Chapter 6
Preeclampsia: Early and Long-Term Clinical Considerations

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Abstract Preeclampsia is a hypertensive disorder of pregnancy characterized by new onset of hypertension after 20 weeks gestational age, in the setting of proteinuria and/or other end organ damage. It is a multisystem disorder and is caused by abnormal placentation and release of angiogenic factors with resultant maternal vascular dysfunction. Preeclampsia complicates 5% of pregnancies and the incidence has increased 25% in the last 20 years. Severe forms of preeclampsia can result in dysfunction of maternal neurologic, renal, cardiac, hepatic, pulmonary function, as well as haematologic disturbances and death. Fetal complications include severe growth restriction, preterm birth and stillbirth/neonatal death. Screening, timely diagnosis and management of preeclampsia are integral to optimizing outcomes, with definitive therapy being delivery of the fetus. However, preeclampsia may also be diagnosed in the postpartum period, highlighting the need for post-partum assessment. Though much work has been done in the antepartum diagnosis and management of preeclampsia, a growing body of evidence has shown an increased risk of long-term cardiovascular disease in patients who develop preeclampsia. Not only must healthcare providers be able to diagnose and manage preeclampsia, providers must also understand the role that preeclampsia plays in the lifelong cardiovascular risk of their patients.

Keywords Preeclampsia · Pregnancy · Hypertension · HELLP · Proteinuria

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Introduction

Hypertensive disorders of pregnancy are one of the leading causes of both maternal and perinatal mortality globally. Preeclampsia is a hypertensive disorder of pregnancy characterized by new onset of hypertension after 20 weeks gestational age (GA), in the setting of proteinuria and/or other end organ damage. It complicates 5% of pregnancies and the incidence has increased by 25% in the last 20 years [1, 2]. Preeclampsia is a multisystem disorder and is caused by abnormal placentation and release of angiogenic factors with resultant maternal vascular dysfunction [3]. Severe forms of preeclampsia can result in dysfunction of maternal neurologic, renal, cardiac, hepatic, and pulmonary function, as well as haematologic disturbances and death. Fetal complications include severe growth restriction, preterm birth and stillbirth/neonatal death. Screening, timely diagnosis and management of preeclampsia are integral to optimizing both maternal and fetal outcomes, with definitive therapy being delivery of the fetus. However, preeclampsia may also be diagnosed in the postpartum period, highlighting the need for post-partum blood pressure assessment. Though much work has been done in the antepartum diagnosis and management of preeclampsia, a growing body of evidence has shown an increased risk of long-term cardiovascular disease in patients who develop preeclampsia. Not only must healthcare providers be able to diagnose and manage preeclampsia in the setting of pregnancy, providers must also understand the role that preeclampsia plays in the lifelong cardiovascular risk of their patients.

Overview

Hypertension in a pregnant patient is defined as a systolic BP $\geq$ 140 mmHg and/or diastolic BP $\geq$ 90 mmHg, based on an average of at least two measurements [4].

There are four major categories of hypertensive disorders in pregnant women:

1. Isolated gestational hypertension—New hypertension after 20 weeks gestational age (GA) in the absence of end organ involvement.
2. Preeclampsia and spectrum conditions (preeclampsia, hemolysis elevated liver enzymes and low platelets (HELLP) syndrome and eclampsia).—New hypertension after 20 weeks GA with variable end-organ damage.
3. Chronic hypertension—hypertension antecedent to pregnancy or present prior to 20 weeks GA.
4. Preeclampsia superimposed on chronic hypertension—worsening/resistant hypertension with new onset proteinuria or end organ involvement after 20 weeks GA, in a woman with pre-existing hypertension.

Diagnosis of Preeclampsia

Preeclampsia is diagnosed when a previously normotensive patient develops hypertension (> 140 mmHg systolic blood pressure or > 90 mmHg diastolic blood pressure) after 20 weeks of gestation along with evidence of end-organ damage.

