Master Class

Preeclampsia, Part 3

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The exact incidence of preeclampsia is unknown, but in its mild form it is estimated to affect up to 10% of all pregnancies. Indeed, it is one of the most common complications of pregnancy. In a smaller number of cases (just under 1% of pregnancies), the disorder develops as severe preeclampsia.

In the past two Master Class installments on preeclampsia, we have discussed how the disorder presents in various ways, afflicting women of different age groups, of varying parity, and with associated medical complications or the lack thereof.

We have also discussed appropriate evaluation and management protocols. The spectrum of disease is such that it spans the very mild (requiring modest intervention) to the very severe (requiring immediate and aggressive intervention strategies). As we saw in the last installment, it is important to view preeclampsia as a multifaceted disease continuum in which designations of "mild" and "severe" are not necessarily fixed.

The variable presentation of the disorder—and the fact that it cannot be precisely predicted or prevented—may in itself be challenging to the practitioner, as he or she counsels patients who are contemplating pregnancies and may be at risk for preeclampsia.

There are certain predisposing medical and sociodemographic factors, however, that are clearly important and that can be useful if they are integrated into an evaluation and management algorithm. Integrating our knowledge of risk factors allows for the most appropriate counseling to be delivered, and the most appropriate management plan to be developed, on a case-by-case basis.

I have invited Dr. Baha Sibai to once again address the topic of preeclampsia in this third and final installment of our series on the disorder. Dr. Sibai is professor of obstetrics and gynecology at the University of Cincinnati and an international expert on preeclampsia and eclampsia, as well as a leader in both clinical care and research in this area.

In this case, we've taken a different approach to presenting the material. We think our case-by-case format will be practical and applicable to the practitioner who is counseling a number of patients who present with varying histories and risk factors. ■

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Identify Patients at Risk Early

BAHA M. SIBAI, M.D.

Despite several decades of extensive research into its pathogenesis, preeclampsia continues to be a syndrome of unknown etiology.

Several theories on the mechanisms leading to preeclampsia have been proposed, all based on numerous pathophysiological abnormalities reported in association with the heterogeneous disorder.

These theories, which have been developed largely during the past 2 decades, involve abnormalities such as impaired trophoblast differentiation and invasion, placental and endothelial dysfunction, immune maladaptation to paternal antigens, an exaggerated systemic inflammatory response, and a state of imbalance between proangiogenic and antiangiogenic factors.

As evidence for these theories has unfolded, investigators have identified numerous risk factors for preeclampsia. Most of them are preexisting risk factors that can be identified either before a patient becomes pregnant or early in the pregnancy. (See box below.)

The disorder's pathogenesis can vary in women with different risk factors or different times of onset. In women with previous preeclampsia, for example, the risk for developing recurrent preeclampsia varies depending on the underlying mechanism and the outcome in the previous pregnancy.

What this means is that even as investigators work to improve our understanding of the disorder, we as clinicians have an immediate opportunity—and responsibility—to identify patients who are at risk for preeclampsia, or recurrent preeclampsia, during preconception counseling or early in gestation.

We can then work with at-risk patients to optimize their health before conception and to carefully manage maternal and fetal well-being during pregnancy.

Women with a history of previous preeclampsia—even those who suffered serious adverse outcomes—should be counseled about their risks and reassured about our ability to optimize outcomes through vigilant monitoring, early detection of complications, and timely delivery.

And in an effort to improve their long-term health, these women should also be counseled about an increased risk for cardiovascular disease and ischemic stroke later in their lives.

Risk Factors for Preeclampsia

Preexisting or Preconceptional Factors	Reported Risk
Chronic hypertension/renal disease	15%-40%
Pregestational diabetes	10%-35%
Obesity/insulin resistance	10%-15%
Connective tissue disease (lupus, rheumatoid arthritis)	10%-20%
Thrombophilia (acquired or genetic)	10%-40%
Age older than 40 years	10%-20%
Limited sperm exposure	10%-35%
Family history of preeclampsia or cardiovascular disease	10%-15%
Partner who fathered preeclamptic pregnancy in another woman	2-fold
Woman born as small for gestational age	1.5-fold
Adverse outcome in previous pregnancy (fetal growth restriction, abruptio placentae, fetal death)	2- to 3-fold

Source: Adapted from Obstet. Gynecol. 2008;112:359-72

Elsevier Global Medical News

Common Scenarios

A healthy 22-year-old woman with an ideal body weight and no preexisting medical risk factors who plans to become pregnant for the first time.

