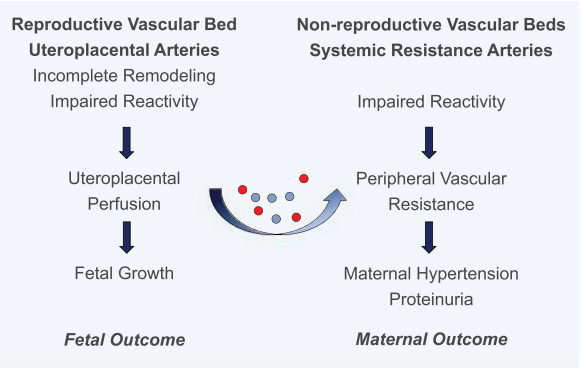
# *Hypertension* Editors' Picks
## Preeclampsia, Pregnancy, and Hypertension

The Editors




The following articles on pregnancy and pregnancy-related hypertension such as preeclampsia are being highlighted as part of *Hypertension*'s Editors' Picks Series. Preeclampsia is one of the leading causes of maternal and perinatal morbidity and mortality. Moreover, hypertensive complications of pregnancy are now considered major risk factors for hypertension and cardiovascular disease in the mother and the offspring. Research in this field has focused on identifying and characterizing new pathways that lead to new-onset hypertension during pregnancy. Over recent years, several innovative biomarkers have been identified in humans and tested for use in prediction and diagnosis of preeclampsia and its complications. In addition, novel animal models have been reported that should aid in the development of targeted therapies for preeclampsia and cardiovascular disease following preeclampsia. We have collated for our readers over 45 full-length basic and clinical articles on pregnancy and preeclampsia published in our Journal between January 2016 and January 2018. It is quite obvious from the articles listed that *Hypertension*, an American Heart Association Journal, continues to be an important home for the publication of high-quality studies on pregnancy hypertension and preeclampsia.

### Chronic Blockade of the Androgen Receptor Abolishes Age-Dependent Increases in Blood Pressure in Female Growth-Restricted Rats[1]

**Abstract**

Intrauterine growth restriction induced via placental insufficiency programs a significant increase in blood pressure at 12 months of age in female growth-restricted rats that is associated with early cessation of estrous cyclicity, indicative of premature reproductive senescence. In addition, female growth-restricted rats at 12 months of age exhibit a significant increase in circulating testosterone with no change in circulating estradiol. Testosterone is positively associated with blood pressure after menopause in women. Thus, we tested the hypothesis that androgen receptor blockade would abolish the significant increase in blood pressure that develops with age in female growth-restricted rats. Mean arterial pressure was measured in animals pretreated with and without the androgen receptor antagonist, flutamide (8 mg kg per day, SC for 2 weeks). Flutamide abolished the significant increase in blood pressure in growth-restricted rats relative to control at 12 months of age. To examine the mechanism(s) by which androgens contribute to increased blood pressure in growth-restricted rats, blood pressure was assessed in rats untreated or treated with enalapril (250 mg/L for 2 weeks). Enalapril eliminated the increase in blood pressure in growth-restricted relative to vehicle- and flutamide-treated controls. Furthermore, the increase in medullary angiotensin type 1 receptor mRNA expression was abolished in flutamide-treated growth-restricted relative to untreated counterparts and controls; cortical angiotensin-converting enzyme mRNA expression was reduced in flutamide-treated growth-restricted versus untreated counterparts. Thus, these data indicate that androgens, via activation of the renin–angiotensin system, are important mediators of increased blood pressure that develops by 12 months of age in female growth-restricted rats.

## Healthful Dietary Patterns and the Risk of Hypertension Among Women With a History of Gestational Diabetes Mellitus: A Prospective Cohort Study[2]


### Abstract

Women who developed gestational diabetes mellitus represent a high-risk population for hypertension later in life. The role of diet in the progression of hypertension among this susceptible population is unknown. We conducted a prospective cohort study of 3818 women with a history of gestational diabetes mellitus in the Nurses' Health Study II as part of the ongoing Diabetes & Women's Health Study. These women were followed up from 1989 to 2011. Incident hypertension was identified through self-administered questionnaires that were validated previously by medical record review. Adherence scores for the alternative Healthy Eating Index 2010, the alternative Mediterranean diet, and the Dietary Approaches to Stop Hypertension were computed for each participant. Cox proportional hazard models were used to evaluate the associations between dietary scores and hypertension while adjusting for major risk factors for hypertension. We documented 1069 incident hypertension cases during a median of 18.5 years of follow-up. After adjustment for major risk factors for hypertension, including body mass index, alternative Healthy Eating Index 2010, alternative Mediterranean diet, and Dietary Approaches to Stop Hypertension, scores were significantly inversely associated with the risk of hypertension; hazard ratio and 95% confidence interval comparing the extreme quartiles (highest versus lowest) were 0.76 (0.61–0.94; *P* for linear trend=0.03) for AHEI score, 0.72 (0.58–0.90; *P* for trend=0.01) for Dietary Approach to Stop Hypertension score, and 0.70 (0.56–0.88; *P* for trend=0.002) for alternative Mediterranean diet score. Adherence to a healthful dietary pattern was related to a lower subsequent risk of developing hypertension among women with a history of gestational diabetes mellitus.


## Maternal Administration of Sildenafil Citrate Alters Fetal and Placental Growth and Fetal–Placental Vascular Resistance in the Growth-Restricted Ovine Fetus[3]


### Abstract

Intrauterine growth restriction (IUGR) causes short- and long-term morbidity. Reduced placental perfusion is an important pathogenic component of IUGR; substances that enhance vasodilation in the uterine circulation, such as sildenafil citrate (sildenafil), may improve placental blood flow and fetal growth. This study aimed to examine the effects of sildenafil in the growth-restricted ovine fetus. Ewes carrying singleton pregnancies underwent insertion of vascular catheters, and then, they were randomized to receive uterine artery embolization (IUGR) or to a control group. Ewes in the IUGR group received a daily infusion of sildenafil (IUGR+SC; n=10) or vehicle (IUGR+V; n=8) for 21 days. The control group received no treatment (n=9). Umbilical artery blood flow was measured using Doppler ultrasound and the resistive index (RI) calculated. Fetal weight, biometry, and placental weight were obtained at postmortem after treatment completion. Umbilical artery RI in IUGR+V fell less than in controls; the RI of IUGR+SC was intermediate to that of the other 2 groups (mean±SEM for control versus IUGR+V versus IUGR+SC: RI, 0.09±0.03 versus −0.01±0.02 versus 0.03±0.02; $F(2, 22)=4.21$; $P=0.03$). Compared with controls, lamb and placental weights were reduced in IUGR+V but not in IUGR+SC (control versus IUGR+V versus IUGR+SC: fetal weight, 4381±247 versus 3447±235 versus 3687±129 g; $F(2, 24)=5.49$; $P=0.01$ and placental weight: 559.7±35.0 versus 376.2±32.5 versus 475.2±42.5 g; $F(2, 24)=4.64$; $P=0.01$). Sildenafil may be a useful adjunct in the management of IUGR. An increase in placental weight and fall in fetal–placental resistance suggests that changes to growth are at least partly mediated by changes to placental growth rather than alterations in placental efficiency.


## Drinking Water Sodium and Elevated Blood Pressure of Healthy Pregnant Women in Salinity-Affected Coastal Areas[4]


### Abstract

Coastal areas in Southeast Asia are experiencing high sodium concentrations in drinking water sources that are commonly consumed by local populations. Salinity problems caused by episodic cyclones and subsequent seawater inundations are likely (partly) related to climate change and further exacerbated by changes in upstream river flow and local land-use activities. Dietary (food) sodium plays an important role in the global burden of hypertensive disease. It remains unknown, however, if sodium in drinking water—rather than food—has similar effects on blood pressure and disease risk. In this study, we examined the effect of drinking water sodium on blood pressure of pregnant women: increases in blood pressure in this group could severely affect maternal and fetal health. Data on blood pressure, drinking water source, and personal, lifestyle, and environmental confounders was obtained from 701 normotensive pregnant women residing in coastal Bangladesh. Generalized linear mixed regression models were used to investigate association of systolic and diastolic blood pressure of these—otherwise healthy—women with their water source. After adjustment for confounders, drinkers of tube well and pond water (high saline sources) were found to have significantly higher average systolic (+4.85 and +3.62 mm Hg) and diastolic (+2.30 and +1.72 mm Hg) blood pressures than rainwater drinkers. Drinking water salinity problems are expected to exacerbate in the future, putting millions of coastal people—including pregnant women—at increased risk of hypertension and associated diseases. There is an urgent need to further explore the health risks associated to this understudied environmental health problem and feasibility of possible adaptation strategies.

## Low Molecular Weight Heparin Improves Endothelial Function in Pregnant Women at High Risk of Preeclampsia[5]


### Abstract

Low molecular weight heparin (LMWH) has been investigated for the prevention of severe preeclampsia, although the mechanisms of action are unknown. The objective of this study was to investigate the cardiovascular effects of LMWH in pregnant women at high risk of preeclampsia. Pregnant women at high risk of preeclampsia (n=25) and low-risk pregnant controls (n=20) at 22 to 26 weeks' gestation underwent baseline cardiovascular assessments. High-risk women were then randomized to LMWH or saline placebo (30 mg IV bolus and 1 mg/kg subcutaneous dose). Cardiovascular function was assessed 1 and 3 hours post-randomization. The in vitro endothelial effects of patient serum and exogenous LMWH on human umbilical venous endothelial cells were determined. High-risk women demonstrated a reduced cardiac output, high resistance hemodynamic profile with impaired radial artery flow-mediated dilation compared with controls. LMWH increased flow-mediated dilation in high-risk women 3 hours after randomization compared with baseline and increased plasma levels of placental growth factor, soluble fms-like tyrosine kinase-1, and myeloperoxidase. Serum from high-risk women impaired endothelial cell angiogenesis and increased PlGF-1 and PlGF-2 transcription compared with serum from low-risk controls. Coexposure of high-risk serum with LMWH improved the in vitro angiogenic response such that it was equivalent to that of low-risk serum and promoted placental growth factor secretion. LMWH improves maternal endothelial function in pregnant women at high risk of developing preeclampsia, possibly mediated through increased placental growth factor bioavailability.