For a diagnosis of preeclampsia, at least one of the following needs to be present in addition to new onset hypertension [5–8]:

- Proteinuria (protein:creatinine ratio ≥ 30 mg/mmol or albumin:creatinine ratio ≥ 8 mg/mmol, ≥ 0.3 g/day in a 24 h urine collection)
- Maternal end organ dysfunction
  - Neurological sequelae (headache, altered mental status, visual scotoma, clonus, eclampsia, blindness, stroke, posterior reversible encephalopathy syndrome (PRES)
  - Cardiovascular (myocardial dysfunction, pulmonary edema)
  - Hematological sequelae (thrombocytopenia, hemolysis, disseminated intravascular coagulation)
  - Renal insufficiency (creatinine > 90 μmol/L)
  - Liver involvement (elevated liver transaminases or right upper quadrant/epigastric pain)
- Uteroplacental dysfunction (fetal growth restriction, abnormal fetal dopplers, placental abruption, stillbirth)

HELLP syndrome is a severe form of preeclampsia with an increased risk of maternal and fetal complications [4]. HELLP syndrome is characterized by hemolysis (with microangiopathy blood smear/schistocytes/burr cells), elevated liver enzymes, and low platelet count.

Eclampsia is diagnosed in the setting of new onset tonic–clonic focal or multifocal seizures or coma in a patient with preeclampsia, and is the manifestation of severe neurologic involvement. Eclamptic seizures are defined as occurring in the absence of other causative conditions such as cerebral ischemia/infarction, epilepsy, intracranial hemorrhage or drug use [7].

Pathophysiology of Preeclampsia:

Preeclampsia is a multisystem disorder of pregnancy with a complex pathophysiology that remains incompletely understood. Suboptimal trophoblast invasion and inadequate remodeling of the maternal spiral arteries in the early stages of placentation is thought to underlie this clinical syndrome [3, 9]. These abnormalities result in a reduction in prefusion to the utero-placental unit and subsequent placental ischemia/hypoxia which in turn causes an increase in angiogenic markers (including fms-like tyrosine kinase-1 and soluble endoglin) [9]. The increase in angiogenic markers,

has been proposed to result in a decrease in vascular growth factor (VEGF) and placental growth factor, and subsequent maternal vascular endothelial dysfunction. Endothelial dysfunction may be accompanied by vasoconstriction, oxidative stress and micro-emboli which can affect multiple organ systems [3, 10]. The degree of maternal inflammatory response and placental ischemia as well as the evolving imbalance in angiogenic and antiangiogenic factors influence the clinical severity of the syndrome [3, 6–8, 11]. Additional mechanisms likely involved in the development of preeclampsia include immunologic aberrations in pregnancy and genetic factors [3]. Abnormal placentation early in pregnancy tends to be a key feature of early-onset preeclampsia (diagnosis < 34 weeks) which carries the highest risk of maternal fetal morbidity and mortality. In contrast, cases of late-onset preeclampsia (> 34 weeks) often demonstrate normal early placental development but develop due to abnormal placental perfusion, inflammation and oxidative stress later in pregnancy [12].

Outcomes and Burden of Preeclampsia:

Globally, preeclampsia has been found to be present in 5% of pregnancies, noting some regional variation [13]. Hypertensive disorders of pregnancy are one of the leading causes of maternal death globally, with 13% being attributed to preeclampsia/eclampsia [14]. The most common cause of death from preeclampsia is cerebral hemorrhage from severe uncontrolled hypertension [2]. Significant morbidity for the mother also takes the form of increased rates of pulmonary edema (0.1–2.3%), renal failure requiring dialysis (2.3%) and HELLP syndrome (8.3%) [15–17]. Preeclampsia increases the rates of various conditions in the fetus, including prematurity, low birth weight, and death. It has been found that in women with preeclampsia the risk of preterm birth ranges from 20 to 55% and the risk of a low-birth-weight infant ranges between 23 and 34% [16, 18, 19]. Many studies globally have examined the cost to health care systems associated with preeclampsia; there is a significant increase in health care spending in patients with preeclampsia with the majority of extra cost (millions to billions of dollars annually, depending on country) attributed to caring for premature infants and increased use of health care services [20–22].