This patient's risk for preeclampsia is low (only 1%-2%). If preeclampsia occurs, it is likely to be mild, with an onset near term or intrapartum, and with generally good outcomes.

Nevertheless, it is important to inquire about any family history of preeclampsia or cardiovascular disease in this type of patient, and to be aware that women who themselves were born small for gestational age have an increased risk for preeclampsia, as does any woman whose husband or partner fathered a preeclamptic pregnancy in another woman.

Certain changes and events can also occur during pregnancy that will increase her risk. If, during antenatal care, ultrasound reveals multifetal gestation or unexplained fetal growth restriction, for instance, her risk of preeclampsia will increase substantially. (See box, page 9, top right.)

Likewise, if she develops gestational hypertension, her risk will increase to 25%-50% based on gestational age at the time the hypertension developed.

Several recently published studies have reported an association between maternal infections and an increased risk of preeclampsia as well. (Infections probably increase a maternal inflammatory response that already is engendered by the pregnancy itself.)

A systematic review published in 2006 found that the odds ratio for preeclampsia was 1.57 in women with urinary tract infections, and 1.76 in women with periodontal disease (N. Engl. J. Med. 2006; 355:992-1005).

Unfortunately, the various biomarkers that have been proposed to predict which women are likely to develop preeclampsia—from serum placental growth factor to asymmetric dimethylarginine—have not been shown to be reliable and are not predictive or specific enough for use in clinical practice.

Likewise, supplementation with fish oil, vitamin E, vitamin C, low-dose aspirin, or calcium is not recommended for the prevention of preeclampsia in the young woman with no risk factors.

A 42-year-old who is trying to become pregnant for the first time.

This patient's older age is itself a risk factor for preeclampsia. An older age also often means more body weight and a higher likelihood of chronic hypertension or diabetes, as well as an increased likelihood that donated gametes were used, all of which can significantly increase risk.

As in the case of the younger patient, risk evaluation and management should begin before conception. Family history, personal birth history, and the history of the patient's husband or partner should be explored.

And because a high body mass index is a proven risk factor—as is insulin resistance, which is often linked with obesity—patients who are overweight or obese should be encouraged to lose weight and achieve a healthy BMI.

The risks associated with preexisting medical conditions like hypertension and diabetes vary depending on the conditions' severity.

Studies show, for instance, that women with mild hypertension before conception or early in pregnancy have a 15% rate of preeclampsia, whereas women with severe prepregnancy hypertension have a nearly 50% risk.

In all cases, women with chronic hypertension or diabetes should have their blood pressure and glucose levels optimized before conception, and then controlled throughout their pregnancy.

When assisted reproductive technology is planned, a discussion about the increased risk for preeclampsia that is caused by donated gametes is important, because donor insemination or the use of donated oocytes affects the maternal-fetal immune interaction and increases the risk of preeclampsia to as much as 35%.

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Because multifetal gestation is more common with ART than with natural birth and is another risk factor for preeclampsia, this patient's overall risk can also be minimized by reducing the number of transferred embryos and by avoiding hyperstimulation when ovulation induction is required.

Just as in the case of the younger woman, unfortunately, we have little if anything else to offer this patient for the prevention of preeclampsia.

These women can be offered calcium, however. A recent review by the Food and Drug Administration concluded that any benefit with respect to preeclampsia is inconclusive and "unlikely" (Nutr. Rev. 2007;65:78-87).

However, in a 2007 Cochrane review of 12 clinical studies, calcium supplementation was associated with a reduction in the rate of preeclampsia, particularly in populations at high risk and in those with diets deficient in calcium (BJOG 2007; 114:933-43).

Management should include a baseline metabolic profile and complete blood count, as well as baseline urinalysis; this information can be helpful if later laboratory studies are needed to assess the function of organ systems likely to be affected by preeclampsia.

