Postpartum preeclampsia or eclampsia: defining its place and management among the hypertensive disorders of pregnancy

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High blood pressure in the postpartum period is most commonly seen in women with antenatal hypertensive disorders, but it can develop de novo in the postpartum time frame. Whether postpartum preeclampsia or eclampsia represents a separate entity from preeclampsia or eclampsia with antepartum onset is unclear. Although definitions vary, the diagnosis of postpartum preeclampsia should be considered in women with new-onset hypertension 48 hours to 6 weeks after delivery. New-onset postpartum preeclampsia is an understudied disease entity with few evidence-based guidelines to guide diagnosis and management. We propose that new-onset hypertension with the presence of any severe features (including severely elevated blood pressure in women with no history of hypertension) be referred to as *postpartum preeclampsia* after exclusion of other etiologies to facilitate recognition and timely management. Older maternal age, black race, maternal obesity, and cesarean delivery are all associated with a higher risk of postpartum preeclampsia. Most women with delayed-onset postpartum preeclampsia present within the first 7 to 10 days after delivery, most frequently with neurologic symptoms, typically headache. The cornerstones of treatment include the use of antihypertensive agents, magnesium, and diuresis. Postpartum preeclampsia may be associated with a higher risk of maternal morbidity than preeclampsia with antepartum onset, yet it remains an understudied disease process. Future research should focus on the pathophysiology and specific risk factors. A better understanding is imperative for patient care and counseling and anticipatory guidance before hospital discharge and is important for the reduction of maternal morbidity and mortality in the postpartum period.

Key words: delayed-onset postpartum preeclampsia, hypertension, new-onset postpartum preeclampsia, postpartum, postpartum eclampsia, postpartum hypertension, pregnancy

Introduction

Hypertensive disorders of pregnancy complicate between 10% and 20% of pregnancies in the United States. They are responsible for a substantial proportion of maternal morbidity and mortality and the number one reason for postpartum hospital readmission.[1–3] Although most cases are diagnosed during the antepartum period, new-onset or de novo postpartum preeclampsia (PE) is increasingly being recognized as an important contributor to maternal morbidity and mortality in the postpartum period.[4] High blood pressure (BP) in the postpartum period is most commonly seen in women with antenatal hypertensive disorders, but it can develop de novo in the postpartum time frame. Although definitions vary, the diagnosis of postpartum PE should be considered in women with new-onset hypertension in the postpartum period. There is a need for improved terminology surrounding immediate postpartum PE (within the first 48 hours after delivery) and delayed-onset postpartum PE, which has traditionally been defined as new-onset PE 48 hours after delivery to 6 weeks after delivery. Most reports on postpartum PE are limited to smaller case series; thus, the overall incidence has not been reliably ascertained in a prospective fashion. Literature estimates on the prevalence range between 0.3% and 27.5% of all pregnancies in the United States.[5] The wide variation likely reflects that milder disease may go unnoticed after delivery, and many women may present to urgent care centers, emergency rooms, or primary care physicians who may be less familiar with this disease process and the potential for adverse maternal outcomes.

Whether postpartum PE or eclampsia represents a distinct entity from PE or eclampsia with antepartum onset is unclear and remains a source of debate. In this review, we do not necessarily propose to label it as a separate disease process but will discuss the limited literature surrounding this entity and highlight its importance in postpartum care and the need for better recognition and timely management. We intend here to review risk factors, clinical manifestations, and management and maternal outcomes for pregnancies complicated by postpartum PE. In addition, we will attempt to address the understudied aspects of the disease, including potential etiologies and implications for future

