Hypertension occurs in approximately 10–20% of pregnancies and is associated with significant maternal and fetal morbidity. Most importantly, it results in preterm delivery and is associated with other conditions in the spectrum of placental ischemic disease such as intrauterine growth retardation and placental abruption. Chronic hypertension increases the risk for gestational hypertension and preeclampsia. Hypertension during pregnancy is also associated with increased future cardiovascular risk in the mother and her offspring. Topics to be discussed in this chapter include the classification of hypertensive disorders in pregnancy, normal blood pressure patterns during pregnancy, the pathophysiology of gestational hypertension and preeclampsia, features unique to the pregnant adolescent, the epidemiology and outcome of hypertension during pregnancy, and treatment guidelines.

<table>
<thead>
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<th>Keywords</th>
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<tr>
<td>Gestational hypertension • Preeclampsia • ABPM • Preterm birth • Adolescence • Placental ischemia</td>
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<th>Abbreviations</th>
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<tr>
<td>2-ME 2-Methoxyestradiol</td>
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<td>ABPM Ambulatory Blood Pressure Monitoring</td>
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<td>ACEi Angiotensin Converting Enzyme inhibitors</td>
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<td>ARB Angiotensin Receptor Blockers</td>
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<td>ANP Atrial Natriuretic Protein</td>
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<td>BP Blood Pressure</td>
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<td>BMI Body Mass Index</td>
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<td>COMT Catechol-O-Methyl Transferase</td>
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<tr>
<td>CI Confidence Interval</td>
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<td>SBP Systolic BP</td>
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<td>DBP Diastolic BP</td>
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<td>sEng Endoglin</td>
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<tr>
<td>GFR Glomerular Filtration Rate</td>
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<td>HELLP Hemolysis, Elevated Liver Enzymes, Low Platelets syndrome</td>
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<tr>
<td>HIF Hypoxia Inducible Factor-1</td>
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<td>MAP Mean Arterial Pressure</td>
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<td>OR Odds Ratio</td>
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<td>PIGF Placental Growth Factor</td>
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<td>sFlt1 Soluble Fms-Like Tyrosine Kinase 1</td>
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<td>VEGF Vascular Endothelial Growth Factor</td>
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© Springer International Publishing AG 2017
J.T. Flynn et al. (eds.), Pediatric Hypertension,
DOI 10.1007/978-3-319-31420-4_28-1
### Introduction

Hypertension occurs in approximately 10–20% of pregnancies and is associated with significant maternal and fetal morbidity. Most importantly, it results in preterm delivery and is associated with other conditions in the spectrum of placental ischemic disease such as intrauterine growth retardation and placental abruption (Roberts et al. 2013; Lindheimer et al. 2010). Both chronic hypertension and obesity increase the risk for worsening hypertension during pregnancy (including preeclampsia) as well as preterm birth and fetal growth insufficiency. Blood pressure (BP) levels during the first half of pregnancy are lower than before pregnancy, a physiologic change that challenges the clinician in the choice of BP thresholds at which to initiate or to achieve with antihypertensive therapy. Hypertension during pregnancy is associated with increased future cardiovascular risk in the mother and her offspring as can be viewed as a stress test for future cardiovascular risk. Topics to be discussed in this chapter include the care of the pregnant adolescent with hypertension, classification of hypertensive disorders in pregnancy, normal BP patterns during pregnancy, the pathophysiology of preeclampsia, features unique to the pregnant adolescent, the epidemiology and outcome of hypertension during pregnancy, and treatment guidelines. There are very few studies which focus on the adolescent with hypertension, and, therefore, most of the references cited in this chapter relate to hypertension during pregnancy in general. If available, studies which specifically address the pregnant teenager will be discussed.

### Case

A 16-year-old female was followed in the pediatric nephrology clinic since the age of 9 years for hypertension secondary to renal scarring and vesicoureteral reflux. She was treated with valsartan 160 mg daily and amlodipine 5 mg daily. Past medical history was remarkable for imperforate anus, s/p repair as an infant, linear growth delay, delayed puberty, and recurrent urinary tract infections. Her electrolytes were normal and serum creatinine 0.7 mg/dl. Her urine protein excretion was abnormal, with a baseline urine protein/creatinine ratio of 0.5 mg/mg (normal, <0.2 mg/mg). Her follow-up to clinic was sporadic, as she missed about 50% of scheduled appointments. Her mother called to report that she was pregnant and requested advice on continuation of her antihypertensive medications. She was advised to discontinue valsartan and was scheduled to see an obstetrician.

This case illustrates several questions which arise in the pregnant adolescent with preexisting hypertension: How is preeclampsia detected in the setting of baseline proteinuria and hypertension? What is the risk to the patient and to her baby? What is the goal for BP levels? Which medications should be used to control BP? Should the pregnancy be terminated due to conception while on valsartan?
The Pregnant Adolescent: General Considerations

Adolescent pregnancy is a significant burden across the world, with an estimated 16 million children born to women between 15 and 19 years of age (www.guttmacher.org 2012). The USA has one of the highest rates among developed countries; however, this number has been steadily decreasing between 1990 and 2010. It is estimated that up to two thirds of adolescent pregnancies in the USA are unplanned (Finer and Henshaw 2006). Approximately two thirds of teenage pregnancies result in live birth and one third end in abortion (Kost and Henshaw 2014). There is considerable variation among regions of the USA, with southern states having the highest teen pregnancy rates. There is also significant variation between races, with African American and Hispanic adolescents becoming pregnant at twice the rate of non-Hispanic white teens in the USA. Finally, lower socioeconomic status and lower levels of parental education also have strong correlations with teenage pregnancy (Hamilton et al. 2011). These statistics emphasize that providers who are dealing with this age group, even on an infrequent basis, will most likely encounter teenage pregnancy in various clinical settings.

There are several features about adolescent pregnancy which cause it to be classified as high risk. Pregnant teenagers have a higher incidence of domestic violence, sexual abuse, sexually transmitted infections, substance use, and nutritional imbalance (Quinlivan and Evans 2005; Lenders et al. 2000; Black et al. 2012). Many comprehensive high risk centers incorporate a multidisciplinary team of providers which can include a social worker, counselor, nutritionist, obstetrician, and adolescent medicine provider. This team can address the multiple factors that will improve outcomes for mothers and infants (Quinlivan and Evans 2004).

Unplanned pregnancy can be viewed as a disruption of the psychosocial development of a teenager. Physical development along with full reproductive potential is usually completed by early and middle adolescence, between the ages of 12 and 16. Emotional and social maturity typically occurs in later adolescence, between the ages of 17 and 20 (Brown and Brown 2006). This incongruous development results in many teen mothers and fathers who are emotionally unprepared to handle a pregnancy and the responsibilities associated with it. Teens are suddenly forced to reckon with the many burdens of prenatal and postpartum care, which include infant care-taking responsibilities, personal health and nutrition, finances, and educational or vocational responsibilities (Paranjothy et al. 2009). Adolescent women who have concurrent chronic medical conditions, such as hypertension or diabetes, face the additional challenge of maintaining optimal control of their health to avoid adverse effects to the child (Sibai 1991). All of these extra tasks of pregnancy and parenting represent a major emotional conflict for teenage women who are still attempting to establish their own identity.

