REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Preeclampsia

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PREECLAMPSIA, WHICH COMPLICATES 2 TO 4% OF PREGNANCIES GLOBALLY, is progressive, unpredictable, and serious. It is associated with approximately 46,000 maternal deaths and approximately 500,000 fetal and newborn deaths annually.[1,2] The disease burden is borne disproportionately by women in low- and middle-income countries or who are otherwise disadvantaged. Much of the literature focuses on preterm preeclampsia, which accounts for up to one third of cases and is associated with a much higher risk of maternal and fetal or newborn complications than preeclampsia at term. However, a much larger number of women have term disease, which makes a substantial contribution to preeclampsia-related morbidity and mortality.

Antepartum care is devoted in large part to blood-pressure screening for hypertension and specifically preeclampsia. Maternal biologic and social risk factors for preeclampsia include certain demographic characteristics (e.g., membership in a minority racial or ethnic group), a history of medical or obstetrical disorders (e.g., chronic hypertension), certain characteristics of the current pregnancy (e.g., conception by means of assisted reproductive technology), physiological abnormalities (e.g., increased blood pressure), abnormal results of laboratory tests (e.g., severe anemia), and ultrasonographic abnormalities (e.g., an abnormal uterine-artery pulsatility index, measured by Doppler ultrasonography)[3] (Fig. 1). These risk factors align with the pathogenesis of preeclampsia, which involves uteroplacental mismatch, syncytiotrophoblast factors, and an imbalance of angiogenic factors, which lead to maternal systemic endothelial dysregulation and inflammation, a process similar to sepsis (Fig. 1).

Most cases of preeclampsia arise at term and are mild and transient and resolve soon after the delivery. However, 5 to 20% of women, especially those in whom preeclampsia arises well before term, have life-altering, life-threatening, or fatal complications. Systemic endothelial damage causes the generalized edema once considered to be a diagnostic criterion. Cardiovascular manifestations are related primarily to increased peripheral vascular resistance, which causes hypertension, despite decreased intravascular volume. With adjustment for factors affecting risk (e.g., maternal age and weight), cardiac output is normal, unless preeclampsia is complicated by peripartum cardiomyopathy. Pulmonary endothelial activation, neutrophil activation, and decreased plasma oncotic pressure increase the risk of pulmonary edema and acute respiratory distress syndrome. Severe hypertension, especially systolic hypertension, increases the risk of hemorrhagic stroke, and the combination of hypertension and endothelial activation can result in reversible ischemic encephalopathy in the posterior hemispheres (manifested as headaches, scotomata, and scintillations) and the seizures of eclampsia. Whether cerebral edema is a cause or consequence of eclampsia is unclear.

Renal involvement is most commonly manifested as proteinuria because of the pathognomonic lesion of glomerular endotheliosis and associated loss of podocyte

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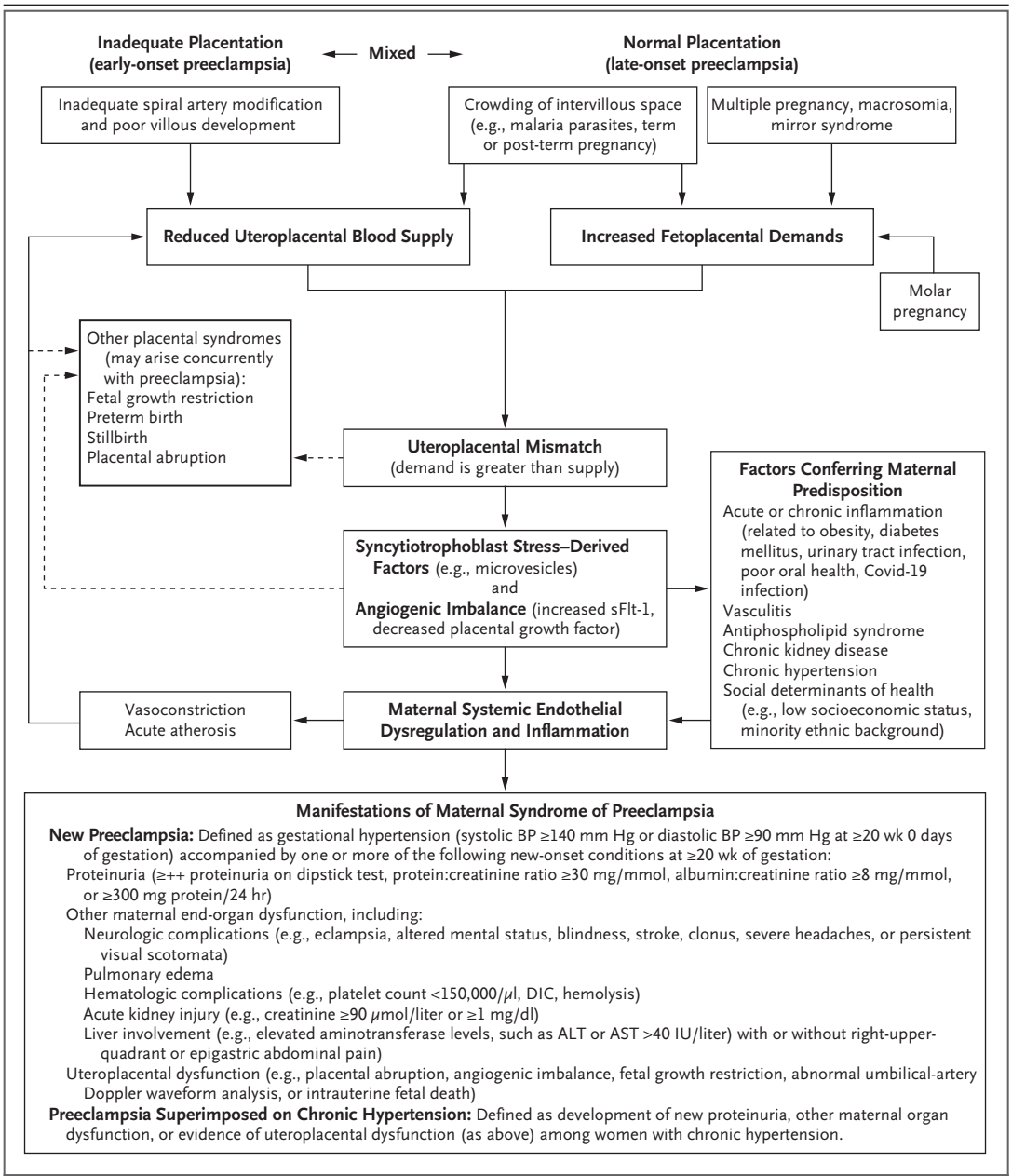


Figure 1. Pathogenesis of Preeclampsia.

