preconception care to whom, where, when, and how, and there are significant barriers to this care including the organization, financing, training, and demand. Finally, much more research on the content and how to effectively market and implement preconception care for men is needed.

Key words: father, health promotion, preconception, risk assessment

In 2005, the Centers for Disease Control and Prevention (CDC) and 35 partner organizations convened a national summit and issued a set of recommendations to promote preconception care in the US. While passing recognition was given to the importance of preconception health promotion "among both men and women," the focus was on women. To date, little attention has been given to men's preconception health and health care.

The belated recognition of men in our efforts parallels efforts to involve men in reproductive health initiatives internationally, which has only gradually recognized that men should be legitimate targets for sexual and reproductive health promotion, and that men should play direct, active, and constructive roles as part of a broader reproductive health agenda.[1] Several international initiatives have taken place with themes such as "Men as Partners in Reproductive Health."[2] In the US, there has been a steady increase in research and programs on men's health and family involvement, but these have not heretofore been conceptualized in a preconception health context. We believe that there are several distinct reasons why preconception care for men is important.

First, as with women, improving men's preconception health is critical for ensuring that all pregnancies are planned and wanted. Men are critical partners in family planning, and until the advent of modern assisted reproductive technologies (ART), necessary partners. The CDC's first Preconception Care recommendation encourages all women, men, and couples to have a reproductive life plan.[3] Men's contribution to the family planning partnership means addressing the utilization, access, and efficacy of male fertility control, including barrier methods and hormonal agents; and not assuming that all reproductive responsibility (and biologic risk) is held by women. Although many assume men are not interested in or supportive of family planning and contraceptive usage, most recent research shows that this is untrue.[4] Men's preconception care should encourage men to positively influence their own and their partner's contraceptive decision making.

Second, improving men's preconception health can result in improved pregnancy outcomes by enhancing men's biologic and genetic contributions to the pregnancy conception. Sperm DNA can get damaged in many ways, including exposures to tobacco, alcohol, drugs (eg, anabolic steroids), caffeine, poor diet, radiation and chemotherapy, and testicular hyperthermia. Medical conditions such as diabetes mellitus, varicoceles, and epididymitis, if left untreated, can also reduce sperm count and quality. A growing number of xenobiotics, including 1,2-dibromo-3-chloropropane, nonylphenol, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), dioxins, phthlates and acrylamide, have been shown to cause oxidative stress and DNA damage to the sperm. Such damage usually results in infertility, subfertility, or spontaneous abortions. However, pregnancy may still be possible despite some degree of DNA damage, and can result in birth defects and even childhood cancers. Because new sperm is made every 42-76 days, damaged sperm can be replaced within 3 months of mitigated exposures. Thus, preconception care offers a window of opportunity to improve sperm quality.

Third, preconception care for men can result in improved reproductive health biology for women. Preconception care for men offers an opportunity for

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screening and treatment of sexually transmitted infections (STIs), including gonorrhea, syphilis, human immunodeficiency virus (HIV), and others, as well as environmental toxins. STI treatment of women only, without treatment of their partners, is doomed to failure. Preconception care also provides the opportunity to address men's behaviors that might result in undesired and unplanned pregnancies, including intimate partner violence, rape, drinking/drug usage, and multiple sexual partners, among others. Violence against women prevention programs have proven beneficial, albeit limited in number and evaluative quality.[1]

Fourth, preconception care for men can result in improved reproductive health practices and outcomes for women. Men can be a vital source of support or stress for women during pregnancy, birth, and parenting. Men often play a controlling/gatekeeper role in decisions around prenatal care, delivery services, and other health-seeking behaviors. While paternal permission for access to modern reproductive health services is not a major issue in the US, this is not true all over the globe. Men also play important roles in fostering or discouraging important maternal health behaviors such as smoking, drinking, physical fitness, and healthy nutrition. Women who live with a smoking partner, for example, are less likely to reduce smoking than women who live with a nonsmoking partner,[5] not to mention the impact of secondhand smoke on the developing fetus. Men's preconception care therefore offers an opportunity to promote male support of women's positive reproductive health and health care-seeking practices.

Fifth, preconception care for men can result in their own improved capacity for parenthood and fatherhood. Men have critical roles to play as a parent during pregnancy and post childbirth to ensure healthy families and children. Men's maturation to be an effective parent (and even to be present) should begin with preconception care. There is a great deal of literature on men's development and men's conceptions of their roles in parenthood, which heretofore has not usually been conceived of as starting in the preconception period, but could and should be. Efforts to address gender and development, including programs to change men's (and especially adolescent men's) social or gender norms, can be conceptualized as men's preconception health programs. Male understanding of his roles and responsibilities as a parent has the capacity to evolve over the course of prepregnancy, pregnancy, and birth.