## Meta-Analysis and Systematic Review to Assess the Role of Soluble FMS-Like Tyrosine Kinase-1 and Placenta Growth Factor Ratio in Prediction of Preeclampsia: The SaPPPhirE Study[6]


### Abstract

Preeclampsia is a major cause of morbidity and mortality worldwide. Numerous candidate biomarkers have been proposed for diagnosis and prediction of preeclampsia. Measurement of maternal circulating angiogenesis biomarker as the ratio of sFlt-1 (soluble FMS-like tyrosine kinase-1; an antiangiogenic factor)/PlGF (placental growth factor; an angiogenic factor) reflects the antiangiogenic balance that characterizes incipient or overt preeclampsia. The ratio increases before the onset of the disease and thus may help in predicting preeclampsia. We conducted a meta-analysis to explore the predictive accuracy of sFlt-1/PlGF ratio in preeclampsia. We included 15 studies with 534 cases with preeclampsia and 19 587 controls. The ratio has a pooled sensitivity of 80% (95% confidence interval, 0.68–0.88), specificity of 92% (95% confidence interval, 0.87–0.96), positive likelihood ratio of 10.5 (95% confidence interval, 6.2–18.0), and a negative likelihood ratio of 0.22 (95% confidence interval, 0.13–0.35) in predicting preeclampsia in both high- and low-risk patients. Most of the studies have not made a distinction between early- and late-onset disease, and therefore, the analysis for it could not be done. It can prove to be a valuable screening tool for preeclampsia and may also help in decision-making, treatment stratification, and better resource allocation.


## Hypertension in Pregnancy and Offspring Cardiovascular Risk in Young Adulthood: Prospective and Sibling Studies in the HUNT Study (Nord-Trøndelag Health Study) in Norway[7]


### Abstract

Women with hypertensive disorders in pregnancy are at increased lifetime risk for cardiovascular disease. We examined the offspring's cardiovascular risk profile in young adulthood and their siblings' cardiovascular risk profile. From the HUNT study (Nord-Trøndelag Health Study) in Norway, 15 778 participants (mean age: 29 years), including 210 sibling groups, were linked to information from the Medical Birth Registry of Norway. Blood pressure, anthropometry, serum lipids, and C-reactive protein were assessed. Seven hundred and six participants were born after exposure to maternal hypertension in pregnancy: 336 mothers had gestational hypertension, 343 had term preeclampsia, and 27 had preterm preeclampsia. Offspring whose mothers had hypertension in pregnancy had 2.7 (95% confidence interval, 1.8–3.5) mm Hg higher systolic blood pressure, 1.5 (0.9–2.1) mm Hg higher diastolic blood pressure, 0.66 (0.31–1.01) kg/m$^2$ higher body mass index, and 1.49 (0.65–2.33) cm wider waist circumference, compared with offspring of normotensive pregnancies. Similar differences were observed for gestational hypertension and term preeclampsia. Term preeclampsia was also associated with higher concentrations of non–high-density lipoprotein cholesterol (0.14 mmol/L, 0.03–0.25) and triglycerides (0.13 mmol/L, 0.06–0.21). Siblings born after a normotensive pregnancy had nearly identical risk factor levels as siblings born after maternal hypertension. Offspring born after maternal hypertension in pregnancy have a more adverse cardiovascular risk profile in young adulthood than offspring of normotensive pregnancies. Their siblings, born after a normotensive pregnancy, have a similar risk profile, suggesting that shared genes or lifestyle may account for the association, rather than an intrauterine effect. All children of mothers who have experienced hypertension in pregnancy may be at increased lifetime risk of cardiovascular disease.

## Continued Investigation Into 17-OHPC: Results From the Preclinical RUPP Rat Model of Preeclampsia[8]


### Abstract

Preeclampsia is characterized by elevated TNF-α (tumor necrosis factor-α), antiangiogenic factors, such as sFlt-1 (soluble vascular endothelial growth factor receptor 1), increased uterine artery resistance index, and decreased of NO during pregnancy. Previously we showed that 17-hydroxyprogesterone caproate (17-OHPC) administered into reduced uterine perfusion pressure (RUPP) rats on day 18 of gestation improved hypertension without improving pup weight. We hypothesized that earlier administration of 17-OHPC on day 15 of gestation could improve pathophysiology of preeclampsia and fetal outcomes in response to placental ischemia. Carotid catheters were inserted on day 18, and mean arterial blood pressure and samples were collected on day 19. Mean arterial blood pressure in normal pregnant rats was 102±2, 105±2 in normal pregnant+day 15 of gestation (GD15) 17-OHPC, 127±2 in RUPP, and 112±1 mm Hg in RUPP+GD15 17-OHPC, $P<0.05$. Pup weight and litter size were improved from 1.9±0.05, 10.1±1.4 in RUPP to 2.1±0.07 g and 13.2±0.6 in RUPP+GD15 17-OHPC, $P<0.05$. Uterine artery resistance index was 0.8±0.03 in RUPP, which was decreased to 0.6±0.04 in RUPP+GD15 17-OHPC, $P<0.05$. Plasma TNF-α levels were 164±34 in RUPP and blunted to 29±9 pg/mL in RUPP+GD15 17-OHPC, $P<0.05$. Plasma nitrate–nitrite levels were 10.8±2.3 in RUPP rats and significantly increased to 25.5±5.2 μmol/L in RUPP+GD15 17-OHPC, $P<0.05$. sFlt-1 levels were 386±141 in RUPP rats, which were reduced to 110.2±11 in RUPP+17-OHPC, $P<0.05$. These data indicate that GD15 17-OHPC improves pathophysiology in RUPP rats, possibly via improving sFlt-1 reduced NO during pregnancy.


## Cyclic Nucleotides Differentially Regulate Cx43 Gap Junction Function in Uterine Artery Endothelial Cells From Pregnant Ewes[9]


### Abstract

Cell–cell communication is dependent on GJ (gap junction) proteins such as Cx43 (connexin 43). We previously demonstrated the importance of Cx43 function in establishing the enhanced pregnancy vasodilatory phenotype during pregnancy in uterine artery endothelial cells from pregnant (P-UAEC) ewes. Cx43 is regulated by elevating cAMP and PKA (protein kinase A)-dependent Cx43 S365 phosphorylation-associated trafficking and GJ open gating, which is opposed by PKC (protein kinase C)-dependent S368 phosphorylation-mediated GJ turnover and closed gating. However, the role of cyclic nucleotide-mediated signaling mechanisms that control Cx43 and GJ function in P-UAECs is unknown. We hypothesize that cAMP will mediate increases in S365 phosphorylation, thereby, enhancing GJ trafficking and open gating, while cGMP will stimulate S368, but not S365, phosphorylation to enhance GJ turnover and closed gating in P-UAECs. Treatment with 8-Bromo (8-Br)-cAMP signal significantly ($P<0.05$) increased nonphosphorylated S365 signal and total Cx43 phosphorylation, but not S368 phosphorylation, while 8-Br-cGMP significantly ($P<0.05$) increased Cx43 C terminus S365 signal, S368, and total Cx43 phosphorylation. Inhibition of PKA, but not PKG (protein kinase G), abrogated the 8-Br-cAMP–stimulated increase in nonphosphorylated S365 and total Cx43 phosphorylation and inhibited S368 below basal levels, whereas inhibition of PKG blocked ($P<0.05$) the 8-Br-cGMP–stimulated rises in nonphosphorylated S365, total Cx43, and S368 phosphorylation levels in P-UAECs. Functional studies showed that 8-Br-cAMP increased dye transfer and sustained calcium bursts, while 8-Br-cGMP decreased both. Thus, in P-UAECs, only 8-Br-cAMP and not 8-Br-cGMP effectively enhances nonphosphorylated S365 and total Cx43 expression that correspondingly reduces S368 phosphorylation, allowing increased GJ communication. This provides new insights into the regulatory mechanisms behind Cx43 function and GJ communication.


## Maternal Urinary Bisphenol A Concentration During Midterm Pregnancy and Children's Blood Pressure at Age 4[10]


### Abstract

Bisphenol A (BPA) has been reported to be associated with adverse health effects, including high blood pressure (BP). BPA is also suspected to cross placenta in pregnancy and might affect children's health. The present study was aimed to evaluate the effect of prenatal exposure to BPA on the BP of the child at the age of 4. We followed up 645 children at the age of 4 who were born from women who participated midterm during their pregnancy in a birth cohort study from August 2008 to July 2011. Because BPA and BP showed nonlinear association, we constructed a piecewise regression model to examine the association between urinary BPA concentration of mother at around 20 weeks of gestation and BP of the child at age 4 and to determine threshold level of BPA for the association. Diastolic BP of the children was positively associated with maternal urinary concentration of BPA above the threshold level measured at around 20 weeks of gestation. For 1 log unit increment of prenatal urinary BPA concentration, diastolic BP was increased by 7.9 mm Hg (SE=2.072; $P=0.0001$) after adjusting potential confounders. Pulse pressure was decreased by −8.0 mm Hg (SE=2.528; $P=0.0015$). However, systolic BP was not significantly associated with prenatal BPA concentration. The present study suggests that exposure to BPA during pregnancy is associated with higher diastolic BP of the children above a certain threshold (4.5 μg/g creatinine).

## Accuracy of Blood Pressure Measurement Devices in Pregnancy: A Systematic Review of Validation Studies[11]


### Abstract

The accurate measurement of blood pressure (BP) in pregnancy is essential to guide medical decision-making that affects both mother and fetus. The aim of this systematic review was to determine the accuracy of ambulatory, home, and clinic BP measurement devices in pregnant women. We searched Ovid MEDLINE, The Cochrane Library, EMBASE, CINAHL EBSCO, Clinicaltrials.gov, International Clinical Trials Registry Platform, and dabl from inception through August 3, 2017, for articles that assessed the validity of an upper arm BP measurement device against a mercury sphygmomanometer in pregnant women. Two independent investigators determined eligibility, extracted data, and adjudicated protocol violations. From 1798 potential articles identified, 41, that assessed 28 devices, met the inclusion criteria. Most articles (n=32) followed a standard or modified American National Standards Institute/Association for the Advancement of Medical Instrumentation/International Organization for Standardization, British Hypertension Society, or European Society of Hypertension validation protocol. Several articles described the results of validation studies performed on >1 device (n=7) or in >1 population of pregnant women (n=12), comprising 64 pairwise validity assessments. The device was validated in 61% (32 of 52) of studies which used a standard or modified protocol. Only 34% (11 of 32) of the studies wherein the device was successfully validated were performed without a protocol violation. Given the implications of inaccurate BP measurement in pregnant women, healthcare providers should be aware of and try to use the BP measurement devices which have been properly validated in this population.


