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Cardiological Society of India

Yearbook of CARDIOLOGY 2024

Hypertension

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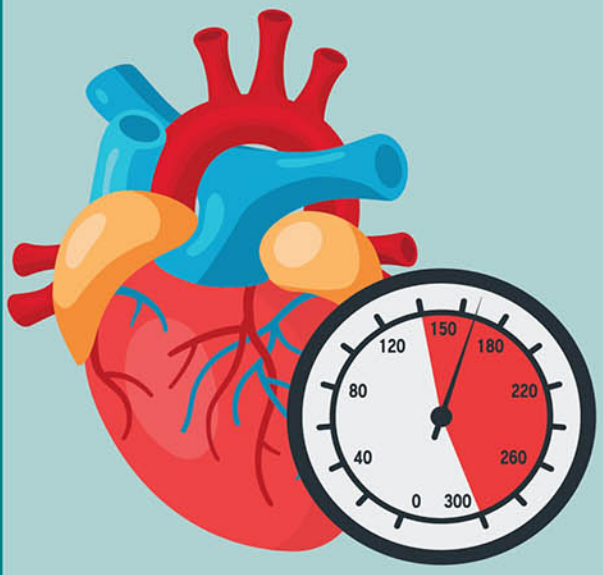

Foreword
Pratap Chandra Rath

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SECTION 4

Hypertension in Woman

***Section Editor*: G Justin Paul**

ARTICLE 1

Maternal Hypertensive Traits and Adverse Outcomes in Pregnancy: A Mendelian Randomization Study

Ardissino M, Reddy RK, Slob EAW, Griffiths J, Girling J, Ng FS. Maternal hypertensive traits and adverse outcome in pregnancy: a Mendelian randomization study.
J Hypertens. 2023;41(9):1438-45.

Abstract

Introduction: First of all, pregnancy-related hypertension problems are linked to unfavorable fetal and mother outcomes. The majority of the data currently available comes from observational research, which are biased and susceptible to confounding. Using Mendelian randomization, this study examined the causative relevance of component hypertensive indices on a number of unfavorable pregnancy outcomes.

Techniques: As instrumental variables, uncorrelated ($r^2 < 0.001$) genome-wide significant ($p < 5 \times 10^{-8}$) single-nucleotide polymorphisms linked to pulse pressure (PP), diastolic blood pressure (DBP), and systolic blood pressure (SBP) were chosen. Preterm delivery, placental abruption, bleeding in the early stages of pregnancy, and preeclampsia or eclampsia outcomes' genetic association estimates were taken from the FinnGen cohort's summary data of genome-wide association studies.

The main technique for analysis was two-sample, inverse-variance weighted Mendelian randomization. The odds ratios (ORs) for each 10 mm Hg increase in the genetically predicted hypertension index are displayed.

Findings: There was a positive correlation between higher genetically predicted SBP and increased risks of preterm birth [OR 1.09; 95% confidence interval (CI) 1.03–1.16; $p = 0.005$], placental abruption (OR 1.33; 95% CI 1.05–1.68; $p = 0.016$), and preeclampsia or eclampsia (OR 1.81; 95% CI 1.68–1.96; $p = 5.45 \times 10^{-49}$). Preeclampsia or eclampsia was linked to higher genetically predicted DBP (OR 2.54; 95% CI 2.21–2.92; $p = 5.35 \times 10^{-40}$).

Preterm birth (OR 1.18; 95% CI 1.06–1.30; $p = 0.002$) and preeclampsia or eclampsia (OR 1.68; 95% CI 1.47–1.92; $p = 1.9 \times 10^{-14}$) were linked to higher genetically predicted PP.

In conclusion this study provides genetic evidence to support causal associations of SBP, DBP and PP on multiple adverse outcomes of pregnancy. Since SBP and PP were linked to the widest variety of unfavorable outcomes, it is likely that optimizing blood pressure (BP) management—especially SBP—is essential to enhancing fetomaternal health.

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COMMENT

Hypertensive disorders of pregnancy, including chronic hypertension, gestational hypertension, and preeclampsia, are significant contributors to maternal and fetal morbidity. Chronic hypertension is either pre-existing or diagnosed before 20 weeks of gestation, while gestational hypertension arises de novo after 20 weeks' without associated proteinuria or biochemical abnormalities. Preeclampsia, a more severe condition, is characterized by new-onset hypertension post-20 weeks' gestation accompanied by proteinuria, intrauterine growth restriction, or end-organ damage. Numerous observational studies have linked maternal blood pressure before pregnancy to adverse maternal and fetal outcomes. However, such studies often face confounding factors and reverse causality issues, especially concerning preterm birth and preeclampsia, where the pathophysiology remains relatively unclear. Enhancing the understanding of the determinants of adverse fetomaternal outcomes is crucial for improving risk stratification and targeted care to better obstetric outcomes.