Teen mothers also face many barriers to high quality preconception and prenatal care. These obstacles include social stigma, transportation issues, confidentiality, financial burden, and lack of information about preconception care. Confidentiality is perhaps the most important of these barriers. Teens are less likely to seek contraceptive or prenatal care due to concerns about confidentiality among family and peers. This is demonstrated by the fact that adolescent females wait an average of 1 year to seek contraceptive counseling after initiating sexual intercourse because they are afraid of their parent finding out (2012). As a result, most teenage pregnancies occur within the first year of becoming sexually active. Most states protect the rights of minors to seek contraception counseling and prenatal care; however, many states still restrict a minor’s right to termination of pregnancy without parental consent (2012).

Pregnant adolescents require additional resources and specialized care, so clinicians can utilize existing relationships amongst the teen and her family, peers, and partners. The initial preference for the teenager may be to conceal the pregnancy from family members or her partner due to fear of negative consequences. Providers are encouraged to engage a close family member
such as a parent or an older sibling during the initial office visit when the pregnancy is confirmed. Family members can provide the teen mother with much-needed support in the tenuous days and weeks ahead when decisions will have to be made about choice of pregnancy outcome and access to prenatal care.

Definitions of Hypertensive Disorders of Pregnancy

Interpretation of epidemiologic studies and outcomes research in the area of gestational hypertension and preeclampsia has been challenged by a lack of agreement on terminology (Lindheimer et al. 2010). Such definitions may differ depending upon the working group from which they originate. Furthermore, the correct categorization may not be clear until postpartum. Diagnostic criteria are designed to be rather loose or highly sensitive, so as to detect all possibly affected individuals early in the course with the goal that maternal and infant morbidity/mortality can be minimized. The following classification of hypertensive disorders in pregnancy was adopted by the International Society for the Study of Hypertension in Pregnancy (ISSHP) (2013): pre-eclampsia, chronic hypertension, preeclampsia superimposed upon chronic hypertension, and gestational hypertension (Table 1). The term pregnancy-induced hypertension which is not included in the classification scheme shown above has been used in some studies and publications; use of this term is discouraged because it might refer to either gestational hypertension or preeclampsia.

Chronic hypertension is defined as SBP \( \geq 140 \) and/or DBP \( \geq 90 \) before pregnancy or before 20 weeks gestation. It is possible that chronic hypertension may be initially designated as gestational hypertension with delay in the final diagnosis until 12 weeks postpartum because hypertension that is diagnosed during pregnancy but that does not resolve postpartum is considered chronic. Preeclampsia is a pregnancy-specific syndrome which usually occurs after 20 weeks gestation; it includes gestational BP elevation (same parameters as above) and proteinuria. In the absence of proteinuria, additional symptoms such as headache, blurred vision, abdominal pain, thrombocytopenia, and elevation of hepatic transaminases also indicate the presence of preeclampsia.

During uncomplicated pregnancy, the urine protein excretion increases to 200–260 mg/24 h with urinary microalbumin excretion levels up to 29 mg/24 h. Proteinuria is defined as \( \geq 300 \) mg per 24 h, by urine protein/creatinine ratio (Upc) \( > 0.3 \) or if those methods are not available, then \( \geq 1 \) by dipstick on at least two random urine samples collected more than 6 h apart (Dekker 2011). There are concerns about use of Upc in place of a timed urine collection. The correlation between 24 h urine protein and Upc was only moderate (\( R^2 = 0.41 \)) and a Upc < 0.3 had a negative predictive value of 47.5% among women with suspected preeclampsia (Durnwald and Mercer 2003). Indeed, while classically, proteinuria has been considered a criterion for preeclampsia, not all women with preeclampsia have

### Table 1

Classification of hypertensive disorders of pregnancy (Adapted from Garovic 2012)

<table>
<thead>
<tr>
<th>&lt;20 gestational weeks</th>
<th>( \geq 20 ) gestational weeks</th>
<th>( \geq 12 ) weeks postpartum</th>
<th>Diagnosis</th>
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</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>Gestational HTN + proteinuria</td>
<td>Resolution of HTN and proteinuria</td>
<td>Preeclampsia</td>
</tr>
<tr>
<td>Normotensive</td>
<td>Gestational HTN – no proteinuria</td>
<td>Resolution of HTN</td>
<td>Gestational HTN</td>
</tr>
<tr>
<td>Normotensive</td>
<td>Gestational HTN – no proteinuria</td>
<td>Persistent HTN</td>
<td>Chronic (incident) HTN</td>
</tr>
<tr>
<td>Chronic (prevalent) HTN</td>
<td>+proteinuria</td>
<td>Resolution of proteinuria</td>
<td>Preeclampsia superimposed upon chronic HTN</td>
</tr>
<tr>
<td>Chronic (prevalent) HTN</td>
<td>–proteinuria</td>
<td>Persistent HTN</td>
<td>Chronic HTN</td>
</tr>
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</table>
proteinuria. More recent definitions allow for inclusion of those individuals without proteinuria to be considered to have preeclampsia if they have evidence for other organ dysfunction, (thrombocytopenia, liver dysfunction, renal dysfunction, CNS symptoms). Eclampsia is defined as seizures without other causes in someone with preeclampsia. Edema has been omitted as a criterion.

Preeclampsia may also occur in the individual with chronic hypertension and may be difficult to distinguish from worsening chronic hypertension. In females such as the illustrative case with hypertension secondary to renal parenchymal disease, detection of preeclampsia may be challenged by preconception proteinuria. Furthermore, chronic hypertension is a significant risk factor for the development of preeclampsia. The onset of proteinuria or marked worsening of proteinuria in the setting or worsening hypertension and development of thrombocytopenia or hepatic transaminase elevation increase the likelihood that preeclampsia is superimposed upon chronic hypertension as opposed to worsening chronic hypertension.

Gestational hypertension describes the scenario of detection of hypertension in a pregnant female without known chronic hypertension or signs of preeclampsia, with the understanding that she may go on to develop preeclampsia or have chronic hypertension postpartum. If BP is normal by 12 weeks postpartum, then chronic hypertension can be excluded. Hypertension during pregnancy can be due to a preexisting condition (chronic hypertension – primary or secondary – most often related to underlying renal disease) or pregnancy-induced hypertension.

### BP Patterns Through the Course of Pregnancy

Physiological changes during pregnancy include upregulation of the renin-angiotensin-aldosterone system and global vasodilation, resulting in increased glomerular filtration rate and renal plasma flow. In addition, there may be increased renal volume (Berry and Atta 2016). During pregnancy, BP typically decreases during the first trimester and early second trimester [first 20 weeks] and then increases in the late second trimester and third trimesters to values similar to those at the beginning of gestation (Lindheimer et al. 2010). Clinic BP patterns were examined during gestation in more than 13,000 women from the Avon Longitudinal Study, 4% of whom were younger than 20 years of age (Macdonald-Wallis et al. 2012). Eighty-percent were normotensive; gestational hypertension developed in 14.6%, preeclampsia in 2.1%, and 3.3% had primary (or chronic) hypertension. BP levels were higher by 8 weeks gestation in women who developed gestational hypertension or preeclampsia (Fig. 1). Baseline BP levels were similar between women who developed gestational hypertension and preeclampsia despite the assumption of divergent etiologies/mechanisms. Those individuals who developed preeclampsia failed to demonstrate the typical decline in BP during the first half of gestation and were characterized by a sharper slope of increase in BP during the second half of gestation (Fig. 1). Those with chronic hypertension had higher BP levels during early gestation but did have a mid-gestational decline in BP, in a fashion similar to normal women. The magnitude of the increase in BP in the second half of gestation was also associated with earlier delivery.