## Maternal Antihypertensive Medication Use and Congenital Heart Defects: Updated Results From the National Birth Defects Prevention Study[12]


### Abstract

Previous NBDPS (National Birth Defects Prevention Study) findings from 1997 to 2003 suggested that maternal antihypertensive use was associated with congenital heart defects (CHDs). We re-examined associations between specific antihypertensive medication classes and specific CHDs with additional NBDPS data from 2004 to 2011. After excluding mothers missing hypertension information or who reported pregestational diabetes mellitus, a multiple birth, or antihypertensive use but no hypertension, we compared self-reported maternal exposure data on 10 625 CHD cases and 11 137 nonmalformed controls. We calculated adjusted odds ratios (95% confidence intervals) to estimate the risk of specific CHDs associated with antihypertensive use during the month before conception through the third month of pregnancy, controlling for maternal age, race/ethnicity, body mass index, first trimester cigarette smoking, and NBDPS site. Overall, 164 (1.5%) case mothers and 102 (0.9%) control mothers reported early pregnancy antihypertensive use for their hypertension. We observed increased risk of 4 CHD phenotypes, regardless of antihypertensive medication class reported: coarctation of the aorta (2.50 [1.52–4.11]), pulmonary valve stenosis (2.19 [1.44–3.34]), perimembranous ventricular septal defect (1.90 [1.09–3.31]), and secundum atrial septal defect (1.94 [1.36–2.79]). The associations for these phenotypes were statistically significant for mothers who reported β-blocker use or renin–angiotensin system blocker use; estimates for other antihypertensive medication classes were generally based on fewer exposed cases and were less stable but remained elevated. Our results support and expand on earlier NBDPS findings that antihypertensive medication use may be associated with increased risk of specific CHDs, although we cannot completely rule out confounding by underlying disease characteristics.


## Estimating the Cost of Preeclampsia in the Healthcare System: Cross-Sectional Study Using Data From SCOPE Study (Screening for Pregnancy End Points)[13]


### Abstract

To estimate the cost of preeclampsia from the national health payer's perspective using secondary data from the SCOPE study (Screening for Pregnancy End Points). SCOPE is an international observational prospective study of healthy nulliparous women with singleton pregnancies. Using data from the Irish cohort recruited between November 2008 and February 2011, all women with preeclampsia and a 10% random sample of women without preeclampsia were selected. Additional health service use data were extracted from the consenting participants' medical records for maternity services which were not included in SCOPE. Unit costs were based on estimates from 3 existing Irish studies. Costs were extrapolated to a national level using a prevalence rate of 5% to 7% among nulliparous pregnancies. Within the cohort of 1774 women, 68 developed preeclampsia (3.8%) and 171 women were randomly selected as controls. Women with preeclampsia used higher levels of maternity services. The average cost of a pregnancy complicated by preeclampsia was €5243 per case compared with €2452 per case for an uncomplicated pregnancy. The national cost of preeclampsia is between €6.5 and €9.1 million per annum based on the 5% to 7% prevalence rate. Postpartum care was the largest contributor to these costs (€4.9–€6.9 million), followed by antepartum care (€0.9–€1.3 million) and peripartum care (€0.6–€0.7 million). Women with preeclampsia generate significantly higher maternity costs than women without preeclampsia. These cost estimates will allow policy-makers to efficiently allocate resources for this pregnancy-specific condition. Moreover, these estimates are useful for future research assessing the cost-effectiveness of preeclampsia screening and treatment.

## Maternal Vascular Physiology in Preeclampsia[14]


### Abstract

Abnormal maternal vascular physiology is a common feature of preeclampsia that affects the reproductive and/or the peripheral (nonreproductive) vasculatures. Dysfunction of the vascular endothelium and smooth muscle, and defects in the mechanisms underlying remodeling of the uterine arteries contribute to impaired systemic and placental hemodynamics, maternal hypertension, and intrauterine growth restriction. The main objective of this brief review is to discuss the molecular mechanisms underlying aberrant maternal vascular physiology in reproductive and nonreproductive vascular beds in preeclampsia.


## Pregnancy Outcome After First Trimester Use of Methyldopa: A Prospective Cohort Study[15]


### Abstract

Published experience on first trimester exposure to methyldopa is still limited, although it is recommended as first-line treatment for hypertensive disorders in pregnancy in most countries. The primary aim of this prospective observational cohort study was to analyze the rate of major birth defects and spontaneous abortions in women with methyldopa therapy for chronic hypertension. Outcomes of 261 pregnancies with first trimester exposure to methyldopa and 526 comparison pregnancies without chronic hypertension reported to the German Embryotox pharmacovigilance institute were evaluated. The rate of major birth defects in the exposed cohort was not significantly increased compared with the comparison cohort (3.7% versus 2.5%; adjusted odds ratio, 1.24; 95% confidence interval, 0.4–4.0). There was a tendency toward a higher rate of spontaneous abortions in exposed women. The risk of preterm birth was significantly higher, and adjusted birth weight scores were significantly lower in the methyldopa group. Head circumferences were significantly reduced in exposed boys only. There was neither evidence for an increased risk for birth defects or increase in early pregnancy loss nor evidence for growth restriction or a reduced head circumference in a sensitivity analysis comparing monotherapies with methyldopa to metoprolol. However, the significantly increased risk of preterm birth in methyldopa-treated pregnancies was confirmed. In conclusion, our study does not indicate a teratogenic risk of methyldopa. Further studies are needed to confirm its safety in the first trimester and clarify the influence of hypertension and methyldopa on preterm birth and intrauterine growth.


## Pregnancy Reprograms Large-Conductance $Ca^{2+}$-Activated $K^+$ Channel in Uterine Arteries: Roles of Ten-Eleven Translocation Methylcytosine Dioxygenase 1–Mediated Active Demethylation[16]


### Abstract

The large-conductance $Ca^{2+}$-activated $K^+$ ($BK_{Ca}$) channel is of critical importance in pregnancy-mediated increase in uterine artery vasodilation and blood flow. The present study tested the hypothesis that active DNA demethylation plays a key role in pregnancy-induced reprogramming and upregulation of $BK_{Ca}$ channel β1 subunit (BKβ1) in uterine arteries. Uterine arteries were isolated from nonpregnant and near-term pregnant sheep. Pregnancy significantly increased the expression of ten-eleven translocation methylcytosine dioxygenase 1 (TET1) in uterine arteries. A half-palindromic estrogen response element was identified at the TET1 promoter, and estrogen treatment increased TET1 promoter activity and TET1 expression in uterine arteries. In accordance, pregnancy and steroid hormone treatment resulted in demethylation of BKβ1 promoter by increasing 5-hydroxymethylcytosine and decreasing 5-methylcytosine at the CpG in the Sp1-380 binding site that is of critical importance in the regulation of the promoter activity and BKβ1 expression. Inhibition of TET1 with fumarate significantly decreased BKβ1 expression in uterine arteries of pregnant animals and blocked steroid hormone–induced upregulation of BKβ1. Functionally, fumarate treatment inhibited pregnancy and steroid hormone–induced increases in $BK_{Ca}$ channel current density and $BK_{Ca}$ channel–mediated relaxations. In addition, fumarate blocked pregnancy and steroid hormone–induced decrease in pressure-dependent myogenic tone of the uterine artery. The results demonstrate a novel mechanism of estrogen-mediated active DNA demethylation in reprogramming of $BK_{Ca}$ channel expression and function in the adaption of uterine circulation during pregnancy.

## MicroRNA-210 Targets Ten-Eleven Translocation Methylcytosine Dioxygenase 1 and Suppresses Pregnancy-Mediated Adaptation of Large Conductance $Ca^{2+}$-Activated $K^+$ Channel Expression and Function in Ovine Uterine Arteries[17]


### Abstract

Gestational hypoxia inhibits large conductance $Ca^{2+}$-activated K+ ($BK_{Ca}$) channel expression and function in uterine arterial adaptation to pregnancy. Given the findings that microRNA-210 (miR-210) is increased in hypoxia during gestation and preeclampsia, the present study sought to investigate the role of miR-210 in the regulation of $BK_{Ca}$ channel adaptation in the uterine artery. Gestational hypoxia significantly increased uterine vascular resistance and blood pressure in pregnant sheep and upregulated miR-210 in uterine arteries. MiR-210 bound to ovine ten-eleven translocation methylcytosine dioxygenase 1 mRNA 3′ untranslated region and decreased ten-eleven translocation methylcytosine dioxygenase 1 mRNA and protein abundance in uterine arteries of pregnant sheep, as well as abrogated steroid hormone–induced upregulation of ten-eleven translocation methylcytosine dioxygenase 1 expression in uterine arteries of nonpregnant animals. In accordance, miR-210 blocked pregnancy- and steroid hormone–induced upregulation of $BK_{Ca}$ channel β1 subunit expression in uterine arteries. Functionally, miR-210 suppressed $BK_{Ca}$ channel current density in uterine arterial myocytes of pregnant sheep and inhibited steroid hormone–induced increases in $BK_{Ca}$ channel currents in uterine arteries of nonpregnant animals. Blockade of endogenous miR-210 inhibited hypoxia-induced suppression of $BK_{Ca}$ channel activity. In addition, miR-210 decreased $BK_{Ca}$ channel–mediated relaxations and increased pressure-dependent myogenic tone of uterine arteries. Together, the results demonstrate that miR-210 plays an important role in the downregulation of ten-eleven translocation methylcytosine dioxygenase 1 and repression of $BK_{Ca}$ channel function in uterine arteries, revealing a novel mechanism of epigenetic regulation in the maladaptation of uterine hemodynamics in gestational hypoxia and preeclampsia.