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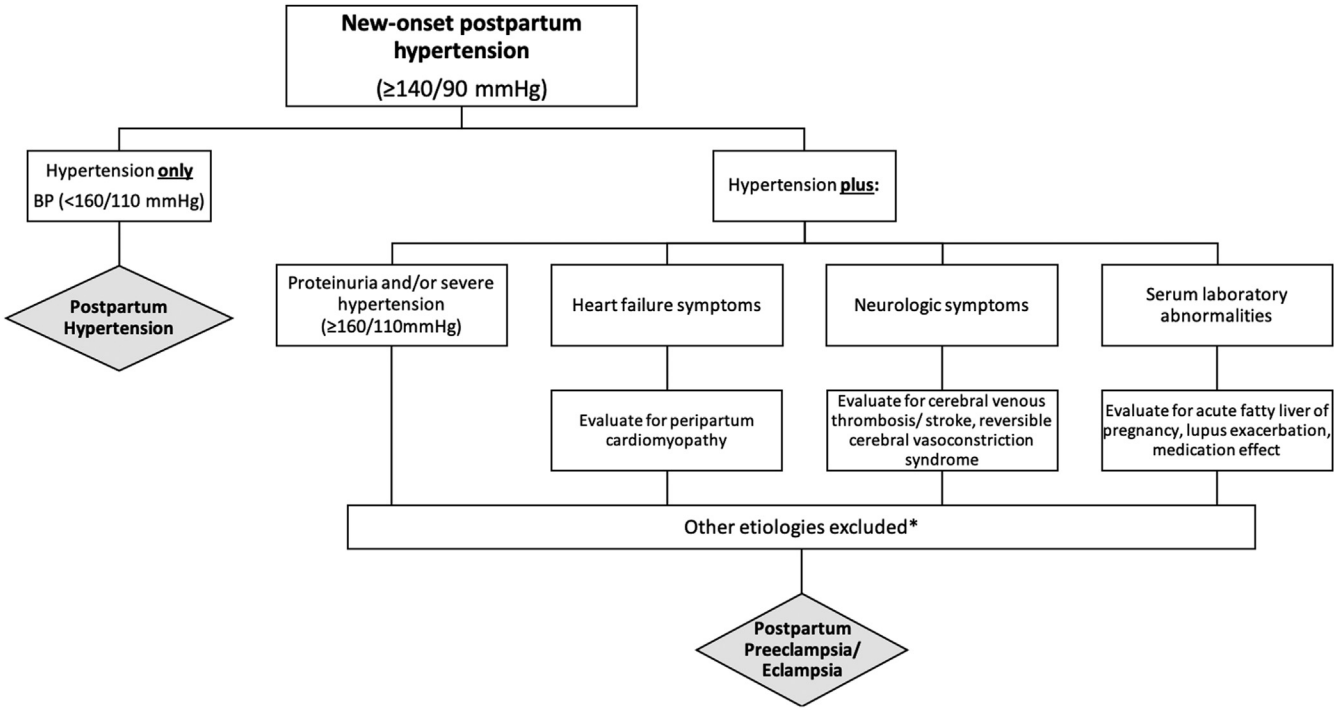
FIGURE 1
Suggested approach to new-onset postpartum hypertension



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maternal health and priorities for future research.

Definition

Few national or international guidelines address new-onset postpartum hypertension, and there are no clear definitions within existing guidelines. The American College of Obstetricians and Gynecologists (ACOG), the Royal College of Obstetricians and Gynaecologists (RCOG)/National Institute for Health and Care Excellence (NICE), and the Society of Obstetricians and Gynaecologists of Canada do not specifically define postpartum PE and do not distinguish between new-onset postpartum PE and new-onset postpartum hypertension.[4,6,7] In our experience, this is a diagnostic question that frequently arises when providing clinical care for this population of women.

With regard to timing, we propose that the diagnosis of postpartum PE should be considered in women with new-onset PE 48 hours after delivery to 6 weeks after delivery. Although this timing is not explicitly defined, this is the terminology used by experts and existing literature on the topic.[8–10] We acknowledge that the postpartum time frame is a continuum, and this time frame may need to be modified as we better understand the pathophysiology of this condition. The duration of 48 hours has traditionally been used because this generally encompasses immediate postpartum changes and usual in-hospital management. Importantly, other causes should be considered in cases of postpartum hypertension and seizures beyond 4 weeks postpartum. We believe further study is needed to determine if new-onset postpartum PE or eclampsia is a distinct entity from PE with antepartum onset; that said, we recommend that this condition be highlighted here and in national and international guidelines, as it is underrecognized by providers.

The definitions of hypertension and PE are extrapolated from guidelines surrounding hypertensive disorders of pregnancy with antepartum onset, that is, 140/90 mm Hg.[4] There is no evidence to suggest that the presence of proteinuria is associated with worse clinical outcomes or that it is helpful in differentiating among potential subtypes of postpartum hypertension. In our clinical experience, women without proteinuria seem to be just as likely to experience adverse clinical outcomes as women with substantial proteinuria. However, recognizing the limited data on clinical outcomes, we suggest continuing to evaluate for proteinuria, consistent with existing guidelines, until further studies evaluating outcomes in this population are available. Extrapolating from ACOG guidelines on the antepartum diagnosis of PE and gestational hypertension, we suggest that less emphasis be placed on the presence of proteinuria among women with new-onset postpartum hypertension.[4] We present a suggested evaluation and diagnostic framework in Figure 1. Of note, in line with ACOG

recommendations regarding PE with antepartum onset, elevated BP should be confirmed on 2 occasions at least 4 hours apart, except in the case of severe hypertension, which should be confirmed within minutes to facilitate timely treatment. In the absence of specific postpartum definitions from ACOG, we propose that the presence of any severe features (including severely elevated BP in women with no history of hypertension) be referred to as *postpartum PE* after exclusion of other etiologies. This is in line with the current guidelines on the antepartum onset of disease with removal of the term "mild preeclampsia" to emphasize the considerable maternal morbidity associated with pregnancy-related hypertension.[11] We suggest reserving the term *postpartum hypertension* for women with nonsevere hypertension (≥140/90 mm Hg but <160/110 mm Hg) and no other end-organ involvement or other severe features (Box and Figure 1). Although severe postpartum hypertension may represent undiagnosed chronic hypertension or exacerbation of chronic hypertension, the presence of severe features warrants further workup and management similar to those outlined for postpartum PE.