### Ambulatory Blood Pressure During Pregnancy

Several studies have measured ambulatory BP in midtrimester in nulliparous females with normal baseline BP and have examined differences in and magnitude of ambulatory BP levels in predicting preeclampsia and pregnancy-induced hypertension (Kyle et al. 1993; Higgins et al. 1997). There were significant differences in both clinic and ambulatory systolic BP (SBP) between the normal and preeclamptic groups at 18 weeks gestation; those who went on to develop preeclampsia had a mean ambulatory SBP 4.7 mmHg greater than those who did not. At 28 weeks, there were significant differences in ambulatory systolic and diastolic BP; those who went on to develop preeclampsia had a mean
ambulatory SBP 6.9 mmHg and DBP 4.4 mmHg greater than those who did not. Diurnal pattern was maintained; those in the highest quartile of BP had the highest incidence of preeclampsia (Kyle et al. 1993). Positive predictive values using the 95th percentile cutoff for daytime, nighttime, and 24-h BP levels were poor.

Differences in diurnal variation were observed in a larger study; this study (in contrast to the previous) distinguished between two outcomes—gestational hypertension and preeclampsia (gestational hypertension + proteinuria) and compared them to a normal group. The group with preeclampsia had significantly higher nighttime BP, with a much smaller nocturnal decline, in contrast to the gestational hypertension group, which had higher daytime and nighttime BP as compared to the normal group but maintained a normal ratio between day/night mean BP. Despite significantly different mean BP levels in both hypertensive groups as compared to the normal group, ambulatory BP levels performed poorly in predicting who would develop gestational hypertension or preeclampsia (Higgins et al. 1997).
The pattern of ambulatory BP throughout pregnancy has been extensively characterized by Ramón Hermida and coworkers, who have argued that use of clinic BP levels with the threshold of 140/90 underestimates the incidence of gestational hypertension. Furthermore, they have offered several methods to define hypertension during pregnancy. Similar to other clinical situations, they argue that clinic BP levels misclassify individuals at risk. Pregnant women with masked gestational hypertension (high ambulatory and normal clinic BP) have comparable outcomes [preterm delivery and IUGR] as those with both abnormal ambulatory and clinic BP (Hermida and Ayala 2002). Differences in mean 24 h BP levels were noted toward the end of the first trimester; those who developed gestational HTN had a mean 24 hr ambulatory BP of 115/67 as compared to normotensive women, whose mean 24 hr ambulatory BP was 103/60. As illustrated in Fig. 2, ambulatory BP 90th percentile threshold levels are lower in the normal pregnant female as compared to the normal nonpregnant female.

Evidence continues to accumulate that reliance on office BP may underdiagnose hypertension during pregnancy. ABPM was performed in 87 women with high-risk pregnancy in whom office BP was considered normal (< 140/90). Thirty-three percent had masked hypertension. Those with nocturnal hypertension had 4.7 times greater risk for preeclampsia/eclampsia (Salazar et al. 2016; Bilo and Parati 2016). Although the supporting evidence was rated as low, the most recent ACOG report recommended ABPM for
pregnant women with suspected white coat hypertension to provide a more accurate representation of BP (2013).

Mechanisms of Gestational Hypertension and Preeclampsia

Preeclampsia, the most severe form of gestational hypertension, resolves with delivery. The occurrence of preeclampsia with molar pregnancies as well, however, points to the crucial role of the placenta, as opposed to the fetus, in its pathophysiology. During normal placentation, embryonic cytotrophoblast cells migrate into the uterine spiral arteries leading to their remodeling into high capacitance, low resistance vascular channels which provide for adequate placental and fetal perfusion (Powe et al. 2011). In so doing, cytotrophoblast cells acquire an endothelial phenotype, and spiral artery remodeling extends through the most superficial uterine layer, the decidua, and into the myometrium. These processes are attenuated in the preeclamptic placenta, in which myometrial-level arterial remodeling was seen in only 27% of arteries in one study (range, 3–41%), compared to 88% for placentae from non-preeclamptic pregnancies (range, 76–100%) (Brosens et al. 2011). Inadequate spiral artery remodeling in preeclampsia leads to reduced placental perfusion. Indeed, Doppler assessment of maternal uterine arterial blood flow demonstrates alterations reflecting this inadequate conversion of spiral arteries. Thus, among >4000 singleton pregnancies, odds ratios for gestational hypertension, preeclampsia, and early-onset preeclampsia were 1.5 [95% CI 1.02–2.26], 2.1 [1.28–3.36], and 4.47 [1.50–13.35], respectively, in the presence of diastolic notching in bilateral uterine arteries (heralding reduced perfusion) showed (Espinoza et al. 2010). The higher occurrence of preeclampsia in patients with preexisting hypertension, renal disease, obesity, and diabetes may relate to preexisting vascular abnormalities which render the spiral arteries resistant to cytotrophoblast cell invasion and remodeling.

The mechanisms and importance of uterine spiral artery remodeling to normal pregnancy have recently been further elucidated to include a prominent role for locally produced (uterine) atrial natriuretic protein (ANP) and the enzyme corin, which converts pro-ANP to ANP. ANP stimulates trophoblast invasion and both ANP and corin null mutant mice, when pregnant, demonstrate impaired trophoblast invasion/spiral artery remodeling as well as hypertension, proteinuria, and renal pathology. Human uterine samples from preeclamptic patients showed corin deficiency and pre-ANP excess compared to unaffected pregnancies (Cui et al. 2012). In a study of nearly 500 blood samples from 122 women throughout gestation, preterm preeclamptic mothers had lower circulating corin levels than those without preeclampsia and higher circulating pro ANP levels (Khalil et al. 2015). Further, two human corin gene mutations have been identified in preeclamptic Chinese women which markedly reduced ANP generation (Cui et al. 2012). More recently, two more common single nucleotide polymorphisms in the human CORIN gene (in almost perfect linkage disequilibrium) were found to be significantly associated with preeclampsia in Caucasians as well (Stepanian et al. 2014).

A poorly perfused, hypoxic placenta is thought to be central to the development of preeclampsia. Reduction in uteroplacental perfusion in a variety of mammals, including primates, has been shown to cause maternal hypertension (Gilbert et al. 2008; Makris et al. 2007). In a well-characterized rat model, 40% reduction in ureteroplacental perfusion on day 14 of a 21-day gestation induces dramatic maternal cardiovascular changes. On gestation day 19, animals displayed increased mean arterial pressure (MAP), increased total peripheral resistance, decreased renal blood flow and GFR, proteinuria, and endothelial dysfunction. Ex vivo investigation of vascular strips from similarly treated animals showed decreased relaxation in response to acetylcholine and decreased nitric oxide generation. Thus, reduced uteroplacental perfusion appears to tip the maternal cardiovascular balance towards vasoconstriction (Goulopoulou and Davidge 2015). Conversely, renal venous occlusion caused by compression of the left renal vein by the gravid uterus has been proposed as an overlooked
contributor to gestational hypertension and preeclampsia. The resultant higher renal interstitial pressure reduces the arterial flow and activates the RAAS as well as the sympathetic nervous system leading to systemic hypertension. Persistence of increased renal interstitial pressure results in ischemia leading to release of endothelin and other vasoactive mediators (Reuter et al. 2016).