## Elevated Adenosine Induces Placental DNA Hypomethylation Independent of A2B Receptor Signaling in Preeclampsia[18]


### Abstract

Preeclampsia is a prevalent pregnancy hypertensive disease with both maternal and fetal morbidity and mortality. Emerging evidence indicates that global placental DNA hypomethylation is observed in patients with preeclampsia and is linked to altered gene expression and disease development. However, the molecular basis underlying placental epigenetic changes in preeclampsia remains unclear. Using 2 independent experimental models of preeclampsia, adenosine deaminase–deficient mice and a pathogenic autoantibody-induced mouse model of preeclampsia, we demonstrate that elevated placental adenosine not only induces hallmark features of preeclampsia but also causes placental DNA hypomethylation. The use of genetic approaches to express an adenosine deaminase minigene specifically in placentas, or adenosine deaminase enzyme replacement therapy, restored placental adenosine to normal levels, attenuated preeclampsia features, and abolished placental DNA hypomethylation in adenosine deaminase–deficient mice. Genetic deletion of CD73 (an ectonucleotidase that converts AMP to adenosine) prevented the elevation of placental adenosine in the autoantibody-induced preeclampsia mouse model and ameliorated preeclampsia features and placental DNA hypomethylation. Immunohistochemical studies revealed that elevated placental adenosine–mediated DNA hypomethylation predominantly occurs in spongiotrophoblasts and labyrinthine trophoblasts and that this effect is independent of A2B adenosine receptor activation in both preeclampsia models. Extending our mouse findings to humans, we used cultured human trophoblasts to demonstrate that adenosine functions intracellularly and induces DNA hypomethylation without A2B adenosine receptor activation. Altogether, both mouse and human studies reveal novel mechanisms underlying placental DNA hypomethylation and potential therapeutic approaches for preeclampsia.


## Dysregulated DNA Methyltransferase 3A Upregulates IGFBP5 to Suppress Trophoblast Cell Migration and Invasion in Preeclampsia[19]


### Abstract

Preeclampsia is a unique multiple system disorder during human pregnancy, which affects ≈5% to 8% of pregnancies. Its risks and complications have become the major causes of maternal and fetal morbidity and mortality. Although abnormal placentation to which DNA methylation dysregulation is always linked is speculated to be one of the reasons causing preeclampsia, the underlying mechanisms still remain elusive to date. Here we revealed that aberrant DNA methyltransferase 3A (DNMT3A) plays a critical role in preeclampsia. Our results show that the expression and localization of DNMT3A are dysregulated in preeclamptic placenta. Moreover, knockdown of DNMT3A obviously inhibits trophoblast cell migration and invasion. Mechanistically, IGFBP5 (insulin-like growth factor-binding protein 5), known as a suppressor, is upregulated by decreased DNMT3A because of promoter hypomethylation. Importantly, IGFBP5 downregulation can rescue the defects caused by DNMT3A knockdown, thereby, consolidating the significance of IGFBP5 in the downstream of DNMT3A in trophoblast. Furthermore, we detected low promoter methylation and high protein expression of IGFBP5 in the clinical samples of preeclamptic placenta. Collectively, our study suggests that dysregulation of DNMT3A and IGFBP5 is relevant to preeclampsia. Thus, we propose that DNMT3A and IGFBP5 can serve as potential markers and targets for the clinical diagnosis and therapy of preeclampsia.

## Activating Transcription Factor 3 Is Reduced in Preeclamptic Placentas and Negatively Regulates sFlt-1 (Soluble fms-Like Tyrosine Kinase 1), Soluble Endoglin, and Proinflammatory Cytokines in Placenta[20]


### Abstract

Preeclampsia is a major pregnancy complication associated with poor placental perfusion and placental hypoxia. Systemic and placental inflammation and elevated placental secretion of the antiangiogenic factors sFlt-1 (soluble fms-like tyrosine kinase 1) and sEng (soluble endoglin) are hallmarks of preeclampsia, causing endothelial dysfunction and multiorgan injury. A molecule that links placental hypoxia, inflammation, and antiangiogenic factor release has not been described. ATF3 (activating transcription factor 3) is highly expressed in placenta. We assessed whether placental ATF3 is dysregulated in preterm preeclampsia, is altered by hypoxia, and regulates proinflammatory cytokine and antiangiogenic factor production. ATF3 mRNA and protein expression was significantly reduced in preterm preeclamptic placentas compared with gestation-matched controls. Hypoxia reduced ATF3 expression in primary cytotrophoblast and placental explants. Silencing ATF3 in primary cytotrophoblast increased proinflammatory cytokine (IL-6 [interleukin 6], TNF-α [tumor necrosis factor-α]) and NF-κB (nuclear factor κB) expression. In silico analysis identified an ATF3-binding site in the promoter of Flt-1 (the transcript from which sFlt-1 is produced). Silencing ATF3 increased sFlt-1 and sEng secretion from primary cytotrophoblast possibly by increasing Rab11a and Arf1, cargo proteins that facilitate exosomal release of sFlt-1. ATF3 knockout mice did not have a preeclampsia phenotype, suggesting that these pathways may be specific to humans (preeclampsia is a uniquely human condition). To conclude, we have shown that ATF3 is decreased in preeclamptic placentas and that this decrease is likely to occur after prolonged hypoxia. We show that ATF3 is a regulator of placental proinflammatory cytokines and antiangiogenic factors sFlt-1 and sEng. Therefore, reduced ATF3 may be centrally involved in the pathology of preeclampsia.


## Mechanisms and Treatment of Halogen Inhalation–Induced Pulmonary and Systemic Injuries in Pregnant Mice[21]


### Abstract

Inhalation of oxidant gases has been implicated in adverse outcomes in pregnancy, but animal models to address mechanisms and studies to identify potential pregnancy-specific therapies are lacking. Herein, we show that inhalation of bromine at 600 parts per million for 30 minutes by pregnant mice on the 15th day of embryonic development results in significantly lower survival after 96 hours than an identical level of exposure in nonpregnant mice. On the 19th embryonic day, bromine-exposed pregnant mice have increased systemic blood pressure, abnormal placental development, severe fetal growth restriction, systemic inflammation, increased levels of circulating antiangiogenic short fms-like tyrosine kinase-1, and evidence of pulmonary and cardiac injury. Treatment with tadalafil, an inhibitor of type 5 phosphodiesterase, by oral gavage 1 hour post-exposure and then once daily thereafter, attenuated systemic blood pressures, decreased inflammation, ameliorated pulmonary and cardiac injury, and improved maternal survival (from 36% to 80%) and fetal growth. These pathological changes resemble those seen in preeclampsia. Nonpregnant mice did not exhibit any of these pathological changes and were not affected by tadalafil. These findings suggest that pregnant women exposed to bromine may require particular attention and monitoring for signs of preeclampsia-like symptoms.


## Trimester-Specific Weight Gain and Midpregnancy Diastolic Blood Pressure Rebound During Normotensive Pregnancy[22]


### Abstract

The longitudinal exposure–response relationship between trimester-specific gestational weight gain (GWG) and blood pressure (BP) during pregnancy is not well understood. We retrospectively assessed 1112 uncomplicated, normotensive pregnant women whose body weight and BP were measured from $12^{+0}$ to $40^{+0}$ weeks of gestation from a hospital-based cohort. By using growth curve modeling, a J-shaped pattern dominated diastolic BP (DBP) changing dynamics, with a midpregnancy drop at $20^{+0}$ to $22^{+0}$ weeks followed by a rebound. Using group-based trajectory modeling, 3 distinctive trajectories of DBP were identified: high-J shaped (18.5%), moderate-J shaped (48.3%), and low-J shaped (33.1%), as well as 3 distinctive GWG trajectories: high increasing (14.7%), moderate increasing (48.6%), and low increasing (36.8%). A temporal coincidence between the maximal rate of GWG and DBP transition from its nadir to rebound was observed during $20^{+0}$ to $22^{+0}$ weeks. Moreover, women in the high-increasing GWG group had the highest probability of being in the high–J DBP group. The GWG rate during the late midsecond trimester ($22^{+0}$ to $26^{+0}$ weeks) was consistently associated with an elevated DBP level: for every 200 g/wk increase, the multivariable-adjusted odds ratio was 1.27 (95% confidence interval, 1.13–1.43) for the trajectory shift to the high–J group and 1.20 (95% confidence interval, 1.07–1.35) for the occurrence of diastolic prehypertension after $37^{+0}$ weeks. Furthermore, adding a trimester-specific GWG rate ($22^{+0}$ to $26^{+0}$ weeks) contributed to the incremental yield for the prediction of diastolic prehypertension after $37^{+0}$ weeks. Our results thus provide the timing and extent of gestational weight control relevant to the optimized BP level during pregnancy.

## Protective Low-Frequency Variants for Preeclampsia in the Fms Related Tyrosine Kinase 1 Gene in the Finnish Population[23]


### Abstract

Preeclampsia is a common pregnancy-specific vascular disorder characterized by new-onset hypertension and proteinuria during the second half of pregnancy. Predisposition to preeclampsia is in part heritable. It is associated with an increased risk of cardiovascular disease later in life. We have sequenced 124 candidate genes implicated in preeclampsia to pinpoint genetic variants contributing to predisposition to or protection from preeclampsia. First, targeted exomic sequencing was performed in 500 preeclamptic women and 190 controls from the FINNPEC cohort (Finnish Genetics of Preeclampsia Consortium). Then 122 women with a history of preeclampsia and 1905 parous women with no such history from the National FINRISK Study (a large Finnish population survey on risk factors of chronic, noncommunicable diseases) were included in the analyses. We tested 146 rare and low-frequency variants and found an excess (observed 13 versus expected 7.3) nominally associated with preeclampsia ($P$<0.05). The most significantly associated sequence variants were protective variants rs35832528 (E982A; $P$=2.49E-4; odds ratio, 0.387) and rs141440705 (R54S; $P$=0.003; odds ratio, 0.442) in Fms related tyrosine kinase 1. These variants are enriched in the Finnish population with minor allele frequencies 0.026 and 0.017, respectively. They may also be associated with a lower risk of heart failure in 11 257 FINRISK women. This study provides the first evidence of maternal protective genetic variants in preeclampsia.


