

Preeclampsia: Updates in Pathogenesis, Definitions, and Guidelines

Elizabeth Phipps,* Devika Prasanna,* Wunnie Brima,[†] and Belinda Jim*

Abstract

Preeclampsia is becoming an increasingly common diagnosis in the developed world and remains a high cause of maternal and fetal morbidity and mortality in the developing world. Delay in childbearing in the developed world feeds into the risk factors associated with preeclampsia, which include older maternal age, obesity, and/or vascular diseases. Inadequate prenatal care partially explains the persistent high prevalence in the developing world. In this review, we begin by presenting the most recent concepts in the pathogenesis of preeclampsia. Upstream triggers of the well described angiogenic pathways, such as the heme oxygenase and hydrogen sulfide pathways, as well as the roles of autoantibodies, misfolded proteins, nitric oxide, and oxidative stress will be described. We also detail updated definitions, classification schema, and treatment targets of hypertensive disorders of pregnancy put forth by obstetric and hypertensive societies throughout the world. The shift has been made to view preeclampsia as a systemic disease with widespread endothelial damage and the potential to affect future cardiovascular diseases rather than a self-limited occurrence. At the very least, we now know that preeclampsia does not end with delivery of the placenta. We conclude by summarizing the latest strategies for prevention and treatment of preeclampsia. A better understanding of this entity will help in the care of at-risk women before delivery and for decades after.

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Introduction

Preeclampsia has been dubbed a disease of theories. Its concept has transformed throughout the century from a disease specific to the kidney leading to chronic nephritis to a state of toxemia caused by circulating toxins. Our understanding of this disorder has significantly advanced since that time: the introduction of circulating antiangiogenic factors contributing to disease and the emphasis away from proteinuria to diagnose preeclampsia. What have also been unraveled, more so in the last decade, are the future cardiovascular and renal implications for women with a history of preeclampsia, especially those with early, severe subtypes. Thus, with much better understanding of this disease, we have optimism for diagnosis and treatment as well as caution for future care of these women. In this review, we will present the latest findings on pathogenesis of preeclampsia, the most recent updates on the classification schema of hypertensive disorders of pregnancy, and a summary of preventive and treatment strategies.

Pathogenesis

The pathogenesis of preeclampsia is not fully elucidated but much progress has been made in the last decades. The placenta has always been a central figure in the etiology of preeclampsia because the removal of the placenta is necessary for symptoms to regress (1,2). Pathologic examination of placentas from pregnancies with advanced preeclampsia often reveals numerous placental infarcts and sclerotic narrowing of arterioles

(3). The hypothesis that defective trophoblastic invasion with associated uteroplacental hypoperfusion may lead to preeclampsia is supported by animal and human studies (4,5). Thus, a two-stage model was developed: incomplete spiral artery remodeling in the uterus that contributes to placental ischemia (stage 1) and the release of antiangiogenic factors from the ischemic placenta into the maternal circulation that contributes to endothelial damage (stage 2) (Figure 1). During implantation, placental trophoblasts invade the uterus and induce the spiral arteries to remodel, while obliterating the tunica media of the myometrial spiral arteries; this allows the arteries to accommodate increased blood flow independent of maternal vasomotor changes to nourish the developing fetus (6). Part of this remodeling requires that the trophoblasts adopt an endothelial phenotype and its various adhesion molecules. If this remodeling is impaired, the placenta is likely to be deprived of oxygen, which leads to a state of relative ischemia and an increase in oxidative stress during states of intermittent perfusion. This abnormal spiral artery remodeling was seen and described over five decades ago in pregnant women who were hypertensive (7). It has since been shown to be the central pathogenic factor in pregnancies complicated by intrauterine growth restriction, gestational hypertension, and preeclampsia (6). One limitation to this theory, hence, is that these findings are not specific to preeclampsia and may explain the difference in manifestations between placental preeclampsia and maternal preeclampsia (see Subtypes of Preeclampsia below).

*Department of Nephrology/Medicine, Jacobi Medical Center at Albert Einstein College of Medicine, Bronx, New York; and
[†]Department of Medicine, James J. Peters Veterans Affairs Medical Center, New York, New York

Correspondence:
Dr. Belinda Jim, Jacobi Medical Center, Department of Nephrology/Medicine, 1400 Pelham Parkway, Building 1, 3 North, Bronx, NY 10461.
Email: Belindajim286@gmail.com