Reduced uteroplacental blood supply, increased fetoplacental demands, or both result in uteroplacental mismatch. This leads to release of placental syncytiotrophoblast stress–derived factors (e.g., proinflammatory cytokines or placental debris) and an imbalance in circulating levels of proangiogenic placental growth factor and antiangiogenic soluble fms-like tyrosine kinase 1 (sFlt-1). Less severe perturbations in these factors will lead to clinical disease in women with maternal predisposition, as indicated. The result is systemic endothelial dysregulation, excessive systemic inflammation, and ultimately, maternal and fetal manifestations of preeclampsia. The dashed arrows indicate that these processes can also result in other placental syndromes, even in the absence of clinical manifestations of preeclampsia. The manifestations of preeclampsia are particularly likely to occur in women with a predisposition that is related to preexisting conditions (e.g., obesity, diabetes, and chronic hypertension). The "Mixed" annotation indicates that the pathogenesis types are not distinct or mutually exclusive. ALT denotes alanine aminotransferase, AST aspartate aminotransferase, BP blood pressure, Covid-19 coronavirus disease 2019, and DIC disseminated intravascular coagulation.

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integrity. When severe, these lesions can result in nephrotic-range proteinuria, acute tubular necrosis, and acute kidney injury.

Liver damage is characterized by periportal inflammation and hepatocellular damage (manifested as right-upper-quadrant or epigastric pain and transaminitis), subcapsular hematoma, and in rare cases, hepatic failure or rupture. Jaundice and hypoglycemia are rare and late findings, which distinguish preeclampsia from acute fatty liver of pregnancy.

Hematologic manifestations include relative hemoconcentration (unless hemolysis occurs), relative neutrophilia, microvascular thrombosis and hemolysis (manifested as an increased lactate dehydrogenase level), platelet consumption, and especially with placental abruption, disseminated intravascular coagulation. Abruption probably results from ischemia–reperfusion injury in maternal uteroplacental vessels.

Fetal manifestations are not uniform and include both fetal growth restriction (as a result of inadequate placentation, usually with early-onset preeclampsia) and macrosomia (as a cause of uteroplacental mismatch, often with late-onset preeclampsia). Both early-onset preeclampsia and late-onset preeclampsia are associated with increased perinatal risks.

Here we review the current understanding of preeclampsia, particularly findings published within the past 5 years. We focus on individualization and integration of concepts concerning the prediction, prevention, diagnosis, and management of preeclampsia during pregnancy and in the long term. Although some of the management strategies we discuss apply to women with chronic or gestational hypertension, our focus is on preeclampsia.

PREDICTION OF PREECLAMPSIA

The following two approaches are commonly used to identify women who are at increased risk for preeclampsia and who could benefit from preventive interventions: a traditional count of clinical risk factors and multivariable modeling of clinical, ultrasonographic, and laboratory assessment of uteroplacental perfusion and function. Although each approach is usually applied in early pregnancy to identify women who can benefit from prophylaxis with low-dose aspirin, assessment later in pregnancy may identify women who could benefit from enhanced surveillance and timed birth.

Traditional screening for the risk of preeclampsia is advocated by most clinical practice guidelines.[4] This approach involves an assessment of clinical risk factors early in pregnancy; the risk factors are treated independently and summarized either without an indication of the level of risk or as a count of any factor that confers a high risk or one or more factors that confer a moderate risk.[5] This approach is simple, but the detection rate (i.e., the sensitivity) is low for both preterm preeclampsia (approximately 40%) and term preeclampsia (approximately 35%), with a positive screening rate (i.e., the screen-positive rate) of approximately 10%.[3]

Multivariable models have high detection rates when used at 11 to 13 weeks' gestation for preterm preeclampsia and at 35 to 36 weeks' gestation for term preeclampsia, with a positive screening rate of approximately 10%. The competing-risks model of the Fetal Medicine Foundation (FMF), which is supported by the largest body of evidence, comprises the components that are most commonly included in other models (i.e., maternal ethnic or racial background, body-mass index, blood pressure, ultrasonographic assessment of the uterine-artery pulsatility index, and angiogenic markers[6]). The FMF competing-risks approach is based on a survival–time model that incorporates a prior distribution of gestational age at delivery with preeclampsia, derived from maternal characteristics, with likelihood functions from biomarkers to estimate an individual woman's risk of delivery with preeclampsia before a specified gestational age (e.g., at <37 weeks).[3]

The internationally validated FMF model of maternal risk factors and biomarkers (i.e., blood pressure, uterine-artery pulsatility index as measured by Doppler ultrasonography, and serum level of placental growth factor) identifies approximately 90% of women at 11 to 13 weeks' gestation in whom early preeclampsia (at <34 weeks' gestation) will develop and approximately 75% of those in whom preterm preeclampsia will develop, with a positive screening rate of 10%.[3] Uterine-artery Doppler ultrasonography and placental growth factor assays are not performed routinely, even in well-resourced clinical settings. However, a two-step screening procedure can be undertaken, in which 70% of

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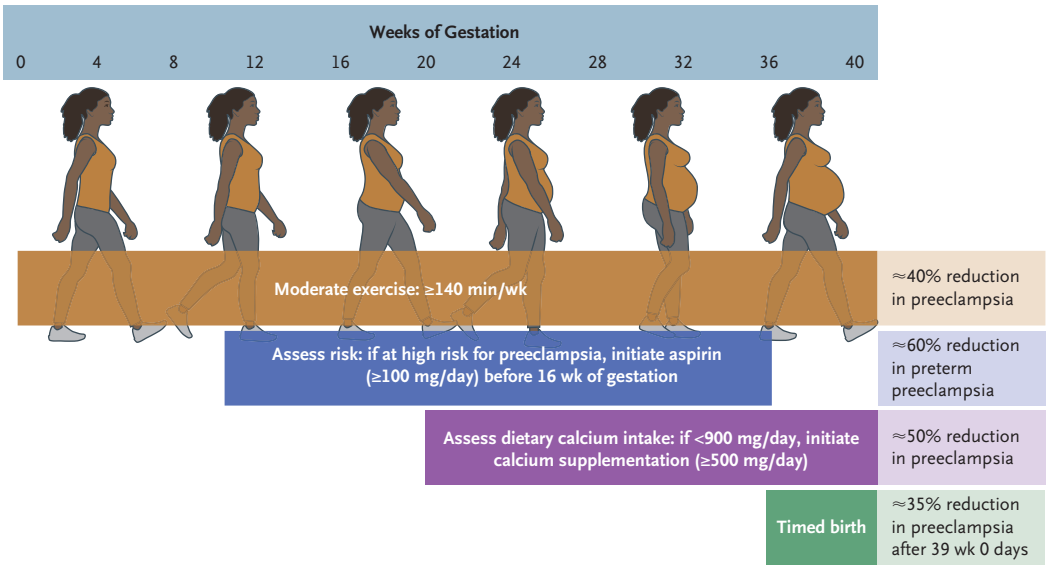


Figure 2. Prevention of Preeclampsia.