Risk Factors

Demographics

Multiple cohort studies have addressed risk factors for postpartum PE and in general have found similar overlap with risk factors for PE with antepartum onset (Figure 1). Older maternal age, black race, and maternal obesity are associated with a higher risk of postpartum PE. The age of ≥35 years has been repeatedly demonstrated to be associated with an approximately 2-fold increased risk for postpartum PE.[13,14] Prepregnancy obesity seems to be consistently associated with an increased risk of postpartum PE in a dose-dependent fashion, with an up to 7.7-fold increased risk associated with body mass index of >40 kg/m^2. Black women have a 2- to 4-fold increased risk of postpartum PE compared with women of other races.[8,15] Unlike antepartum PE, postpartum PE does not seem to be more common among primiparous women.[8,16] Postpartum PE develops more commonly among women with a history of a hypertensive disorder in a previous pregnancy.[8,14]

Intrapartum risk factors

Cesarean delivery increases the risk of postpartum PE by 2- to 7-fold compared with vaginal delivery, which is a consistent finding across multiple studies.[8,13–16] Higher rates of intravenous (IV) fluid infusion on labor and delivery are also associated with an increased risk of postpartum PE.[15] To the best of our knowledge, published studies do not distinguish between prelabor cesarean deliveries and intrapartum cesarean deliveries, which would likely affect the amount of IV fluids administered. Women who receive greater volumes of IV crystalloids during labor and delivery may shift more fluid to the interstitial compartment and may subsequently be more likely to develop volume overload and hypertension when the fluid is remobilized to the intravascular space after delivery. Overall, studies have not shown an increased risk of postpartum PE associated with the use of epidural anesthesia and pharmacologic agents that might be hypothesized to raise BP, such as vasopressors or ergot derivatives in labor or after delivery.[14,15]

Clinical Presentation

As noted earlier, postpartum PE can develop after a pregnancy with no antecedent diagnosis of a hypertensive disorder of pregnancy or after a pregnancy complicated by gestational hypertension or in women with underlying chronic hypertension. Approximately 60% of patients with new, delayed-onset postpartum PE have no antecedent diagnosis of a hypertensive disorder of pregnancy.[10] Most women with delayed-onset postpartum PE present within the first 7 to 10 days after delivery; however, this varies widely in the literature with onset of up to 3 months after delivery reported.[17] Women most frequently present with neurologic symptoms, typically headache, which has consistently been reported as the most common symptom in approximately 60% to 70% of women across multiple studies (Figure 2).[8,10,15,18] Postpartum headache is exceedingly common; however, there are certain characteristics that should prompt additional investigation with imaging and/or consultation with a neurologist or neurosurgeon. In particular, refractory or thunderclap headaches or any headache associated with altered mental status, seizures, visual disturbances, or focal neurologic deficits should prompt an evaluation for other cerebrovascular etiologies. In addition to postpartum PE, the differential diagnosis for postpartum headache should include migraine headache, postdural puncture headache, medication-related headache, cerebral venous thrombosis, and reversible cerebral vasoconstriction syndrome.[19,20]

In previous studies, 21% of eclampsia occurs after delivery.[21] Less commonly, eclampsia has been reported as the presenting symptom in up to 10% to 15% of women with delayed postpartum PE or eclampsia.[10,22] Other symptoms include those associated with volume overload such as shortness of breath, chest pain, and peripheral edema. Less commonly, women may present with BP elevations noted in either a physician's office or as noted on home BP monitoring; however, postpartum BP monitoring is not universally recommended for women without signs or symptoms of a hypertensive disorder.[8] These findings emphasize the importance of appropriate patient education regarding signs and symptoms that should prompt evaluation after discharge from the delivery hospitalization. Furthermore, because women without an antenatal hypertensive disorder of pregnancy typically do not have a visit with an obstetrical provider for 2 to 6 weeks after delivery, appropriate education of other providers who may interact with women during the initial postpartum period, such as pediatricians, is critical to ensure timely identification and management. In an effort to facilitate early detection of postpartum PE, our institution has initiated a quality improvement initiative to screen women with BP measurement and for symptoms of PE during well newborn examinations. Similar efforts and education are imperative for all

BOX

Approach to women with postpartum PE

Postpartum PE proposed diagnostic criteria

BP: new-onset hypertension on >1 occasion, ≥4 hours apart (systolic BP of ≥140 mm Hg or diastolic BP of ≥90 mm Hg) within 6 weeks of delivery with no other identifiable etiology

And

- Proteinuria: protein-to-creatinine ratio of ≥0.3
- Thrombocytopenia: platelet count of <100,000
- Renal insufficiency: serum creatinine concentrations of >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
- Impaired liver function: elevated blood concentrations of liver transaminases to twice the normal concentration for individual laboratory study
- Other severe features: pulmonary edema, vision changes, or new-onset headache unresponsive to medication and not accounted for by alternative diagnoses

Or

Systolic BP of ≥160 mm Hg or diastolic BP of ≥110 mm Hg within 6 weeks of delivery with no other identifiable etiology in the absence of any of the abovementioned features