Serial ultrasonography as well as uterine Doppler studies at 18-20 weeks should also be employed. The Doppler studies are a useful tool for assessing the velocity of the uterine artery blood flow.

An increased resistance index and/or the presence of uterine artery diastolic notching suggests an increased risk of preeclampsia (as much as a sixfold increased risk) and the need for more vigilant monitoring and care.

How to Manage Recurrence Risk

Preconception

► Identify risk factors.
► Review outcome of previous pregnancy.
► Optimize maternal health.

First Trimester

► Perform ultrasonography for dating and assessing fetal number.
► Order baseline metabolic profile and complete blood count.
► Perform baseline urinalysis.
► Offer first-trimester combined screening.
► If antiphospholipid syndrome is documented, start low-dose aspirin and heparin. Otherwise, offer low-dose aspirin therapy at 12 weeks' gestation.

Second Trimester

► Monitor for signs and symptoms of preeclampsia.
► Perform ultrasonography at 18-22 weeks' gestation for fetal anomaly evaluation and to rule out molar gestation.
► Perform uterine Doppler studies at 18-20 weeks.

Third Trimester

► Monitor for signs and symptoms of preeclampsia.
► As indicated by the clinical situation, perform laboratory testing, serial ultrasonography (for fetal growth and amniotic fluid assessment), and umbilical artery Doppler with a nonstress test and/or biophysical profile.
► Hospitalize for severe gestational hypertension, fetal growth restriction, or recurrent preeclampsia.

Post Partum

► Counsel patient about an increased risk for cardiovascular disease and ischemic stroke.
► Encourage close follow-up and prevention.

Source: Adapted from Obstet. Gynecol. 2008;112:359-72

A woman who developed severe preeclampsia at 26 weeks' gestation in her first pregnancy. She wants a child but is afraid—terribly and understandably frightened—of a second pregnancy because her first baby was born prematurely and died after about 100 days in the NICU.

We can and should reassure this patient that her loss does not mean she should forego becoming pregnant again, and that with proper monitoring, she has a significant chance of having a healthy baby.

A woman's risk of preeclampsia recurrence will depend on whether or not she has any preexisting risk factors, as well as the gestational age at the time of onset of preeclampsia in her first pregnancy.

The reported rate of recurrent preeclampsia ranges from 11.5% to 65%, with the highest rates being reported in women whose previous preeclampsia occurred in the second trimester. This patient's risk of recurrent preeclampsia is about 50%.

In general, recurrent preeclampsia is more likely to be severe and to develop preterm than is first-time preeclampsia. We can reassure this patient, however, that an early onset of preeclampsia in the first pregnancy does not necessarily mean that the disorder will have an early onset in the second pregnancy.

In a study published in 1991, among women with previous preeclampsia in the second trimester, preeclampsia recurred in the second trimester in 21%, at 28-36 weeks in 21%, and at term in 23% (Am. J. Obstet. Gynecol. 1991;165:1408-12).

Women with a history of eclampsia have a rate of recurrence of 1%-2% and a rate of subsequent preeclampsia of 22%-35%. Women with a history of HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome have a rate of preeclampsia in subsequent pregnancies of 16%-52% and, according to the most reliable data, a rate of recurrent HELLP syndrome of less than 5%.

Management for this patient ideally begins before conception, with an extensive evaluation and an in-depth history to uncover preexisting risk factors and/or medical conditions associated with the disorder.

This will allow proper counseling about the magnitude of risk for preeclampsia recurrence, and will guide you as you manage the pregnancy. (See box, bottom left.)

Knowing when she developed preeclampsia is important, as are details about maternal complications such as HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome, pulmonary edema, or renal failure, for instance; about fetal complications, such as fetal growth restriction; and about previous laboratory test results, as well as placental pathology.

The status of any comorbidities, such as high BMI or high blood pressure, should be optimized before conception, and vigilant monitoring—including early and serial ultrasonography, uterine Doppler assessment at 18-20 weeks, and laboratory testing as indicated—should be instituted to minimize and manage her risk.