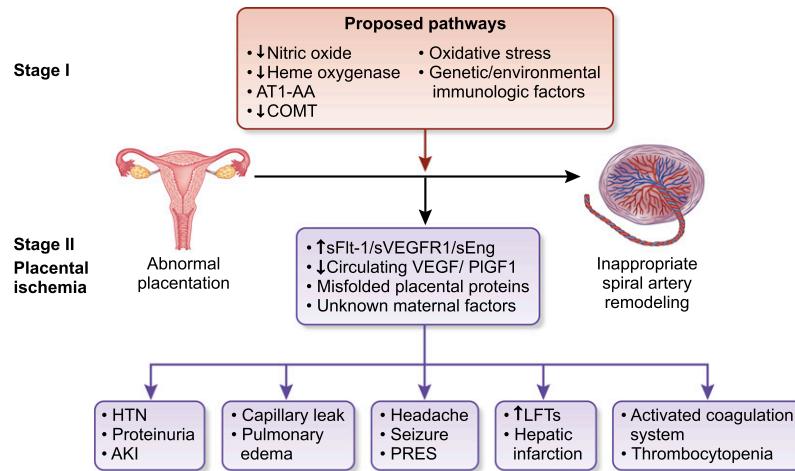


Figure 1. | Pathogenesis of preeclampsia: two-stage model. AT1-AA, autoantibodies to angiotensin receptor 1; COMT, catechol-*O*-methyltransferase; HTN, hypertension; LFT, liver function test; PlGF1, placental growth factor 1; PRES, posterior reversible encephalopathy syndrome; sEng, soluble endoglin; sFlt-1, soluble fms-like tyrosine kinase 1; sVEGFR1, soluble vascular endothelial growth factor receptor 1; VEGF, vascular endothelial growth factor. Reprinted from reference 35, with permission.

Angiogenic Factors

In 2003, Maynard *et al.* (8) showed that such a substance, soluble fms-like tyrosine kinase 1 (sFlt-1), was upregulated in the circulation of preeclamptic women. sFlt-1 is a splice variant of the vascular endothelial growth factor (VEGF) receptor fms-like tyrosine kinase 1. Not containing the cytoplasmic and membrane domains of the receptor, sFlt-1 is allowed to circulate and bind to VEGF and placental growth factor (PlGF), essentially antagonizing their binding to cell surface receptor fms-like tyrosine kinase 1 (VEGF receptor 1). When sFlt-1 was injected into rats using an adenovirus, they developed significant hypertension and albuminuria and histologic changes consistent with preeclampsia (*i.e.*, glomerular enlargement, endotheliosis, and fibrin deposition within the glomeruli). Thus, sFlt-1 seems to be a key mediator in the development of preeclampsia (8). Subsequently, a second placenta-derived protein, soluble endoglin (sEng), was also found to be upregulated in preeclampsia (9). sEng, a circulating coreceptor of TGF- β , can bind to TGF- β in the plasma. Antagonizing TGF- β , a proangiogenic factor, is analogous to sFlt-1 antagonizing VEGF. In fact, elevated levels of sEng in the circulation have been shown to induce signs of severe preeclampsia in pregnant rats (9). The true significance of these angiogenic markers, however, may be in their ability to predict adverse maternal or fetal outcomes. Rana *et al.* (10) showed that, in a group of women with the clinical diagnosis of preeclampsia, an elevated level of sFlt-1-to-PlGF ratio (angiogenic form) is associated with worse maternal and fetal outcomes compared with in women with a lower ratio (nonangiogenic form). Recently, the Prediction of Short-Term Outcome in Pregnant Women with Suspected Preeclampsia Study, a multicenter trial among 14 countries that studied high-risk pregnant women in their second and third trimesters using angiogenic markers, showed that an sFlt-1-to-PlGF ratio of 38 or lower drawn at 24–37 weeks of gestation can reliably predict the absence of preeclampsia and fetal adverse outcomes within 1 week, with negative predictive values of 99.3% (95% confidence interval [95% CI], 97.9% to 99.9%) and 99.5% (95% CI, 98.1% to 99.9%),

respectively (11). Hence, the incorporation of angiogenic markers may help to risk stratify women with high suspicion for preeclampsia. Similarly, angiogenic markers have proved to be useful in distinguishing between confounding diagnoses, such as chronic hypertension, CKD, and lupus nephritis (12–15). The potential to target sFlt-1 as a therapy is also exciting and currently being studied using an apheresis technique (16). The results are promising, although they need to be validated in a randomized, controlled trial.

Heme Oxygenase Pathway

Most recent studies have focused on the proximal pathways of sFlt-1 induction. One such pathway is promulgated by heme oxygenase (HO). The HO enzyme, which exists in two forms, Hmox1 and Hmox2, degrades heme into carbon monoxide (CO) and other products. Hmox is upregulated in states of hypoxia and ischemia; its product, CO, acts as a vasodilator and has been shown to decrease perfusion pressure in the placenta (17–19). HO is expressed by trophoblasts, and its inhibition has been shown to result in defective trophoblast invasion *in vitro* (20). Human studies have also shown that levels of Hmox are decreased in patients with preeclampsia (21–27). Furthermore, the addition of sera from patients with preeclampsia led to decreased levels of Hmox *in vitro* (28). Conversely, increased gene expression of Hmox was shown to decrease circulating levels of sFlt-1 (29). Interestingly, CO levels have been found to be increased in smokers, which may explain the smoking paradox, because smoking seems to confer a protection against preeclampsia (29–32). Indeed, lower levels of CO have been shown in the exhaled breath of patients with preeclampsia and gestational hypertension (33,34),