Diagnostic considerations

- Laboratory studies:
  - Complete blood count
  - Complete metabolic panel
  - Urine protein-to-creatinine ratio
  - Women with signs or symptoms of volume overload: consider brain natriuretic peptide
- Imaging: based on clinical presentation
  - Chest imaging to include chest X-ray or CT
  - Neuroimaging to include brain MRI or CT
  - Women with signs or symptoms of volume overload: consider echocardiogram

Management considerations

- Short-acting antihypertensive medications (IV labetalol, IV hydralazine, oral nifedipine)[a]:
  - Administered within 30–60 min
  - Threshold for treatment: BP of ≥160/110 mm Hg
  - Goal BP: <150/100 mm Hg
- Long-acting antihypertensive medications (most commonly oral labetalol, oral extended-release nifedipine)[a]:
  - Administered to maintain BPs of <140s–150s/90s–100s mm Hg
- Magnesium for seizure prophylaxis:
  - Recommended in women with neurologic symptoms
  - Weighted discussion of risks and benefits among women with other severe features, particularly 1 wk after delivery
- Diuresis (most commonly IV or oral furosemide)[a]:
  - Guided by clinical assessment of volume status
  - Should be given routinely in women with pulmonary edema or volume overload
- Follow-up:
  - Home BP monitoring and management where feasible; where not feasible, recommend short-interval in-office BP check (within 5–7 d)
  - BP assessment at comprehensive postpartum visit
  - Education on long-term morbidity associated with hypertensive disorders of pregnancy, risk factor identification, and management and at least annual assessment of BP

BP, blood pressure; *CT*, computed tomography; *IV*, intravenous; *MRI*, magnetic resonance imaging; *PE*, preeclampsia.

[a]Specific doses and frequency discussed in detail elsewhere.[4,6,12]

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providers who interact with women in the postpartum period, including Emergency Medicine providers and Primary Care and Family Practice physicians. A review of maternal death in California from 2002 to 2007 demonstrated that the emergency department was a site with several improvement opportunities. Among

women who died from pregnancy-related causes, two-thirds received care in an emergency department at some point during the prenatal or postpartum time frame.[23] Multidisciplinary approaches to care of women in the postpartum period are critical to early detection and reduction of maternal morbidity and mortality.

Evaluation of New-Onset Postpartum Hypertension

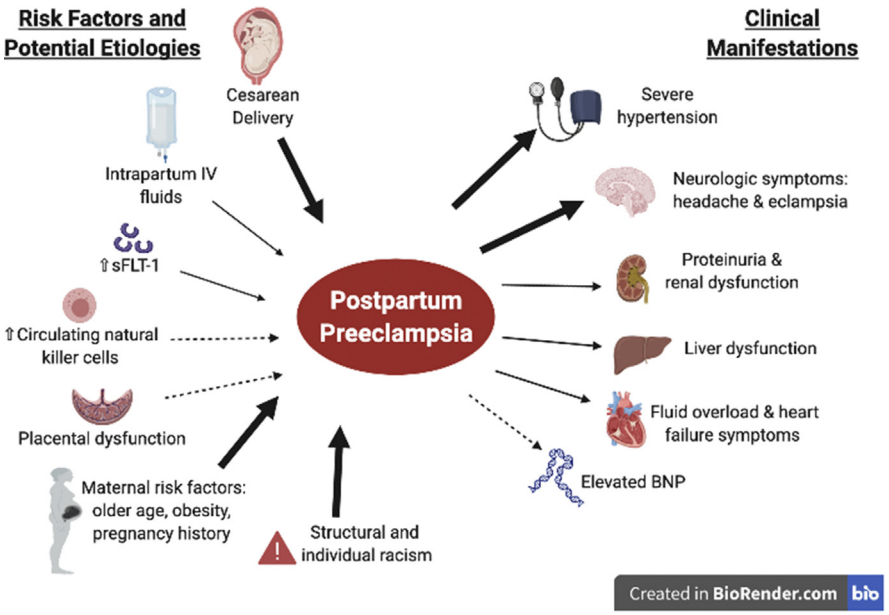
Laboratory studies and imaging

Diagnostic evaluation of new-onset postpartum hypertension should include a detailed history and physical examination, with close attention to clinical volume status, and cardiopulmonary and neurologic examination based on presenting signs and symptoms (Box). Serum laboratory evaluation should include assessment of electrolytes and renal function, platelet count, liver enzymes, and urine protein assessment. Previous studies have demonstrated that approximately 25% of women have abnormal serum laboratory values and approximately 20% to 40% have an elevated urine protein-to-creatinine ratio ($\geq$0.3).[8,10] Further laboratory assessment and imaging studies should be guided by the clinical presentation. Most women presenting with postpartum PE undergo at least 1 radiologic study (74%).[8] We review below the most common clinical presentations of postpartum PE and suggested workup.