Risk Factors and Primary Prevention of Preeclampsia:

There have been multiple risk factors associated with the development of preeclampsia (Table 6.1) [6–8, 23]. However, it is important to understand that most cases of preeclampsia occur in women with no overt risk factors. The identification of risk factors for preeclampsia is clinically important as it can guide care providers to initiate preventative therapy.

Given the burden and scope of disease, prevention of preeclampsia is a healthcare priority. In high-risk women (Table A), acetylsalicylic acid (ASA) has been shown

Table 6.1 Risk factors for the development of preeclampsia [4, 8, 24]

	"High risk" factor	"Moderate risk" factor
Maternal demographics	• Pre-pregnancy body mass index > 30 kg/m^2	• Maternal age (≥ 35 years)
Maternal history	• Preexisting hypertension • Type 1 or 2 diabetes • Chronic renal disease • Autoimmune disease (e.g. SLE) • Antiphospholipid antibody syndrome	• Family history of preeclampsia • Interpregnancy interval (> 10 years)
Reproductive history	• Previous hypertensive disorder of pregnancy/preeclampsia	• Prior placental abruption/fetal growth restriction or stillbirth
Current pregnancy	• Assisted reproductive technology	• Multifetal gestation • Nulliparity

SLE systemic lupus erythematosus
*Patients are typically considered "high risk" if they have at least one risk factor from the high-risk category or two or more from the moderate risk category

to reduce rates of preterm preeclampsia by 70%, in addition to reducing preterm birth and severe disease [6, 25, 26]. It is recommended to start ASA > 100 mg daily prior to 12 weeks GA and to continue to 36 weeks or delivery, depending on obstetrical plan [7, 26]. Exercise in pregnancy is recommended for all women without contraindications, to decrease the odds of developing preeclampsia. It has been demonstrated that 140 min of moderate-intensity exercise weekly can reduce the risk of developing preeclampsia by 25% [27]. In patients with low calcium intake (< 900 mg/day), calcium supplementation (> 500 mg/day) has been associated with reduced risk and severity of preeclampsia by up to 50% [28–30]. There is no clear role for vitamins C or E, metformin, statins, oral magnesium, low molecular weight heparin or folic acid in the prevention of preeclampsia currently, although studies assessing these are in progress [11].

Antepartum Management of Preeclampsia

Screening for the Development of Preeclampsia

Screening for preeclampsia begins at the first prenatal (or antenatal) visit by screening for maternal risk factors (Table 6.1). Integral to assessment is accurate blood pressure measurement. This is done with an appropriately sized cuff, while the patient is in the sitting position and the arm is placed at the level of the heart. Two measurements should be taken in the same arm, at least 15 min apart [8]. Blood pressure should be measured at each clinical encounter to identify pre-existing hypertension (< 20 weeks GA) or the development of a hypertensive disorder of pregnancy (> 20 weeks GA).

At 11–14 weeks, women should be screened again with blood pressure measurement, risk factor assessment, uterine artery pulsatility index and placental growth factor (PlGF) if available [6, 8, 11]. This integrated approach assessing maternal characteristic/risk factors, blood pressure, biomarkers and fetal flow characteristics demonstrates improved accuracy at predicting development of preeclampsia compared to maternal risk factors alone [6]. In addition to blood pressure monitoring screening for preeclampsia includes assessment for maternal proteinuria. Urine dipstick is a sufficient screening method for new onset proteinuria however, 24 h urine collection or spot urine PCR should be used to confirm proteinuria if the urine dipstick is > + 1 or if preeclampsia is suspected [8].