Pregnant women should be encouraged to exercise to reduce the risk of preeclampsia and for general health. Before 16 weeks' gestation, women at high risk for preeclampsia should be identified and offered aspirin (≥100 mg per day). Women in low-calcium-intake populations should be offered supplemental calcium, at a dose of at least 500 mg per day, in the second half of pregnancy. Low-risk nulliparous women benefit from labor induction during the 39th week of gestation, between 39 weeks 0 days and 39 weeks 4 days of gestation.

women who have positive screening results on the basis of maternal risk factors undergo second-stage screening (with ultrasound assessment and serum biomarker measurements), which results in a similar overall detection rate for preterm preeclampsia, at a reduced cost.[3] Black women and women of South Asian descent are more likely than women of other races or ethnic groups to require second-stage screening, but the detection rate for preterm preeclampsia among Black and South Asian women is higher (>95%).[3] If the first step in two-step screening includes either uterine-artery Doppler ultrasonography or a placental growth factor assay, then in the second step, measurement of placental growth factor or assessment of the uterine-artery pulsatility index can be reserved for only 30 to 40% of women.[3]

For the 90% of women identified as being at low risk for preterm preeclampsia at 11 to 13 weeks' gestation, rescreening during the second and third trimesters can refine the risk stratification and identify women who require closer monitoring. At the routine ultrasound scanning at 19 to 24 weeks' gestation, rescreening identifies almost all women in whom preeclampsia will develop by 32 weeks. At 32 weeks' gestation, rescreening identifies 90% of women in whom preeclampsia will develop at 32 to 35 weeks. However, only at 35 to 36 weeks' gestation is the prediction of term preeclampsia possible, with soluble fms-like tyrosine kinase 1 (sFlt-1) making an independent contribution[7]; this screening approach at 35 to 36 weeks' gestation identifies 75% and 85% of women in whom term preeclampsia will develop, with positive screening rates of 10% and 20%, respectively.

PREVENTION

Prevention of preeclampsia is a health care priority, given that only delivery of the placenta has been proved to initiate the resolution of preeclampsia once it has developed. Preventive therapies have been based on the pathogenesis of preeclampsia and focused on redressing angiogenic imbalance, endothelial activation, oxidative stress, inflammation, vasoconstriction, or a combination of these factors (Fig. 1). Evidence supports the use of exercise, aspirin, calcium,

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and labor induction as effective preventive strategies (Fig. 2).

EXERCISE

A systematic review of 15 randomized, controlled trials, involving a total of 3322 women, showed that exercise reduces the risk of preeclampsia (odds ratio, 0.59; 95% confidence interval [CI], 0.37 to 0.90) without adverse fetal effects.[8] To achieve these benefits, women must undertake at least 140 minutes per week of moderate-intensity exercise, sufficient to raise the heart rate and allow speaking but not singing.

ASPIRIN

A meta-analysis of 60 trials involving a total of 36,716 women at increased risk for preeclampsia primarily on the basis of clinical risk factors showed that aspirin (50 to 162 mg per day, usually ≤75 mg per day) reduces the risk of preeclampsia in a dose-dependent manner (relative risk, 0.82; 95% CI, 0.77 to 0.88), in addition to lowering the rates of serious maternal complications, preterm birth, delivery of a small-for-gestational age infant, and fetal or newborn death.[9] In the ASPRE (Combined Multimarker Screening and Randomized Patient Treatment with Aspirin for Evidence-Based Preeclampsia Prevention) trial, multivariable first-trimester screening was used to identify a high-risk group of women randomly assigned to receive aspirin (150 mg per day) or placebo from 11 to 13 weeks' gestation until 36 weeks' gestation. In the aspirin group, the risk of preterm preeclampsia was reduced by more than 60% (odds ratio, 0.38; 95% CI, 0.20 to 0.74), but no significant reduction in term disease was observed (odds ratio, 0.95; 95% CI, 0.57 to 1.57).[10] This approach was cost-effective in Canada[11] and Israel.[12]

A subsequent meta-analysis of 16 trials involving a total of 18,907 women showed that aspirin is beneficial in preventing preterm preeclampsia (relative risk, 0.62; 95% CI, 0.45 to 0.87) but not term disease (relative risk, 0.92; 95% CI, 0.70 to 1.21), provided treatment is initiated by 16 weeks' gestation and at a dose of at least 100 mg per day.[13] This effect may be related to differences in the predominant pathogenesis or a shift in diagnosis to a later gestational age, so cases of preeclampsia at term that are prevented are replaced by cases that would have involved preterm delivery. The dose of aspirin available is affected by geographic variation; 75-mg and 81-mg tablets can be used interchangeably, and an approximation of the recommended doses may be required. Further research must clarify why women with chronic hypertension did not benefit from aspirin.[10]

Aspirin prophylaxis against preeclampsia is associated with a very small increase in antepartum and postpartum bleeding, as well as neonatal bleeding in rare cases, on the basis of data from a population-based cohort study involving a total of 4088 women treated with aspirin[14] and data from 29 randomized, controlled trials involving a total of 30,775 women.[9] These risks could be mitigated by discontinuing aspirin by 36 weeks' gestation and are far outweighed by the benefits of preventing preterm preeclampsia in women at increased risk. Nevertheless, the risks argue against universal aspirin prophylaxis as an alternative to risk screening.