Placenta-derived circulating factors have been identified which link abnormal placentation and the aberrations seen in maternal physiology with preeclampsia. Gene expression profiling of placental tissue from women with and without preeclampsia identified upregulation of soluble fms-like tyrosine kinase 1 (sFlt1) and elevated circulating sFlt1 in those with preeclampsia. As a splice variant of a vascular endothelial growth factor (VEGF) receptor lacking cytosolic and transmembrane domains, sFlt1 is circulating yet still able to bind VEGF, though without downstream effects, and thus acts to inactivate VEGF and placental growth factor (PIGF) as well. Normally, VEGF is a proangiogenic factor which promotes the proliferation and survival of endothelial cells. VEGF fosters vasodilation through interaction with the endothelial KDR receptor which upregulates endothelial nitric oxide synthase (eNOS) and also maintains endothelial fenestration and vascular permeability (He et al. 1999; Facemire et al. 2009), while the VEGF Flt1 receptor also contributes to endothelial permeability and survival (Takahashi et al. 2004). With 53% homology to VEGF, PIGF potentiates VEGF endothelial maintenance (Powe et al. 2011). Deprived of normal VEGF signal through increasing circulating sFlt1, maternal endothelium becomes dysfunctional (Fig. 3). This includes the renal circulation, where podocyte to endothelial VEGF signaling is essential to maintenance of normal glomerular capillaries, so that diminished VEGF leads to endothelial cell swelling, loss of the intact filtration barrier, and proteinuria. Infusion of sFlt1 (acting as a VEGF trap) into animals (pregnant or not) induced hypertension, proteinuria, and recapitulated the renal findings of severe preeclampsia, including glomerular endothelial

**Fig. 3** Soluble fms-like tyrosine kinase 1 (sFlt1) and soluble endoglin (sEng) cause endothelial dysfunction by antagonizing vascular endothelial growth factor and transforming growth factor-β1 (TGF-β1) signaling. VEGF and TGF-β1 maintain endothelial health. During normal pregnancy, vascular homeostasis is maintained by physiological levels of VEGF and TGF-β1 signaling in the vasculature; however, in preeclampsia, excess placental secretion of sFlt1 and sEng, which are endogenous antiangiogenic protein, inhibits VEGF and TGF-β1 signaling in the vasculature, resulting in endothelial dysfunction and the accompanying decreased prostacyclin and nitric oxide production as well as release of procoagulant proteins. TβRII indicates TGF-β1 receptor (From Powe et al. (2011))
Cell swelling and intracapillary fibrin deposition. This is similar to observations of hypertension and proteinuria with pharmacologic inhibition of VEGF for cancer therapy (Patel et al. 2008). Because sFlt1 also binds placental growth factor (PIGF), reduced free VEGF and free PIGF levels have been found in preeclamptic women, and these levels were even lower with worsening severity of preeclampsia (Maynard et al. 2003).

In a larger cohort of 120 pairs of nulliparous women with and without preeclampsia, non-preeclamptic women showed an increase in sFlt1 in the last few weeks of gestation which was dramatically surpassed (two to threefold higher) in those with preeclampsia (Levine et al. 2004). Lower PIGF levels were seen (8–45% control level in the last trimester) though depletion of circulating VEGF was harder to demonstrate in this larger cohort in part because of lower VEGF levels in all women (5–10 pg/ml) compared to PIGF levels (50–1000 pg/ml); circulating VEGF represents a small fraction, as the majority of VEGF is membrane bound. Further implicating sFlt1 in the pathophysiology of preeclampsia are observations that its placental expression and maternal circulating level are augmented by hypoxia/hypoperfusion (Hornig et al. 2000; Makris et al. 2007). Lastly, apheresis with a dextran sulfate cellulose column reduced circulating sFlt1 level in severe preterm preeclamptic women and was accompanied by reduction in BP and proteinuria as well as prolongation of pregnancy (Thadhani et al. 2011). This initial whole blood apheresis strategy has recently been improved upon (decreasing procedure-associated hypotension) by first separating out plasma before passing it through a plasma-specific dextran sulfate (PSDS) column (Thadhani et al. 2016). Among women with very preterm preeclampsia (23–32 weeks gestation), lowering sFlt through PSDS apheresis allowed continuation of pregnancy for 8 days (range 2–11) and 15 days (range 11–21) after single and multiple treatments, respectively, compared to 3 days prolongation of pregnancy in untreated contemporaneous controls.

Similarly, excess placenta-derived soluble endoglin (sEng) circulating at higher than normal levels in the preeclamptic mother causes important endothelial effects. This is because membrane bound endoglin is a necessary coreceptor for endothelial TGF beta signaling. In addition to its recognized function to promote cellular proliferation and differentiation, TGF beta is also crucial to normal vascular functioning including vasodilatation through nitric oxide (Venkatesha et al. 2006). As with sFlt1 and VEGF, sEng acts as a ligand trap for TGF beta, lessening its endothelial receptor binding and downstream eNOS signaling and vascular relaxation (Venkatesha et al. 2006). In preeclamptic mothers, reduction in circulating nitrite (metabolic by product of nitric oxide metabolism) correlated with elevations in sEng (as well as sFlt1) (Sandrim et al. 2008).

Effects of sEng and sFlt1 appear synergistic. Thus, while experimental infusion of sFlt1 causes hypertension and proteinuria, coinfusion of sFlt1 and sEng together causes more severe hypertension and proteinuria as well as hemolysis, thrombocytopenia, and elevated hepatic transaminases, recapitulating the HELLP syndrome (hemolysis, elevated liver enzymes, low platelets) (Venkatesha et al. 2006). In assessing for risk of preeclampsia, elevation in either sFlt1 or sEng alone was associated with adjusted odds ratio (OR) of 1.5–2.3 (95% CI 0.4–8.7). Elevation in both produced an OR for term preeclampsia of 31.6 (95% CI 10.7–93.4) (Levine et al. 2006).

Measurements of maternal levels of circulating anti- and proangiogenic factors are being used to improve the diagnostic accuracy of current clinical signs and symptoms of preeclampsia. In a large, urban American obstetric practice, patients with a ratio of PIGF/sFlt1 less than 0.05 multiples of the median (MoM) (a low level of pro-/antiangiogenic factors) had a dramatically increased risk for preterm delivery (<34 weeks) due to preeclampsia (adjusted odds ratio 7.4). Among those presenting at less than 34 weeks gestation, the addition of the PIGF/sFlt1 ratio to standard clinical tests improved the sensitivity of detecting those at risk of delivery in less than 2 weeks. Thus, for PIGF/sFlt1 ratios of ≤0.035 MoM, 0.036—0.34 MoM, and ≥0.35 MoM the rates of preterm delivery <34 weeks gestation were 94%, 27%, and 7%, respectively (Chaiworapongs
et al. 2014). A multicenter prospective European trial produced similar results in that a low ratio of sFlt1/PlGF (anti-/proangiogenic factors) was able effectively to rule out preeclampsia. A sFlt1/PlGF ratio < 38 had a negative predictive power (no preeclampsia in the following week) of 99.3% (99% CI 97.9–99.9) (Zeisler et al. 2016). Such results should allow more precise stratification of preeclampsia risk so that resources can be directed towards those most clearly affected.

Increased expression of sFlt1 is mediated at least in part by hypoxia inducible factor-1 (HIF), credibly linking placental hypoperfusion and findings of increased circulating sFlt1 in preeclampsia (Nevo et al. 2006). 2-Methoxyestradiol (2-ME), which is elevated in normal pregnancies, suppresses HIF. The enzyme responsible for production of 2-ME, catechol-O-methyltransferase (COMT), is reduced in the placentas of women with preeclampsia (Barnea et al. 1988). COMT null mutant mice, absent 2-ME, have elevated HIF and sFlt1 and preeclampsia, all ameliorated by exogenous 2-ME administration (Kanasaki et al. 2008). Interestingly, genetic variants associated with lower COMT levels have been associated with recurrent preeclampsia raising the possibility that 2-ME administration might have therapeutic potential for treatment of preeclampsia (Roten et al. 2011; Hernandez et al. 2013).