In women with neurologic symptoms, such as headache or vision changes that persist after management of severe hypertension, neuroimaging should be considered to evaluate for cerebrovascular accident or posterior reversible cerebral encephalopathy. The differential diagnosis may include other etiologies of postpartum headache, such as postdural puncture headache, subarachnoid hemorrhage, central venous sinus thrombosis, thrombotic thrombocytopenic purpura, and migraine. For women with clinical evidence of volume overload, assessment of brain natriuretic peptide (BNP) can be useful to both confirm the diagnosis of fluid overload and guide management. BNP has an established role in the diagnosis, prognosis, and risk stratification of heart failure outside of pregnancy.[24] Secreted predominantly by the left ventricular cardiac myocytes in response to increased wall tension, BNP increases diuresis and decreases vascular tone.[25] Previous studies have demonstrated a high correlation of serum BNP levels with echocardiography findings of fluid overload in pregnancy.[26–28] Among women with postpartum PE at our institution with a BNP measured at the time of presentation (n=22), the median value was noted to be 424 (interquartile range, 190–645) pg/mL (upper limit of normal, <100 pg/mL).[8] Women with clinical evidence of volume overload or signs and symptoms of heart failure, such as shortness of breath, orthopnea, or palpitations, should also be evaluated for peripartum cardiomyopathy with a transthoracic echocardiogram.

There is conflicting evidence about the benefit of uterine curettage at shortening resolution time of hypertension and laboratory abnormalities among women with PE with antepartum onset.[29,30] Based on this, we do not routinely recommend uterine curettage for women with postpartum PE in the absence of retained products of conception. Thus, we recommend pelvic ultrasound to evaluate for retained products of conception only in women with a suggestive history.

FIGURE 2
Risk factors, etiology, and clinical manifestations of postpartum preeclampsia



BNP, brain natriuretic peptide; *IV*, intravenous; *sFLT-1*, soluble fms-like tyrosine kinase-1.

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Other etiologies of hypertension

The most common cause of hypertension in the postpartum period is a hypertensive disorder of pregnancy.[5] However, if the patient does not clearly meet the criteria for a hypertensive disorder of pregnancy, then secondary causes of hypertension should be considered (Figure 1). Other etiologies include preexisting renal disease, peripartum cardiomyopathy, lupus exacerbation, hyperthyroidism, primary hyperaldosteronism, renal artery stenosis, cerebrovascular accident, drug or medication use, and pheochromocytoma. Appropriate workup should be guided by the clinical presentation and may include additional laboratory studies and imaging such as renal artery ultrasound, thyroid function studies, basic metabolic panel, and urine metanephrines. Involvement of additional

consultants would clearly be warranted for further evaluation and management of these conditions. A previously published review article on this topic provides a comprehensive framework detailing the differential diagnosis and approach to workup of alternative etiologies of hypertension in this period.[5]

Management

Antihypertensive agents

Similar to the management of PE with antepartum onset, the cornerstone of management of postpartum PE is acute treatment of severe hypertension. There is clear evidence that sustained, severe hypertension is associated with an increased risk of maternal morbidity, including cerebrovascular accident and eclampsia.[31] Cerebral perfusion pressure is increased in PE compared with healthy pregnant women. During the postpartum period, mean cerebral blood flow velocities increase in women with PE. Both cerebral hyperperfusion and increased cerebral perfusion pressure increase wall tension of cerebral vessels and can therefore increase the risk of intracerebral hemorrhage.[32] ACOG recommends treating women with sustained, severe hypertension (≥160/110 mm Hg) with rapid-acting antihypertensive agents within 30 to 60 minutes. Agents used for management of acute, severe hypertension in the postpartum period are similar to those used during pregnancy and include IV labetalol, IV hydralazine, and oral nifedipine as first-line agents.[12] Previous studies have addressed differences in time to BP control with the use of IV hydralazine compared with IV labetalol and have found no difference.[33] Some indirect evidence suggests that oral nifedipine may be superior to hydralazine or labetalol for the management of acute, severe hypertension; however, these studies predominantly enrolled women during pregnancy, and there is a dearth of evidence regarding the efficacy of specific antihypertensive agents in the postpartum period.[34,35] Because there are no longer fetal considerations after delivery, a lower threshold for initiating treatment such as 150/100 mm Hg may be considered to prevent progression to severe hypertension.[36] Further studies are needed to determine optimal BP targets and ranges for initiation and maintenance in the setting of postpartum PE.