CALCIUM

A meta-analysis of 30 trials involving a total of 20,445 women showed that calcium supplementation during pregnancy reduces the risk of preeclampsia (relative risk, 0.49; 95% CI, 0.39 to 0.61) at term or preterm gestational age, regardless of whether calcium supplementation is initiated before, at, or after 20 weeks' gestation, whether it is given with or without vitamin D, and whether the dose is high (≥1 g per day) or low (usually 500 mg per day).[15] However, calcium was effective only in the subgroup of 24 trials involving a total of 15,050 women with a low average calcium intake at baseline (<900 mg per day; relative risk, 0.45; 95% CI, 0.35 to 0.58).[15] In a network meta-analysis of 25 trials involving 15,038 women, high-dose and low-dose calcium were similarly effective (relative risk, 0.79; 95% CI, 0.43 to 1.40).

OTHER PREVENTIVE MEASURES

A trial involving 6106 low-risk, nulliparous women showed that labor induction at 39 weeks 0 days to 39 weeks 4 days of gestation, as compared with expectant care, reduced the risks of gestational hypertension and preeclampsia.[16]

Pravastatin has received considerable attention as a potential preventive agent. In a study involving 1120 women identified at 35 to 36 weeks' gestation as being at high risk for term preeclampsia on the basis of multivariable screen-

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ing, pravastatin (20 mg per day) reduced neither the incidence of preeclampsia nor circulating levels of angiogenic markers, despite good adherence to the medication regimen.[17] A number of trials evaluating the initiation of pravastatin prophylaxis in early pregnancy are ongoing.

Folic acid (4 mg per day) did not prevent preeclampsia in a trial involving 2464 women at high risk.[18] The effectiveness of low-molecular-weight heparin remains uncertain, and its use is not recommended outside a study protocol unless high-quality data on safety and efficacy become available.[19] Newer candidates being evaluated (e.g., metformin[20]) have been repurposed from other indications for which safety is accepted.[21]

SURVEILLANCE FOR WOMEN AT INCREASED RISK

For women identified as having an increased risk of preeclampsia on the basis of multivariable or clinical risk factor screening in early pregnancy, no standardized program of maternal and fetal surveillance has been shown to reduce maternal or perinatal risk. Women should be encouraged to self-monitor for symptoms that may reflect preeclampsia, whether maternal (e.g., headache) or fetal (e.g., reduced fetal movement). Self-monitoring of blood pressure has become common, particularly since the start of the coronavirus disease 2019 (Covid-19) pandemic, but it remains uncertain whether this will result in earlier detection of preeclampsia. Pragmatic approaches of potential effectiveness include an increased frequency of antenatal care visits, maternal self-monitoring for proteinuria, monthly maternal laboratory testing for end-organ involvement (thrombocytopenia, elevated creatinine or aminotransferase levels, or angiogenic imbalance), and third-trimester fetal assessment (ultrasonographic monitoring of growth or Doppler velocimetry of the pulsatility indexes of the umbilical and middle cerebral arteries).

DIAGNOSIS

The purpose of diagnosing preeclampsia is to identify women at risk for adverse outcomes and determine the best course of management. The traditional definition of preeclampsia is new-onset hypertension and proteinuria at 20 weeks or more of gestation. The growing international consensus is that the definition should be broad in order to include other relevant forms of maternal end-organ involvement and uteroplacental dysfunction (Fig. 1). A systematic review of 33 observational studies involving a total of 9426 women with suspected preeclampsia showed an association between angiogenic imbalance and adverse pregnancy outcomes,[22] including those at term.[23] On the basis of these findings, angiogenic imbalance is part of the 2021 International Society for the Study of Hypertension in Pregnancy (ISSHP) definition of preeclampsia.[24] Challenges with the use of angiogenic markers include limited availability and various assays with different cutoff points, particularly those that are not adjusted for maternal characteristics or gestational age.[3] In women with preexisting hypertension, the diagnosis of superimposed preeclampsia should be based on nonhypertensive manifestations and not solely on worsening hypertension.[24]

Preeclampsia has been subgrouped by gestational age at onset. Women with early-onset disease (at <34 weeks' gestation) are more likely than women with late-onset disease (at ≥34 weeks' gestation) to have end-organ involvement, associated fetal growth restriction, and a hemodynamic profile of low cardiac output and high peripheral vascular resistance.[25] In women with late-onset preeclampsia, who account for at least 70% of all women with preeclampsia, birth weight is usually normal or even increased, cardiac output may be increased, and peripheral vascular resistance is variable (i.e., decreased[25] or increased[26]).

MANAGEMENT

PLACE OF CARE

It is reasonable to consider a component of outpatient care for women with preeclampsia that is not associated with severe hypertension or serious maternal or fetal compromise (Table 1). To be eligible for outpatient care, women must understand the symptoms of disease progression, have the capacity to measure their own blood pressure, have open lines of communication with care teams, and live within 30 minutes of a hospital.

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MONITORING

In preeclampsia, adverse maternal outcomes (as a Delphi-derived composite of mortality and major morbidity and consistent with the 14 core maternal outcomes[27] [Table 2]) can be predicted with the externally validated fullPIERS (Preeclampsia Integrated Estimate of Risk) model, provided its components are assessed at least twice weekly. The components are gestational age, chest pain or dyspnea, pulse oximetry measurement, platelet count, serum creatinine level, and aspartate or alanine aminotransferase level.[28,29] An online calculator is available (https://pre-empt.obgyn.ubc.ca/home-page/past-projects/fullpiers/).

Prospective studies involving women with suspected preeclampsia have shown that the measurement of placental growth factor or the ratio of sFlt-1 to placental growth factor is useful in identifying women who will give birth with preeclampsia in the next 1 to 4 weeks.[30,31] However, the addition of angiogenic markers may not improve the prediction of adverse maternal outcomes over prediction with the use of fullPIERS.[32,33] A stepped-wedge randomized trial involving 1035 women who presented primarily with worsening hypertension, new proteinuria, or headache or visual symptoms showed that knowledge of placental growth factor levels reduced the incidence of adverse maternal outcomes.[34] In contrast, a similar stepped-wedge clinical trial showed no benefit of knowing placental growth factor levels in 2291 women, who most commonly had suspected fetal growth restriction and could have had blood tests consistent with preeclampsia.[35] Finally, a single-center, randomized trial involving 370 women with suspected preeclampsia showed that knowledge of the ratio of sFlt-1 to placental growth factor did not reduce hospital admissions or gestational age at birth.[36]

Various fetal surveillance strategies, including assessment of fetal growth and Doppler ultrasonography, are often used in the management of preeclampsia. Data from high-quality studies that support a particular strategy are limited.