Hydrogen Sulfide Pathway

The hydrogen sulfide (H₂S)–generating system has also been implicated in the pathogenesis of preeclampsia. H₂S is a gas known to have vasodilatory, cytoprotective, and

angiogenic properties similar to CO. H₂S is generated by three enzymes, cystathionine γ -lyase, cystathionine β -synthase, and 3-mercaptopyruvate sulfurtransferase, using the substrates cystathionine, homocysteine, cysteine, and mercaptopyruvate (36). H₂S levels have not only been shown to be decreased in preeclampsia, but they seem to modulate levels of sFlt-1 and sEng (29,37). This mechanism may be dependent on VEGF. When rats that were injected with adenovirus overexpressing sFlt-1 were treated with H₂S donor sodium hydrosulfide, they showed decreased levels of serum sFlt-1 and increased serum VEGF (38). Gene expression of VEGF in the kidneys was also increased, suggesting that the proangiogenic effects of H₂S are mediated by VEGF. Clinically, the rats showed decreased proteinuria, hypertension, and glomerular injury (38). Conversely, decreased levels of the precursor molecules of H₂S have been found in patients with preeclampsia (37,39,40). Chronic administration of a cystathionine γ -lyase inhibitor, DL-propargylglycine, to pregnant mice resulted in elevated mean BP, liver damage, and decreased fetal growth. However, subsequent administration of an H₂S-generating compound to these pregnant mice inhibited the sFlt-1 and sEng levels and restored fetal growth (37). The closest existing compound to H₂S in clinical use is sodium thiosulfate. Sodium thiosulfate was studied in an angiotensin-induced hypertensive rat model and showed that it reduced hypertension, proteinuria, oxidative stress, and functional and structural renal parameters (41). In practice, however, sodium thiosulfate has been mainly used for the treatment of calciphylaxis and resulted in case reports of severe anion gap metabolic acidosis *via* an unknown mechanism (42,43). Although these findings may give hope that a version of H₂S may offer benefits in preeclampsia, its safety profile must first be well established in pregnancy.

Nitric Oxide Pathway

The nitric oxide (NO)/nitric oxide synthase (NOS) system is also deranged in preeclampsia. NO is a potent vasodilator that acts to induce relaxation in vascular smooth muscle cells *via* a cyclic guanosine monophosphate pathway (44). Decreased levels of NO (45,46) and increased levels of arginase (which degrades a precursor molecule in the NOS pathway) have been reported in preeclampsia (47,48). A deficiency in NO has been shown to correlate with metabolic derangements seen in preeclampsia, such as hypertension, proteinuria, and platelet dysfunction (45). NO deficiency induces the uteroplacental changes characteristic of preeclampsia in pregnant mice, including decreased uterine artery diameter, spiral artery length, and uteroplacental blood flow (49). These findings suggest that an intact NOS system is essential for normal spiral artery remodeling and pregnancy.

Oxidative Stress

From early pregnancy on, the placenta assumes a state of oxidative stress arising from increased placental mitochondrial activity and production of reactive oxygen species (ROS), mainly superoxide anion (50,51). In preeclampsia, a heightened level of oxidative stress is encountered (51). The source had been attributed to the placenta, where free radical synthesis occurs, with maternal leukocytes

and the maternal endothelium likely contributors (53). The superoxide-producing enzyme NADPH oxidase, for example, has been shown to be present in placental trophoblast. Women with early onset of preeclampsia have been found to have higher superoxide production compared with those with late-onset disease (53). However, clinical trials of antioxidant therapy with vitamins C (1000 mg) and E (400 IU) have been disappointing and were associated with an increased number of low-birth weight babies in the treatment arm (54). It is not entirely clear if these doses, although superphysiologic, would be high enough to affect the ROS system. Higher doses, although permitted, were avoided in pregnancy to avoid unknown side effects.