Mendelian randomization (MR) uses genetic variants as proxies for exposures in instrumental variable analysis to explore exposure-outcome relationships. Given the independent and random distribution of genetic variants during meiosis, MR is less susceptible to the limitations of phenotypic observational studies, such as confounding and reverse causality. Despite the importance of blood pressure (BP) control in pregnancy, the causal relevance of BP indices like diastolic BP (DBP) and pulse pressure (PP) on key obstetric outcomes, such as preterm birth and placental abruption, has not been thoroughly explored.

In this study, the researchers extended their previous MR research to investigate the causal impact of genetically predicted systolic BP (SBP), DBP, and PP on a range of maternal and fetal outcomes, including preterm birth, placental abruption, and early pregnancy hemorrhage. We extracted instrumental variants for SBP, DBP, and PP from a sex-adjusted genome-wide association study (GWAS) involving 738,168 individuals. These instrumental single-nucleotide polymorphisms (SNPs) were selected based on their genome-wide significance level [$p < 5 \times 10^{-8}$].

The findings provide genetic evidence supporting a causal role of higher genetically predicted SBP, DBP, and PP in multiple adverse pregnancy outcomes, including preeclampsia, preterm birth, and placental abruption. These results have significant implications. First, they corroborate recent clinical trial findings showing improved pregnancy outcomes with strict BP control in women with gestational hypertension. Second, they highlight key adverse outcomes associated with elevated BP, which are crucial for risk stratification and surveillance in high-risk pregnancies. Finally, they confirm a causal relationship between all three BP indices and adverse pregnancy outcomes.

The association between genetically predicted SBP and preeclampsia/eclampsia was extended in this study to include DBP and PP, consistent with previous observational studies and meta-analyses. This genetic evidence suggests that higher maternal BP may impair spiral artery formation through hemodynamic effects and resultant vascular damage or alter the balance of circulating vasoactive mediators, leading to failed cytotrophoblast invasion of spiral arteries and the development of high-resistance vessels.

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For preterm birth, this study identified associations with genetically predicted SBP and PP, aligning with prior research. A plausible mechanism is that increased hypertensive indices raise the risk of pre-eclampsia, leading to preterm deliveries. Regarding placental abruption, the link with higher genetically predicted SBP is supported by earlier meta-analyses and large-scale data analyses, suggesting that elevated maternal BP may initiate and propagate placental abruption due to increased resistance in placental circulation. Given the severe nature of placental abruption, further investigation into the role of strict BP control in at-risk women is warranted.

This study did not find a significant relationship between genetically predicted hypertensive indices and early pregnancy hemorrhage, despite its known association with higher risks of preterm delivery and other complications. This may reflect either a true lack of biological association or insufficient power in the genetic instruments used.

Strengths of this study include the use of a large, nationwide cohort, and the application of validated devices for BP measurement, reducing confounding and reverse causality risks. However, limitations include the inability to distinguish between early and late-onset preeclampsia, the conservative nature of the Bonferroni correction potentially leading to type II errors, and the study's focus on individuals of European ancestry, limiting generalizability.

Clinically, the results underscore the importance of optimal BP management for improving maternal and fetal outcomes. Further research is needed to define precise BP targets in pregnancy for various clinical scenarios. The Chronic Hypertension and Pregnancy (CHAP) trial recently demonstrated that a lower treatment threshold for chronic hypertension in pregnancy (140/90 mm Hg) significantly reduced adverse outcomes compared to a higher threshold (160/105 mm Hg). Additionally, optimizing BP management has long-term benefits for maternal health, as hypertensive disorders of pregnancy are associated with increased risks of cardiovascular and cerebrovascular diseases and cardiovascular death. Future trials should aim to establish clear antenatal BP targets tailored to different clinical situations, ensuring the best possible outcomes for both mother and child.

Take Home Messages

- ***Adverse fetomaternal outcomes are common in hypertensive disorders of pregnancy. However, it is not yet established if this association is causal. This could be because the evidence for this association comes predominantly from observation studies, and the pathophysiology of adverse outcomes like preterm birth and preeclampsia are yet to be well understood. This study attempted to provide genetic evidence to support causal associations of SBP, DBP and PP on adverse pregnancy outcomes.***
- ***The authors have used data from the genome-wide association study (GWAS) on 738,168 individuals to conduct this Mendelian randomization study. Higher genetically predicted SBP, DBP and PP were associated with higher odds of preeclampsia or eclampsia. SBP and PP were associated with the broadest range of adverse outcomes. This suggests that optimal management of blood pressure, particularly SBP, is a key priority to improve fetomaternal health.***
- ***Genetic evidence for the causal effects of hypertensive indices on a adverse pregnancy outcomes have been identified for the first time.***

