Etiology and management of postpartum hypertension-preeclampsia

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Postpartum hypertension can be related to persistence of gestational hypertension, pre-eclampsia, or preexisting chronic hypertension, or it could develop de novo postpartum secondary to other causes. There are limited data describing the etiology, differential diagnosis, and management of postpartum hypertension-preeclampsia. The differential diagnosis is extensive, and varies from benign (mild gestational or essential hypertension) to life-threatening such as severe preeclampsia-eclampsia, pheochromocytoma, and cerebrovascular accidents. Therefore, medical providers caring for postpartum women should be educated about continued monitoring of signs and symptoms and prompt management of these women in a timely fashion. Evaluation and management should be performed in a stepwise fashion and may require a multidisciplinary approach that considers predelivery risk factors, time of onset, associated signs/symptoms, and results of selective laboratory and imaging findings. The objective of this review is to increase awareness and to provide a stepwise approach toward the diagnosis and management of women with persistent and/or new-onset hypertension-preeclampsia postpartum period.

Key words: etiology, management, postpartum hypertension-preeclampsia

Hypertensive disorders of pregnancy are a major cause of maternal mortality and morbidity, especially in developing countries. Hypertension may be present before or during pregnancy or postpartum. Postpartum hypertension can be related to persistence of gestational hypertension (GH), preeclampsia, or preexisting chronic hypertension, or it could develop de novo secondary to other causes.

During the past decades, there has been extensive research regarding the incidence, risk factors, pathogenesis, prediction, prevention, and management of GH-preeclampsia. However, patients who were readmitted with postpartum hypertension-preeclampsia were not considered in reported studies. In addition, the available data in the medical literature have primarily focused on antenatal and peripartum management of such patients, even though some patients can develop de novo eclampsia and hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome in the late postpartum period. Thus, there are few data regarding the evaluation, management, and complications in women who are rehospitalized with diagnosis of postpartum hypertension. Therefore, this report will focus on the prevalence, etiology, and evaluation and management of women who have de novo or persistent postpartum hypertension.

Incidence

The exact incidence of postpartum hypertension is difficult to ascertain. In clinical practice, most women will not have their blood pressure (BP) checked until the 6 weeks’ postpartum visit in physician’s offices or in postpartum clinics. As a result, women with mild hypertension who are asymptomatic are usually not reported. In addition, postpartum women who have hypertension in association with symptoms such as headaches or blurred vision are often seen and managed in the emergency department and will not be coded as hypertensive unless they are hospitalized.

Research studies dealing with postpartum hypertension are usually limited by analysis of data from a single center, focused on inpatients in the immediate postpartum period (2-6 days), or describing patients who were readmitted because of preeclampsia-eclampsia, severe hypertension, or complications related to hypertension. Despite the limitations, the reported prevalence of de novo postpartum hypertension or preeclampsia ranges from 0.3–27.5%.

Etiology and differential diagnosis

The etiology and different diagnosis of postpartum hypertension is extensive (Table), but it can be focused based on clinical and laboratory findings as well as response to treatment of BP. GH-preeclampsia (new onset or preexisting prior to delivery) is the most common cause, however, other life-threatening conditions such as pheochromocytoma and cerebrovascular accidents should also be considered.

New-onset postpartum hypertension-preeclampsia

Normal pregnancy is characterized by increased plasma volume in association with sodium and water retention in the interstitial tissue. This is further exaggerated in women with multifetal gestation. In addition, many women receive intravenously a large volume of fluids during labor, delivery, and postpartum. Large volumes of fluids are also given because of regional analgesia-anesthesia or during cesarean section. In some women, acute or delayed mobilization of large
volume of fluid into the intravascular space, particularly in association with suboptimal renal function, can lead to a state of volume overload resulting in hypertension.\textsuperscript{11,13}

Some medications that cause vasoconstriction are often used for pain relief, in women having perineal lacerations, episiotomy, or cesarean delivery. Such women usually require large doses of nonsteroidal antiinflammatory drugs such as ibuprofen or indomethacin that are associated with vasoconstriction and sodium and water retention, both of which can result in severe hypertension.\textsuperscript{18} In addition, some women receive frequent injections of ergot alkaloids (ergometrine or methylergonovine) for treatment of uterine atony. The action of these medications is mediated through alpha adrenergic receptors, which can lead to peripheral vasoconstriction with resultant hypertension or aggravation of hypertension, cerebral vasoconstriction, and stroke.\textsuperscript{19} These medications are also associated with nausea, vomiting, and headaches, symptoms that are similar to those in severe GH–preeclampsia.