TIMED BIRTH

Resolution of preeclampsia is initiated with delivery, but maternal end-organ complications may still worsen in the postpartum period, particularly during the first 3 days. Although earlier planned birth minimizes the risk for the mother, it may increase the risk for the newborn, particularly at preterm gestational ages.

In cases of preeclampsia, initiation of birth is recommended at an early gestational age (<24 weeks 0 days) when the risks of maternal complications and fetal mortality are high, at any gestational age when serious maternal or fetal complications are noted, and at term gestational age (≥37 weeks 0 days), even in the absence of complications, to minimize the risk for the mother without increasing the risk for the newborn.[24]

If care for sick mothers and newborns is readily available, expectant management of preeclampsia (i.e., watchful waiting and close monitoring for indications for birth) should be discussed in preference to initiation of birth from fetal viability to 36 weeks 6 days of gestation.[24] A meta-analysis of six trials involving a total of 748 women showed that expectant care until 33 weeks 6 days of gestation, as compared with early delivery, is associated with reduced newborn morbidity.[37] Two trials, with a total of 1604 women, showed that from 34 weeks 0 days to 36 weeks 6 days of gestation, expectant care is associated with increased maternal morbidity but a reduced risk of admission to the neonatal unit and of respiratory morbidity,[38,39] particularly when antenatal glucocorticoids are administered routinely to accelerate fetal lung maturity and reduce other prematurity-related risks.[38]

PHARMACOTHERAPY

Currently, no disease-modifying therapy is available for established preeclampsia. Randomized trials of potential interventions have focused almost entirely on preeclampsia of early onset and the outcome of pregnancy prolongation. Many trials are under way. Among those targeting pathways involved in the pathogenesis of preeclampsia (Fig. 1), one trial, involving 180 women, suggests that metformin (at a dose of 3 g per day) shows particular promise.[40] New approaches include plasmapheresis to remove antiangiogenic factors (i.e., sFlt-1), monoclonal antibodies (against tumor necrosis factor α or complement), and gene silencing targeting sFlt-1 production or angiotensinogen.[21]

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Table 1. Preeclampsia Risks and Management According to Weeks of Gestation at Diagnosis.*

Risks and Management	<24 wk	24 wk 0 days to 33 wk 6 days	34 wk 0 days to 36 wk 6 days	≥37 wk 0 days
Risks				
Preeclampsia (%)	<0.05	0.2	0.4	2.9
Associated short-term risks				
Maternal complications (%)[23,25]	≤70	Approximately 15	Approximately 5	2–4
Fetal or newborn death (%)	50–82	2–40	<1	<1
Newborn death without serious health problems (%)	98–55	4–12	4	4
Management				
Antepartum care				
Place of care	Where resources are sufficient to deal with sick mothers or babies (especially for expectant care); after initial assessment, a component of outpatient care can be considered but should be individualized	Where resources are sufficient to deal with sick mothers or babies (especially for expectant care); after initial assessment, a component of outpatient care can be considered but should be individualized	Where resources are sufficient to deal with sick mothers or babies (especially for expectant care); after initial assessment, a component of outpatient care can be considered but should be individualized	Where resources are sufficient to deal with sick mothers or babies (especially for expectant care); after initial assessment, a component of outpatient care can be considered but should be individualized
Maternal monitoring (at minimum)†	Daily BP; blood tests twice/wk (platelet count, creatinine and liver-enzyme levels); use fullPIERS model to evaluate risk of adverse maternal outcome	Daily BP; blood tests twice/wk (platelet count, creatinine and liver-enzyme levels); use fullPIERS model to evaluate risk of adverse maternal outcome	Daily BP; blood tests twice/wk (platelet count, creatinine and liver-enzyme levels); use fullPIERS model to evaluate risk of adverse maternal outcome	Daily BP; blood tests twice/wk (platelet count, creatinine and liver-enzyme levels); use fullPIERS model to evaluate risk of adverse maternal outcome
Fetal monitoring (at minimum)‡	Fetal growth (repeated every 2 wk) and fetal Doppler (at <32 wk of gestation, umbilical artery and ductus venosus)	Fetal growth (repeated every 2 wk) and fetal Doppler (at <32 wk of gestation, umbilical artery and ductus venosus; at ≥32 wk of gestation, umbilical and middle cerebral arteries; repeated at least weekly)	Fetal growth (repeated every 2 wk) and fetal Doppler (at ≥32 wk of gestation, umbilical and middle cerebral arteries; repeated at least weekly)	Fetal growth (repeated every 2 wk) and fetal Doppler (at ≥32 wk of gestation, umbilical and middle cerebral arteries; repeated at least weekly)
Timed birth§	Initiation of birth (within 24–48 hr)	Consider expectant care if no indications for timed birth	Consider expectant care if no indications for timed birth	Initiation of birth (within 24–48 hr)
Antihypertensive agents	Treat hypertension, whether severe (BP ≥160/110 mm Hg) or nonsevere (140–159/90–109 mm Hg); target diastolic BP of 85 mm Hg, to be achieved more slowly if BP severely elevated	Treat hypertension, whether severe (BP ≥160/110 mm Hg) or nonsevere (140–159/90–109 mm Hg); target diastolic BP of 85 mm Hg, to be achieved more slowly if BP severely elevated	Treat hypertension, whether severe (BP ≥160/110 mm Hg) or nonsevere (140–159/90–109 mm Hg); target diastolic BP of 85 mm Hg, to be achieved more slowly if BP severely elevated	Treat hypertension, whether severe (BP ≥160/110 mm Hg) or nonsevere (140–159/90–109 mm Hg); target diastolic BP of 85 mm Hg, to be achieved more slowly if BP severely elevated