Angiotensin Receptor 1 Autoantibodies

Turning to immune mechanisms, there have been many studies to show the link between autoantibodies to angiotensin receptor 1 (AT1-AA) and preeclampsia. The presence of AT1-AA was first described by Wallukat *et al.* (55) in 1999 in patients with preeclampsia. These autoantibodies seem to be pathogenic in a variety of proposed pathways. Dechend *et al.* (52) discovered that AT1-AA isolated from sera of preeclampsia women cause upregulation of ROS and the NADPH oxidase components as well as NK- κ B. Blockade with an angiotensin receptor 1 (AT1) receptor blocker, such as losartan, was able to attenuate these changes. Interestingly, the same group showed that infusion with an endothelin antagonist in an AT1-AA-infused hypertensive rat was able to decrease its BP. Hence, another possible pathway of AT1-AA-induced hypertension may be *via* endothelin (56). The fact that transfer of purified human AT1-AA from women with preeclampsia into pregnant mice induced a clinical phenotype of preeclampsia further shows its pathogenicity. This phenotype was prevented by the coinjection of losartan, an AT1 receptor antagonist, or an antibody neutralizing peptide (57). Ironically, the only available class of medication that seems to ameliorate AT1-AA-induced preeclampsia is the angiotensin receptor blocker, which happens to be teratogenic. Hence, safe blockers of the AT1 system need to be explored. Evidence of a relationship between AT1-AA and angiogenic factors also exists. In mice, the presence of AT1-AA seems to induce sFlt-1 release *via* activation of the calcineurin/nuclear factor of activated t cells pathway (58). Furthermore, AT1-AA stimulates sFlt-1 and sEng by inducing TNF- α and overcoming its negative regulator, HO (59). In terms of human studies, Stepan *et al.* (60) did not find a correlation between AT1-AA and sFlt-1 levels, whereas Siddiqui *et al.* (61) did. Given these mixed results in humans, it remains questionable whether AT1-AA and sFlt-1 levels share the same pathophysiologic mechanism.

Misfolded Proteins

Preeclamptic placentas have been shown to accumulate clusters of misfolded protein, which may contribute to the pathophysiology of the disease (62). Buhimschi *et al.* (62) proposed that urine samples in preeclampsia exhibited congophilia, a well recognized marker of protein instability and misfolding. The urine congophilic material includes proteoforms of ceruloplasmin, Ig free light chains, serpin peptidase inhibitor 1, albumin, IFN-inducible

protein 6–16, and Alzheimer β -amyloid. The presence of β -amyloid aggregates in placentas of women with preeclampsia and fetal growth restriction further supports the notion that such protein aggregates might be directly pathogenic to the placenta. Urine congophilia was found to be significantly elevated in high-risk women with severe preeclampsia and medically indicated deliveries compared with in women who were healthy pregnant controls and those with chronic or gestational hypertension (62). (High risk was defined as women with chronic hypertension, history of severe preeclampsia, twin pregnancy, diabetes, diabetic nephropathy, nephrolithiasis, membranous nephropathy, autoimmune disease, or sickle cell disease with history of crises.) Furthermore, in a longitudinal portion of this study where 56 high-risk women were followed, 78% of the women who developed preeclampsia requiring delivery had high congophilia levels (defined by Congo red retention of $\geq 15\%$ after removal of unbound Congo red) at study entry, which was >10 weeks before clinical manifestation of the disease. However, for low- and high-risk women who did not develop preeclampsia, there was no significant difference in their congophilia levels at study entry. These findings suggest that congophilia plays a pathophysiologic role early in disease and may be used as a predictive marker (62).

Subtypes of Preeclampsia

Ness and Roberts (63) in 1996 had proposed to distinguish preeclampsia into two broad categories: placental and maternal. Others have categorized into early onset (<34 weeks of gestation) versus late onset (>34 weeks of gestation) (64). These two subtypes seem to have different etiologies and phenotypes. In placental or early-onset preeclampsia, the etiology is abnormal placentation under hypoxic conditions with higher levels of sFlt-1, lower PIGF, and higher sFlt-1-to-PIGF ratio compared with in maternal preeclampsia (65,66). Uterine Doppler studies have also been shown to have a higher accuracy in identifying patients who will subsequently develop early- rather than late-onset preeclampsia (67–69). These findings support the abnormal high impedance to blood flow in the uterine arteries that has been associated with failure of physiologic transformation of spiral arteries (70–72). In maternal preeclampsia or late-onset preeclampsia, the problem arises from the interaction between a presumably normal placenta and maternal factors that are plagued with endothelial dysfunction, making them susceptible to microvascular damage. These commonly used classifications seem to have prognostic value, because placental or early-onset preeclampsia carries a significantly higher risk of maternal and fetal complications (64,73,74). They also harbor a greater prevalence of placental lesions, especially between 28 and 32 weeks of gestation (75). Hence, placental or early-onset preeclampsia is associated with fetal growth restriction and adverse maternal and neonatal outcomes (76,77). However, maternal or late-onset preeclampsia seems to be a decompensated response to the oxidase stress in the placenta by a dysfunctional maternal endothelium. Endothelial dysfunction, which is one aspect of a systemic maternal inflammatory response, may result in generalized vasoconstriction and reduced blood to

multiple organs, including the heart, kidney, and brain (78). However, because the level of pathology does not seem to be at the placenta, it is generally associated with a lower rate of fetal involvement and more favorable perinatal outcomes (77,79). Despite the pathophysiologic differences between these subtypes of preeclampsia, one must recognize that the distinction is not always clear cut, because the two subtypes may harbor significant overlap, such as in the older woman with vascular disease who experiences abnormal placentation. Thus, although subtyping may be helpful in the understanding and prognostication of the condition, most patients with preeclampsia have elements of both pathologies.