After the initial stabilization of BP, women should be initiated on oral antihypertensive agents if hypertension persists. Both ACOG and the RCOG/NICE recommend achieving a range of 140 to 150/90 to 100 mm Hg.[4,12,37] Because there are no standardized management guidelines for specific antihypertensive agents or parameters for medication titration in the postpartum period, physician preference, experience, cost of drug, safety during breastfeeding, and frequency of administration become important factors that affect the choice of therapy.[38] Options for oral antihypertensive agents are discussed in detail elsewhere and are beyond the scope of this review.[6]

Magnesium sulfate

Although magnesium sulfate for seizure prophylaxis is a key component of management of antepartum-onset PE with severe features, few evidence-based recommendations exist to guide the use of magnesium sulfate in women with postpartum PE.[39] ACOG recommends the use of magnesium sulfate for women with new-onset hypertension associated with headaches or blurred vision or PE with severe hypertension in the postpartum period, while acknowledging that this recommendation is based on low-quality evidence.[11] Eclampsia most commonly presents within 48 hours after delivery, with the highest risk time period extending through the first week after delivery.[10,40] However, as noted earlier, women with postpartum PE most frequently present with neurologic symptoms, including headache and eclampsia, that have been documented in 10% to 15% of women in larger case series.[10,22] Therefore, the authors recommend the use of magnesium for new-onset postpartum PE with any associated neurologic symptoms, particularly within the first week after delivery. Among women with severe disease as diagnosed by other non-neurologic features, such as severe hypertension, a discussion of risks and benefits of treatment is reasonable, particularly beyond the first week after delivery.

Diuresis

Multiple studies have noted the prevalence of clinical signs and symptoms of volume overload among women with postpartum PE, including shortness of breath (20% to 30%), peripheral edema (11% to 18%), and pulmonary edema (11%).[8,10] Diuretics lower BP by promoting natriuresis and decreasing intravascular volume that help to decrease cardiac preload and cardiac output.[41] The authors recommend thoughtful assessment of clinical volume status, using such parameters as urine output, weight change from delivery hospitalization, and clinical examination findings. In women with clinical evidence of volume overload, we recommend the use of diuresis to potentially further lower BP and shorten postpartum readmission. As noted earlier, the use of BNP as an adjunctive tool to inform decision making concerning volume status also seems to be promising.[42] Adequate diuresis can typically be achieved with the use of IV or oral furosemide and concurrent monitoring and repletion of serum electrolytes. For women with volume overload, consideration for a short course of daily oral furosemide is reasonable (3−5 days). Several randomized controlled trials have investigated the use of prophylactic diuresis with furosemide among women with PE with antepartum onset. In 1 study, women who had PE with severe features randomized to treatment with furosemide 20 mg orally daily were found to have significantly lower BP at postpartum day 2 and require significantly less antihypertensive therapy on discharge compared with women treated with placebo.[43] A more recent study demonstrated improved BP control and less need for antihypertensive medication among all women with hypertensive disorders of pregnancy randomized to furosemide 20 mg orally daily for the first 5 days postpartum compared with women treated with placebo.[44] Although further study is needed to support the routine use of prophylactic diuresis among women without clinical evidence

of volume overload, in women with evidence of volume overload, we recommend a short course of diuresis to potentially lower BP and shorten postpartum readmission.

Home blood pressure monitoring

Among women with antepartum hypertensive disorders, BP increases at 3 to 7 days after delivery.[41] The etiology for this exacerbation is unclear; however, others have speculated that it may be caused by mobilization of fluid during this time period.[41] Among women with antepartum-onset hypertensive disorders, remote hypertension monitoring improves compliance with ACOG recommendations surrounding BP assessment within the first 3 to 10 days after delivery, reduces disparities in BP ascertainment, and may identify women with otherwise unrecognized BP elevations requiring medication in this period.[4,45–47] Although home BP monitoring has not been studied specifically among a population of women with postpartum PE, based on existing data, the authors would advocate for its use because it has the potential to shorten the time of rehospitalization after delivery and allow for the detection and management of severe hypertension after hospital discharge without relying on in-office assessment. This may be particularly useful in light of overall low attendance rates at in-person postpartum follow-up visits and initiatives by ACOG to develop innovative approaches to delivering postpartum care.[45]

Etiology of Postpartum Preeclampsia

Typically, hypertension resolves relatively rapidly after delivery, with BP returning to prepregnancy range in the ensuing days to weeks. The traditional adage in obstetrics has always been that delivery of the placenta "cures" PE; thus, the onset of PE days to weeks after placental delivery raises questions about whether delayed postpartum PE is a subtype of antepartum PE or whether it represents a separate disease entity. Studies of angiogenic factors, inflammatory profiles, and placental pathology have been useful in informing this distinction. Antiangiogenic soluble fms-like tyrosine kinase-1 (sFlt-1) is a well-established pathogenic factor in PE, and imbalances between sFlt-1 and the proangiogenic placental-derived growth factor (PlGF) have been linked to the pathogenesis of PE with antepartum onset.[48] A prospective study that collected blood samples before cesarean delivery noted that women who developed new-onset postpartum PE had significantly higher sFlt-1 levels and a higher sFlt-1-to-PlGF ratio than women who remained normotensive postpartum.[49] This pattern is identical to that observed in PE with antepartum onset, leading the authors to hypothesize that women who develop postpartum PE may represent a group with subclinical PE that manifests as postpartum hypertension. Most women within this cohort (62%) developed postpartum hypertension between 48 and 72 hours after delivery, with only 5% developing hypertension 5 days after delivery.[49] Whether these imbalances in pro- and antiangiogenic factors are consistent among women who present days to weeks after delivery has not been studied, particularly considering sFlt-1 declines rapidly after delivery.[50]