Sixth, preconception care can be a venue for enhancing the health of men through access to primary health care. A man's health is an issue of importance both for himself and for his capacity to be a parent. Topics such as paternal depression, smoking behavior, physical fitness, nutritional status, etc, all impact on his own health and his parenting/spousal responsibilities. Increasing obesity, for example, is directly associated with increasing male infertility.[6] Preconception care offers an opportunity for disease prevention and health promotion among men, similar to the opportunity among women—that can have an impact on his lifetime health and the nation's reproductive health overall.

As defined by the CDC Select Panel, preconception care is a set of interventions that aims to identify and modify biomedical, behavioral, and social risks to women's health or reproductive outcomes through prevention and management. This definition can be applied to preconception care for men if the focus is changed from "women's health" to "men's health." The basic components of preconception care for women consist of 1) risk assessment, 2) health promotion, and 3) clinical and psychosocial interventions. A model framework of the content of preconception care for men, which can be applied in clinical practice, is outlined below.

Risk Assessment

The primary objective of risk assessment is to identify ongoing problems that need to be addressed.

Reproductive life plan

Risk assessment begins with evaluation of the couple's reproductive life plan. As defined by the CDC, a reproductive life plan is a set of personal goals about having (or not having) children based on personal values and resources, and a plan to achieve those goals. The patient is queried as to whether he plans to have any (more) children, and how long he and his partner plan to wait. If they plan to wait less than a year, the patient should return for a full preconception assessment. If greater than a year, the patient should continue to receive recommended age-appropriate preventive health services, but the provider should make sure that he and his partner are using effective contraception, and update their reproductive life plan at every routine visit.

Past medical and surgical history

The provider should inquire about the patient's past medical and surgical history, including any ongoing medical conditions that may impair his reproductive health. Several medical conditions have been associated with reduced sperm quality, including obesity, diabetes mellitus, varicocele, and sexually transmitted infections. In men with diabetes mellitus type 1, it has been demonstrated that semen volume, motility, and morphology are all significantly lowered compared to controls; furthermore, diabetic men with unsatisfactory glycemic control had lower sperm count, motility, velocity, and viability characteristics than men with satisfactory glycemic control.[7] In terms of male reproductive function, diabetes can affect more than just sperm quality: in a study of 541 diabetic patients, 35% reported erectile dysfunction, with associations found between impotence and age, retinopathy, peripheral and autonomic neuropathy, and treatment with either insulin or an oral medication.[8]

Medications

The patient's past and current medication use, including prescription, nonprescription and herbal products, should be reviewed. A number of medications can affect sperm count and quality, including alkylating agents, calcium channel blockers, cimetidine, colchicine, corticosteroids, cyclosporine, erythromycin, gentamicin, methadone, neomycin, ni-

trofurantoin, phenytoin, spironolactone, sulfasalazine, tetracycline, and thioridazine. Any medication use, including over-the-counter medications, should be guided by a risk-benefit calculus weighing benefits for men's health against known or potential risks to offspring.

Family history and genetic risks

Genetic risk assessment should be based on family history, paternal age, and ethnicity. A 3-generation family history of genetic disorders should be obtained, as certain disorders (sex-linked or autosomal recessive) may skip generations. A number of genetic disorders, such as cystic fibrosis, Klinefelter syndrome, Kartagener syndrome, and polycystic kidney disease, may impair fertility and sperm quality. In a review article on Klinefelter syndrome, the study authors collected data consistent with symptomatic azoospermia, and only 8.4% of their adult patients had spermatozoa in their ejaculate, out of the 69.3% of their population that were willing and able to provide an ejaculate sample.[9] A small study of pre- and peripubertal boys with Klinefelter syndrome found that half (7) of the subjects had no spermatogonia; this study also found an association between the beginning of puberty and loss of spermatogonia.[10]

In an early study of adult men with cystic fibrosis, all patients examined had azoospermia. The study authors also pointed to a high number of abnormal sperm forms seen.[11] Obstructive azoospermia of males with cystic fibrosis is due to a condition known as congenital absence of the vas deferens.[12,13]

Discussion of paternal age-related decline in sperm quality may help inform the couple's reproductive life planning, as many men are not aware of the growing body of evidence linking paternal age to schizophrenia in the offspring. In a Swedish cohort study, the offspring's risk for schizophrenia had a hazard ratio of 1.47 for each 10-year increase in paternal age, even after adjustment for familial schizophrenia history, socioeconomics, birth exposures, and early parental death.[14] Another cohort study revealed that the relative risk for offspring with schizophrenia increases with every 5-year increase in paternal age, culminating in fathers of 50 and over having an adjusted relative risk of 2.96.[15] Furthermore, these authors indicated that for fathers 30-35 years, 1 out of 99 offspring are estimated to have schizophrenia, compared to 1 out of 47 for fathers aged 50 or older.