## Polymerization-Incompetent Uromodulin in the Pregnant Stroke-Prone Spontaneously Hypertensive Rat[24]


### Abstract

The kidney is centrally involved in blood pressure regulation and undergoes extensive changes during pregnancy. Hypertension during pregnancy may result in an altered urinary peptidome that could be used to indicate new targets of therapeutic or diagnostic interest. The stroke-prone spontaneously hypertensive rat (SHRSP) is a model of maternal chronic hypertension. Capillary electrophoresis-mass spectrometry was conducted to interrogate the urinary peptidome in SHRSP and the control Wistar–Kyoto strain at 3 time points: prepregnancy and gestational days 12 and 18. The comparison within and between the Wistar–Kyoto and SHRSP peptidome at all time points detected 123 differentially expressed peptides (fold change >1.5; $P$<0.05). Sequencing of these peptides identified fragments of collagen α-chains, albumin, prothrombin, actin, serpin A3K, proepidermal growth factor, and uromodulin. Uromodulin peptides showed a pregnancy-specific alteration in SHRSP with a 7.8-fold ($P$<0.01) and 8.8-fold ($P$<0.05) increase at gestational days 12 and 18, respectively, relative to the Wistar–Kyoto. Further investigation revealed that these peptides belonged to the polymerization-inhibitory region of uromodulin. Two forms of uromodulin (polymerization competent and polymerization incompetent) were found in urine from both Wistar–Kyoto and SHRSP, where the polymerization-incompetent form was increased in a pregnancy-specific manner in SHRSP. Nifedipine-treated pregnant SHRSP showed only polymerization-competent uromodulin, indicating that calcium may be mechanistically involved in uromodulin polymerization. This study highlights, for the first time, a potential role of uromodulin and its polymerization in hypertensive pregnancy.


## Placental Vesicles Carry Active Endothelial Nitric Oxide Synthase and Their Activity is Reduced in Preeclampsia[25]


### Abstract

Preeclampsia, a multisystem hypertensive disorder of pregnancy, is associated with increased systemic vascular resistance. Placentae from patients with preeclampsia have reduced levels of endothelial nitric oxide synthase (eNOS) and, thus, less nitric oxide (NO). Syncytiotrophoblast extracellular vesicles (STBEV), comprising microvesicles (STBMV) and exosomes, carry signals from the syncytiotrophoblast to the mother. We hypothesized that STBEV-bound eNOS (STBEV-eNOS), capable of producing NO, are released into the maternal circulation. Dual-lobe ex vivo placental perfusion and differential centrifugation was used to isolate STBEV from preeclampsia (n=8) and normal pregnancies (NP; n=11). Plasma samples of gestational age–matched preeclampsia and NP (n=6) were used to isolate circulating STBMV. STBEV expressed placental alkaline phosphatase, confirming placental origin. STBEV coexpressed eNOS, but not inducible nitric oxide synthase, confirmed using Western blot, flow cytometry, and immunodepletion. STBEV-eNOS produced NO, which was significantly inhibited by $N^G$-nitro-L-arginine methyl ester (eNOS inhibitor; $P$<0.05) but not by N-(3-(aminomethyl) benzyl) acetamidine; inducible nitric oxide synthase inhibitor). STBEV-eNOS catalytic activity was confirmed by visualizing eNOS dimerization. STBEV-eNOS was more abundant in uterine vein compared with peripheral blood, indicating placental origin. STBEV isolated from preeclampsia-perfused placentae had lower levels of STBEV-eNOS (STBMV; $P$<0.05) and overall lower NO activity (STBMV, not significant; syncytiotrophoblast extracellular exosomes, $P$<0.05) compared with those from NP. Circulating plasma STBMV from preeclampsia women had lower STBEV-eNOS expression compared with that from NP women ($P$<0.01). This is the first observation of functional eNOS expressed on STBEV from NP and preeclampsia placentae, as well as in plasma. The lower STBEV-eNOS NO production seen in preeclampsia may contribute to the decreased NO bioavailability in this disease.

## Proton Pump Inhibitors Decrease Soluble fms-Like Tyrosine Kinase-1 and Soluble Endoglin Secretion, Decrease Hypertension, and Rescue Endothelial Dysfunction[26]


### Abstract

Preeclampsia is a severe complication of pregnancy. Antiangiogenic factors soluble fms-like tyrosine kinase-1 (sFlt-1) and soluble endoglin are secreted in excess from the placenta, causing hypertension, endothelial dysfunction, and multiorgan injury. Oxidative stress and vascular inflammation exacerbate the endothelial injury. A drug that can block these pathophysiological steps would be an attractive treatment option. Proton pump inhibitors (PPIs) are safe in pregnancy where they are prescribed for gastric reflux. We performed functional studies on primary human tissues and animal models to examine the effects of PPIs on sFlt-1 and soluble endoglin secretion, vessel dilatation, blood pressure, and endothelial dysfunction. PPIs decreased sFlt-1 and soluble endoglin secretion from trophoblast, placental explants from preeclamptic pregnancies, and endothelial cells. They also mitigated tumor necrosis factor-α–induced endothelial dysfunction: PPIs blocked endothelial vascular cell adhesion molecule-1 expression, leukocyte adhesion to endothelium, and disruption of endothelial tube formation. PPIs decreased endothelin-1 secretion and enhanced endothelial cell migration. Interestingly, the PPI esomeprazole vasodilated maternal blood vessels from normal pregnancies and cases of preterm preeclampsia, but its vasodilatory effects were lost when the vessels were denuded of their endothelium. Esomeprazole decreased blood pressure in a transgenic mouse model where human sFlt-1 was overexpressed in placenta. PPIs upregulated endogenous antioxidant defenses and decreased cytokine secretion from placental tissue and endothelial cells. We have found that PPIs decrease sFlt-1 and soluble endoglin secretion and endothelial dysfunction, dilate blood vessels, decrease blood pressure, and have antioxidant and anti-inflammatory properties. They have therapeutic potential for preeclampsia and other diseases where endothelial dysfunction is involved.


## Sildenafil During Pregnancy: A Preclinical Meta-Analysis on Fetal Growth and Maternal Blood Pressure[27]


### Abstract

Sildenafil is a new approach to treat fetal growth restriction (FGR) and preeclampsia. We performed a systematic meta-analysis to evaluate effects of sildenafil. Our search identified 22 animal studies (mouse, rat, rabbit, sheep, and guinea pigs) and 2 human randomized controlled trials. Data were pooled using ratio of means and mean differences with 95% confidence intervals for fetal growth and maternal blood pressure, respectively. Meta-regression analyses were performed for study-related factors that might affect efficacy of sildenafil, including the model used (healthy pregnancy versus FGR/preeclampsia) and route of administration. Dose–response curves with dose per metabolic weight (mg/kg$^{0.75}$ per 24 hours) were fitted using splines. Our analyses show that sildenafil increases fetal growth during FGR/preeclampsia pregnancy compared with healthy pregnancy (1.10 [1.06–1.13] versus 1.03 [0.99–1.06]; $P$=0.006). There was no significant effect on fetal growth in the absence of FGR/preeclampsia. Effects were similar among different species and largest after oral and continuous administration. There was a positive relation between dose and fetal growth up to a human equivalent dose of ≈450 mg/d. A significant blood pressure–lowering effect of sildenafil is present during FGR/preeclampsia pregnancy only (−19 [−25 to −13] mm Hg; $P$<0.01), with the effect size being highly dependent on baseline blood pressure and without effect in the absence of hypertension. This meta-analysis supports that sildenafil improves fetal growth and maternal blood pressure regulation during FGR and preeclampsia pregnancy. The greatest beneficial effects on fetal growth are with dosages greater than those currently used in human studies.


## Association of Pregnancy Complications and Characteristics With Future Risk of Elevated Blood Pressure: The Västerbotten Intervention Program[28]


### Abstract

Pregnancy characteristics are associated with risk of cardiovascular diseases, but their independent associations with hypertension or blood pressure (BP) levels remain uncertain. We linked the Swedish Medical Birth Register with Västerbotten Intervention Program data (Northern Sweden). Using linear and logistic regression, we related pregnancy factors in any prior pregnancy with BP and hypertension at 40 years of age in 15 896 parous women free of prepregnancy hypertension. Pregnancy factors included parity, age at first delivery, preeclampsia, gestational diabetes mellitus, placental abruption, shortest gestational age small for gestational age baby (<third percentile for birth weight), or stillbirth. We defined hypertension as systolic BP ≥140 mm Hg and diastolic BP ≥90 mm Hg or antihypertensive use. Multivariable models were adjusted for all pregnancy factors and potential lifestyle and sociodemographic confounders. At 40 years of age, 1535 women (9.6%) had hypertension. In multivariable models, lower parity, younger age at first birth, preeclampsia, small for gestational age, and placental abruption were independently associated with higher systolic and diastolic BP levels at 40 years of age. Younger age at first birth, preeclampsia, gestational age <32 versus ≥37 weeks, and small for gestational age were independently associated with hypertension. Our findings raise the possibility that earlier and more frequent BP screening may be desirable in women with these pregnancy characteristics.

## Age at First Childbirth and Hypertension in Postmenopausal Women[29]

### Abstract

Whether age at first childbirth has an effect on hypertension incidence is unclear. The objectives of this study were to examine the relationship between age at first childbirth and hypertension and to examine whether degree of obesity, measured as body mass index, mediates age at first childbirth-related hypertension in postmenopausal women. This study analyzed 4779 postmenopausal women data from the Korea National Health and Nutrition Examination Survey 2010 to 2012. Logistic regression analyses were used to investigate relationship between age at first childbirth and hypertension. Mediation analysis was performed to examine the contribution of body mass index to age at first childbirth-related hypertension. Mean of participants' age at first childbirth and current age were 23.8 and 63.4 years, respectively. The prevalence of hypertension was 51.1%. Age at first childbirth was significantly associated with the prevalence of hypertension (odds ratio, 0.963; 95% confidence interval, 0.930–0.998; *P*=0.036). Women with age at first childbirth ≤19 years had significantly higher risk of hypertension (odds ratio, 1.61; 95% confidence interval, 1.17–2.23; *P*=0.004) compared with those >19 years. Multivariable-adjusted prevalence of hypertension was significantly lower in women who delivered the first infant at 20 to 24 (45.5%), 25 to 29 (46.1%), and ≥30 (39.9%) years compared with those at ≤19 years (58.4%). Body mass index completely mediated age at first childbirth–hypertension relationship (indirect effect: odds ratio, 0.992; 95% confidence interval, 0.987–0.998; *P*=0.008). Age at first childbirth was significantly associated with hypertension in postmenopausal women. Body mass index mediated the effects of age at first childbirth on hypertension.