Vasoconstrictor responses of maternal vasculature are potentiated by increased angiotensin type I receptor signaling. Autoantibodies to the angiotensin AT1 receptor (AT1-AA) have been detected in the serum of preeclamptic women which function as receptor agonists. Increased receptor activity might explain the exaggerated pressor response to angiotensin II observed in preeclamptic compared with normal pregnancies (Wallukat et al. 1999). Various AT1-mediated effects have been demonstrated for these autoantibodies including vasoconstriction, stimulation of plasminogen activator inhibitor-1 (PAI-1) from mesangial cells, and tissue factor expression by vascular cells – all potentially relevant to maternal cardiovascular and renal changes observed in preeclampsia (Dechend et al. 2003). Importantly, AT1-AA recovered from patients with preeclampsia produced preeclampsia when administered to pregnant mice (Zhou et al. 2008). Underscoring the levels of complexity of preeclampsia causation are observations that AT1-AA leads to increased sEng, as well as the potent vasoconstrictor endotheлин-1 (Zhou et al. 2010, 2011). Moreover, recombinant VEGF administration ameliorates experimental AT1-AA mediated preeclampsia, suggesting VEGF blockade by sFlt1 to be an important post AT1 receptor mediator of preeclampsia as well (Siddiqui et al. 2011).

Emerging evidence points to a role for complement dysregulation in preeclampsia and gestational hypertension as well. Placental trophoblasts express three membrane bound complement regulatory proteins: membrane cofactor protein (MCP, CD46), delay accelerating factor (DAF, CD55), and MAC inhibitory protein (MAC-IP, CD59), an inhibitor of terminal complement (Regal et al. 2015). These function to quell the complement activation of normal pregnancy and maintain the health and integrity of the fetal placental unit. In preeclamptic Chinese women, the terminal complement product C5b-9 was elevated in plasma together with C3a and C5a (complement metabolites indicative of activation). As the terminal product of the complement cascade, elevated C5b-9, the soluble membrane attack complex (sMAC), indicates unrestrained complement activation (He et al. 2016). Renal autopsy tissue from women with preeclampsia showed a dramatic increase in glomerular staining for C4d compared to normal pregnancy and chronic hypertensive controls as well as a moderate increase in C1q (Penning et al. 2015). To further investigate these observations, this group used a murine model of preeclampsia induced by injection of exogenous sFLt-1 during pregnancy. These mice subsequently showed marked increase in renal C4d as well. Given the model of preeclampsia induction, these data indicate a link of complement activation to the antiangiogenic state of preeclampsia (increased sFlt-1). Similar results have been found in women with severe preeclampsia, in whom elevated urine C5b-9 correlated significantly with urine sFlt-1 ($r = 0.77; p < 0.0001$) as well as the overall antiangiogenic state of marked elevation in sFlt-1 and suppression of PI GF and VEGF in plasma.
Sera from patients with severe preeclampsia and HELLP syndrome indicated complement activation which could be blocked in vitro by the anti-C5 monoclonal antibody, eculizumab (Vaught et al. 2016). Indeed, eculizumab has been used to treat severe HELLP syndrome at 26-weeks gestation, resulting in improvement in liver function studies, LDH, haptoglobin, and platelet count, allowing pregnancy to be prolonged by 17 additional days (Burwick and Feinberg 2013).

The pathophysiology of gestational hypertension shares many components with preeclampsia. A significant elevation in the ratio of sFlt1:PlGF in women with gestational hypertension has been observed, though elevation was relatively smaller than the marked elevation in preterm and term preeclampsia (Levine et al. 2004). In the same group of patients, however, sEng was elevated to the same degree as those with preeclampsia, leading the authors to consider/recommend gestational hypertension as a milder form of preeclampsia. In another study, sFlt1 and sEng were both intermediate in patients with gestational hypertension (23.5, 23.6 pg/ml) compared to normal pregnant controls (16.5, 15.5 pg/ml) and preeclamptic women (74.7, 69.2 pg/ml) (Salahuddin et al. 2007). Since the advent of normative data for sFlt1 and sEng levels in pregnancy, it has been shown that circulating levels above the 95th percentile were seen in 67% and 67% of women with gestational hypertension as opposed to 94% and 89% of women with standard preeclampsia (Hirashima et al. 2011). Women with gestational hypertension demonstrate a reduction in circulating nitrite (reflecting reduced endothelial nitric oxide) though to a lesser degree than preeclampsia (Salahuddin et al. 2007). Similarly, glomerular endotheliosis on renal biopsy (once considered pathognomonic of preeclampsia) has been documented in women with gestational hypertension as well, though milder than in preeclampsia (Strevens et al. 2003). Even AT1-AA levels were intermediate in patients with gestational hypertension between those with preeclampsia (higher) and normotensive pregnancies (low) (Siddiqui et al. 2010). Though not a universal view, these observations speak to diffuse endothelial dysfunction underlying both gestational hypertension and preeclampsia, differing mainly by degree (Noori et al. 2010).

### Risk Factors for Preeclampsia

Risk factors for preeclampsia are listed in Table 2. Although young maternal age was originally thought to increase the risk of gestational hypertension, there is conflicting evidence to support that younger age alone increases the risk of gestational hypertension or preeclampsia (some studies did not differentiate between the two outcomes). Younger maternal age was not found to be an independent risk factor in more recent studies (see section on factors unique to the adolescent). The increased risk observed for younger women

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nulliparity</td>
<td>2.91</td>
<td>1.28–6.61</td>
</tr>
<tr>
<td>Previous preeclampsia</td>
<td>7.19</td>
<td>5.85–8.83</td>
</tr>
<tr>
<td>Previous AKI</td>
<td>4.70</td>
<td>2.10–10.10</td>
</tr>
<tr>
<td>Family history of preeclampsia</td>
<td>2.90</td>
<td>1.70–4.93</td>
</tr>
<tr>
<td>High BMI at first evaluation</td>
<td>1.55</td>
<td>1.28–1.88</td>
</tr>
<tr>
<td>Before pregnancy</td>
<td>2.47</td>
<td>1.66–3.67</td>
</tr>
<tr>
<td>SBP ≥ 130mmHg at first evaluation</td>
<td>2.37</td>
<td>1.78–3.15</td>
</tr>
<tr>
<td>DBP ≥ 80mmHg at first evaluation</td>
<td>1.38</td>
<td>1.01–1.87</td>
</tr>
<tr>
<td>Preexisting DM</td>
<td>3.56</td>
<td>2.54–4.99</td>
</tr>
<tr>
<td>Preexisting HTN</td>
<td>Increased risk</td>
<td></td>
</tr>
<tr>
<td>Preexisting renal disease</td>
<td>Increased risk</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Duckitt and Harrington (2005), Steegers et al. (2010), Sibai et al. (1998), Tangren et al. (2016)
may be related to several of the known risk factors which are common to the adolescent, including nulliparity, limited sperm exposure, and primipaternity (Duckitt and Harrington 2005). Obesity is a significant risk factor for preexisting hypertension, gestational hypertension, and development of preeclampsia. Results reported from the Generation R Study indicate that higher prepregnancy body mass index (BMI) was associated with greater SBP throughout pregnancy, with the highest levels among the morbidly obese group (Gaillard et al. 2011). There was a pattern of consistently higher SBP and DBP for higher BMI throughout pregnancy (Fig. 4). The odds ratios for gestational hypertension (the term pregnancy-induced hypertension was used) for the overweight/obese/morbidly obese groups as compared to the group with normal BMI were 2.12 (CI 1.54–2.91), 4.67 (3.07–7.09), and 11.34 (6.80–18.86) and for preeclampsia: 1.82 (CI 1.16–2.83), 2.49 (CI 1.29–4.78), and 3.40 (1.39–8.28), respectively (Gaillard et al. 2011). Additionally, greater gestational weight gain was also associated with increased risk of gestational hypertension (<7 g vs. >7 kg) but was not associated with increased risk of preeclampsia. Among the 2637 women participating in the BIRTH study, a dose response effect of BMI on risk of preeclampsia was observed. Indeed, obesity was the most important risk factor for preeclampsia and severe preeclampsia in this cohort, with an attributable risk of 64.9% and 64.4%, respectively (Pare et al. 2014).