If the patient belongs to an ethnic group at increased risk for certain genetic disorders (eg, Ashkenazi Jews, African Americans, Southeast Asians, and Mediterranean), the provider should screen the patient if his partner's genetic screen is positive or unknown. For mixed couples, the partner at increased genetic risk based on ethnicity should be screened first.

Social History

The patient's social history, including potential occupational exposures, should be reviewed. Ongoing exposures to metals, solvents, endocrine disruptors, and pesticides at work can impair sperm quality, which may lead to infertility, miscarriage, and birth defects. The patient may obtain a copy of the Material Safety Data Sheet (MSDS) of any chemical exposure at work from his employer, for review for potential reproductive toxicity.

Risk Behaviors

The patient's major and potential risk behaviors, including tobacco, alcohol, drug use, and hobbies, should be reviewed.

Tobacco use has been associated with decreased sperm count and abnormal sperm morphology, motility, and fertilizing capacity. Recent evidence suggests that nicotine and other chemicals in cigarettes can also induce oxidative damage to sperm DNA.

The effects of alcohol use on sperm quality are unclear. Some studies have shown that moderate drinking may be protective against DNA damage, perhaps in part due to the antioxidant effect of some alcoholic beverages.[16] Other studies have shown that alcohol may be damaging to sperm DNA. The data are clearer on heavy drinking (> 2 drinks a day). In a study of alcoholics in an addiction treatment center, testosterone level, semen volume, sperm count, and the number of sperm with normal morphology and motility were lower among alcoholic than nonalcoholic men.[17] The CAGE questions can be easily used to screen for alcohol abuse.

Several recreational drugs have also been linked to male infertility, including marijuana, cocaine, and anabolic steroids. Marijuana has been shown to reduce testosterone production, sperm count, and semen quality. Cocaine has also been associated with decreased sperm count and abnormal sperm morphology and motility, and the effects can linger for up to 2 years from last use. Anabolic steroids can also reduce testosterone level and sperm quality. In a small study of 15 men who were using anabolic steroids, 11 had low testosterone level and 9 had no sperm production at all. Even after quitting, only 2 men resumed normal sperm production.[18]

A study of anabolic steroid use in bodybuilders and semen quality found that compared to a control group, the group of men using steroids exhibited lower sperm concentration and a lower amount of morphologically normal spermatozoa.[19] Patient steroid abuse gives the physician potential for positive intervention, as a study of 18 anabolic androgenic steroid and human chorionic gonadotrophin (HCG) users demonstrated that the mean sperm concentration more than doubled 6 months after cessation of steroid use.[20] This study also showed that the percent of spermatozoa with abnormal morphology was positively correlated with cumulative HCG dose taken.[20] CAGE questions can also be used to screen for recreational drug use.

Certain hobbies may expose the patient to reproductive hazards. Hobbies that involve refinishing furniture, repairing cars, painting, building models, or anything that requires the use of strippers, degreasers, or nonwater-based glues or paints may expose the patient to organic solvents. Hobbies that involve painting, pottery, making stained glass windows, or handling, shooting, or cleaning guns may expose the patient to lead or other heavy metals.

Nutrition

Nutritional screening should review current dietary patterns and use of restrictive diets. Both zinc and folate have antioxidant properties that counteract reactive oxygen species (ROS) and protect sperm against oxidative stress and DNA damage. In a randomized controlled trial of 99 fertile and 94 subfertile men, daily administration of 66 mg zinc sulfate and 5 mg folic acid significantly increased sperm concentration of the subfertile men, suggesting the importance of multiple nutrients impacting fertility; the study authors also found an increase in median percentage abnormal forms from 80-84%.[21] A study of 33 subfertile men from a male infertility clinic who received an intervention consisting of twice daily oral 220 mg zinc sulfate for 3 months significantly increased mean percentage progressive and total motility of sperm.[22] In a randomized controlled trial giving 250 mg zinc sulfate 2 times per day, investigators found that for asthenozoospermic men, 3 months of zinc therapy yielded increases in progressive motility of sperm, sperm count, and sperm membrane integrity, while decreasing percentage of nonmotile sperm.[23] An early study in which normospermic and oligospermic men were given 10 mg folic acid 3 times a day for 1 month found that treatment resulted in no change in sperm characteristics.[24]

Other antioxidants have also been used to treat male infertility, including vitamin C, vitamin E, selenium, glutathione, ubiquinol, carnitine, and carotenoids. However, the safety and efficacy of such treatments have not been clearly established. In 1 study, the combination of vitamins C and E at high doses resulted in sperm DNA damage in vitro, raising concerns about the potential harms of high-dose antioxidant supplementation.[25]