## Myeloperoxidase in Hypertensive Disorders of Pregnancy and Its Relation With Nitric Oxide[30]

### Abstract

Elevated levels of myeloperoxidase have been demonstrated in women with preeclampsia where it may contribute to endothelial dysfunction mediated, in part, by nitric oxide impairment. In this study, we investigated myeloperoxidase in hypertensive disorders of pregnancy and its contribution to the impairment of the vasodilator nitric oxide. We found higher levels of myeloperoxidase in supernatant from human umbilical vein endothelial cells cultures incubated with plasma from preeclampsia group compared with healthy pregnant women. Further, we measured plasma concentration and activity of myeloperoxidase in 219 healthy pregnant women, 130 gestational hypertension (on antihypertensive therapy or not), and 143 preeclampsia patients (on antihypertensive therapy or not). We found that patients with preeclampsia and gestational hypertension without antihypertensive treatment showed higher levels and activity of this enzyme, respectively. Moreover, the inhibition of myeloperoxidase activity in vitro improved nitric oxide bioavailability. Our results indicate a higher cardiovascular risk in pregnant women with hypertensive disorders, and that active myeloperoxidase may play a role in endothelial dysfunction in these conditions by impairment of nitric oxide availability. Besides, the use of antihypertensive drugs seems to decrease enzyme levels suggesting a new protective feature for these drugs.

## Low Soluble Fms-Like Tyrosine Kinase-1, Endoglin, and Endothelin-1 Levels in Women With Confirmed or Suspected Preeclampsia Using Proton Pump Inhibitors[31]

### Abstract

Patients with preeclampsia display elevated placenta-derived sFlt-1 (soluble Fms-like tyrosine kinase-1) and endoglin levels and decreased placental growth factor levels. Proton pump inhibitors (PPIs) decrease trophoblast sFlt-1 and endoglin secretion in vitro. PPIs are used during pregnancy to combat reflux disease. Here, we investigated whether PPIs affect sFlt-1 in women with confirmed/suspected preeclampsia, making use of a prospective cohort study involving 430 women. Of these women, 40 took PPIs (6 esomeprazole, 32 omeprazole, and 2 pantoprazole) for 8 to 45 (median 29) days before sFlt-1 measurement. Measurements were only made once, at study entry between weeks 20 and 41 (median 33 weeks). PPI use was associated with lower sFlt-1 levels, with no change in placental growth factor levels, both when compared with all non-PPI users and with 80 gestational age–matched controls selected from the non-PPI users. No sFlt-1/placental growth factor alterations were observed in women using ferrous fumarate or macrogol while, as expected, women using antihypertensive medication displayed higher sFlt-1 levels and lower placental growth factor levels. The PPI use-associated decrease in sFlt-1 was independent of the application of antihypertensive drugs and also occurred when restricting our analysis to patients with hypertensive disease of pregnancy at study entry. PPI users displayed more cases with preexisting proteinuria, less gestational hypertension, and a lower number of neonatal sepsis cases. Finally, their plasma endoglin and endothelin-1 levels were lower while sFlt-1 levels correlated positively with both. In conclusion, PPI use associates with low sFlt-1, endoglin, and endothelin-1 levels, warranting prospective trials to investigate the therapeutic potential of PPIs in preeclampsia.

## Angiogenic Markers Predict Pregnancy Complications and Prolongation in Preeclampsia: Continuous Versus Cutoff Values[32]


### Abstract

To assess the incremental value of a single determination of the serum levels of sFlt-1 (soluble Fms-like tyrosine kinase 1) and PlGF (placental growth factor) or their ratio, without using cutoff values, for the prediction of maternal and fetal/neonatal complications and pregnancy prolongation, 620 women with suspected/confirmed preeclampsia, aged 18 to 48 years, were included in a prospective, multicenter, observational cohort study. Women had singleton pregnancies and a median pregnancy duration of 34 (range, 20–41) weeks. Complications occurred in 118 women and 248 fetuses. The median duration between admission and delivery was 12 days. To predict prolongation, PlGF showed the highest incremental value ($R^2$=0.72) on top of traditional predictors (gestational age at inclusion, diastolic blood pressure, proteinuria, creatinine, uric acid, alanine transaminase, lactate dehydrogenase, and platelets) compared with $R^2$=0.53 for the traditional predictors only. sFlt-1 showed the highest value to discriminate women with and without maternal complications (C-index=0.83 versus 0.72 for the traditional predictors only), and the sFlt-1/PlGF ratio showed the highest value to discriminate fetal/neonatal complications (C-index=0.86 versus 0.78 for the traditional predictors only). Applying previously suggested cutoff values for the sFlt-1/PlGF ratio yielded lower incremental values than applying continuous values. In conclusion, sFlt-1 and PlGF are strong and independent predictors for days until delivery along with maternal and fetal/neonatal complications on top of the traditional criteria. Their use as continuous variables (instead of applying cutoff values for different gestational ages) should now be tested in a prospective manner, making use of an algorithm calculating the risk of an individual woman with suspected/confirmed preeclampsia to develop complications.


## Testosterone Represses Estrogen Signaling by Upregulating miR-22: A Mechanism for Imbalanced Steroid Hormone Production in Preeclampsia[33]


### Abstract

Preeclampsia, a multisystem syndrome occurring during mid- to late gestation in humans, is a leading cause of maternal and perinatal morbidity and mortality. Patients usually present with high circulating testosterone and reduced estradiol production, but the mechanisms remain unclear. Revealing the mechanism that modulating the imbalance of testosterone and estradiol in preeclampsia is of great value in understanding the cause of the disease. The placenta is the predominant source of steroid hormone production during gestation, and we observed markedly increased 17β-HSD3 (17β-hydroxysteroid dehydrogenase 3) levels and downregulated aromatase expression, the key enzymes responsible for synthesis of testosterone and estradiol, respectively, in preeclamptic placentas compared with controls. Furthermore, we found a significant upregulation of microRNA (miR)-22 in preeclamptic placentas. In a trophoblast cell line, JEG-3 cells, testosterone repressed the expression of aromatase and estrogen receptor alpha and the production of estradiol while promoting miR-22 expression. miR-22 directly targeted and inhibited estrogen receptor alpha expression while indirectly decreasing aromatase expression and estradiol production by interfering with estrogen receptor α signaling. Furthermore, inhibition of miR-22 expression significantly reversed the inhibitory effect of testosterone on de novo estradiol synthesis in human trophoblastic cells. The findings reveal a mechanism underlying the balanced production of androgen and estrogen modulated by miR-22 in the human placenta and provide new insights into the pathogenesis of preeclampsia from the aspect of endocrine regulation.


## Prediction of Preeclampsia Using the Soluble fms-Like Tyrosine Kinase 1 to Placental Growth Factor Ratio: A Prospective Cohort Study of Unselected Nulliparous Women[34]


### Abstract

We sought to assess the ratio of sFlt-1 (soluble fms-like tyrosine kinase 1) to PlGF (placental growth factor) in maternal serum as a screening test for preeclampsia in unselected nulliparous women with a singleton pregnancy. We studied 4099 women recruited to the POP study (Pregnancy Outcome Prediction; Cambridge, United Kingdom). The sFlt-1:PlGF ratio was measured using the Roche Cobas e411 platform at ≈20, ≈28, and ≈36 weeks of gestational age (wkGA). Screen positive was defined as an sFlt-1:PlGF ratio >38, but higher thresholds were also studied. At 28 wkGA, an sFlt-1:PlGF ratio >38 had a positive predictive value (PPV) of 32% for preeclampsia and preterm birth, and the PPV was similar comparing women with low and high prior risk of disease. At 36 wkGA, an sFlt-1:PlGF ratio >38 had a PPV for severe preeclampsia of 20% in high-risk women and 6.4% in low-risk women. At 36 wkGA, an sFlt-1:PlGF ratio >110 had a PPV of 30% for severe preeclampsia, and the PPV was similar comparing low- and high-risk women. Overall, at 36 wkGA, 195 (5.2%) women either had an sFlt-1:PlGF ratio of >110 or an sFlt-1:PlGF ratio >38 plus maternal risk factors: 43% of these women developed preeclampsia, about half with severe features. Among low-risk women at 36 wkGA, an sFlt-1:PlGF ratio ≤38 had a negative predictive value for severe preeclampsia of 99.2%. The sFlt-1:PlGF ratio provided clinically useful prediction of the risk of the most important manifestations of preeclampsia in a cohort of unselected nulliparous women.

## Increased Angiotensin II Sensitivity Contributes to Microvascular Dysfunction in Women Who Have Had Preeclampsia[35]


### Abstract

Women who have had preeclampsia have increased cardiovascular disease risk; however, the mechanism(s) responsible for this association remain unclear. Microvascular damage sustained during a preeclamptic pregnancy may persist postpartum. The putative mechanisms mediating this dysfunction include a reduction in NO-dependent dilation and an increased sensitivity to angiotensin II. In this study, we evaluated endothelium-dependent dilation, angiotensin II sensitivity, and the therapeutic effect of angiotensin II receptor blockade (losartan) on endothelium-dependent dilation in vivo in the microvasculature of women with a history of preeclampsia (n=12) and control women who had a healthy pregnancy (n=12). We hypothesized that preeclampsia would have (1) reduced endothelium-dependent dilation, (2) reduced NO-mediated dilation, and (3) increased sensitivity to angiotensin II. We further hypothesized that localized losartan would increase endothelium-dependent vasodilation in preeclampsia. We assessed microvascular endothelium-dependent vasodilator function by measurement of cutaneous vascular conductance responses to graded infusion of acetylcholine (acetylcholine; $10^{-7}$–102 mmol/L) and a standardized local heating protocol in control sites and sites treated with 15 mmol/L L-NAME ($N^G$-nitro-L-arginine methyl ester; NO-synthase inhibitor) or 43 μmol/L losartan. Further, we assessed microvascular vasoconstrictor sensitivity to angiotensin II ($10^{-20}$–$10^{-4}$ mol/L). Preeclampsia had significantly reduced endothelium-dependent dilation (−0.3±0.5 versus −1.0±0.4 $\log_{EC50}$; $P<0.001$) and NO-dependent dilation (16±3% versus 39±6%; $P=0.006$). Preeclampsia also had augmented vasoconstrictor sensitivity to angiotensin II (−10.2±1.3 versus −8.3±0.5; $P=0.006$). Angiotensin II type I receptor inhibition augmented endothelium-dependent vasodilation and NO-dependent dilation in preeclampsia but had no effect in healthy pregnancy. These data suggest that women who have had preeclampsia have persistent microvascular dysfunction postpartum, mediated, in part, by increased sensitivity to angiotensin II.