**Persistence/exacerbation of hypertension-proteinuria in women with preexisting GH–preeclampsia**

Maternal hypertension and proteinuria will usually resolve during the first week postpartum in most women with GH or preeclampsia, however, there are conflicting data regarding the time it takes for resolution in such women.\textsuperscript{20–25} The differences among various studies are due to the population studied, severity of disease process (mild, severe, with superimposed preeclampsia, HELLP syndrome), duration of follow-up, management (aggressive vs expectant), and criteria used for hypertension or proteinuria.\textsuperscript{21–25} In women with preeclampsia, there is a decrease in BP within 48 hours, but BP increases again between 3–6 days postpartum.\textsuperscript{20} In some patients, cerebral manifestations and/or deterioration in maternal laboratory findings will manifest for the first time postpartum leading to the development of eclampsia and/or HELLP syndrome.\textsuperscript{5,8,26–31}

**Persistence/exacerbation of hypertension in chronic hypertension**

Women with chronic hypertension during pregnancy are at increased risk for exacerbation of hypertension and/or superimposed preeclampsia.\textsuperscript{32} The risk depends on severity of hypertension, presence of associated medical conditions (obesity, type 2 diabetes, renal disease), or whether antihypertensive medications were used during pregnancy.\textsuperscript{32,33} Hypertension or exacerbation of hypertension postpartum may be due to either undiagnosed essential chronic hypertension (women with limited medical care prior to or early in pregnancy), or due to exacerbation of hypertension after delivery in those with superimposed preeclampsia.

Two studies in patients with superimposed preeclampsia suggest that systolic and diastolic BP increases at 3–6 days postpartum in such women.\textsuperscript{17,33}
Postpartum hypertension or preeclampsia can also be secondary to ≥1 of the underlying medical disorders listed in the Table.\textsuperscript{11,17,34-47}

### Maternal complications

Maternal complications depend on ≥1 of the following: severity and etiology of the hypertension, maternal status at presentation (presence of organ dysfunction), and the quality of management used. Potential life-threatening complications include cerebral infarction or hemorrhage, congestive heart failure or pulmonary edema, renal failure, or death. Maternal outcome is usually good in those with only isolated hypertension or preeclampsia, whereas it is poor with pheochromocytoma,\textsuperscript{38,39} stroke, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome,\textsuperscript{44,45} and with delayed diagnosis and inadequate control of persistent severe hypertension.

### Evaluation and management of postpartum hypertension

Evaluation of patients with postpartum hypertension should be performed in a stepwise fashion and may require a multidisciplinary approach. Consequently, management requires a well-formulated plan that takes the following factors into consideration: predelivery risk factors, time of onset in relation to delivery, presence of signs/symptoms, results of laboratory/imaging findings, and response to initial therapy (Figure).

The most common cause for persistent hypertension beyond 48 hours after delivery is GH, preeclampsia, or essential chronic hypertension (either preexisting prior to delivery or developing de novo).

Initial management will depend on their history, clinical findings, presence or absence of associated symptoms, results of laboratory findings (urine protein, platelet count, liver enzymes, serum creatinine, and electrolytes), and response to treatment of hypertension.