Maternal Outcomes

Multiple clinical studies of women with preeclampsia show an increased risk of developing cardiovascular diseases later in life (80). An often-quoted meta-analysis of prospective and retrospective cohort studies of 3,488,160 women showed that the relative risk for hypertension was 3.70 (95% CI, 2.70 to 5.05) after 14.1 years weighted mean follow-up and that the relative risks for ischemic heart disease and stroke were 2.16 (95% CI, 1.86 to 2.52) after 11.7 years and 1.81 (95% CI, 1.45 to 2.27) after 10.4 years, respectively (81). Three individual studies performed in Norway, California, and Taiwan indicated that women with preeclampsia have a ≤ 12 -fold increase in risk for developing cardiovascular disease (73,82,83). Additional adverse outcomes, such as the increased risk of renal disease (84), metabolic disorders (85,86), and death (73), have also been reported. Early-onset preeclampsia conferred a higher risk of end organ damage in terms of cardiovascular, respiratory, central nervous, renal, and hepatic systems compared with late onset (87). These clinical studies, however, do not delineate whether preeclampsia is a cause or a marker for long-term vascular disease.

Guidelines

The classification schema of hypertensive disorders in pregnancy in general and the definition of preeclampsia in particular have been variably modified in recent years. The well known classification system was adopted by the National High Blood Pressure Education Program (NHBPEP) Working Group in 1990 and subsequently endorsed by 46 medical organizations. The updated version in 2000 has become a standard that the American College of Obstetrics and Gynecology (ACOG) follows (88). Since the NHBPEP original reports, guidelines from international societies have emerged, each with their own evidence, although many with similar recommendations. Of note, one of the most important advances or amendments is the ACOG definition of preeclampsia: it no longer requires the presence of proteinuria as long as there is evidence of other end organ damage (Table 1). Diagnosing preeclampsia in the setting of CKD may be one of the most difficult if not an impossible task, because they share many of the same features. Interestingly, none of the societies address this issue in their guidelines. However, the angiogenic markers (as mentioned above in Angiogenic Factors) sFlt-1 and PIGF have been shown to be able to distinguish

Table 1. Comparison of definitions among different societies

| Category | ACOG (89) | SOGC (90) | RCOG (www.nice.org.uk/guidance/cg107) | SOMANZ (91) | ISSHP (92) |
|-------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
| Chronic HTN/ essential HTN | sBP \geq 140 mmHg and/or dBP \geq 90 mmHg known to predate conception or detected before 20 wk of gestation, with no underlying cause | sBP \geq 140 mmHg and/or dBP \geq 90 mmHg that develops either pre-pregnancy or at $<20+0$ wk of gestation Preexisting HTN with comorbid conditions Preexisting HTN with superimposed preeclampsia | HTN that is present at the booking visit or before 20 wk or if the woman is already taking antihypertensive medication when referred to maternity services | sBP \geq 140 mmHg and/or dBP \geq 90 mmHg confirmed before pregnancy or before 20 completed wk of gestation without a known cause | High BP predating the pregnancy |
| Gestational HTN | New-onset elevations of BP after 20 wk of gestation, often near term, in the absence of accompanying proteinuria | HTN that develops for the first time at $\geq 20+0$ wk of gestation Gestational HTN with comorbid conditions Gestational HTN with evidence of preeclampsia | New HTN presenting after 20 wk without significant proteinuria | New onset of HTN after 20 wk of gestation without any maternal or fetal features of preeclampsia followed by return of BP to normal within 3 mo postpartum | When <i>de novo</i> HTN is present after 20 wk of gestation in the absence of proteinuria and maternal organ/uteroplacental dysfunction |
| Preeclampsia/ eclampsia | HTN as defined above, associated with proteinuria (24-h excretion \geq 300 mg), diagnosed after 20 wk of uneventful gestation up to 2 wk postpartum In the absence of proteinuria, new-onset HTN with new onset of any of the following Platelet count $<100,000/\mu\text{L}$, serum creatinine >1.1 mg/dl, or doubling of concentration in absence of other renal disease Transaminitis to twice normal concentration Pulmonary edema Cerebral/visual symptoms | Gestational HTN with one or more of the following New proteinuria One or more adverse conditions ^a One or more severe complications ^b | Preeclampsia is new HTN presenting after 20 wk with significant proteinuria Eclampsia is a convulsive condition associated with preeclampsia Hemolysis, elevated liver enzymes, and low platelet count syndrome Severe preeclampsia: preeclampsia with severe HTN and/or symptoms and/or biochemical and/or hematologic impairment | Multisystem disorder unique to human pregnancy characterized by HTN and involvement of one or more other organ systems and/or the fetus | When <i>de novo</i> HTN is present after 20 wk of gestation in the presence of proteinuria and maternal organ/uteroplacental dysfunction |