Mental Health

Routine screening for mental health disorders should be performed. Estimates of lifetime risk of major depression for men range from 1.4% in the Epidemiologic Catchman Area to 11% in the National Comorbidity Study. Recent evidence suggests that depression of the father during the postnatal development of their child was found to be significantly associated with poor childhood emotional and behavioral outcomes, even after adjusting for maternal depression and paternal depression during a different developmental stage of the child[26]; such long-term detriments can be averted with identification and referral of at-risk fathers-to-be for mental health services. Furthermore, depressed fathers can have a negative impact on the mother-child interaction behaviors, and are less likely to engage in certain father-child interactions, such as playing outdoors with their children.[27] On the other hand, fathers with good mental health have been shown to reduce the impact of a mother's depression on the child.[28]

Physical Examination and Laboratory Testing

Physical examination and laboratory testing should be guided by clinical history. For example, men at increased risk for sexually transmitted infections should be offered screening for HIV, syphilis, and other STIs. The United States Preventive Services Task Force (USPSTF) recommends screening all adult men for high blood pressure and obesity; men aged 35 and older for lipid disorders (as well as men aged 20-35 with diabetes, family history of cardiovascular disease or familial hyperlipidemia, or multiple coronary heart disease risk factors); men with hypertension or hyperlipidemia for type 2 diabetes mellitus; and men aged 50 and older for colorectal cancer.[29] Routine screening for testicular cancer in young men or prostate cancer in men aged 50 and older ($\geq$ 45 for men at increased risk, eg, African Americans or those with family history of prostate cancer) may also be considered.

Health Promotion

Healthy weight and nutrition

There is a national epidemic of obesity. In 2003-2004, 62.2% of men aged 20-39 were overweight or obese, categorized as having a body mass index (BMI) of 25 or higher.[30] Males who are overweight or obese have been associated with lower testosterone level, poorer sperm quality, and reduced fertility, compared to nonoverweight or obese men; the odds of infertility increases by 10% for every 20 lbs overweight.[6]

An important objective of preconception care is to achieve healthy weight before conception. Clinical guidelines have been established for the identification, evaluation, and treatment of overweight and obesity. Men should be encouraged to set weight loss goals, to develop a plan to reach those goals, and to exercise at least 30 minutes a day on most days of the week. A referral to a nutritionist and/or a structured weight loss program may be useful. After successful weight loss, the likelihood of weight loss maintenance is enhanced by a program consisting of dietary therapy, physical activity, and behavior therapy, which should be continued until pregnancy.

Stress reduction and enhancing resilience

The impact of chronic stress on men's cardiovascular health has been well demonstrated; much less is known about the impact of chronic stress on men's reproductive health. Stress can disrupt hypothalamic-pituitary-gonadal functions, resulting in decreased steroidogenesis and spermatogenesis. Stress can also increase susceptibility to infection and inflammation, which may cause oxidative damage to sperm. However, the literature on stress and semen quality has been inconsistent. Stress has been shown to negatively impact semen quality variables for in vitro fertilization (IVF) patients and patients visiting andrology clinics,[30-34] but has also been shown to have no impact on semen quality for these patients.[35] Weekly time at job and stress have been shown to negatively impact sperm quality variables for fertile men,[36] but job strain and stress have also shown no impact on sperm for infertile men[37] and men of unknown fertility.[38] In other studies of unknown male fertility, stress levels were not associated with variables of sperm quality,[39] but acute stress stemming from an event like a family death,[40] or physiologic, psychological, and overall stress levels can impact sperm quality variables.[41]

It appears prudent to recommend steps that promote stress reduction and resilience in the context of male precon-

ception care. Elements to consider include regular exercise, adequate sleep, and balanced nutrition. Programs or selected readings that enhance the patient's emotional intelligence, capacity for interpersonal communication, and positive mental health should be helpful as well. As is recommended for women, men should be screened for the adequacy of their social support systems. Activities that strengthen social support should be encouraged.

Inflammation and immunization

Chronic inflammation can cause oxidative damage to sperm. Sources of chronic inflammation include chronic, untreated infections such as periodontal disease or STIs, stress, diet, and xenobiotics. Screening for such disorders or exposures should be included as a routine part of health promotion during preconception care.

The immunization status of men should be reviewed as part of a preconception evaluation, and appropriate vaccines should be offered. Immunization recommendations are updated annually by the CDC, the American College of Physicians (ACP), and the American Academy of Family Physicians (AAFP).

