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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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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