Though the diagnosis of preeclampsia is typically made in the prenatal period, a diagnosis of hypertensive disorders of pregnancy and/or preeclampsia can be made up to 6 weeks post-partum, highlighting the need for appropriate post-partum follow-up [8]. For women who did not develop hypertension or preeclampsia antenatally, routine post-partum care is typically done with assessment at 6 weeks post-partum. Women with preeclampsia are typically seen frequently in the immediate post-partum period, as blood pressures tend to rise in the first week post-partum. Patient education is critical as blood pressures still need to be checked and medications should not be stopped until it is safe to do so. Thereafter, the frequency of appointments tends to wane as blood pressures settle. Patients without pre-existing hypertension are slowly weaned off medication as the cardiovascular changes of pregnancy and delivery subside.

Clinical Presentation of Preeclampsia and Assessment of Complications

Preeclampsia affects multiple organ systems; as such, clinical and laboratory assessment is necessary for both diagnosis, identification of severe disease and management. Affected organ systems include the central nervous system, cardiovascular, renal, hepatic, haematologic and the fetal-placental unit (Fig. 6.1). During pregnancy, management of preeclampsia is based on the severity of blood pressure elevation in addition to the degree of end-organ damage that develops, including complications in the fetus. Adverse conditions are features of preeclampsia that increase the risk of negative maternal or fetal outcomes and require urgent management (typically expedient delivery) in order to mitigate severe complications. (Fig. 6.1) [8].

Antepartum Management of Preeclampsia:

Once the diagnosis of preeclampsia has been established, frequent clinical assessment is recommended [5, 11]. Further monitoring is dependent on maternal and fetal status

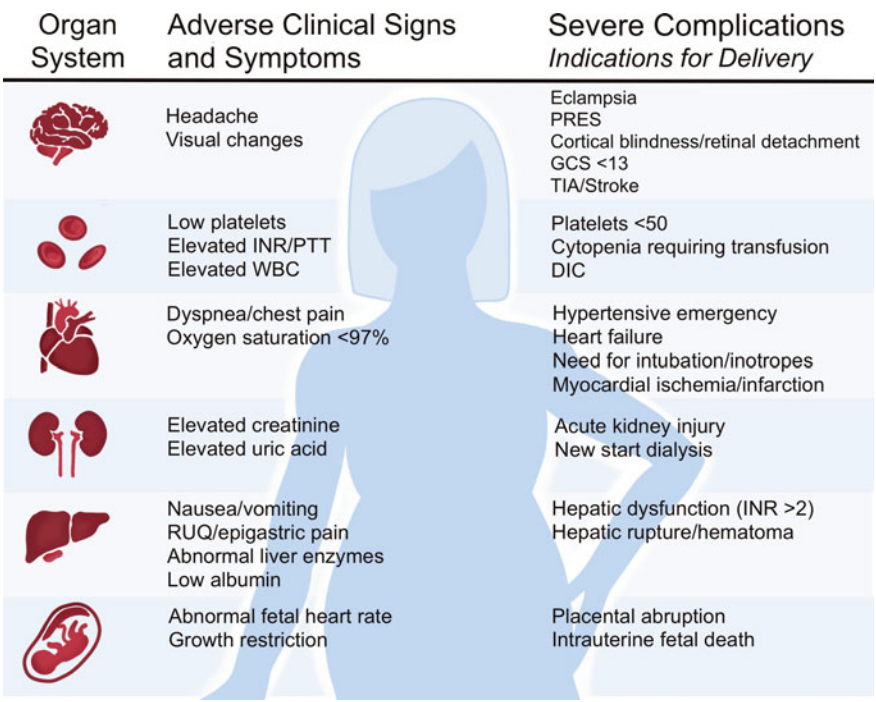

Fig. 6.1 Clinical presentation and indications for delivery in preeclampsia. DIC = disseminated intravascular coagulopathy; GCS = Glasgow coma scale; INR = international normalised ratio; PRES = posterior reversible encephalopathy syndrome; PTT = prothrombin time; RUQ = right upper quadrant; TIA = transient ischemic attack; WBC = white blood cell

and close clinical follow up is used to help guide indications for medical therapy and planning for delivery.