Avoidance of harmful exposures

An increasing number of environmental exposures, including phthlates (a type of plasticizer used in food-can linings and many household products), acrylamide (produced during frying, baking, and overcooking), and pesticides and dioxins, have also been shown to cause sperm DNA damage. According to the National Institute for Occupational Safety and Health, male reproductive health can be negatively affected by the following workplace exposures: lead, dibromochloropropane, carbaryl, toluenediamine, dinitrotoluene, ethylene dibromide, plastic production (styrene and acetone), ethylene glycol monoethyl ether, welding, perchloroethylene, mercury vapor, heat, military radar, kepone (in large doses), bromine vapor (in large doses), radiation (in large doses), carbon disulfide, and 2, 4-dichlorophenoxy acetic acid.[42] Additional substances have been identified as potential causes of male infertility, including chlordecone, beta-chloroprene, lead azide, lead II thiocyanate, manganese, manganese tetroxide, tetraethyl lead, and tetramethyl lead.[43] Physical exposures like heat, sedentary work positions, and radiation have the potential to affect male fertility, though the evidence supporting a direct effect remains unclear.[44]

Clinical and Psychosocial Interventions

The integration of preconception care into the ongoing primary care of women is an acknowledged challenge for the recommendations of the CDC's Select Panel. However, an even greater challenge will be to apply the science and principles outlined in this paper to the primary care of men. Even when adequate access and health insurance coverage are available, men do not often seek primary care for their own health promotion and disease prevention. Obstetricians-gynecologists and other clinical professionals providing primary care to women can help by encouraging the woman's partner to seek such care. Additionally, the clinical content of male preconception health care must be integrated into both graduate and continuing medical education for both family medicine and general internal medicine physicians.

Preconception care also offers an opportunity to address the psychosocial needs of men before pregnancy and parenting. Three types of psychosocial services should be made available to men during preconception care: 1) social services, 2) clinical support, and 3) partner and parenting support. Social services may include financial literacy training or assistance with job placement to help men get ready to start a family. The preconception care visit can offer a platform for accessing these services. Men who have mental health problems including depression could benefit from some forms of psychological support and therapy. Many men can use some guidance on how to provide emotional support to their partners, with emphasis on strengthening their capacities for communication and nurturance. Similarly, most men can use some lessons to help them prepare for fatherhood, and preconception is a good time to start.

Recommendation. In spite of the challenges and barriers, we recommend that each male, planning with their partner to conceive a pregnancy, should undergo a comprehensive medical evaluation for the purposes of disease prevention and detection, and preconception education. Management should be optimized for any high risk behaviors or poorly controlled disease states prior to attempting conception. *Strength of recommendation:* B; *quality of evidence:* III.

Conclusion

In this paper, we have outlined the key elements of a comprehensive approach to optimizing the preconception health status of men. Preconception care for men is important for improving family planning and pregnancy outcomes, enhancing the reproductive health and health behaviors of their female partners, and preparing men for fatherhood. Most importantly, preconception care offers an opportunity, similar to the opportunity it presents for women, for disease prevention and health promotion in men.

However, we recognize that to improve preconception health and health care for men in the US, significant barriers must be overcome. Issues that need to be addressed include organization, financing, training, and demand. There is currently no consensus on service delivery of preconception care for men—who should provide preconception care to whom, where, when, and how. To ask busy clinicians to provide preconception care to men at every visit ("every man, every visit") may not be feasible, and some components of preconception care may not be indicated or appropriate for every man at every visit. Furthermore, preconception care for men is not currently a billable diagnosis under most health plans. Many clinicians who provide care to men are not trained to provide preconception care; most obstetricians-gynecologists are not trained to provide care for men. As a starting

point, each couple seeking infertility services should be encouraged to have the male partner medically evaluated by either a urologist or reproductive endocrinologist with an interest in andrology.

Perhaps the most difficult issue is a social marketing one. Men are notorious about not seeking preventive and primary health care. In order to make preconception care for men relevant to every man, targeted health messaging, the buy-in of partners and peers, cultural competency, and appropriate language will be critical. Further evidence is needed on how to effectively market and implement preconception care for men. Additionally, much more research is needed on men's preconception health; research in this newly identified area is virtually nonexistent. ■

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The clinical content of preconception care: environmental exposures

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Environmental origins of disease risk and harm to health have been increasingly acknowledged for numerous outcomes, in both adult and pediatric populations. Adverse reproductive and developmental effects have also been linked to environmental exposures. In addition to the current queries about a patient's alcohol and smoking history, key determinants of a future pregnancy outcome should also be elicited during the preconception visit. These determinants include: (1) mercury intake via fish consumption; (2) nitrate exposure from well water sources; (3) exposure to chemical, physical, or biologic hazards on the job; and (4) lead and other toxic exposures—possibly from hobbies or the use of lead-glazed dinnerware in the home. Eliciting a detailed environmental history permits tailored recommendations to optimize the woman's health and that of her future pregnancy.