There are several medications that are frequently prescribed in the postpartum period such as ibuprofen, ergonovine, and anticongestants. Use of large or frequent doses of these agents can aggravate preexisting hypertension or results in new-onset hypertension.\textsuperscript{18,19} The use of these drugs is also associated with cerebral symptoms, nausea, and vomiting. Many physicians and consultants are not familiar with the effects of such medications. Therefore, all women with postpartum hypertension should be evaluated

\[AFLP,\text{ acute fatty liver of pregnancy; APAS, antiphospholipid antibody syndrome; HELLP, hemolysis, elevated liver enzymes, and low platelet; HUS, hemolytic uremic syndrome; RCVS, reversible cerebral vasoconstriction syndrome; TTP, thrombotic thrombocytopenic purpura.}\]


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\[\text{FIGURE}\]

Recommended evaluation and management of women with postpartum hypertension

- **Persistent hypertension postpartum**
  - Detailed history & physical examination
  - Presence of cerebral/gastrointestinal symptoms
  - Laboratory evaluation including proteinuria

<table>
<thead>
<tr>
<th>Hypertension only</th>
<th>Hypertension plus</th>
<th>Hypertension plus</th>
<th>Hypertension plus</th>
<th>Hypertension plus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
<td>Palpitations, tachycardia</td>
<td>Proteinuria</td>
<td>Recurrent symptoms</td>
<td></td>
</tr>
<tr>
<td>Anxiety, short breath</td>
<td>Cerebral symptoms</td>
<td>Neurologic deficits</td>
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- **Response to treatment**
  - Stop vasoactive drugs
  - Antihypertensive drugs

- **Response to treatment**
  - Evaluate for arterial stenosis & adrenal tumors
  - Seek consultation

- **Response to treatment**
  - Neurologic consultation
  - Cerebral imaging

- **Response to treatment**
  - Consultation & evaluation for:
    - Thyrotoxicosis
    - Cardiomyopathy
    - Pheochromocytoma
    - Pre/eclampsia
    - Magnesium sulfate
    - Antihypertensives
  - RCVS
  - Stroke
  - HELLP syndrome
  - Magnesium sulfate
  - Antihypertensives
  - Supportive care

- **Response to treatment**
  - Consultation & evaluation for:
    - Exacerbation of lupus
    - TTP/HUS
    - APAS
    - AFLP

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\[\text{AFLP, acute fatty liver of pregnancy; APAS, antiphospholipid antibody syndrome; HELLP, hemolysis, elevated liver enzymes, and low platelet; HUS, hemolytic uremic syndrome; RCVS, reversible cerebral vasoconstriction syndrome; TTP, thrombotic thrombocytopenic purpura.}\]
in regards to receiving these medications, and discontinued if they are being used. Subsequent management includes control of hypertension and close observation until resolution of hypertension and associated symptoms.\textsuperscript{18,29}

If the patient has hypertension only with absent symptoms, no proteinuria, and normal laboratory findings, the next step is to control BP. Antihypertensive medications are recommended if systolic BP remains persistently >150 mm Hg and/or if diastolic BP persists >100 mm Hg.\textsuperscript{5,10,17} Bolus intravenous injections of either labetalol or hydralazine are used initially if there is persistent elevations in BP to levels ≥160 mm Hg systolic or ≥110 mm Hg diastolic; this is subsequently followed by oral medication to keep systolic BP <150 mm Hg and diastolic BP <100 mm Hg. There are several antihypertensive drugs to treat postpartum hypertension.\textsuperscript{10,11,48} In GH-pre eclampsia, I recommend short-acting oral nifedipine (10-20 mg every 4-6 hours) or long-acting nifedipine XL (10-30 mg every 12 hours). Alternatively, one can use oral labetalol 200-400 mg every 8-12 hours. As compared to labetalol, oral nifedipine is associated with improved renal blood flow with resultant diuresis, which makes it the drug of choice in postpartum women with volume overload.\textsuperscript{30} In some, it is necessary to switch to a new agent such as angiotensin-converting enzyme inhibitor, which is the drug of choice in those with pregestational diabetes mellitus or cardiomyopathy. In addition, thiazide or loop diuretics may be needed in women with circulatory congestion (overload) and in those with pulmonary edema. In this case, it is necessary to add potassium supplementation. Antihypertensive agents such as methyl dopa, hydrochlorothiazide, furosemide, captopril, propranolol, and enalapril are compatible with breast-feeding.\textsuperscript{11,14,49} If the BP is well controlled and there are no maternal symptoms, the patient is then discharged home with instructions for daily BP measurements (self or by a visiting nurse) and reporting of symptoms until her next visit in 1 week. Antihypertensive medications are then discontinued if the BP remains below the hypertensive levels for at least 48 hours. This may take one or several weeks to resolve. Both nifedipine and labetalol are safe to use in breast-feeding women.\textsuperscript{29}