## Maternal Serum B-Cell Activating Factor Levels: Candidate Early Biomarker for Hypertensive Disorders of Pregnancy[36]


### Abstract

Hypertensive disorders of pregnancy are a leading cause of maternal and perinatal morbidity and mortality. Early suppression of B-cell lymphopoiesis is necessary for a normal pregnancy. Dysregulation of factors critical to B-cell survival may result in pregnancy complications, including hypertension. In this prospective observational study at a single medical center, serum levels of BAFF (B-cell activating factor) were measured in pregnant participants at each trimester, at delivery, and postpartum and in nonpregnant controls at a single time point. Comparisons were made between nonpregnant and pregnant subjects and between time periods of pregnancy. First-trimester serum BAFF levels were further tested for association with hypertensive disorders of pregnancy. The study included 149 healthy pregnant women, 25 pregnant women with chronic hypertension, and 48 nonpregnant controls. Median first-trimester serum BAFF level (ng/mL) for healthy women (0.90) was lower than median serum BAFF levels for women with chronic hypertension (0.96; $P=0.013$) and controls (1.00; $P=0.002$). Serum BAFF levels steadily declined throughout pregnancy, with the median second-trimester level lower than the corresponding first-trimester level (0.77; $P=0.003$) and the median third-trimester level lower than the corresponding second-trimester level (0.72; $P=0.025$). The median first-trimester serum BAFF level was elevated in women who subsequently developed hypertension compared with women who remained normotensive (1.02 versus 0.85; $P=0.012$), with the area under the receiver operating characteristic curve being 0.709. First-trimester serum BAFF level may be an early and clinically useful predictor of hypertensive disorders of pregnancy.


## All Hypertensive Disorders of Pregnancy Increase the Risk of Future Cardiovascular Disease[37]


### Abstract

Hypertensive disorders of pregnancy are associated with vascular dysfunction in the pregnancy and an increased risk of long-term cardiovascular disease (CVD) in the mother. What remains to be understood is whether the length, severity of the disease, the treatment of hypertension in pregnancy, or the subtype of hypertensive disorders of pregnancy are significant predictors of future CVD. We undertook a retrospective cohort study to review all women who gave birth at a tertiary hospital in Sydney between the years 1980 and 1989 (n=31 656). A cohort of women was further defined by having hypertension during the antenatal, intrapartum, or postnatal periods (n=4387). Randomly selected records of women (n=1158) with a hypertensive disorder of pregnancy were individually reviewed to collect data on their pregnancy and pregnancy outcomes. The entire cohort then underwent linkage analysis to future CVDs. Women who presented with gestational hypertension were at greater risk of future hypertension and ischemic heart disease compared with the women who were diagnosed with preeclampsia. There was no significant difference between the women who were treated with antihypertensive medication and the women who did not receive antihypertensive medication or the duration of hypertensive disorders of pregnancy and future admission for CVD, although severity of hypertension tracked with increased risk of future hypertension in all groups. This study demonstrated that all women who present with any of the subtypes of hypertensive disorders in pregnancy are at significant risk of future CVD compared with women who remain normotensive during their pregnancy.

## Catechol-O-Methyltransferase Deficiency Leads to Hypersensitivity of the Pressor Response Against Angiotensin II[38]


### Abstract

Catechol-O-methyltransferase (COMT) metabolizes 2-hydroxyestradiol into 2-methoxyestradiol (2-ME); COMT deficiency has shown to be associated with hypertension in men and preeclampsia, the disease associated with hypersensitivity of pressor response against angiotensin II (Ang II). Here, we found that COMT deficiency could explain the hypersensitivity of pressor response against Ang II in mice because of the lack of 2-ME–dependent suppression of angiotensin II receptor type 1 (AT1R). Male C57BL/6 mice were subjected to COMT inhibitor (COMTi: 25 mg/kg per day) or oil (control) for 4 weeks, with or without low-dose Ang II infusion (ANGII: 70 ng/kg per minute) for the last 3 weeks. The Ang II–infused mice were treated with 2-ME (10 ng/d) or vehicle for the last 1 week. We obtained the following experimental groups: control, ANGII, COMTi, COMTi+ANGII, and COMTi+ANGII+2-ME. We performed similar experiments using the in vivo administration of small interfering RNA of COMT instead of COMTi. Neither ANGII nor COMTi exhibited significant alterations in systolic blood pressure. Compared with ANGII or COMTi, COMTi+ANGII displayed significantly higher systolic blood pressure, albuminuria, and glomerular endotheliosis; 2-ME normalized such alterations. Similar phenotypes were observed in COMT small interfering RNA-treated mice. In the aorta of COMT-deficient mice, AT1R expression was increased; 2-ME suppressed AT1R expression. The 2-ME exhibited peroxisome proliferator–activated receptor γ agonistic activity in vitro and ex vivo plasma from pregnant female mice as well. In vitro, 2-ME suppressed both basal and Ang II–induced AT1R levels in a peroxisome proliferator–activated receptor γ–dependent manner. The 2-ME is relevant to combat COMT deficiency–associated hypertensive disorders via suppression of AT1R by its peroxisome proliferator–activated receptor γ activity.


## Placental Growth Factor as a Prognostic Tool in Women With Hypertensive Disorders of Pregnancy: A Systematic Review[39]


### Abstract

The PlGF (placental growth factor) has been largely demonstrated to be associated with the diagnosis of the hypertensive disorders of pregnancy (HDPs); however, it is unclear how useful it is for the prognosis of the condition. Our objective was to provide a summary of important findings of its prognostic ability by systematically reviewing studies that examined the ability of the PlGF, either independently or combined with other factors, to predict maternal and fetal complications resulting from the HDPs. We included studies published before January 30, 2017, reporting on the use of the PlGF as a prognostic test for women with confirmed HDPs or suspected preeclampsia. Of the 220 abstracts identified through MEDLINE, Embase, and CINAHL (Cumulative Index to Nursing and Allied Health Literature), 17 studies were eligible for our review. Prognostic performance was evaluated by sensitivity, specificity, likelihood ratios, and area under the receiver operating characteristic curve. PlGF showed moderate-to-high evidence (likelihood ratios of ≥5 or ≤0.2 or area under the receiver operating characteristic curves ≥0.70) for identifying women at the highest risk of preterm delivery or neonatal outcomes (10/12 studies) but showed no clinically useful performance for the prediction of adverse maternal outcomes. PlGF may aid in the management of women with HDPs to avert fetal complications. Future studies should determine an optimum threshold for the marker to guide delivery and should examine whether its use for predicting adverse maternal outcomes in women with HDPs can be improved.


## Diagnostic Performance of Placental Growth Factor in Women With Suspected Preeclampsia Attending Antenatal Facilities in Maputo, Mozambique[40]


### Abstract

In well-resourced settings, reduced circulating maternal-free placental growth factor (PlGF) aids in either predicting or confirming the diagnosis of preeclampsia, fetal growth restriction, stillbirth, preterm birth, and delivery within 14 days of testing when preeclampsia is suspected. This blinded, prospective cohort study of maternal plasma PlGF in women with suspected preeclampsia was conducted in antenatal clinics in Maputo, Mozambique. The primary outcome was the clinic-to-delivery interval. Other outcomes included: confirmed diagnosis of preeclampsia, transfer to higher care, mode of delivery, intrauterine fetal death, preterm birth, and low birth weight. Of 696 women, 95 (13.6%) and 601 (86.4%) women had either low (<100 pg/mL) or normal (≥100 pg/mL) plasma PlGF, respectively. The clinic-to-delivery interval was shorter in low PlGF, compared with normal PlGF, women (median 24 days [interquartile range, 10–49] versus 44 [24–81], $P$=0.0042). Also, low PlGF was associated with a confirmed diagnosis of preeclampsia, higher blood pressure, transfer for higher care, earlier gestational age delivery, delivery within 7 and 14 days, preterm birth, cesarean delivery, lower birth weight, and perinatal loss. In urban Mozambican women with symptoms or signs suggestive of preeclampsia, low maternal plasma PlGF concentrations are associated with increased risks of adverse pregnancy outcomes, whether the diagnosis of preeclampsia is confirmed. Therefore, PlGF should improve the provision of precision medicine to individual women and improve pregnancy outcomes for those with preeclampsia or related placenta-mediated complications.

## External Validation of the fullPIERS Model for Predicting Adverse Maternal Outcomes in Pregnancy Hypertension in Low- and Middle-Income Countries[41]


### Abstract

The hypertensive disorders of pregnancy are leading causes of maternal mortality and morbidity, especially in low- and middle-income countries. Early identification of women with preeclampsia and other hypertensive disorders of pregnancy at high risk of complications will aid in reducing this health burden. The fullPIERS model (Preeclampsia Integrated Estimate of Risk) was developed for predicting adverse maternal outcomes from preeclampsia using data from tertiary centers in high-income countries and uses maternal demographics, signs, symptoms, and laboratory tests as predictors. We aimed to assess the validity of the fullPIERS model in women with the hypertensive disorders of pregnancy in low-resourced hospital settings. Using miniPIERS data collected on women admitted with hypertensive disorders of pregnancy between July 2008 and March 2012 in 7 hospitals in 5 low- and middle-income countries, the predicted probability of developing an adverse maternal outcome was calculated for each woman using the fullPIERS equation. Missing predictor values were imputed using multivariate imputation by chained equations. The performance of the model was evaluated for discrimination, calibration, and stratification capacity. Among 757 women with complete predictor data (complete-case analyses), the fullPIERS model had a good area under the receiver operating characteristic curve of 0.77 (95% confidence interval, 0.72–0.82) with poor calibration ($P$<0.001 for the Hosmer–Lemeshow goodness-of-fit test). Performance as a rule-in tool was moderate (likelihood ratio: 5.9; 95% confidence interval, 4.23–8.35) for women with ≥30% predicted probability of an adverse outcome. The fullPIERS model may be used in low-resourced setting hospitals to identify women with hypertensive disorders of pregnancy at high risk of adverse maternal outcomes in need of immediate interventions.