Table 1. (Continued)

| Category | ACOG (89) | SOGC (90) | RCOG (www.nice.org.uk/guidance/cg107) | SOMANZ (91) | ISSHP (92) |
|----------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Preeclampsia/eclampsia superimposed on chronic HTN | HTN diagnosed before or in early gestation and development of associated proteinuria | HTN along with the development of one or more of the following at ≥20 wk Resistant HTN New or worsening proteinuria One or more adverse conditions ^a One or more severe complications ^b | None specified | Woman with chronic HTN developing one or more of the systemic features of preeclampsia after 20 wk of gestation | One or more of the above features of preeclampsia (<i>i.e.</i> , proteinuria and maternal organ/uteroplacental dysfunction) occur in addition to HTN |
| Other HTN effects | White coat HTN; elevated BP primarily in the presence of health care providers | White coat HTN: BP that is elevated in the office but consistently normal outside of the office (<135/85 mmHg) by ABPM or HBPM Transient hypertensive effect: elevated BP may be caused by environmental stimuli (<i>e.g.</i> , the pain of labor) Masked hypertensive effect: BP that is consistently normal in the office (sBP <140 mmHg or dBP <90 mmHg) but elevated outside of the office (≥135/85 mmHg) by ABPM or repeated HBPM | None specified | White coat HTN: raised BP in the presence of a clinical attendant but normal BP otherwise as assessed by ABPM or HBPM Secondary HTN: raised BP in the presence of an inciting factor such as CKD (<i>e.g.</i> , GN, reflux nephropathy, and adult polycystic kidney disease) Renal artery stenosis Systemic disease with renal involvement (<i>e.g.</i> , diabetes mellitus or SLE) Endocrine disorders (<i>e.g.</i> , pheochromocytoma, Cushing syndrome, and primary hyperaldosteronism) Coarctation of the aorta | White coat HTN: normal BP using 24-h ABPM in the first half of pregnancy |

ACOG, American College of Obstetrics and Gynecology; SOGC, Society of Obstetricians and Gynecologists of Canada; RCOG, Royal College of Obstetricians and Gynecologists; SOMANZ, Society of Obstetric Medicine of Australia and New Zealand; ISSHP, International Society for the Study of Hypertension in Pregnancy; HTN, hypertension; sBP, systolic BP; dBP, diastolic BP; ABPM, ambulatory BP monitoring; HBPM, home BP monitoring.

^aAdverse condition: involvement of organ systems, such as central nervous (headache, visual symptoms, seizure, *etc.*), cardiorespiratory (chest pain, hypoxia, poorly controlled HTN, *etc.*), hematologic (low platelet count, elevated international normalized ratio [INR] or partial thromboplastin time [PTT], *etc.*), renal (elevated creatinine, elevated uric acid, new indication for dialysis, *etc.*), hepatic (right upper quadrant pain, transaminitis, low plasma albumin, *etc.*), or fetoplacental system (abnormal fetal heart rate, oligohydramnios, stillbirth, *etc.*)

^bSevere complications: complications of central nervous (*e.g.*, eclampsia, posterior reversible encephalopathy syndrome [PRES]), cortical blindness, Glasgow coma scale <13, stroke, transient ischemic attack [TIA], or reversible ischemic neurological deficit [RIND]), cardiorespiratory (*e.g.*, uncontrolled severe HTN over 12 hours, despite use of three antihypertensive agents, oxygen saturation <90%, pulmonary edema, positive inotropic support, or myocardial ischemia or infarction), hematologic (platelet count <50×10⁹/L or transfusion of any blood product), renal (AKI or new indication for dialysis), hepatic (INR >2 in the absence of disseminated intravascular coagulopathy [DIC] or warfarin), or fetoplacental system (abruption with evidence of maternal or fetal compromise, reverse ductus venosus A wave, or stillbirth).

preeclampsia from CKD (13,14) and thus, may be potentially incorporated in practice for more clarity.

Comparison of Guidelines from International Societies

Although there may be myriad societal guidelines, we chose to review those that have been most impactful and used. In the United States, however, the classification scheme as per the ACOG in 2013 comprising four categories remains unchanged (89). In 2014, the Society of Obstetricians and Gynecologists of Canada released revised recommendations on hypertension in pregnancy on the basis of literature reviews and criteria from the Canadian Task Force on Preventative Health Care (90). The National Institute for Health and Care Excellence in the United Kingdom in 2010 introduced evidence-based guidelines on the diagnosis and management of hypertension during pregnancy, birth, and the postnatal period (www.nice.org.uk/guidance/cg107). The Society of Obstetric Medicine of Australia and New Zealand has expanded its definition of chronic hypertension (91). Finally, the International Society for the Study of Hypertension in Pregnancy submitted a revised statement in 2014 that includes the categories of chronic hypertension, gestational hypertension, preeclampsia (*de novo* or superimposed on chronic hypertension), and white coat hypertension (92). The main categories from each society have been summarized in Table 1.