Those who continue to have persistent hypertension despite the use of maximum doses of antihypertensive medications require evaluation for the presence of either renal artery stenosis or primary hyperaldosteronism. In most women with hyperaldosteronism, the elevated progesterone levels act like spironolactone reversing the hypokalemia and the hypertension as well, with rapid exacerbations of hypertension and falling potassium levels in the postpartum period. The diagnosis should be suspected in the presence of hypokalemia (serum potassium levels <3.0 mEq/L) in association with metabolic acidosis, and then confirmed by either computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen revealing presence of adrenal tumor.\textsuperscript{17,38} Evaluation and management should be made in consultation with a nephrologist.\textsuperscript{17}

Women presenting with hypertension in association with shortness of breath, orthopenia, tachycardia, or palpitations should be evaluated for possible pulmonary edema and/or postpartum cardiomyopathy, hyperthyroidism, or pheochromocytoma.\textsuperscript{36,37,50,51} Indeed, 23-46% of women with peripartum cardiomyopathy will have associated hypertension.\textsuperscript{50,51} Such women should receive a chest x-ray and echocardiography and then be managed in association with a cardiologist according to the demonstrated etiology.\textsuperscript{50,51}

Patients with Graves’ disease during pregnancy can develop exacerbation of the hyperthyroidism in the postpartum period.\textsuperscript{36,37} In addition, new-onset hyperthyroidism postpartum can be due to the hyperthyroid phase of postpartum thyroiditis (first 1-2 months postpartum).\textsuperscript{37} The hyperthyroidism in hyperthyroidism is mainly systolic, and is associated with wide pulse pressure, tachycardia, palpitations, and heat intolerance.\textsuperscript{36,37} Women with these findings should receive thyroid function tests (thyroid stimulating hormone and free thyroid 4 levels) and then be managed in consultation with an endocrinologist. Women with Graves’ disease are treated with prophythiouracil (100-300 mg daily) or methimazole (10-20 mg daily), and then followed with measurements of thyroid stimulating hormone and free thyroid 4 levels. Both of these medications are compatible with breast-feeding.\textsuperscript{36} Women with hyperthyroid phase of postpartum thyroiditis do not require antithyroid drugs since the condition resolves spontaneously.

Pheochromocytoma is a rare adrenal or extraadrenal tumor that produces catecholamines resulting in paroxysmal hypertension, headaches, palpitations and excessive sweating, chest pain, dizziness, and postural hypotension.\textsuperscript{38,39} Maternal mortality can be as high as 25% if there is a delay in diagnosis and treatment.\textsuperscript{38,39} Diagnosis is usually made by measurements of 24-hour urine epinephrine, norepinephrine, and their metabolites (metanephrine and normetanephrine) and is then confirmed by CT scan or MRI of the abdomen. Management of pheochromocytoma should be made in consultation with a nephrologist and a surgeon and will include initially medical therapy with alpha blockers followed by surgical removal of the adrenal tumor.\textsuperscript{38,39}

Women with postpartum hypertension in association with new-onset persistent headaches and/or visual changes or new-onset proteinuria should be considered to have severe preeclampsia. If there is hypertension with seizure, she should be initially treated as having eclampsia. It is important to emphasize that many of these women will be first seen and evaluated in the emergency department, and many emergency room physicians may not be aware that preeclampsia-eclampsia can present postpartum.\textsuperscript{8,16} In patients presenting with these findings, magnesium sulfate therapy must be initiated promptly for seizure prophylaxis and/or treatment. In addition, intravenous antihypertensive medications are recommended to lower BP to the desired goal while considering an alternative cause for the cerebral symptoms. Magnesium sulfate is given intravenously as a 4- to 6-g loading dose over 20-30 minutes, followed by a maintenance dose of 2 g per hour for at least 24 hours.\textsuperscript{2} If the patient continues to have cerebral symptoms and/or if she develops seizures or neurologic deficits despite magnesium sulfate and adequate
BP control, then she should receive neurodiagnostic evaluation and be managed in consultation with a neurologist.