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ARTICLE 2

Appraising the Preclinical Evidence of the Role of the Renin–Angiotensin–Aldosterone System in Antenatal Programming of Maternal and Offspring Cardiovascular Health Across the Life Course: Moving the Field Forward: A Scientific Statement from the American Heart Association

Alexander BT, South AM, August P, Bertagnolli M, Ferranti EP, Grobe JL, et al. Appraising the Preclinical Evidence of the Role of the Renin–Angiotensin–Aldosterone System in Antenatal Programming of Maternal and Offspring Cardiovascular Health Across the Life Course: Moving the Field Forward: A Scientific Statement from the American Heart Association.

Hypertension. 2023;80(5):e75-e89.

Abstract

The long-term cardiovascular health of women who had difficult pregnancies and the children they had is a topic of growing attention. Preeclampsia is one of the emerging prenatal risk factors that seems to raise the lifetime risk of hypertension and cardiovascular disease in both the kids and the postpartum mother. The prenatal programming mechanisms responsible, however, are intricate and poorly understood, with roots in changes to the kidney, heart, brain, and vasculature's growth, shape, and function. The development and function of kidney and cardiovascular tissues, as well as maternal-fetal health through the placental interface, are all significantly regulated by the renin–angiotensin–aldosterone system (RAAS).

Dysregulation of the RAAS is a major factor in the development of pregnancy-related problems like preeclampsia and the establishment of long-term detrimental cardiovascular health in both the mother and the offspring. In order to identify individuals who are at-risk and to aid in the development of innovative medicines for the prevention and treatment of disease throughout the life course, a deeper knowledge of the programming of the prenatal RAAS is necessary. Preclinical and translational research studies must follow best practices to precisely and rigorously measure the various components of the RAAS, given the system's inherent complexity.

This thorough synthesis of preclinical and translational scientific data regarding the mechanistic function of the RAAS in the prenatal programming of hypertension and cardiovascular disease will be useful in three ways: (1) identifying critical needs; (2) ensuring that future research adheres to best practices in the field; and (3) directing future studies to optimize potential results. Better health outcomes will result from this, as well as more swift and effective translation to clinical care.

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COMMENT

Antenatal period, the time between conception to birth of offspring, is very crucial for both mother and baby. Any adverse maternal health condition or environmental stress has the potential to alter structural and metabolic fetal development. This antenatal programming though beneficial for short term "survival", has long term, cardiovascular consequences (developmental plasticity).

The exact mechanism of developmental plasticity is not completely explored, but it is related to renin–angiotensin–aldosterone system (RAAS) system components [angiotensin-converting enzyme (ACE)/angiotensin II (Ang II)/Ang-II type 1 receptor (AT1R)], which regulate the development and function of kidney and cardiovascular system (CVS).

Antenatal pregnancy-related conditions such as preeclampsia, hypertension in pregnancy, and long-term cardiovascular (CV) ill health in offspring are associated with RAAS dysregulation.

Exact characterization of dysregulation of RAAS and its effects on fetomaternal CV health is still lacking. This scientific statement summarizes the current evidence and knowledge related to antenatal programming of fetomaternal CV health in relation to RAAS pathway.

Maternal-placental Fatal Interface and the Renin–angiotensin–aldosterone System

There is increasing stress on mother as the fetus grows along with placenta. Reduction of systemic vascular resistance (SVR) and blood pressure (BP) start occurring as early as 4–6 weeks' gestation with consequent stimulation of maternal circulating RAAS. This leads to sodium and water retention and increases in plasma volume, cardiac output and glomerular filtration rate (GFR) 40–50% over and above baseline.

Renin–angiotensin–aldosterone System in Normal Pregnancy Physiology

In normal healthy pregnant women, serum plasma renin activity (PRA) remains elevated, but BP remains lower. This is due to activation of additional RAAS pathway despite reduced serum ACE activity. This phenomenon helps to increase blood volume. Dynamic expression of various RAAS components in local tissue and placenta is key to normal physiological processes such as placentation, trophoblast invasion, and migration and spiral artery formation. ACE is predominantly expressed in fetal side of fetomaternal circulation and enhances angiotensin type II production which helps in fetal angiogenesis. There occurs upregulation of ACE-2/Ang-(1–7) pathway which balance, increase ACE/Ang-II and helps maternal hemodynamic adaptation. This pathway maintains uterine artery tone and at the same time reduces material systemic vascular resistance. Intracellular signaling between AT1R and Mas receptor and conversion of Ang-II into Ang-(1–7) are key factors which regulate Ang-II effects in normal pregnancy. There remains knowledge gap in understanding additional RAAS pathways and Ang II–Ang-(1–7) balance, prorenin receptors function, and various signaling pathway interfaces like Wnt/β-catenin, mitogen-activated protein (MAP) kinase, neprilysin, etc., are also less well understood.