Acute kidney injury (AKI) prior to conception significantly increases the risk for preeclampsia. A single center retrospective study over 10 years, including over 25,000 pregnancies, found that the adjusted odds ratio for preeclampsia was 4.7 [2.1–10.1] among women with previous history of AKI and recovery of renal function (no CKD). In addition, risk for adverse fetal outcomes was also significantly increased by prior AKI (OR 2.1, 1.2–3.7) (Tangren et al. 2016).
Features Unique to the Pregnant Teenager

There are no guidelines as to the definition of gestational hypertension in the adolescent female. The threshold of 140/90 used in adult women is based upon the definition of hypertension for adults in general. It could be argued that this threshold should be decreased for all pregnant women and particularly for adolescent females, because BP levels are lower during the first half of pregnancy (as discussed in previous section). Furthermore, 140/90 is significantly higher than the current definition of stage 1 hypertension among adolescent females (clinic BP at or above the 95th percentile for age and height percentile). A SBP threshold of 140 mmHg is greater than the 99th percentile for females aged 13–17 years of age, whereas the DBP threshold of 90 mmHg approaches the 99th percentile for taller adolescent females. Among a cohort of women with mild gestational HTN, BP levels in teenagers were compared to those of adult women: SBP was 133.4 ± 15 mmHg at the beginning of monitoring for the teenage group and 139.5 ± 15 mmHg for the adult group. Similarly, DBP levels were lower in the teenagers, 84.1 ± 13.6 mmHg versus 90.1 ± 11.5 mmHg in the adults (Barton et al. 1995). A small retrospective study among mothers 15–19 years of age found that a second trimester MAP > 80 mmHg (in contrast to a threshold MAP of 90 mmHg used for adult women) had a sensitivity of 60% and specificity of 93% in predicting gestational hypertension, with a positive predictive value of 76% and negative predictive value of 82% (Gavette and Roberts 1987).

Earlier studies reported a higher incidence of hypertension (preeclampsia/eclampsia) among younger mothers (Treffers et al. 2001; Eure et al. 2002); however, this has been disputed by more recent epidemiologic studies, including a meta-analysis (Sibai et al. 1997; de Vienne et al. 2009; Gupta et al. 2008; Duckitt and Harrington 2005). There was a lower incidence of hypertension in teenage mothers (mean age 18.3, range 13.7–19.9 years) as compared to mothers 20–35 years of age (3.7% vs. 6.6%) (Gupta et al. 2008). The authors did not further classify the underlying hypertension (i.e., preeclampsia); however, they did subdivide the adolescent group into those aged less than 17 years to investigate whether the very youngest had increased risk and found none. Younger maternal age was associated with a lower risk of preeclampsia in a study of more than 8000 primiparous women at the University Hospital of Caen, France (de Vienne et al. 2009). A systematic review of controlled cohort studies that examined the risk of preeclampsia and age concluded that younger maternal age was not a significant risk factor (Duckitt and Harrington 2005).

A retrospective case-control study using the Finger Lakes Regional Perinatal Data System categorized adolescents (maternal age < 19 years) according to prepregnancy BMI into control (BMI 18.5–24.9 35 kg/m²), overweight (BMI 25–29.9 kg/m²), obese (BMI 30–34.9 kg/m²), and morbidly obese (BMI >35 kg/m²). Preexisting chronic hypertension was present in 0.5% of the control group and 1.1% of the combined overweight-obese group. Pregnancy-induced hypertension was present in 4.5% of the control group and 7.8% of the combined overweight and obese group, and preeclampsia in 2.4% of the control versus 4.0% of the overweight and obese group. The odds ratio for gestational hypertension was 1.8 (CI 1.4, 2.3) in women with a BMI >25 kg/m² (Sukalich et al. 2006). This emphasizes the multiple levels of risk associated with the overweight/obese adolescent with respect to pregnancy-associated hypertension: not only are they at increased risk for primary hypertension, they are also at increased risk for pregnancy-related hypertension due to their higher prepregnancy BP levels and BMI.

Impact of Chronic Hypertension on Pregnancy Outcome

The prevalence of chronic hypertension among females of child-bearing age appears to be increasing largely due to the increased prevalence of obesity, and this is equally true for the increasing prevalence of hypertension among adolescent females (Wang and Beydoun 2007). Females with chronic hypertension who become pregnant are at
increased risk for developing preeclampsia and of developing preeclampsia relatively earlier in gestation (Seely and Ecker 2011). Preeclampsia occurred in 10–25% of women with mild chronic HTN, with an average prevalence of 20.8% across the four available studies. Chronic hypertension without preeclampsia increases the risk for fetal growth restriction (8–15.5%), preterm birth (12–33.3%), placental abruption (0.7–1.4%), and stillbirth (Seely and Ecker 2011; Sibai et al. 1998). Chronic HTN was associated with a fivefold increase in risk of delivering preterm and 1.5 times increased risk of offspring who are small for gestational age (Seely and Ecker 2011). Although some women with chronic hypertension experience lower BP levels during pregnancy as a result of the typical physiological decrease in BP in the first half of gestation, others develop preeclampsia or worsening hypertension (Sibai et al. 1998). Proteinuria in the setting of chronic hypertension prior to pregnancy is a risk factor for preeclampsia and/or fetal growth restriction (Sibai et al. 1998). It has been recommended that increased risk be assigned to women with chronic hypertension who become pregnant. Women considered to have low risk for developing preeclampsia include those with mild essential hypertension without target organ damage. Among women with chronic hypertension, the higher risk group includes those with secondary hypertension, target organ damage, previous perinatal loss, and SBP > 180 mmHg or DBP > 110 mmHg (Sibai 2002). The case presented at the outset of the chapter illustrates this concept – previous diagnosis of chronic, severe HTN with baseline proteinuria is associated with markedly increased risk for our patient to develop preeclampsia and for her infant to be premature and small for gestational age.

Because of the increased risk of poor outcome in the setting of chronic hypertension, prepregnancy counseling and evaluation is recommended. Prepregnancy counseling is unlikely to be offered in the setting of adolescent pregnancy which is most often unplanned. This raises the question of whether hypertensive adolescents should be counseled regarding the risks that HTN has in the event of pregnancy – this could be added to the warning regarding pregnancy prevention in those taking angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs).