Key words: environment, exposure, lead, mercury, preconception

Links between environmental exposures and risk of disease or other health harm have been increasingly acknowledged for numerous outcomes ranging from cancer development to childhood asthma. Adverse reproductive and developmental effects have also been linked to environmental exposures. The Institute of Medicine (IOM) describes a patient's environment as comprising 3 sectors—the home, the community, and the workplace—wherein chemical and physical hazards may be encountered via various media such as contaminated soil, water, and air.[1,2] Although the American College of Obstetrics and Gynecology (ACOG) Ante Partum Record already includes environmental history queries regarding smoking and alcohol use,[3] a broader review of the patient's home, community, and work life must be added to gain a more complete picture. Diet history including fish consumption can be considered under the "home" environment and drinking water source under "community." Specifics of work duties and agents handled enable tailored recommendations to optimize the woman's health and that of her future pregnancy. Routine assessment of hobbies, habits, and home and work environments might identify exposures associated with adverse reproductive consequences that can be minimized during the preconception period. Although the effects on human pregnancy of many of the chemicals in occupational use are unknown, several classes of elements and compounds—such as heavy metals and organic solvents—have been implicated in a variety of reproductive disorders.

Recommendation. It is prudent to educate women for whom pregnancy is a possibility about environmental hazards, and to provide them with the facts available about the teratogenic potential or reproductive toxicity of any chemical or environmental agent to which they are exposed. *Strength of recommendation:* A; *quality of evidence:* III.

Mercury

National norms exist for mercury levels in both blood and urine collected during the National Health and Nutrition Examination Survey (NHANES) conducted by Center of Disease Control (CDC).[4] Measures of mercury exposure in women of childbearing age generally fall below levels of concern. Several scenarios, however, if elicited during history taking at the preconception visit, merit follow-up and possibly intervention. Exposure to methylmercury is of particular concern because it is a well-established human neurotoxin and the developing fetus is most sensitive to its adverse effects.[5-7] Methylmercury bioaccumulates through the food chain so that concentrations are highest in large predatory fish. Exposure occurs primarily through consumption of seafood, freshwater fish, and shellfish.[8-12] Thus, consumption of fish high in mercury, which has been organified and concentrated through the food chain and is found in highest concentrations in large game fish, is of concern during the preconception period. The 2004 United States Environmental Protection Agency (EPA) and the Food and Drug Administration (FDA) issued a joint consumer advisory regarding methylmercury in fish and shellfish, advising pregnant women, those likely to become pregnant, and those breastfeeding to avoid any consumption of shark, swordfish, King mackerel, and tile fish.[13] Other fish consumption (such as tuna) should also be limited but is allowed in up to 2 meals of 6 ounces each per week. Counseling about fish consumption is especially important in nonmeat eating patients and those who supplement a meager diet with fish that the family catches (subsistence fish eaters). The National Academies of Science's IOM has issued a more recent recommendation on seafood con-

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sumption,[14] updating the 2004 EPA/FDA advisory. Generally, the IOM agrees with the EPA/FDA advisory but is a bit more cautious with portion size recommendations for pregnant women, those who could become pregnant, and those breastfeeding, stating that a "reasonable intake" of fish with lesser mercury content is 2 meals weekly of 3 ounces each (a typical can of tuna contains 7 ounces), but the 12-ounce total intake recommended by the EPA/FDA advisory can be "safely consumed."

Active controversy regarding dietary sea food limitation reigns in the literature due to the documented benefit of essential fatty acids in the maternal diet to both mother and the fetus.[15] A reasonable approach here is to recommend alternative sources of dietary fatty acids such as purified fish oil.

Recommendation. Women of childbearing age who may become pregnant should avoid consumption of shark, swordfish, King mackerel, and tile fish. Other fish consumption (such as tuna) should also be limited but is allowed in up to 2 meals of 3 ounces each per week. Many state government agencies issue fish advisories and bans relating to mercury concentration in locally caught fish. In addition the maternal diet may be supplemented with essential fatty acids from nonseafood sources. *Strength of recommendation:* B; *quality of evidence:* III.