Renin–angiotensin–aldosterone System: In Pregnancy Pathologies

For proper development of fetus (including kidney and cardiovascular health) and

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uneventful pregnancy outcome sufficient placental perfusion is very important. Intrauterine growth retardation, a surrogate of placental insufficiency, is associated with higher cord blood. Ang-II concentration and reduced glomerular number and hypertension in offspring. A soluble isoform of vascular endothelial growth factor (VEGF), FMS-like tyrosine kinase, which has antiangiogenic properties, is found increased in early pregnancy placental ischemia and causes imbalance between pro- and anti-angiogenic factors, resulting in maternal endothelial dysfunction.

Ang-II type 1 receptor autoantibody induced vasoconstriction, hypertension, and hypercoagulability are well established in preeclampsia. But, gap exists between complete understanding of their significance. Gap also exists in complete understanding of cause–effect relation between preeclampsia and RAAS dysregulation. Some theories suggest that abnormal placentation, defective spiral artery remodeling, reduced placental perfusion and increased oxidative stress contribute to preeclampsia. Abnormal RAAS expression may be the consequence of abnormal placenta development and adverse fetomaternal outcome.

Evidence for Renin–angiotensin–aldosterone System-mediated Antenatal Programming and Fetomaternal Health

Offspring's CV health and renal development is dependent on RAAS. Hence, RAAS blockade is contraindicated in pregnancy as it causes renal agenesis, fetal birth defect, kidney failure. The higher blood pressure noted adolescents who were born preterm, could be a result of in utero-shifts in the delicate balance between the ACE/Ang II pathway and the ACE2/Ang-(1–7) pathway.

Though the exact mechanism is incompletely understood, various models also established association of maternal RAAS alteration and maternal hypertension.

Second Hits: Additive Multiplicative Programming Effects

Programmed RAAS modification in antenatal period sensitizes both mother and fetus and on further exposure to another insult often result to hypertension and CV disease—this is called second hit. This sensitization of both the mother and child to subsequent second hit is yet to be explored.

Additional Renin–angiotensin–aldosterone System Programming Mechanism

Epigenetic mechanisms like deoxyribonucleic acid (DNA) methylation, histone modification, noncoding ribonucleic acid (RNA) can modify gene expression without alteration of DNA sequences. This can sensitize the mother and fetus to programmed RAAS modification. This phenomenon is supported by models of maternal nutrient deprivation or excess. Modification of AT1R as a component of RAAS system is a potential mechanism of RAAS programming. Recent evidence on exosome and micro-RNA established these facts.

Methodological Limitation

There remain challenges for experimental manipulation of different RAAS modification methods which can affect maternal and offspring health adversely, and these methods need to be validated. The costs of various models, measurement of plasma levels of various RAAS components, which are differentially distributed in various maternal and fetal components are still an issue.

Future Direction

Renin–angiotensin–aldosterone system modification, environmental exposure, genetic difference in pregnancy outcomes

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in various maternal disease conditions are gray areas which need to be explored especially in the post-coronavirus disease 2019 (COVID-19) era where ACE receptors are proved to play major role in CV outcomes. Socio-demographic influences in primordial prevention of RAAS programming need to be explored and established.

Take Home Messages

- *Renin–angiotensin–aldosterone system (RAAS) plays an enormous role in both healthy and pathological pregnancies.*
- *Dysregulation of the RAAS not only contributes to the development of pregnancy complications, such as preeclampsia, but also to the programming of long-term adverse cardiovascular health in both the mother and her offspring.*
- *Numerous preclinical models using different programming events in various animal species have demonstrated consistently that programmed RAAS alterations in the antenatal period can lead to development of cardiovascular abnormalities in women and their offspring.*
- *The programming of maternal and fetal RAAS is still poorly understood.*
- *Considering the inherent complexities of the RAAS, it is crucial for preclinical and translational research studies to follow best practices in assessing the system's components accurately and rigorously.*
- *Guidance is provided as how to plan these preclinical and translational research studies so as to enable a quicker and more efficient transition to clinical care, ultimately enhancing health outcomes.*

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Hypertension

Salient Features

- The book is aimed for the Physicians and Cardiologists dealing with the patients suffering with Hypertension.
- There are 7 Sections with articles from high impact factor journals.
- The commentary discussions on the articles and relevant issues, emphasizing the current evidence-based thinking on the subject.
- This will be helpful resource toward day-to-day practice for the practicing physicians and cardiology fellows.

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