## Angiogenic Markers and Cardiovascular Indices in the Prediction of Hypertensive Disorders of Pregnancy[42]


### Abstract

Angiogenic and antiangiogenic factors have proven to be an accurate predictive means of preeclampsia. Echocardiographic studies have shown that women with preeclampsia exhibit significant cardiovascular strain, especially early-onset preeclampsia. The aim of this study is to determine preeclampsia risk with soluble fms-like tyrosin kinase 1/placental growth factor ratio, serum NT-proBNP (N-terminal pro-B-type natriuretic peptide), and biophysical markers of cardiovascular function in a prospective case–control study. We examined a cohort of 110 pregnant women with uneventful pregnancy outcome (controls) and 129 with hypertensive pregnancy disorders, including 77 with preeclampsia and 52 with pregnancy-induced hypertension. Cardiac indices were obtained with a USCOM-1A monitor, and soluble fms-like tyrosin kinase 1, placental growth factor, and NT-proBNP were measured in serum samples on automated platforms. Logistic regression, as well as Cox proportional hazard analysis, was performed. There were significant contributions from all variables tested, except for heart rate, stroke volume index, and cardiac index to the prediction model. When testing accuracy of respective markers in combination (full model) versus individual markers (soluble fms-like tyrosin kinase 1/placental growth factor ratio and total peripheral resistance) was compared. The soluble fms-like tyrosin kinase 1/placental growth factor ratio and total peripheral resistance performed as good as the full model, except for hypertensive pregnancy disorders and pregnancy-induced hypertension, where the full model performed better. The additional assessment of biophysical and biochemical markers of cardiovascular strain in pregnancy increases the detection of the composite group of hypertensive pregnancy disorders, while not significantly improving detection of preeclampsia alone. This offers a more precise insight into the pathogenesis of the disease, as well as offering a window for intervention, possibly decreasing cardiovascular mortality in these women.


## Labetalol Versus Nifedipine as Antihypertensive Treatment for Chronic Hypertension in Pregnancy: A Randomized Controlled Trial[43]


### Abstract

Data from randomized controlled trials to guide antihypertensive agent choice for chronic hypertension in pregnancy are limited; this study aimed to compare labetalol and nifedipine, additionally assessing the impact of ethnicity on treatment efficacy. Pregnant women with chronic hypertension ($12^{+0}$–$27^{+6}$ weeks' gestation) were enrolled at 4 UK centers (August 2014 to October 2015). Open-label first-line antihypertensive treatment was randomly assigned: labetalol- (200–1800 mg/d) or nifedipine-modified release (20–80 mg/d). Analysis included 112 women (98%) who completed the study (labetalol n=55, nifedipine n=57). Maximum blood pressure after randomization was 161/101 mm Hg with labetalol versus 163/105 mm Hg with nifedipine (mean difference systolic: 1.2 mm Hg [−4.9 to 7.2 mm Hg], diastolic: 3.3 mm Hg [−0.6 to 7.3 mm Hg]). Mean blood pressure was 134/84 mm Hg with labetalol and 134/85 mm Hg with nifedipine (mean difference systolic: 0.3 mm Hg [−2.8 to 3.4 mm Hg], and diastolic: −1.9 mm Hg [−4.1 to 0.3 mm Hg]). Nifedipine use was associated with a 7.4-mm Hg reduction (−14.4 to −0.4 mm Hg) in central aortic pressure, measured by pulse wave analysis. No difference in treatment effect was observed in black women (n=63), but a mean 4 mm Hg reduction (−6.6 to −0.8 mm Hg; $P$=0.015) in brachial diastolic blood pressure was observed with labetalol compared with nifedipine in nonblack women (n=49). Labetalol and nifedipine control mean blood pressure to target in pregnant women with chronic hypertension. This study provides support for a larger definitive trial scrutinizing the benefits and side effects of first-line antihypertensive treatment.

## Maternal Gestational Hypertension-Induced Sensitization of Angiotensin II Hypertension Is Reversed by Renal Denervation or Angiotensin-Converting Enzyme Inhibition in Rat Offspring[44]


### Abstract

Numerous findings demonstrate that there is a strong association between maternal health during pregnancy and cardiovascular disease in adult offspring. The purpose of the present study was to test whether maternal gestational hypertension modulates brain renin–angiotensin–aldosterone system (RAAS) and proinflammatory cytokines that sensitizes angiotensin II–elicited hypertensive response in adult offspring. In addition, the role of renal nerves and the RAAS in the sensitization process was investigated. Reverse transcription polymerase chain reaction analyses of structures of the lamina terminalis and paraventricular nucleus indicated upregulation of mRNA expression of several RAAS components and proinflammatory cytokines in 10-week-old male offspring of hypertensive dams. Most of these increases were significantly inhibited by either renal denervation performed at 8 weeks of age or treatment with an angiotensin-converting enzyme inhibitor, captopril, in drinking water starting at weaning. When tested beginning at 10 weeks of age, a pressor dose of angiotensin II resulted in enhanced upregulation of mRNA expression of RAAS components and proinflammatory cytokines in the lamina terminalis and paraventricular nucleus and an augmented pressor response in male offspring of hypertensive dams. The augmented blood pressure change and most of the increases in gene expression in the offspring were abolished by either renal denervation or captopril. The results suggest that maternal hypertension during pregnancy enhances pressor responses to angiotensin II through overactivity of renal nerves and the RAAS in male offspring and that upregulation of the brain RAAS and proinflammatory cytokines in these offspring may contribute to maternal gestational hypertension-induced sensitization of the hypertensive response to angiotensin II.


## Cerebrovascular Reactivity and Vascular Activation in Postmenopausal Women With Histories of Preeclampsia[45]


### Abstract

Cerebrovascular reactivity (CVR) is reduced in patients with cognitive decline. Women with a history of preeclampsia are at increased risk for cognitive decline. This study examined an association between pregnancy history and CVR using a subgroup of 40 age- and parity-matched pairs of women having histories of preeclampsia (n=27) or normotensive pregnancy (n=29) and the association of activated blood elements with CVR. Middle cerebral artery velocity was measured by Doppler ultrasound before and during hypercapnia to assess CVR. Thirty-eight parameters of blood cellular elements, microvesicles, and cell–cell interactions measured in venous blood were assessed for association with CVR using principal component analysis. Middle cerebral artery velocity was lower in the preeclampsia compared with the normotensive group at baseline (63±4 versus 73±3 cm/s; $P$=0.047) and during hypercapnia ($P$=0.013–0.056). CVR was significantly lower in the preeclampsia compared with the normotensive group (2.1±1.3 versus 2.9±1.1 cm·s·mm Hg; $P$=0.009). Globally, the association of the 7 identified principal components with preeclampsia ($P$=0.107) and with baseline middle cerebral artery velocity ($P$=0.067) did not reach statistical significance. The interaction between pregnancy history and principal components with respect to CVR ($P$=0.084) was driven by a nominally significant interaction between preeclampsia and the individual principal component defined by blood elements, platelet aggregation, and interactions of platelets with monocytes and granulocytes ($P$=0.008). These results suggest that having a history of preeclampsia negatively affects the cerebral circulation years beyond the pregnancy and that this effect was associated with activated blood elements.


## Prevalence of Hypertensive Phenotypes After Preeclampsia: A Prospective Cohort Study[46]


### Abstract

Preeclampsia is associated with increased cardiovascular and renal risk. The aim of this prospective cohort study was to characterize the early postpartum blood pressure (BP) profile after preeclampsia. We enrolled 115 women with preeclampsia and 41 women with a normal pregnancy in a prospective cohort study. At 6- to 12-week postpartum, we assessed the prevalence of different hypertensive phenotypes using 24-hour ambulatory BP monitoring (ABPM), as well as the risk of salt sensitivity and the variability of BP derived from ABPM parameters. Among patients with preeclampsia, 57.4% were still hypertensive at the office. Daytime ABP was significantly higher in the preeclampsia group (118.9±15.0/83.2±10.4 mm Hg) than in controls (104.8±7.9/71.6±5.3 mm Hg; $P$<0.01). Differences between groups were similar for nocturnal BP values. Fifty percent of preeclampsia women remained hypertensive on ABPM in the postpartum, of whom 24.3% were still under antihypertensive treatment; 17.9% displayed a white-coat hypertension and 11.6% had masked hypertension. In controls, 2.8% had white-coat hypertension; none had masked hypertension or needed hypertensive treatment. The prevalence of nondippers was similar 59.8% in the preeclampsia group versus 51.4% in controls. High-risk class of salt sensitivity of BP was increased in preeclampsia women (48.6%) compared with controls (17.1%); $P$<0.01. In conclusion, ABPM 6 to 12 weeks after delivery reveals a high rate of sustained ambulatory, nocturnal, and masked hypertension after preeclampsia. This finding may help identify women who should be included in a postpartum cardiovascular risk management program.

## Fetal Microsatellite in the Heme Oxygenase 1 Promoter Is Associated With Severe and Early-Onset Preeclampsia[47]


### Abstract

Preeclampsia is a vascular pregnancy disorder that often involves impaired placental development. HO-1 (heme oxygenase 1, encoded by HMOX1) is a stress response enzyme crucial for endothelial and placental function. Long version of the guanine–thymine ($GT_n$) microsatellite in the HMOX1 promoter decreases HO-1 expression, and the long maternal repeat is associated with late-onset preeclampsia. Our aim was to study whether the length of fetal repeat is associated with mother's preeclampsia, whether the length of fetal and maternal repeats affect HO-1 levels in placenta and maternal serum, and whether HO-1 levels are altered in preeclampsia. We genotyped the repeat in the cord blood of 609 preeclamptic and 745 nonpreeclamptic neonates. HO-1 levels were measured in 36 placental samples, and in the first (222 cases/243 controls) and third (176 cases/53 controls) pregnancy trimester serum samples using enzyme-linked immunosorbent assay. The long fetal $GT_n$ repeat was associated with preeclampsia and its severe and early-onset subtypes. Interaction analysis suggested the maternal and fetal effects to be independent. Placental or serum HO-1 levels were not altered in preeclamptics, possibly reflecting heterogeneity of preeclampsia. Carriers of the long fetal and maternal repeats had lower placental and serum HO-1 levels, respectively, providing functional evidence for the association. We conclude that the long fetal $GT_n$ repeat may increase mother's risk for especially severe and early-onset preeclampsia. The fetal and maternal risk alleles likely predispose to different disease subtypes.





## Acknowledgments

We thank Drs Joey Granger and S. Ananth Karumanchi for contributing the introduction to this article.


## Disclosures

None.

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Journal of the American Heart Association

# *Hypertension* Editors' Picks: Preeclampsia, Pregnancy, and Hypertension

The Editors

*Hypertension.* 2018;72:e1-e18
doi: 10.1161/HYPERTENSIONAHA.118.11037
*Hypertension* is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0194-911X. Online ISSN: 1524-4563