Lead

Lead is a known neurotoxin, especially for vulnerable populations such as young children and the fetus. Lead is most commonly found in lead-based paint, occupational settings, and contaminated soil. Hobbies may also provide a source of lead exposure, as may use of dishes and pottery with lead glaze (see below). Exposures, even early in pregnancy can pose a risk to the fetus. Lead levels of 10-15 μg/dL may lead to central nervous system (CNS) damage; hydroceles; skin tags; hemangiomas, lymphangiomas, and undescended testicles in males; miscarriage; and stillbirth. Adverse effects of elevated maternal blood lead levels (BLLs) during pregnancy include spontaneous abortion, intrauterine fetal demise, premature delivery, intrauterine growth restriction, and postnatal neurologic sequellae.[16] About 0.5% of childbearing-age women in the United States overall may have blood lead levels exceeding 10 mcg/dL.[17] In 1996, blood lead surveillance of women aged 18-45 years old in New York State found that 2% of BLLs exceeded 10 mcg/dL. Although there is no documented safe threshold for BLLs, the adverse effects of antepartum lead levels on the fetus in the range typically found in the United States have not been established. It is also difficult to interpret BLLs in pregnancy because of the potential for hemodilution and the frequent presence of coexisting anemia.[18] This, however, does not preclude measuring the BLL in a preconception or pregnant patient who gives a history suggestive of past or current exposure. The history of present or remote past exposure to lead suggests the need for a BLL and for monitoring of this level if found to be elevated during pregnancy and while breastfeeding.[19] This is due to the mobilization of lead stores from bone during pregnancy and lactation. Lead in breast milk is passed to the feeding infant, as well. If lead levels are elevated, calcium dietary supplements may minimize lead mobilization modestly,[20] and consultation with an occupational medicine specialist is reasonable to assist with management. Risk factors for lead exposure include occupational risks and home renovation. Lead may also be found in some cosmetics, especially from sources outside the United States.[21] The most common categories for occupational exposure include precision production, crafts, and repairs. A study from the New York City Health Department reported on incident BLLs $>$ 20 mcg/dL between 1996 and 1999 ($n = 33$), and found that levels were inversely associated with maternal age and length of time in the United States, and directly correlated with gestational age and pica behavior.[22]

How detectable is the condition? Prevention strategies for childhood lead poisoning include the identification of at-risk pregnant women. The CDC recommends the use of a questionnaire to assess children's risk of lead exposure; this questionnaire has been successfully adapted for use in pregnant women.[23] The New York State Health Department has used questionnaires and BLLs as part of routine screening in pregnancy since 1995.[24] Other states have subsequently adopted their approach.

How effective are the current treatments? Treatment such as chelation has been reported in pregnancy[25] but is reserved only for symptomatic women with very high levels of lead in their blood.

Impact of preconception care: For women of childbearing age who are not pregnant, no recommendations and little data exist. A risk-assessment questionnaire that incorporates questions about potential lead exposure may be useful in identifying areas of risk reduction for further counseling. Recommendations for women with affirmative responses should include screening of any children in the household, education about methods of environmental cleanup, removal from the exposure source, and nutritional counseling—such as increasing the amount of iron and calcium in the diet—to reduce absorption of ingested lead. These recommendations have been extrapolated from pediatric data and are not promoted by national organizations nor studied in this population.

Recommendations by other groups: No national organizations currently recommend screening pregnant women for elevated BLLs. The United States Preventive Services Task Force recommends against routine screening for elevated BLLs in asymptomatic pregnant women.[26]

Recommendation. There is insufficient evidence to recommend that all women should be screened for elevated lead for the purpose of improving perinatal outcomes. However, women exposed to high levels of lead or with a history of known high lead levels, including childhood lead poisoning, should be counseled on the risk of lead to the unborn child. For women with a history of high BLLs, it is reasonable to test the BLL and, if elevated, to initiate activities to lower the levels before conception. *Strength of recommendation:* C; *quality of evidence:* II-2.

Soil and water hazards

Hazards encountered in the soil, water, or air often originate from a current or former industrial source. Polluted sites that are tracked on the US EPA's National Priority Listed (NPL) site program[27] generally do not result in human health effects to the wider community but may threaten residents of a home in close proximity by allowing for soil or drinking water contamination. Although not uniformly true, many residents know when they are living near an NPL or toxic waste site. Documentation of chemical intrusion into soil or drinking water can be obtained from local health departments. Another community-based environmental hazard is the patient's source of drinking water. If the source of water is a private well, documentation of water quality should be sought. Private wells are not regulated for water quality by the EPA, in contrast to public water sources. Several reports of adverse pregnancy outcomes have been attributed to contaminated well water.[28]

Recommendation. During preconception visits, women should be asked if their well water has ever been tested or if there have been questions about their municipal water quality in the past. Any possible water quality problems should be investigated by the local health department and, if concerns are identified, women should use alternative sources of water for drinking and cooking. (Note: avoidance of water bottled in containers containing Bisphenol A [BPA], identified by the number 7 on the bottom of the bottle, is prudent) (see below). Depending on the contaminant and its concentrations, alternative locations for bathing may also be required. *Strength of recommendation:* B; *quality of evidence:* III.