Women presenting with hypertension in association with refractory and/or thunderclap headaches, visual disturbances, or neurologic deficits should be evaluated for possible cerebrovascular complications such as reversible cerebral vasoconstriction syndrome (RCVS) or stroke. These women will require selective diagnostic neuroimaging and consultation with neurology and/or neurosurgery. Such an evaluation may include CT scan for hemorrhage, MRI for detection of vasogenic edema and/or ischemia or infarction, cerebral angiography for diagnosis of RCVS, and cerebral venography for detection of cerebral venous thrombosis (CVT). Subsequent treatment will depend on the etiology.43-45

RCVS is a poorly understood form of angiohypertension that develops between postpartum days 3-14.40,41 The presenting symptoms are a thunderclap headache (89%) in association with other neurologic manifestations such as seizures and visual disturbances. Hypertension is present in 60% of cases, and multifocal neurologic deficits may be present.40 MRI findings in this syndrome overlap with those of eclampsia (posterior reversible encephalopathy syndrome), however, cerebral MRI or traditional angiography reveal the presence of segmental vasoconstriction.41 These latter findings are consistently absent in eclampsia.20,42 Prognosis is favorable in most cases, however, if the vasoconstriction is severe and persistent or recurrent, it can lead to cerebral hemorrhage or infarction with permanent neurologic deficits.40-42 In some patients, serum creatinine may be extremely low suggesting massive volume overload as a cause and thus rapid diuresis with diuretics is beneficial in such cases.82 Additional therapy may include the use of a calcium channel blocker such as nimodipine as a cerebral vasodilator.

Stroke is a rare occurrence postpartum. Reported risk factors for postpartum stroke include hypertension, advanced maternal age, and dehydration.43-45 Potential causes of stroke include CVT, aneurysmal subarachnoid hemorrhage, intraparenchymal hemorrhage, and hypertensive encephalopathy.43-45 Cerebral hemorrhage and CVT secondary to major dural sinus thrombosis can lead to increased intracranial pressure with compensatory peripheral vascular hypertension. In addition, the signs and symptoms of stroke (headache, visual changes, seizures, nausea, or vomiting) and the laboratory findings (elevated liver enzymes, low platelets) can be similar to those in severe preeclampsia, eclampsia, and HELLP syndrome.43,45 The definitive diagnosis is made by cerebral MRI and/or angiography (both arterial and venous).43-45

Women with hypertension with persistent nausea, vomiting, or epigastric pain should be evaluated for HELLP syndrome since up to 30% who develop the syndrome do so postpartum.6 The time of onset of the clinical and laboratory findings ranges from 1-7 days postpartum. 6 Management of these women is similar to that before delivery, which includes the use of magnesium sulfate, antihypertensives, and close monitoring of vital signs and laboratory values.6 In general, patients with HELLP syndrome will demonstrate an improvement in clinical and laboratory findings within 48 hours after treatment. If there is either no improvement or a deterioration in these findings, then it is important to obtain consultation with appropriate specialists for evaluation and subsequent management.6 The differential diagnosis should include thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, acute fatty liver of pregnancy, and exacerbation of lupus nephritis.6,46,47

In summary, there are several causes for postpartum hypertension; some may be benign (mild GH or mild chronic hypertension) whereas others can be life threatening such as severe preeclampsia or stroke. Therefore, a high index of suspicion for secondary dangerous causes of hypertension should be considered when evaluating such women. By directing efforts and educating health care providers about the continued monitoring, reporting, and prompt evaluation of symptoms in the postpartum period, it is expected that some of the maternal complications will be avoided. Evaluation and management of women with postpartum hypertension should be guided by obtaining a detailed history, careful physical examination, selective laboratory and imaging studies, and response to initial treatment.

REFERENCES
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