With regards to blood pressure management, blood pressure > 140/90 mmHg typically can be managed with oral medications to a target blood pressure of systolic < 140 and diastolic < 85 mmHg. Oral antihypertensive medications of choice typically include labetalol, methyldopa and/or nifedipine [23]. When blood pressure is severely elevated (> 160/ > 110 mmHg), intravenous medications (labetalol or hydralazine) or shorter acting oral medications (nifedipine) may be used in order to bring the blood pressure down more rapidly [7, 8, 11]. Though antihypertensive therapy in preeclampsia is typically given to mitigate maternal adverse outcomes, planning for delivery is one of the most important aspects of preeclampsia management as this is the definitive treatment. Management of preeclampsia needs to be individualized. Important considerations include the gestational age, disease severity, end-organ involvement and patient preference. Women with a diagnosis of preeclampsia < 24 weeks GA should receive counselling regarding the pros and cons of continuing the pregnancy. In general, expectant management would be recommended between 24 and 33 + 6 weeks GA [8, 11]. Once a patient reaches 34 weeks GA, there is

insufficient evidence to recommend continued expectant management [5, 8, 11]. For women > 37 weeks GA, delivery is typically recommended [5]. Regardless of GA, women with preeclampsia who have developed severe complications require immediate delivery (Fig. 6.1). If preterm delivery is clinically indicated, consideration should be given to administering antenatal corticosteroids to women presenting < 34 + 6 weeks GA in order to accelerate fetal lung maturity [8, 11, 31]. It is important to note that exercise (beyond typical activities of daily living) is considered contraindicated in women with established preeclampsia and relatively contraindicated in women with gestational hypertension [32]. Women with gestational hypertension should speak with their health care provider regarding participation in moderate- to vigorous activities.

Management During Delivery

In the absence of obstetrical indications, most women with preeclampsia may have a trial of vaginal delivery with diligent intrapartum blood pressure monitoring and pharmacologic management. In cases of abnormal fetal testing, labour may not be tolerated and delivery by caesarean section is indicated. It is important to avoid excess IV fluid to reduce the risk of pulmonary edema. Antihypertensives are to be continued during labour and it is suggested to continue active management of the 3rd stage of labour with oxytocin, especially if the patient has thrombocytopenia or a coagulopathy. However, it is important to avoid ergometrine for women with gestational hypertension and preeclampsia as it increases the risk of uncontrolled hypertension [8].

Management and Prevention of Eclampsia:

For women having preeclampsia with severe features or those with a formal diagnosis of eclampsia magnesium sulfate (MgSO4) should be given to prevent initial or recurrent seizures [11]. Antihypertensive therapy is also used to prevent stroke. Severe features warranting MgSO4 administration include: severe hypertension, headaches/visual disturbances, RUQ/epigastric pain, platelets < 100, progressive renal insufficiency, and /or elevated liver enzymes. A loading dose of MgSO4 is typically given, followed by an infusion. Dose adjustments should be made in renal insufficiency or oliguria [2]. All patients should be monitored for signs of magnesium toxicity every 1–2 h (including absent deep tendon reflexes, respiratory distress or altered level of consciousness) [8, 11].

Post-partum Diagnosis and Management of Preeclampsia

Diagnosis of Post-partum Preeclampsia

Though preeclampsia is typically diagnosed antepartum, about 5% of cases can present in the post-partum period, (typically within the first week post-partum, but can be seen up to 6 weeks) and can be responsible for significant maternal morbidity; as some studies have shown that up to 50% of patients who develop eclampsia will do so in the postpartum period, with approximately 26% occurring > 48 h post-partum [33–36]. It is important to ensure that blood pressure is measured 3–7 days post-partum as this is the anticipated peak secondary to the extravascular fluid redistribution [11]. Target blood pressure remains < 140/90 mmHg (target in patients with diabetes < 130/80 mmHg) [37]. Options for medical therapy include those used in antepartum management in addition to captopril and enalapril, which may be used with breastfeeding [8]. If breastfeeding is not pursued standard/guideline directed antihypertensive therapy may be used [37]. It is important to continue antihypertensive treatment for women with antenatal preeclampsia and those who delivered preterm, in the post-partum period. Women with ongoing hypertension at > 6 weeks post-partum, should be screened for pre-existing hypertension or a secondary cause [5, 8].