In contrast, the immune and inflammatory profile at the time of disease seems to differ significantly between postpartum and antepartum PE.[51] The maternal circulating immune profile in women with antepartum PE has been well characterized, with a consistently noted increase in T lymphocytes compared with women with uncomplicated pregnancies.[51–53] In addition to an increase in T lymphocytes compared with controls, women with postpartum PE also have elevated natural killer and natural killer T cells not seen in women with antepartum PE.[51]

Similarly, placental findings from women with postpartum PE may further inform the etiology of the disease. Placental evidence of maternal vascular malperfusion is the pathognomonic lesion of PE and is thought to develop secondary to defective trophoblastic invasion and inadequate maternal uterine spiral artery remodeling.[54] This impaired transformation of the maternal vessels and the resultant lesions are a common pathologic finding proposed to be secondary to impaired delivery of nutrients and oxygen.[54,55] Comparison of placentas from women with early-onset PE, late-onset PE, and postpartum PE demonstrates that women with postpartum PE have similar rates of decidual vasculopathy as women with late-onset PE and controls.[56] This study is limited by its small sample size (<40 placentas per group) and inclusion of women with chronic hypertension, which is known to be associated with an increased frequency of placental lesions.[57] Larger-scale studies to fully understand the placental findings among women with postpartum PE are needed.

Overall, it is clear from the limited data that the etiology of postpartum PE and whether it is a subtype of antepartum PE remain unanswered.

Maternal Outcomes

Short-term morbidity

Emerging evidence suggests that the risk of severe maternal morbidity is higher among women with postpartum PE than women with antepartum disease. One recent study utilizing the Nationwide Readmissions Database assessed outcomes among women readmitted with postpartum-onset hypertension compared with women with a hypertensive disorder during pregnancy who were readmitted after delivery.[58] Although this study is limited by its use of administrative database–level data, the authors demonstrated a higher risk of severe maternal morbidity associated with new-onset postpartum hypertension than women with hypertension during pregnancy (12.1% vs 6.9%; $P<.01$). Women with a readmission associated with new-onset postpartum hypertension had a higher risk of eclampsia and stroke. They demonstrate that most cases of eclampsia, stroke, and overall severe morbidity associated with postpartum readmissions for hypertension occurred among women without a previous diagnosis of pregnancy-associated hypertension. These findings underscore the potential need for earlier identification of elevated BP among this population, which may allow for closer surveillance and prevention of these

TABLE
Research priorities in postpartum PE

Gaps in knowledge	Proposed methods and specific questions
Prospective determination of disease incidence and risk factors	• Prospective postpartum BP measurement after uncomplicated deliveries. • Telehealth and remote monitoring may be useful to address this gap.
In-depth understanding of etiology and pathophysiology	• Prospective biomarker identification both before disease onset and at the time of diagnosis • Placenta pathology to evaluate features of vascular malperfusion, if available • Biorepositories may assist in answering these questions.
Development of evidence-based management algorithms	• Prospective studies examining outcomes with varying treatment. • Priority should be given to the need for magnesium after delivery and the role of specific antihypertensive agents and routine use of diuretics. Determining optimal threshold for acute treatment and targets (for postpartum). Priority should also be given to the development of the most effective strategies for patient and provider education surrounding postpartum PE recognition and diagnosis.
Understanding the risk of recurrence and future pregnancy risk and optimal management	• Large-scale multicenter studies will likely be needed to address these questions. • Specific questions include the use of low-dose aspirin in future pregnancies and postpartum prophylaxis with home BP monitoring or diuresis in future pregnancies.
Assessing future risk to maternal health	• Clear definitions and classification will aid in determination of future cardiovascular risk. • Of particular interest is the risk of heart failure among women with postpartum PE, which is known to be increased among women with PE with antepartum onset.

BP, blood pressure; *PE*, preeclampsia.

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morbidities. They also emphasize the importance of education about signs and symptoms of postpartum PE in all women at the time of discharge from the delivery hospitalization. In addition to indicating serious postpartum morbidity, maternal hospital readmission after delivery is associated with high healthcare costs, disruption of early parenting, and increased family burden and is increasingly being tracked as a quality measure with financial implications.[59] Finally, it remains of critical importance to continue the broader education of other health professionals, such as Emergency Medicine providers, pediatricians, and primary care providers, who may be front-line providers for postpartum patients. New-onset hypertension postpartum should be distinguished from underlying prepregnancy chronic hypertension, because BP goals and short-term morbidity differ substantially.