BP Targets

Treatment targets for BP, although similar, may also be slightly different between societies and may depend on the presence of end organ damage or comorbidities. We have summarized the treatment goals in Table 2.

In being more aggressive with BP treatments, we are somewhat reassured by the results of the recent multicenter, randomized, controlled study: the Control of Hypertension in Pregnancy Study (93). This study showed that a tighter target of diastolic BP of 85 mmHg had nonsignificant maternal and fetal outcomes compared with a less tight control level of 100 mmHg. The less tight control group, however, had a higher incidence of severe hypertension, thrombocytopenia, elevated liver enzymes with symptoms, and a trend toward a higher incidence of hemolysis, elevated liver enzymes, and low platelets syndrome. Thus, it seems that tighter control of BP is not only safe for the fetus but potentially beneficial to the mother. However, one must be realistic and mindful of the evidence of treating mild to moderate hypertension in pregnancy. Abalos *et al.* (94) showed in their Cochrane Database review that, although the risk of developing severe hypertension was cut in half in women with the use of antihypertensive medications compared with those not using them, there was no clear evidence of a reduction in the development of preeclampsia or eclampsia. It seems that the development of preeclampsia/eclampsia is independent of the BP level, which limits our ability to prevent and treat this condition.

Preconception Counseling, Prevention, Treatment, and Postpartum Care in Preeclampsia

The care of the woman at risk for preeclampsia starts with preconception counseling followed by prevention, treatment, and appropriate postpartum follow-up. An extensive review of this topic is beyond the scope of this paper. However, we would like to highlight a few salient points. The ACOG recommends that women who had

| Society | When to Start Treatment | Treatment Goals |
|---------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|
| ACOG (89) | ≥160/105 for chronic HTN or 160/110 for gestational HTN or preeclampsia | 120–160/80–105 for chronic HTN |
| SOGC (90) | BP lowered to <160/110 in severe HTN or BP of 140–159/90–109 for nonsevere HTN with comorbid conditions | 130–155/80–105 for nonsevere HTN without comorbid conditions ^a or <140/90 nonsevere HTN with comorbid conditions |
| NICE (www.nice.org.uk/guidance/cg107) | >150/100 for uncomplicated chronic HTN/gestational HTN/preeclampsia or >140/90 for target organ damage secondary to chronic HTN | <150/100 but diastolic BP >80 for chronic HTN or <150/80–100 for gestational HTN and preeclampsia |
| SOMANZ (91) | ≥160/110 for mild to moderate HTN or ≥170/110 for severe HTN | None recommended |
| ISSHP (92) | 160–170/110 for preeclampsia | None recommended |

Numbers indicate systolic BP/diastolic BP in millimeters of mercury. ACOG, American College of Obstetrics and Gynecology; HTN, hypertension; SOGC, Society of Obstetricians and Gynecologists of Canada; NICE, National Institute for Health and Care Excellence; SOMANZ, Society of Obstetric Medicine of Australia and New Zealand; ISSHP, International Society for the Study of Hypertension in Pregnancy.

^aComorbid conditions: pregestational type 1 or 2 diabetes mellitus or kidney disease.

Table 3. Preventive and treatment strategies in preeclampsia/eclampsia

| Intervention | Evidence | Benefit(s) | Quality of Data | Comments |
|---------------------------------|---------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Calcium supplementation | 13 RCTs, 15,730 women analyzed by a Cochrane review (97) | RR, 0.45 (95% CI, 0.31 to 0.65) (97) | High | High-dose calcium (>1 g/d) reduced the risk of preeclampsia in subgroups with low calcium intake of <1 g/d and women at high risk of preeclampsia |
| Vitamin C and E supplementation | Multicenter RCT involving 1877 women (98) Multicenter RCT involving 2410 women (54) | RR, 1.20 (95% CI, 0.82 to 1.75) (98) RR, 0.97 (95% CI, 0.80 to 1.17) (54) | High | Patients were given 1000 mg vitamin C and 400 IU vitamin E; associated with low-birth weight babies (54) |
| Aspirin | Meta-analysis of 34 RCTs involving 11,348 women (99) Meta-analysis of 13 RCTs involving 12,184 women (100) | Before 16 wk of gestation: RR, 0.47 (95% CI, 0.34 to 0.65); after 16 wk of gestation: RR, 0.81 (95% CI, 0.63 to 1.03) (99) ARR=2%–5% (100) | High (99); fair to good (100) | Reduction in preeclampsia, especially if used before 16 wk of gestation in high-risk women The USPSTF Study suggests that low-dose aspirin in high-risk women has important benefits when used as early as the second trimester |
| UFH and LMWH | Meta-analysis of 10 RCTs involving 1139 women (101) | RR, 0.43 (95% CI, 0.28 to 0.65) (101) | Fair to good | Significant reduction in secondary outcome of preeclampsia in high-risk patients; significant reduction in risk of perinatal mortality, preterm birth before 34 and 37 wk of gestation, and infant birth weight <10th percentile; it was not possible to evaluate the effect of UFH compared with LMWH |
| Magnesium sulfate | RCTs ranging from 1687 to 2138 women (102,103) | 0.009% versus 0% of phenytoin versus magnesium to prevent eclampsia ($P=0.004$) (102); 52% lower risk of recurrent convulsion than diazepam (95% CI, 64% to 37% reduction); 67% lower risk of recurrent convulsions than phenytoin (95% CI 79% to 47% reduction) (103) | High | Significant reduction in the incidence of initial and recurrent seizures in women with gestational HTN compared with use of anticonvulsants, like phenytoin and diazepam |