### Treatment of Hypertension During Pregnancy

The goal for treatment of hypertension during pregnancy is to maintain a healthy BP for the mother while minimizing the risk for the fetus. At the initial visit when pregnancy is diagnosed several important steps should be taken by the provider. The provider should diagnose the duration of pregnancy based on last menstrual period and then stratify the young woman based on other risk factors. A thorough history of chronic disease such as hypertension, diabetes, thyroid disease, or chronic kidney disease should also be elicited. In addition to placing the mother on a prenatal vitamin, the provider should document all medications and herbal supplements being used and then determine if they pose a risk to the mother or fetus. We also assess each patient for certain parameters including nutritional status and food security, risk for domestic violence, substance use, family and social support system, and accessibility to prenatal care. For adolescent women with chronic medical conditions such as hypertension we establish early communication with subspecialist providers to assess any further risks. At the end of the visit we clearly communicate plans for pregnancy options and follow-up care.

Ideally, adolescent females with hypertension should be followed in a clinic where preconception counseling can be offered confidentially and conveniently. Preconception counseling offers the opportunity for both primary care providers and subspecialists to discuss the efficacy and safety of contraceptive methods in conjunction with potential harm from antihypertensive medications (CDC 2012). As a practice, most teens in our clinic that are on potentially teratogenic drugs are placed on some sort of hormonal contraception and are encouraged to use barrier protection as an adjunctive method.

The costs of managing gestational hypertension include the expense of more frequent visits to the obstetrician’s office or emergency
department, more frequent laboratory tests and fetal monitoring, as well as hospitalizations, sometimes for prolonged periods (Sibai 2007). In addition, pregnancies complicated by hypertension have higher rates of cesarean delivery and preterm infants who require longer postnatal hospitalization, often in a critical care unit.

Treatment to lower BP during pregnancy is controversial, as guidelines published by different organizations do not agree on the threshold for initiation of treatment or on the goal BP levels after treatment is initiated (Seely and Ecker 2011). The American College of Obstetricians and Gynecologists recommends initiation of antihypertensive therapy if the SBP is $\geq 180$ mmHg and/or DBP $\geq 100$ mmHg. The JNC7 Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends initiation of antihypertensive therapy if SBP is $>150–160$ mmHg and/or DBP $>100–110$ mmHg. Canadian guidelines recommend treatment if the SBP $>150$ mmHg and/or DBP $>109$ mmHg and the Australasian guidelines for SBP $>170$ mmHg and DBP $110$ mmHg (Seely and Ecker 2011). In contrast, the European Society of Hypertension/European Society of Cardiology guidelines recommend initiation of antihypertensive medication for BP $\geq 140/90$ (Moser et al. 2012).

In the pregnant female with chronic hypertension, maintenance antihypertensive medications may be continued during pregnancy with the exception of ACEi or ARB, but the recommendations for optimum BP levels are conflicting. The NHBPEP recommendations state that for women with chronic hypertension, antihypertensive medications would not be continued or restarted unless the SBP is 150–160 mmHg or DBP is 100–110 mmHg. Therefore, according to these guidelines antihypertensive medications might have to be discontinued or modified if BP levels decline. The choice of antihypertensive agent is challenged by paucity of information regarding safety and efficacy of specific agents during pregnancy. The most commonly used antihypertensive drugs during pregnancy include methyldopa, labetalol, hydralazine, metoprolol, extended-release nifedipine, and hydrochlorothiazide (Seely and Ecker 2011). Methyldopa is not an agent of choice in adolescents or adult women as a first or second line agent; however, it is the agent of choice during pregnancy due to its record of safety and proven lack of effect on uterine artery Doppler flow. A Cochrane systematic review of available trials reported a reduction in risk for development of severe hypertension (RR 0.50 (0.41–0.61) associated with the use of antihypertensive medication to treat mild to moderate gestational hypertension (Abalos et al. 2007). Recent Cochrane analysis now suggests that there is a reduction in the overall risk of proteinuria/pre-eclampsia when beta-blockers and calcium channel blockers (analyzed together) are compared with methyldopa (RR 0.73; 95% CI 0.54–0.99) (Abalos et al. 2014). Recommendations from a recent review article include the following two proposals (Moser et al. 2012):

1. For women with chronic hypertension that has been adequately controlled, continue the same medication regimen, with the exception of ACEi and/or ARB
2. For the normotensive female who develops increased BP over 140/90 mmHg, initiate treatment with small doses of beta-blockers (labetalol not metoprolol), thiazide diuretic, or calcium channel blocker (in addition to methyldopa and hydralazine)

Treatment of hypertension reduces maternal morbidity but has no proven effect on fetal outcomes. Treatment to lower maternal BP was not associated with differences between treatment and placebo on fetal outcomes such as preterm birth, intrauterine growth restriction, or fetal death (Abalos et al. 2007). An analysis including 12 trials of the effect of beta blockers (vs. placebo or an agent other than beta blocker) on the incidence of small-for-gestational age infants reported a summary relative risk of 1.36 (1.02–1.82) (Magee and Duley 2003). Beta blockers also increased the risk for neonatal bradycardia (RR 1.93 (1.05–3.53) and decreased the risk for respiratory distress syndrome (RR 0.29, 0.12–0.67) with no effect on the risk for preterm birth (Magee and Duley 2003). Concerns about overtreatment of hypertension during pregnancy include the potential risk for reduction of placental blood flow and the
exposure of the fetus to potentially teratogenic medications. A meta-analysis of the effect of antihypertensive therapy on fetal outcome reported that every 10 mmHg reduction in MAP resulted in a birth weight reduction of 145 grams (von Dadelszen et al. 2000). This study has been criticized for overestimation of the effect of BP reduction on birth weight (only 16% of variability of birth weight was related to maternal BP) and selection bias, since a trial which indicated an opposite relationship between birth weight and BP reduction was not included (Moser et al. 2012). Since chronic hypertension is associated with significant morbidity for the mother and her baby, one could argue that treatment would be beneficial for both.

The control of hypertension in pregnancy study (CHIPS) trial randomized women with hypertension (defined by DBP) to either tight or less tight BP control to determine whether BP levels were associated with adverse maternal or fetal outcomes. They found comparable primary and secondary outcomes for both groups; however, the incidence of severe hypertension was greater in the less tight control group. There was an association between severe hypertension and serious maternal complications in the less tight control group; this association remained significant after adjusting for presence of preeclampsia. In addition, severe hypertension was associated with low birth weight and preterm delivery among all participants (Magee et al. 2015, 2016). This study raises the question of whether use of ABPM might have characterized BP more completely to avoid misclassification (Bilo and Parati 2016). Editorial comments regarding the CHIPS Trial concluded that tighter BP control does not appear to increase fetal morbidity; in addition thrombocytopenia was more common in the less tight control group (adjusted OR 2.63 [1.15–6.05]) as was abnormal elevation of hepatic transaminase levels (adjusted OR 2.33 [1.05–5.16]) (Easterling 2016).

In spite of the CHIPS findings, the ACOG group recommends that the threshold to initiate pharmacologic therapy remain at ≥160/105. The agents of choice for oral therapy are labetalol, followed by a calcium channel blocker; the dose of labetalol should be maximized before adding the second agent. For acute hypertension, they recommend IV labetalol or hydralazine, or oral nifedipine (Amro et al. 2016). The ACOG report recommended labetalol, nifedipine, and methyl-dopa as first-line agents for treatment of hypertension during pregnancy (2013). The goal for BP for pregnant women with hypertension is 120–160/80–105 mmHg (2013).