Long-term morbidity

The American Heart Association and ACOG have identified hypertensive disorders of pregnancy as risk factors for later-life cardiovascular disease, including chronic hypertension, heart failure, and cardiovascular mortality.[60–63] Recent high-quality evidence suggests that the risk of chronic hypertension is 30% to 40% after a pregnancy complicated by PE as soon as 2 to 7 years after delivery, with an even higher risk observed among women with iatrogenic preterm birth secondary to PE.[64] Whether this risk is the same among women with postpartum PE has not been well studied. Most longer-term follow-up studies do not differentiate the time of onset of PE (antepartum vs postpartum). One study demonstrated that more than one-third of women with postpartum PE remained on antihypertensive agents at their postpartum visit and had significantly higher BP both at the postpartum visit and on longer-term follow-up, with 45% of women remaining hypertensive at follow-up (median, 1.1 years).[8] Further studies are needed to assess the risk of future cardiovascular disease among women with postpartum PE.

Future pregnancy outcomes

To the best of our knowledge, no studies have addressed the prevention of postpartum PE, recurrence risk of postpartum PE in future pregnancies, or management of future pregnancies specifically related to postpartum PE. Given the overlapping risk factors with antepartum PE, the authors advocate for a similar approach to that employed among women with a history of antepartum-onset PE, while acknowledging the lack of evidence in this population. In our practice, we recommend confirmation of normalization of BPs in the interpregnancy period. For women with a history of postpartum PE who remain on antihypertensive agents (21% in the aforementioned study),[8] we recommend ensuring women are on a medication with a favorable pregnancy safety profile. For women with a history of postpartum PE, we suggest a baseline assessment of renal and liver function and baseline urinary protein assessment depending on other risk factors. We also recommend low-dose aspirin for PE prevention, while acknowledging that no studies have specifically assessed efficacy in this population. In our experience, there is anecdotal evidence of recurrent postpartum PE; thus, for women who remain normotensive during pregnancy, we typically recommend at least a single BP check in the first week after delivery and close assessment of fluid status before discharge from the delivery hospitalization.

Research Recommendations

Clearly, there remain many unanswered questions in the etiology, diagnosis, and management of postpartum PE, which are outlined in the Table. As noted earlier, there is a wide range of the incidence reported in the literature, likely secondary to the fact that women with less severe disease may not present for care and thus may go undetected. Large prospective postpartum studies among women with uncomplicated pregnancies are needed to document the natural history of BP trajectory delivery, which could inform the true incidence of disease. Such large-scale studies would also allow more complete identification of risk factors and development of risk scores to assist in the determination of the need for closer postpartum follow-up. The lack of clear definitions from ACOG and others also limits the ability to distinguish whether there may be subtypes of disease or a different disease entity entirely. The identification of which women with postpartum PE are at highest risk for postpartum morbidity would allow for the development of evidence-based management algorithms and allow for prospective studies to evaluate algorithms and assess whether they affect postpartum morbidity. For example, it is very likely that not all women with postpartum PE necessitate hospital readmission or treatment with magnesium. A more in-depth understanding of disease subtypes, anticipated clinical course, risk factors, and biomarkers could facilitate the development of evidence-based management algorithms.

The authors note that one positive change that may result from the ongoing coronavirus disease 2019 pandemic is the increasing implementation of telehealth as an integral part of prenatal care. A component of this is the provision of home BP monitors for BP documentation during pregnancy. With an increasing proportion of the reproductive-aged population having access to self-monitoring devices, we may be able to implement widespread closer BP follow-up in first 1 to 2 weeks after delivery without requiring an in-person visit. Whether this should become standard of care or could be implemented successfully with women at risk for postpartum PE remains uncertain because prospective studies have not addressed this strategy. The authors suggest a shorter interval follow-up or home BP monitoring among women at high risk of developing postpartum PE. The use of biomarkers, such as anti- and proangiogenic factors, seems to be quite promising in risk prediction; however, whether these factors are useful for women who develop disease beyond 5 days after delivery is less clear. Perhaps biomarkers may provide useful insight into the pathophysiology of postpartum PE and assist in informing whether it is truly a distinct entity from PE with antepartum onset. Furthermore, the identification of biomarkers that can predict onset or need for rehospitalization could substantially reduce postpartum morbidity in this population. This should be a research priority in future studies. The use of biorepositories and multicenter approaches will be critical to address these issues. Finally, a more in-depth understanding of short- and long-term risk for women with a history of postpartum PE is needed. Whether the risk of recurrent PE is similar to women with a history of antepartum PE has not been studied. Finally, to inform long-term health, further studies are needed to address whether women with postpartum PE have an increased risk of cardiovascular disease.

Conclusions

Postpartum PE or eclampsia may be associated with a higher risk of maternal morbidity than PE with antepartum onset.[58] This highlights the need for timely recognition of symptoms and signs by patients and obstetrical and nonobstetrical providers. Postpartum PE remains an understudied disease process. Studies of delayed-onset postpartum PE are limited to case reports or small case series.[10] Here, we have outlined our approach to evaluation and management coupled with the most critical questions to be addressed by future research. Similar to much of the care we deliver in the fourth trimester, postpartum PE has been underrecognized and overlooked for too long. Understanding the etiology and each postpartum woman's risk of the disease is imperative for patient care and counseling and anticipatory guidance before hospital discharge and is crucial for the reduction of maternal morbidity and mortality in the postpartum period. ■

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