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Magnesium sulfate (4 g IV over 5 min, then 1 g/hr IV; or 5 g IM into each buttock, then 5 g IM every 4 hr)	Use for eclampsia treatment and prevention; use for women with preeclampsia who have severe hypertension and proteinuria or any hypertension and neurologic symptoms or signs[23]	Use for eclampsia treatment and prevention; use for women with preeclampsia who have severe hypertension and proteinuria or any hypertension and neurologic symptoms or signs[23]; use for fetal neuroprotection	Use for eclampsia treatment and prevention; use for women with preeclampsia who have severe hypertension and proteinuria or any hypertension and neurologic symptoms or signs[23]	Use for eclampsia treatment and prevention; use for women with preeclampsia who have severe hypertension and proteinuria or any hypertension and neurologic symptoms or signs[23]
Antenatal glucocorticoids	NA	Use to accelerate fetal pulmonary maturity and reduce risks of fetal or newborn death, IVH, and developmental delay¶	Use to accelerate fetal pulmonary maturity and reduce risks of fetal or newborn death, IVH, and developmental delay¶	Not recommended for HELLP syndrome
Postpartum care				
Maternal monitoring†	Watch for peak BP on days 3–6 after birth; daily BP and twice/wk blood tests (platelet count and creatinine and liver-enzyme levels) until discharge	Watch for peak BP on days 3–6 after birth; daily BP and twice/wk blood tests (platelet count and creatinine and liver-enzyme levels) until discharge	Watch for peak BP on days 3–6 after birth; daily BP and twice/wk blood tests (platelet count and creatinine and liver-enzyme levels) until discharge	Watch for peak BP on days 3–6 after birth; daily BP and twice/wk blood tests (platelet count and creatinine and liver-enzyme levels) until discharge
Antihypertensive agents‖	Treat hypertension; most agents can be used during breast-feeding	Treat hypertension; most agents can be used during breast-feeding	Treat hypertension; most agents can be used during breast-feeding	Treat hypertension; most agents can be used during breast-feeding
Counseling about future risks	Discuss preeclampsia recurrence, long-term health risks (particularly CVD**), lifestyle modifications	Discuss preeclampsia recurrence, long-term health risks (particularly CVD**), lifestyle modifications	Discuss preeclampsia recurrence, long-term health risks (particularly CVD**), lifestyle modifications	Discuss preeclampsia recurrence, long-term health risks (particularly CVD**), lifestyle modifications

* BP denotes blood pressure; CVD cardiovascular disease; fullPIERS Preeclampsia Integrated Estimate of Risk; HELLP hemolysis, elevated liver-enzyme levels, and low platelet count; IM intramuscular; IV intravenous; IVH intraventricular hemorrhage; and NA not applicable.

† Maternal monitoring should continue after delivery, particularly in the first week.

‡ There is no program of surveillance that has been shown to minimize the risk of an adverse fetal or newborn outcome.

§ Approximately 40% of women with preterm preeclampsia are eligible for expectant care. Indications for timed birth (at any gestational age) include abnormal neurologic features (e.g., eclampsia, severe intractable headache, or repeated visual scotomata), repeated episodes of severe hypertension despite maintenance treatment with three classes of antihypertensive agents, pulmonary edema, progressive thrombocytopenia or platelet count of less than 50×10^9 per liter, transfusion of any blood product, abnormal and increasing serum creatinine levels, abnormal and increasing liver-enzyme levels, hepatic dysfunction (international normalized ratio >2 in the absence of disseminated intravascular coagulation and warfarin therapy), hematoma or rupture, abruption with evidence of maternal or fetal compromise, or nonreassuring fetal status (including death). If considering timed birth, discuss with anesthesiology, neonatology, maternal–fetal medicine, and obstetrical medicine (if possible).

¶ The upper gestational age limit should be determined by local policy.

‖ See the LactMed database (https://www.ncbi.nlm.nih.gov/books/NBK501922/) for more information.

** The My Health beyond Pregnancy tool provides information about CVD risk and facilitates tracking of BP, weight, and other CVD risk factors (https://www.preeclampsia.org/public/frontend/assets/img/gallery/pream21/MyHealthBeyondPregnancyFINAL.pdf).

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Table 2. Core Maternal and Perinatal Outcomes in Preeclampsia.*

Outcome	Definition or Explanation
Maternal outcomes	
Maternal death	Death during pregnancy or within 42 days after the end of pregnancy
Eclampsia	Onset of convulsions (documented as fits, generalized convulsions, tonic–clonic seizures, or seizures) not attributable to causes other than preeclampsia
Stroke	High-income countries: acute symptoms of focal brain injury lasting >24 hr; ischemic or hemorrhagic stroke confirmed by neuroimaging Low- and middle-income countries: acute symptoms of focal brain injury lasting >24 hr
Cortical blindness	Visual impairment in the presence of intact papillary response to light
Retinal detachment	A condition in which the retina peels away from its underlying layer of support tissue; diagnosed by ophthalmologic examination
Pulmonary edema	Clinical diagnosis of excess fluid in lungs, confirmed by chest radiography, or requirement for directive (i.e., appropriate) treatment and oxygen saturation <95%
Acute kidney injury	Fulfills any of the following criteria: increase in serum creatinine level ≥26 μmol per liter (≥0.29 mg/dl) within 48 hr, >50% rise in serum creatinine level within the past 7 days, urine output <0.5 ml/kg/hr for >6 hr, or serum creatinine level >150 μmol per liter (>1.7 mg/dl) in the absence of a baseline serum creatinine value
Liver capsule hematoma	Blood collection under hepatic capsule, as confirmed by ultrasonography, computed tomography, magnetic resonance imaging, or laparotomy
Abruption	In the absence of placenta previa on ultrasound, vaginal bleeding in second or third trimester, with uterine irritability, labor, clinical signs of hypovolemic shock or coagulopathy, or placental abnormalities with histologic evidence of a chronic abruption
Postpartum hemorrhage	Perceived abnormal bleeding after delivery and either hypotension or medical or surgical intervention for postpartum hemorrhage
Elevated liver-enzyme levels	Aspartate and alanine aminotransferase levels at least twice the upper limit of the normal range
Low platelet count	Acute reduction in the number of platelets in the blood to <100,000/μl
Admission to intensive care unit required	Need for advanced respiratory support alone or monitoring and support for two or more organ systems
Need for respiratory support, not for childbirth	Need for continuous positive airway pressure, noninvasive positive pressure ventilation, or intubation and mechanical ventilation
Perinatal outcomes	
Stillbirth	Gestational age ≥22 wk 0 days, birth weight ≥500 g, or crown–heel length ≥25 cm
Gestational age at delivery	Dating of pregnancy from the first day of the last menstrual period, with confirmation by (in order of most to least accurate dating) first-trimester ultrasonography, first-trimester examination consistent with last menstrual period, detection of fetal heartbeat consistent with last menstrual period and uterine size, second-trimester ultrasonography, third-trimester ultrasonography, or examination of the fetus or, if applicable, known date of fertilization (e.g., with assisted reproductive technology)
Birth weight	High-income countries: birth weight should be recorded within 24 hr after birth and assessed with the use of a calibrated electronic scale with 10-g resolution Low- and middle-income countries: if a calibrated electronic scale is unavailable, the type and calibration of the scale used should be carefully documented
Small for gestational age	Weight below the 10th percentile for gestational age, as assessed against a validated global, regional, or local customized growth chart; should be reported for all births, including stillbirths
Neonatal mortality	Death of a live-born infant before 28 completed days of life
Neonatal seizures	High-income countries: clinical recognition of neonatal seizures confirmed by electroencephalographic monitoring Low- and middle-income countries: clinical recognition of neonatal seizures
Respiratory support required	Need for continuous positive airway pressure, noninvasive positive pressure ventilation, or intubation and mechanical ventilation
Admission to neonatal special care or intensive care unit required	Meeting the local, regional, or national criteria for admission to the neonatal special care or intensive care unit