Although not derived from the ambient environment, dietary exposure to BPA from canned food liners or water bottles is an emerging hazard generating conflicting recommendations from public health agencies. BPA, a high production (by volume) organic chemical compound with estrogenic properties is used as a building block of hard (polycarbonate) plastics and epoxy resins used in some food and drink containers. Recently the Center for the Evaluation of Risk to Human Reproduction (CERHR) of the National Toxicology Program issued a report based on an evaluation of the state of science regarding BPA. Although based largely on animal evidence, mechanisms of toxic action of BPA are shared with humans and the doses at which outcomes were observed occurred at those seen in humans. The NTP therefore issued a statement voicing "some concern" for effects on the brain, behavior, and prostate gland when the fetus, infants or children are exposed at current human exposure levels to BPA. They also determined there is "minimal concern" for effects on the mammary gland and an earlier onset of puberty for females exposed or fetuses, infants, and children at current human exposures to BPA.[29] Prudent practice would therefore suggest avoidance of exposure. This is accomplished by avoiding canned food packed in epoxy (white plastic container liners) and bottled water with the number 7 stamped on the bottom.

During the preconception visit women should be advised about BPA avoidance in their diet. *Strength of recommendation:* B; *quality of evidence:* II.

Workplace exposure

The workplace represents the principal opportunity for exposure to environmental reproductive or developmental toxicants. Although some chemicals are regulated by public health agencies, the majority of chemicals considered for regulation are not evaluated for reproductive endpoints. Therefore, many chemicals with unambiguous reproductive or developmental effects are still in regular commercial use and thus pose a risk to women before pregnancy. Several employment sectors with such toxicants in common use—including laboratory and clinical healthcare, printing, and dry cleaning—employ women in large numbers.[30] Healthcare especially presents exposure opportunities to undisputed reproductive and developmental toxicants, including hazardous anticancer and antiviral agents.[31] Aspects of other industrial sectors, including the use of pesticides and herbicides in the agricultural sector, the use of solvents and heavy metals in the manufacturing sector, and the use of solvents and inks in the printing sector, also present potential risks to underprotected workers. An initial evaluation of a patient's job-related exposures can be obtained by screening questions regarding employment and job sectors.[19,32] If there is a potential chemical, biologic, or physical agent hazard identified, then a more detailed assessment can be made by asking about frequency of exposure, duration, timing, and exposure route (inhalation, dermal contact, or ingestion). This assessment should include questions about the use of additional protective apparel or the use of a respirator for some job tasks. However, there are some jobs in which both governmental safety and health agencies and professional organizations recommend alternative duty (ie, different job duties without exposure to hazards of concern) for pregnant workers or those actively trying to conceive,[33] such as nurses who handle cancer chemotherapeutic agents[34] and workers with organic solvent exposure.[35] The work of the patient's partner should also be inquired about as secondary contamination of the household or maternal exposure opportunity is posed during laundering of work clothes.[36]

Recommendation. During preconception visits, women should be asked about the work environment. If potential exposures are identified, consultation with an occupational medicine specialist may assist in carrying out a more detailed investigation regarding recommendations for work modification. *Strength of recommendation:* B; *quality of evidence:* III.

Household exposures

A woman's residential activities and hobbies pose potential risks for her before pregnancy. Hobbies of concern include those involving solvents such as oil-based paints; heavy metals, such as lead, which are used in stained glass work; and paint-stripping agents that often contain methylene chloride, which metabolizes to carbon monoxide and can be toxic to the fetus.[37] Jewelry mak-

ing and metal tempering can involve the melting and soldering of metals and should also be avoided. Pesticides, herbicides, and rodenticides are among the chemical hazards most likely to be encountered in the home. Application of any of these should be avoided by the preconception patient. A home may be secondarily contaminated by a family member's soiled work clothes and shoes that are brought home and contain pesticides or other toxins. Painting projects with nonlatex-based paints that are solvent based and contain metals for pigment and antifoulant agents, common in exterior paints, should be avoided. Some home-rehabbing projects are also potentially hazardous. The use of heat guns to remove old paint and wallpaper from walls containing lead-based paint should be avoided.

Recommendation. During preconception visits, women should be asked about the home environment. If potential exposures are identified, consultation with an occupational medicine specialist may assist with a more detailed investigation regarding recommendations for modifying exposures. *Strength of recommendation:* A; *quality of evidence:* III.

Conclusion

Elements of the environmental history elicited during the preconception visit may identify key determinants of a future healthy pregnancy. Three sectors of a woman's environment—the home, the community, and the workplace—should be asked about to identify hazards to the pregnancy outcome. The workplace represents the principal source of exposure to toxicants with unambiguous reproductive and developmental effects. These toxicants are often found in industry sectors, such as healthcare, in which many women work. A woman's diet and drinking water source, as well as her hobbies, may also pose a threat to the pregnancy. Exposure opportunities identified in the preconception visit may allow tailored recommendations to be made to the patient to modify exposure and thus reduce the risk of an adverse outcome. ■

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