By detecting complications early and monitoring for signs and symptoms of preeclampsia—and then hospitalizing her if you detect severe gestational hypertension, fetal growth restriction, or recurrent preeclampsia—you can ensure optimal outcomes.

This patient will probably want to know about the value of various biomarkers and supplements, such as fish oil and vitamins C and E, and again, we need to explain that the best studies have shown minimal to no benefit and do not support their use.

The three large randomized trials looking at vitamin E supplementation, for example, showed no effect on the rate of preeclampsia, its severity, or the rate of adverse neonatal outcomes.

None of the randomized trials on calcium supplementation included women with a previous history of preeclampsia, so the benefit for this indication remains unclear. Nevertheless, because calcium is beneficial for any pregnancy, we recommend it.

The greatest benefits of low-dose aspirin may come for this patient. A recent meta-analysis of 31 randomized trials found a 14% reduction in recurrent preeclampsia—higher than that seen for first-time preeclampsia (Lancet 2007; 369:1791-8). Low-dose aspirin has also proved to be safe. We recommend 81 mg daily beginning at 12 weeks' gestation, and suggest discontinuing aspirin with the development of preeclampsia.

If the patient has documented evidence of antiphospholipid antibody syndrome, she should receive prophylactic-dose heparin in addition to low-dose aspirin once fetal viability is confirmed.

A woman who had late-occurring mild preeclampsia in her first pregnancy, and is planning a second child.

This patient experienced the most common presentation of preeclampsia, and fortunately has a fairly low risk for recurrence (about 10%). Chances are also likely that if preeclampsia recurs, it will recur at term.

This risk can be minimized and a good outcome ensured by following the same approach to history taking, counseling, and optimizing health before conception, as well as careful monitoring during pregnancy to detect complications early.

Risks Later in Life

Today, counseling women with a history of preeclampsia involves more than assessing and minimizing risks for recurrence of the disorder. It also involves discussing the now-substantial body of literature that suggests that women whose pregnancies are complicated by preeclampsia and/or fetal growth restriction have an increased risk for future cardiovascular disease and ischemic stroke.

These women require close follow-up after their pregnancies so that their long-term risks can be reduced or avoided through the use of preventive strategies and approaches to care.

Preeclampsia and fetal growth restriction are both vascular-related pregnancy complications, and they share similar risk factors and pathophysiological abnormalities, such as endothelial dysfunction.

It's unclear exactly what mechanisms account for the relationship among these complications and the increased risk of subsequent cardiovascular disease, but it increasingly seems likely that these women have a predisposition to vascular and metabolic disease: a constitutional risk.

Epidemiologic and case-control studies published in the last 10 years—many of them in the nonobstetric literature—have evaluated the associations, and last year a systematic review and meta-analysis of these studies reported a relative risk for chronic hypertension of 3.7 after approximately 14 years of average follow-up, a relative risk of 2.16 for ischemic heart disease after about 11 years of follow-up, and a relative risk of 1.8 for ischemic stroke after about 10 years (BMJ 2007;335:974-85).

In addition, overall mortality after preeclampsia was increased by a relative risk of approximately 1.5 after 14.5 years of follow-up.

In a recently published intergenerational case-control study, Dutch investigators looked at 106 women whose pregnancies were complicated by preeclampsia or fetal growth restriction, a control group of 106 women with normal pregnancies, and each woman's mother and father.

They found significant intergenerational similarities in cardiovascular risk profiles between the women after preeclampsia or fetal growth restriction and their parents, such as higher fasting glucose levels that could not be explained by differences in BMI.

Intergenerational similarities were also found for hypertension, waist circumference, and metabolic syndrome (Hypertension 2008;51:1034-41). ■

Risk Factors for Preeclampsia

The magnitude of risk depends on the number of factors, which include the following:

► Multifetal gestation.
► Unexplained fetal growth restriction.
► Gestational hypertension.
► Hydrops/hydropic degeneration of placenta (triploidy, trisomy 13).
► Urinary-tract and periodontal infections.
► Biophysical and biochemical markers.

Source: Adapted from Obstet. Gynecol. 2008;112:359-72