* Outcomes are from Duffy et al.[27]

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Severe Hypertension

Manifestation: Systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg
Objective: Systolic BP <160 mm Hg and diastolic BP <110 mm Hg within 180 min
Management: Choose one of the following four classes of drugs and the preferred route and timing of administration
If BP control is not achieved despite maximal doses, move to another class of medication
If BP control is not achieved by 360 min despite 2 medications, consult critical care, consider ICU admission, stabilize and deliver (if undelivered)

First-Line Drug	Route of Administration and Dosage Units	0 Min	30 Min	60 Min	90 Min	120 Min	150 Min
Labetalol	Oral — mg	200	—	200	—	200	—
	Intermittent IV — mg	10–20	20–40	40–80	40–80	40–80	40–80
	IV infusion — mg/min	0.5–2.0	→	→	→	→	→
Nifedipine	Oral capsule — mg	5–10	10	—	10	—	10
	Oral tablet (PA/MR) — mg	10	—	10	—	10	—
Hydralazine	Intermittent IV — mg	5	5–10	5–10	5–10	—	—
Methyldopa	Oral (if other medications unavailable or for in utero transfer without monitoring) — mg	1000	—	—	—	—	—

If BP is controlled, continue with maintenance oral medication

If systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg, use medication from a class other than maintenance

Nonsevere Hypertension

Manifestation: Systolic BP 140–159 mm Hg or diastolic BP 90–109 mm Hg
Objective: Systolic BP 135 mm Hg and diastolic BP 85 mm Hg
Management: Start with one of the three classes of drugs and use a low–medium dose
If BP control is not achieved within a week with a medium dose, consider adding a low–medium dose from another class, rather than a high dose of the same medication, for a maximum of three medications
Consider expectant care if antenatal

First-Line Drug	Formulation	Low–Medium Dose	High Dose	Maximum Dose
Labetalol		100–200 mg, 3 or 4 times daily	300 mg, 3 or 4 times daily	1200 mg/day
Nifedipine	Intermediate-acting (PA/MR)	10–20 mg, 2 or 3 times daily	30 mg, 2 or 3 times daily	120 mg/day
	Long-acting (XL/LA)	30 mg, 1 or 2 times daily or 60 mg daily	30 mg every morning and 60 mg every evening	120 mg/day
Methyldopa		250–500 mg, 3 or 4 times daily	750 mg, 3 times daily	2500 mg/day

Figure 3. Management of Blood Pressure.

The information presented is modified from Magee et al.[24] Severe hypertension (systolic BP ≥160 mm Hg or diastolic BP ≥110 mm Hg) requires urgent treatment, as shown in the red box. Oral or parenteral treatment is administered to achieve a target BP of less than 160/110 mm Hg within a few hours. In the hours that follow, a BP of 135/85 mm Hg is the target, with the approach shown in the orange box. ICU denotes intensive care unit, IV intravenous, LA long-acting, MR modified release, PA prolonged action, and XL extended length of action.

ANTIHYPERTENSIVE THERAPY

Severe hypertension is associated with maternal and perinatal adverse outcomes independent of preeclampsia and of similar magnitude to preeclampsia[41] and warrants antihypertensive therapy[4] (Fig. 3). Most guidelines recommend oral nifedipine, parenteral labetalol, or parenteral hydralazine.[4] A network meta-analysis and trial sequential analyses of 32 trials involving a total of 3236 women showed that for achieving a target blood pressure, the efficacy of parenteral labetalol appears to be similar to that of paren-

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teral hydralazine or oral nifedipine,[42] but oral nifedipine may be more effective than parenteral hydralazine, according to a meta-analysis of 17 trials involving a total of 1591 women.[43] Oral labetalol is as effective as oral nifedipine, with fewer babies of low birth weight admitted to neonatal intensive care (10%, vs. 18% with nifedipine).[44] Oral methyldopa alone achieves the target blood pressure in at least 60% of women.[44]

Treatment of nonsevere hypertension in pregnancy is recommended by the World Health Organization, the ISSHP, the International Federation of Gynecology and Obstetrics, and six non-U.S. national guidelines,[4,45,46] on the basis of the results of the international Control of Hypertension in Pregnancy Study, involving 987 women.[47] In women with chronic or gestational hypertension, antihypertensive therapy (most commonly oral labetalol) administered to achieve a target diastolic blood pressure of 85 mm Hg resulted in a mean blood pressure of 133/85 mm Hg after randomization, and the women were less likely than women with minimal medication use to have severe hypertension (as in prior small trials[48]), a platelet count of less than 100×10^9 per liter, or elevated liver-enzyme levels with symptoms[47]; the women with preeclampsia remained in their assigned group. A nonsignificant increase in babies with birth weight below the 10th percentile was balanced by a nonsignificant decrease in preterm births, and there was no increase in fetal or newborn deaths or need for prolonged neonatal care.[49] The recently published Chronic Hypertension and Pregnancy trial (involving 2408 women) also showed that blood pressure control (to <140/90 mm Hg and most commonly with oral labetalol) was associated with a reduction in a composite adverse outcome (of preeclampsia with severe features, medically indicated preterm birth at <35 weeks' gestation, placental abruption, or fetal or neonatal death), with no significant increase in babies with birth weight below the 10th percentile for gestational age.[50]

Oral labetalol, methyldopa, or nifedipine is usually recommended, according to 49 small randomized, controlled trials involving a total of 4723 women.[48] No clear differences have been noted between any two of these agents in 22 trials involving 1723 women, but 95% confidence intervals include clinically relevant benefits and risks, and pediatric developmental follow-up data are reassuring although limited.[51] Labetalol, an alpha- and beta-blocker, or pure beta-blockers may warrant neonatal monitoring for hypoglycemia and bradycardia.[52] Renin–angiotensin–aldosterone inhibitors are fetotoxic and therefore contraindicated during pregnancy.[53]