Recurrence and Secondary Prevention

The recurrence rate of preeclampsia in a subsequent pregnancy is approximately 15% [38]. Importantly, early onset preeclampsia has a recurrence rate of roughly 50%. Women with a history of preeclampsia who are seen in preconception counselling or in early subsequent pregnancy should be counselled on the risk of recurrent preeclampsia and offered the established primary prevention interventions [7, 8].

Lifelong Cardiovascular Risk and Outcomes

In 1964, Epstein showed for the first time ever that women who had developed preeclampsia were at increased risk of developing cardiovascular disease later in life [39]. Since that time, a robust body of literature has evolved to show that there is a strong connection between preeclampsia and long-term maternal cardiovascular risk. One of the landmark studies exploring the link between hypertensive disorders of pregnancy and long-term cardiovascular risk was the CHAMPS study. This was a retrospective Canadian population-based cohort study involving over 1 million women without pre-existing cardiovascular disease before their first delivery. In these women, 7% developed a maternal placental syndrome (hypertensive disorders

of pregnancy, abruption or infarction of the placenta). They found a doubling of the risk of premature cardiovascular disease in women who had developed a maternal placental syndrome compared with those who had not. The mean and maximum age at the time of first cardiovascular event in this group was 38 years and 60 years, respectively, which was significantly earlier than in women who had not developed maternal placental syndromes [40]. Numerous other works have shown similar findings in women with a history of preeclampsia. A robust metanalysis of over 50 studies and 10 million women demonstrated at a twofold higher incidence of cardiovascular events (including: death, myocardial infarction, stroke, hypertension, diabetes and dyslipidemia) in women with previous preeclampsia compared to those with previous normotensive pregnancy. In addition, this meta-analysis highlighted a fourfold higher burden of cardiovascular disease/outcomes in women who had early onset preeclampsia (preeclampsia requiring delivery before or at 34 weeks gestational age) [1].

Preeclampsia is associated with fourfold increase risk of hypertension [41], with 30% of women having hypertension at 2-years post-delivery and 25% with metabolic syndrome at that time [42, 43]. Women who have developed preeclampsia have at least twice the risk of type 2 diabetes and dyslipidemia [44]. Early onset heart failure and dysrhythmias are also more common in women with maternal placental syndromes (including preeclampsia), and the mean age at composite outcome in another retrospective cohort study of > 1 million women was 37.8 years [45]. Similar associations are also seen between preeclampsia and dementia, chronic kidney disease, seizures, and even overall death from any cause [41].

Factors Associated with Lifelong Risk

Our current understanding of the role preeclampsia plays in long term adverse health risk is incomplete. It is unknown if the antecedents of preeclampsia were present in women long before pregnancy, emphasizing the importance of a comprehensive history in these women. It is possible that these women had subclinical risk factors, such as increased peripheral vascular resistance, childhood obesity or a strong family history of vascular disease, which predisposed them to developing preeclampsia and then subsequently overt cardiovascular disease later in life [3]. Alternatively, preeclampsia could be the first "hit" on a phenotype which then becomes susceptible to cardiovascular and metabolic disease later on. In this hypothesis, the direct effects of endothelial dysfunction in pregnancy may have initiated and then accelerated atherosclerosis in these individuals [46]. Further research is required to develop a better understanding of the role preeclampsia plays in life-long disease.