RCT, randomized, controlled trial; RR, relative risk; 95% CI, 95% confidence interval; ARR, absolute risk reduction; USPSTF, US Preventive Services Task Force; UFH, unfractionated heparin; LMWH, low molecular weight heparin; HTN, hypertension.

preeclampsia in a prior pregnancy seek preconception counseling and assessment. In addition, they recommend that for women who have a history of chronic hypertension, the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers is contraindicated for those desiring pregnancy (<http://www.acog.org/Resources-And-Publications/Task-Force-and-Work-Group-Reports/Hypertension-in-Pregnancy>). We agree with preconception counseling in high-risk individuals; however, we do not recommend against the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in women with comorbidities, such as diabetes, proteinuria, or CKD, because of the weak evidence of congenital malformations in the first trimester (95,96). We do recommend that these agents be discontinued after pregnancy has been confirmed. We have also summarized important therapies in the prevention and treatment of preeclampsia and eclampsia

in Table 3. First-line antihypertensive agents are presented in Table 4. Postpartum surveillance, as per the ACOG guidelines, includes obtaining a cardiovascular profile, including yearly assessment of BP, lipids, fasting blood glucose, and body mass index, in women with a history of preterm preeclampsia or recurrent preeclampsia (89). It is recognized that the evidence behind these recommendations is low and thus, health care providers must individualize their decisions on the basis of the value of this information versus convenience and cost.

In summary, with our ever-expanding insight into the pathogenesis of preeclampsia and now, a revised definition of preeclampsia, we hope to more accurately diagnose and treat these patients. Furthermore, the recognition of the long-term consequences of this entity will hopefully enhance our care for these women during pregnancy and for decades afterward.

Table 4. First-line medication choices in treatment of hypertension of pregnancy

| Drug | Dose | Adverse Events in Pregnancy | Comments |
|--------------------|------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|
| Methyldopa (PO) | 500 mg to 3 g in two divided doses | Peripheral edema, anxiety, nightmares, drowsiness, dry mouth, hypotension, maternal hepatitis, no major fetal adverse events | Contraindicated in depression |
| Labetalol (PO) | 100–1200 mg/d in two to three divided doses | Persistent fetal bradycardia, hypotension, neonatal hypoglycemia, asthma | Risk of bronchospasm, bradycardia |
| Labetalol (IV) | 10–20 mg; repeat 20–80 mg iv every 30 min or 1–2 mg/min; maximum of 300 mg/d | Persistent fetal bradycardia, hypotension, neonatal hypoglycemia, asthma | Avoid in asthma or heart failure |
| Nifedipine (PO) | 30–120 mg/d | Hypotension and inhibition of particularly if used in combination with magnesium sulfate | Contraindicated in aortic stenosis; Immediate release nifedipine not recommended |
| Hydralazine (PO) | 50–300 mg/d in two to four divided doses | Hypotension, neonatal thrombocytopenia, lupus-like syndrome, tachycardia | Flushing, headache |
| Hydralazine | 5–10 mg iv/im; may repeat every 20–30 min to a maximum of 20 mg | Tachycardia, hypotension, headache, fetal distress | Hypotension and inhibition of labor, especially when combined with magnesium sulfate |
| Nicardipine (IV) | Initial: 5 mg/h increased by 2.5 mg/h every 15 min to a maximum of 15 mg/h | Headache, edema, tachycardia | Increased risk of hypotension and inhibition of labor, especially when combined with magnesium sulfate |
| Nitroprusside (IV) | 0.3–0.5 to 2 μ g/kg per minute; maximum duration of 24–48 h | Risk for fetal cyanide toxicity | Use >4 h and dose >2 μ g/kg per minute associated with increased risk of cyanide toxicity; use only as a last resort |

PO, oral; IV, intravenous.

Disclosures

None.

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