It has been suggested that antihypertensive therapy should be guided by hemodynamic assessment in women with preeclampsia, with a vasodilator for increased peripheral vascular resistance (along with intravascular fluid) or a beta-blocker for high cardiac output. No randomized trial of hemodynamically guided antihypertensive treatment (as compared with empirical therapy) to achieve a common target blood pressure has been conducted. However, plasma volume expansion (as compared with usual care) was associated with a shorter time to delivery and a higher incidence of pulmonary edema and cesarean deliveries in the largest published trial, involving 216 women.[54] A cautious approach to fluid administration is recommended for women with preeclampsia (i.e., approximately 80 ml per hour during labor) that is not associated with acute kidney injury.[55]

MAGNESIUM SULFATE

Magnesium sulfate is effective for the prevention and treatment of preeclampsia, but implementation has been challenging (Table 1).[4,24,56] Evaluation of alternative regimens (a lower dose or abbreviated duration), more targeted administration in women who may benefit the most, and the complementary strategy of achieving good blood-pressure control is ongoing.[44]

GLUCOCORTICOIDS

Antenatal glucocorticoids should be administered according to local gestational age–based guidance for acceleration of fetal pulmonary maturity and prevention of fetal or newborn death, intraventricular hemorrhage, and developmental delay (Table 1). Glucocorticoids are not recommended for HELLP (hemolysis, elevated liver-enzyme levels, and low platelet count) syndrome; a meta-analysis of 11 trials involving a total of 550 women with HELLP syndrome showed that the transient improvements in laboratory values did not result in improved clinical outcomes.[24]

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POSTPARTUM MANAGEMENT

Preeclampsia may first develop in the postpartum period, when the risk of associated maternal complications and death is highest.[57] As a result of the redistribution of extravascular fluid, blood pressure peaks approximately 3 to 6 days after delivery, when most women have been discharged from the hospital. Postpartum hypertension is a common indication for readmission.[58] Although nonsteroidal antiinflammatory drugs for postpartum analgesia may elevate blood pressure, the results of two trials involving a total of 213 women are inconsistent.[59,60] Limited data suggest that antihypertensive agents are effective in the postpartum period,[61] and most (including some angiotensin-converting–enzyme inhibitors) are acceptable for use during breast-feeding (see the LactMed database).[62] In a study involving 61 women, blood pressure self-monitoring and tapering of antihypertensive therapy for 6 weeks after delivery increased the percentage of women with normotension at 6 months (80%, vs. 62% with usual care), with an approximate reduction of 7 mm Hg in diastolic blood pressure maintained 3.6 years later.[63]

Preeclampsia in the postpartum period is associated with an increased incidence of mental health problems, on the basis of a systematic narrative review of 17 studies.[64]

RISKS IN A FUTURE PREGNANCY

A meta-analysis of data from individual participants in 22 studies, involving a total of 99,415 women with preeclampsia during a previous pregnancy, showed that 15% of the women had gestational hypertension and 15% had preeclampsia during a subsequent pregnancy.[65] The recurrence rate may be as high as 50% if prior preeclampsia was of early onset or associated with complications. Measures undertaken between pregnancies, such as weight loss and exercise, have the potential to reduce the risk of recurrent preeclampsia.

LONG-TERM RISKS

The incidence of preeclampsia doubles when assessed on a per-woman (rather than a per-pregnancy) basis, because on average, women have at least two children.[66] Therefore, 4 to 8% of women will have at least one episode of preeclampsia during their lifetime.

Robust epidemiologic data link preeclampsia with long-term maternal cardiovascular risk factors and disease, which is the leading killer of women. Preeclampsia (as compared with a normotensive pregnancy) is associated with an increase by a factor of approximately 4 in the risk of hypertension, particularly within 2 years after delivery, on the basis of data from 15 studies (1646 women with hypertensive pregnancies and 6395 women with uncomplicated pregnancies),[67] as well as approximately twice the risk of type 2 diabetes and dyslipidemia.[68] Preeclampsia at least doubles the odds of cardiovascular disease (on the basis of two systematic reviews of a total of 26 studies), particularly when preeclampsia is severe[69] or recurrent (on the basis of 7 studies involving a total of 52,544 women).[70] Similar adverse cardiovascular outcomes are reported among the offspring.[71] In addition, preeclampsia is associated with other health problems, such as seizures, dementia, chronic kidney disease, and even death from any cause.[68]

The basis for the link between preeclampsia and cardiovascular risk is complex. Well-established risk factors (e.g., preexisting hypertension) are shared by preeclampsia and cardiovascular disease. Women may have other preexisting, subclinical cardiac or vascular abnormalities (e.g., increased peripheral vascular resistance) that predispose them to vascular or metabolic disease in pregnancy.[68,72] Furthermore, it is theoretically possible that preeclampsia itself damages the maternal cardiovascular system. However, adjustment for conventional cardiovascular risk factors eliminates entirely[73,74] or almost entirely[75] any association observed between hypertension during pregnancy (including preeclampsia) and cardiovascular disease. In addition, studies have yielded inconsistent estimates of the effect of prolonged maternal exposure to preeclampsia, as a result of expectant care, on cardiovascular disease.[76,77]

The American Heart Association lists hypertension during pregnancy (including preeclampsia) as a major cardiovascular risk factor and recommends that affected women undergo cardiovascular risk screening within 3 months after giving birth.[78] However, no cardiovascular prediction model adequately captures the 10-year

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risks among young women, and the development of a bespoke model in a large, population-based cohort was not successful.[79] To further complicate matters, postpartum cardiovascular risk reduction has been challenged by suboptimal patient engagement, high attrition, and a lack of proven effectiveness in reducing the long-term risk of cardiovascular events. Nevertheless, many cardiovascular risk factors are modifiable and related to lifestyle,[80] so at minimum, all women with prior preeclampsia should be offered lifestyle advice in accordance with national or international guidelines.[24]

FUTURE DIRECTIONS

Therapeutic progress may emerge from a research focus on the use of biomarkers (maternal, fetal, or placental) and multivariable, dynamic modeling. Such biomarkers and modeling could provide new insights into preeclampsia phenotypes, improve prediction and management of preeclampsia, and individualize care during and after pregnancy.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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