As mentioned earlier, ACEi and ARBs should never be used during pregnancy; they increase the risk for fetal developmental anomalies (Cooper et al. 2006). Fetal renin-angiotensin system blockade syndrome (fetal RAS blockade syndrome) was recognized in the early 1980s as a result of intrauterine exposure to ACEi, originally termed ACE inhibitor fetopathy. Pregnancies in women on ACEi were complicated by oligohydramnios, and infants with the syndrome exhibited intrauterine growth retardation, hypertension, renal failure, and other developmental anomalies. It was initially thought that first trimester exposure was not a risk for the fetus; however, a study which used Medicaid records to link maternal antihypertensive medication use to infant outcomes found increased risk of congenital malformations as compared to exposure to other antihypertensive medication or no antihypertensive medications with a risk ratio of 2.71 (95% CI 1.72–4.27) (Cooper et al. 2006). A systemic review of ACEi and ARB exposure reported the prevalence of fetal RAS blockade syndrome by trimester and duration of exposure (Bullo et al. 2012). Risk for fetal RAS blockade syndrome was lowest for isolated first trimester exposure as compared to exposure during the second and/or third trimesters (Polifka 2012). Based upon the currently available studies first trimester exposure to ACEi or ARB has a similar risk for congenital malformations as exposure to other antihypertensive agents or untreated hypertension during the first trimester (Polifka 2012). Due to concern about fetal risk for congenital malformations due to continued exposure during the second and third trimester, women treated with ACEi or ARB who become pregnant should be treated with alternative anti-hypertensive agents (Polifka 2012).
Risk of Future Cardiovascular Disease and Renal Disease

The presence of hypertension during pregnancy increases the risk of the woman’s and her offspring’s future risk of developing cardiovascular disease (CVD). Not only are women with gestational hypertension more likely to develop chronic hypertension, they do so at an earlier age. Women with gestational hypertension also have a greater incidence of coronary heart disease and stroke. Data from women participating in the Family Blood Pressure Program study found that women whose pregnancies were complicated by gestational hypertension demonstrated hazard ratios for stroke of 2.0, for coronary artery disease of 1.5, and for hypertension of 1.5 (Garovic 2012). The adjusted hazard ratio for developing chronic hypertension was 1.88 in a model that controlled for traditional cardiovascular risk factors such as race, family history of CVD, diabetes mellitus, smoking, and dyslipidemia (Garovic et al. 2010). The hazard ratio for stroke after controlling for the aforementioned risk factors as well as hypertension was 2.1. Since the risk factors for developing hypertension during pregnancy may be similar to those risk factors associated with CVD in general, it is unclear whether the association of gestational hypertension and future cardiovascular risk is causal or due to common etiologies.

Recent evidence suggests that preeclampsia may do more than unmask preexisting risk of CVD. A murine preeclampsia model was used in which sFlt was overexpressed in pregnancy leading to hypertension and glomerular disease. Two months postpartum, after normalization of sFlt level, hypertension, and cardiac and renal parameters, the mice were subjected to unilateral carotid artery injury. The injured carotid arteries of animals with prior preeclampsia showed dramatically increased smooth muscle cell proliferation and vascular fibrosis (180% and 216% increase, respectively) compared to those from mice which did not previously have preeclampsia. Notably, no preeclampsia-induced differences were observed in the uninjured carotid arteries. Thus, vessels exposed to preeclampsia had an amplified vascular response to subsequent injury (Pruthi et al. 2015). These data appear to suggest that after preeclampsia, the vasculature retains a phenotype with the potential for future maladaptive remodeling and increased risk of CVD. Importantly, proteomic analysis of plasma from human mothers with and without preeclampsia showed persistent differences postpartum as well. Thus, 6 months after delivery, the proteome of women with a history of preeclampsia showed altered expression of coagulation cascade factors favoring thrombophilia (increased Factor X and decreased tetranection) and complement activation, suggesting a potential ongoing link to subsequent cardiovascular risk (Murphy et al. 2015). It is not known whether these or similar alterations in circulating factors may contribute to the observed increased incidence of albuminuria (McDonald et al. 2010) and increased risk of end stage renal disease in mothers with a history of preeclampsia (Vikse et al. 2008; Wang et al. 2013).

Offspring of hypertensive pregnancies are also at risk of developing increased BP. A single center study published in 1979 examined BP of pregnant teenagers during and following pregnancy and BP in their offspring 3–6 years later (Kotchen et al. 1979). Mean BP measured using a mercury sphygmomanometer in the hypertensive group during the mid-third trimester was 121.4 ± 1.2/78.8 ± 0.9 mmHg compared to 112 ± 1.1/69.5 ± 0.9 mmHg in the normal group. The postpartum BP levels 3–6 years postpartum remained higher as did maternal weight in the hypertensive group (119.4 ± 2.4/78.3 ± 1.6 mmHg) versus the normal group (117.1 ± 1.2/73.4 ± 1.3 mmHg). Offspring of the gestational hypertensive mothers had higher mean SBP compared to those with normal maternal BP: 97.6 ± 1.3 versus 93.1 ± 1.5, at a mean age of 4.5 years.

Gestational hypertension was associated with increased body weight and higher BPs and body weight in the mothers and infants at follow-up. This study is mentioned because it included only pregnant teenagers as part of the Young Mothers’ Program at the University of Kentucky and aimed to determine the impact of gestational hypertension on future cardiovascular status (Kotchen et al. 1979).

More recently, a meta-analysis which summarized 18 studies with data from 45,249 individuals
reported that in utero exposure to preeclampsia was associated with a 2.39 mmHg increase in SBP and 1.35 mmHg higher DBP during childhood and young adulthood. BMI was increased by 0.62 kg/m² after exposure to preeclampsia (Davis et al. 2012). In a study which used data from the Helsinki Birth Cohort Study, adult children born to mothers with preeclampsia and gestational hypertension had a greater risk for stroke with hazard ratio of 1.9 (CI 1.2, 3.0) and 1.4 (CI 1.0, 1.8), respectively. Preeclampsia was also associated with smaller head circumference at birth (Kajantie et al. 2009). In conclusion, females with hypertension during pregnancy – including preeclampsia – appear to have increased risk for significant future cardiovascular morbidity. Furthermore, their offspring have higher BP levels and may also have increased risk for future cardiovascular events as adults.

Concluding Remarks

Hypertensive disorders of pregnancy represent a major cause of maternal deaths in the USA as well as increased infant mortality and morbidity. Teenagers with chronic hypertension who become pregnant are more likely to be in a higher risk group if they have secondary cause for hypertension such as chronic kidney disease and may also be at greater risk for preeclampsia due to nulliparity and primipaternity. The presence of hypertension during pregnancy increases the future risk for CVD in the mother and her offspring. Exposure to certain antihypertensive medication classes such as ACEi or ARB poses risk for the developing fetus, some of whom have RAS inhibition fetopathy or other congenital malformations. Clinicians caring for the pregnant adolescent with hypertension are challenged by the lack of evidence from which to development guidelines for treatment. Issues which are specific to this unique group include the appropriate threshold for classification as hypertensive (likely to be lower than for adult women during pregnancy), as well as the choice of antihypertensive agents and the goal for BP levels after initiation of therapy.

Cross-References

- Ambulatory Blood Pressure Monitoring Methodology and Norms in Children
- Endothelial Dysfunction and Vascular Remodeling in Hypertension
- Vasoactive Factors and Blood Pressure in Children

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