Screening for the Development of Cardiovascular Disease

Post-partum management of women with preeclampsia has evolved over a number of years, and now hypertension during pregnancy is recognized as a major cardiovascular risk factor amongst many national and international associations. As of 2016, the Canadian Cardiovascular Society's Dyslipidemia Guidelines were changed to include screening for all women regardless of age if they had a hypertensive disorder in pregnancy [47]. As of 2019, the UK NICE guidelines made similar recommendations, advising women who have had a hypertensive disorder of pregnancy that this is associated with an increased risk of cardiovascular disease later in life, and advising these women to avoid smoking, and to maintain a healthy lifestyle and weight [5]. Finally, the American Heart Association recommends that these women undergo cardiovascular screening within 3 months after delivery [48].

Currently, there is no clear consensus on when is the optimal time to screen patients for cardiovascular disease after the diagnosis of preeclampsia. The Mother's Clinic in Kingston, Ontario is one of the longest running Canadian post-partum risk factor reduction clinics, whereby women are seen 6 months post-partum and both modifiable (e.g. smoking) and non-modifiable (e.g. total cholesterol) risk factors are assessed. Women are then given a sense of their lifetime cardiovascular disease risk estimate based on 5 different risks factors (total cholesterol, systolic blood pressure, diastolic blood pressure, elevated fasting glucose and smoking) [49]. However, no consensus has yet been reached on the best way to assess and characterize risk in all individuals, nor the optimal timing of assessment/intervention post-partum. Furthermore, many post-partum cardiovascular risk reduction clinics are challenged by high attrition, lack of proven effectiveness, and low patient engagement [50].

Long Term Pharmacologic Management:

The literature exploring long term pharmacologic management of women who have developed preeclampsia is underway but far from robust. Women have long been underrepresented in the cardiovascular literature and only recently has there been concerted efforts to address the specific needs of this population [51]. Currently, the pharmacologic management of women who have experienced hypertensive disorders of pregnancy is focused mainly on early and aggressive treatment of their other cardiovascular risk factors including: diabetes, hypertension, chronic kidney disease and dyslipidemia. Without literature specific to this population of women, these conditions are treated in the usual fashion with the same targets as the general population.

Statins

The role of statin therapy in the post-partum period is controversial. Current recommendations support screening at-risk women with a lipid panel in late post-partum period and focus primarily on lifestyle modifications to optimize lipid profile with the decision to start a statin guided by cardiovascular age estimates [52]. Though there has been some early work using pravastatin in an animal model, demonstrating improved cardiac remodelling and cardiac output post-partum [53], much more research in this area is required to understand the role that statins might play in the long term management of women who develop preeclampsia.

Acetylsalicylic Acid and Angiotensin Converting Enzyme Inhibitors

The use of ASA and angiotensin converting enzyme inhibitors in the post-partum period, after pregnancy complicated by hypertensive disorder have been evaluated. In one small placebo controlled trial, women who took ASA for 2 months after pregnancy complicated by preeclampsia, had increased arterial flow mediated dilation indicating an improvement in endothelial function [54]. Another small feasibility randomized controlled trial showed improved diastolic dysfunction and left ventricular remodelling in women with a history of preeclampsia who took enalapril for 6 months post-partum [55]. Both studies had small sample sizes and were testing feasibility only. Larger studies are needed to determine if these interventions impact long term cardiovascular risk.

With an increasing interest and awareness around the cardiovascular health of women, we can expect more robust research in this area of medicine in the coming years. This will help to formalize and guide the management of women who have experienced preeclampsia and hypertensive disorders of pregnancy, in order to optimize their health and reduce their long-term cardiovascular risk.

Summary

Preeclampsia remains one of the leading causes of adverse maternal and fetal pregnancy outcomes. It complicates millions of pregnancies globally, however, with a growing understanding of risk factors, improved screening programs and interventions for prevention, health care providers have tools to help optimize pregnancy outcomes for both mothers and their offspring. Women who have developed preeclampsia are at a significantly increased risk of adverse multisystem outcomes and premature death after pregnancy. Though the mechanisms for the increased burden of disease are not entirely well understood, it is imperative for healthcare

providers and patients to recognize development and history of preeclampsia as a maker of increased lifelong risk. Continued research is required to evaluate strategies to reduce the increased lifelong risk of adverse events in these women.

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