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# PREECLAMPSIA AND HIGH BLOOD PRESSURE IN EARLY PREGNANCY AS RISK FACTORS OF SEVERE MATERNAL CARDIOVASCULAR DISEASE.


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## ABSTRACT

**Background:** The associations between pregnancy hypertensive disorders and common cardiovascular disorders have not been investigated at scale in a contemporaneous population.

**Aims And Objective:** Studies suggest preeclampsia as a risk factor for long term cardiovascular diseases (CVD), while evidence is limited regarding the risk of high blood pressures (BP) in early pregnancy

**Methods And Materials:** A Prospective cohort study consisting all women (n = 150) with pregnancies diagnosed between September 2020 to August 2021 in Gynecology department of Madhubani Medical College, Madhubani district area who delivered at the hospital were considered eligible for inclusion. At the first antenatal visit, the date of the last menstrual period and weight before pregnancy were recorded. Blood pressure and weight were measured at three points in time during pregnancy, i.e., at the first antenatal visit, mid-third trimester, and just before delivery. Blood pressures were rounded to the nearest 5 mmHg at the examination. Edema and proteinuria were assessed in the third trimester and just before delivery. Previous obstetric history was obtained at the first visit from the participants. Gestational age was calculated as the time period between the date of the first day of the latest menstrual period and the date of birth expressed in weeks.

**Result:** Of the included women, 86 (4.9%) had high SBP, 22 (2%) high DBP, 34 (4.3%) high MAP in early pregnancy; and 98 (4.7%) developed preeclampsia. During 12 months of follow-up, 95 (21.9%) women experienced a CVD event. Women with preeclampsia had a higher risk of developing CVD compared to women without preeclampsia.

**Conclusion:** Hypertensive disorders of pregnancy, including preeclampsia, have a similar pattern of increased risk across all 12 cardiovascular disorders and chronic hypertension, and the impact was evident soon after pregnancy. It should be considered as a natural screening tool for cardiovascular events.


**KEYWORDS :** Preeclampsia, high blood pressure and cardiovascular disease

## INTRODUCTION:

Preeclampsia affects 2% to 8% of pregnancies worldwide manifesting as hypertension and proteinuria in the second half of pregnancy [1] Globally, preeclampsia is responsible for around 14% of maternal deaths [2] and is a major cause of perinatal morbidity and mortality. Two decades of research have documented an association between preeclampsia and major cardiovascular disorders in later life [3–8]. However, there are several limitations with the current evidence that prevent its translation into clinical care. Firstly, most research to date has focused on the use of composite end points such as ischemic heart disease and cerebrovascular disorders, which include a heterogeneous group of disorders with diverse etiologies and clinical management. Secondly, over the past 2 decades the pattern of initial presentation of cardiovascular disorders has changed substantially in high-income countries such as the United Kingdom, with most of the events being neither myocardial infarction nor ischemic stroke [9]. Thirdly, only a minority of studies [4, 10, 11] have been able to adjust for post pregnancy cardiovascular risk factors, such as hypertension, limiting their ability to examine potential mediating factors underlying this association. Cardiovascular diseases (CVDs) are the leading cause of deaths globally, i.e., an estimated 31% of all deaths worldwide [12]. Established evidence suggests that hypertensive disorders of pregnancy, such as gestational hypertension and preeclampsia, are associated with an increased risk of future hypertension, stroke, and other CVDs [13, 14]. However, there is uncertainty as to whether preeclampsia is merely an expression of an already existing, prior to pregnancy, vulnerability in the maternal cardiovascular system, or whether the development of preeclampsia itself is a causal factor causing permanent damage to the cardiovascular system [15, 16]. Findings from several studies report that women with preeclampsia in their obstetric history have an earlier onset of subsequent hypertension and CVDs compared to women without preeclampsia [14]. However, the majority of studies are limited by short follow-up time, which is crucial as most of the incidences occur after the age of 50 years [17]. There is emerging evidence of the association between elevated blood pressure in pregnancy and future risk of hypertension and cardiovascular morbidity [18–21]. The blood pressure in early pregnancy is relatively low and decreases to a nadir at around 18 gestational weeks as a result, it may not necessarily transform into hypertension [22].

## AIMS AND OBJECTIVE:

To show preeclampsia acts as a risk factor for long term cardiovascular diseases (CVD), while evidence is limited regarding the risk of high blood pressures (BP) in early pregnancy.

## MATERIAL AND METHODS:

This study is a prospective cohort study consisting of almost all women ($n$ =150) with pregnancies diagnosed by gynecologists between September 2020 to August 2021 in Gynecology department of Madhubani Medical College, Madhubani district area who delivered at the hospital were considered eligible for inclusion. Ethical clearance was obtained by the ethical approval committee of the institute.

At the first antenatal visit, the date of the last menstrual period and weight before pregnancy were recorded. Blood pressure and weight were measured at three points in time during pregnancy, i.e., at the first antenatal visit, mid-third trimester, and just before delivery. Blood pressures were rounded to the nearest 5 mmHg at the examination. Edema and proteinuria were assessed in the third trimester and just before delivery. The smoking history of the women was obtained regularly throughout the pregnancy. Previous obstetric history was

obtained at the first visit from the participants. Gestational age was calculated as the time period between the date of the first day of the latest menstrual period and the date of birth expressed in weeks. Weeks. MAP was calculated from SBP and DBP using the formula:
MAP = DBP+SBP – DBP / 3

Cardiovascular outcomes were identified by the International Classification of Diseases (ICD) versions 8,9and10 for ischemic disease, stroke, and transient ischemic attack. Ischemic heart disease was identified.

**Exclusion Criteria:**
Women who had miscarriages, duplex pregnancies, abortions, molar pregnancies, extra-uterine pregnancies, and second pregnancy were excluded ($n$ = 25) from the study. Due to incorrect or missing personal numbers of mothers, an additional sample of 25 pregnancies was lost. Further, 25 women were excluded due to missing information about study variables or those reporting the use of medications for heart disease or vascular disease during the first, second, or third trimester. The final cohort included 125 women.

**Participants**
Participants were eligible for inclusion in the study if they were female, Preeclampsia and the exposure of interest. Preeclampsia is a syndrome of the latter half of pregnancy. Therefore, to avoid measurement error in the exposure, only non-preeclamptic pregnancies with a minimum length of 20 weeks' gestation were considered as the non-exposed group. Maternity File was used to identify women who had a completed pregnancy record and were between 18 to 38 years old (inclusive) at each estimated pregnancy end date.

**Cardiovascular System In Pregnancy And Preeclampsia**

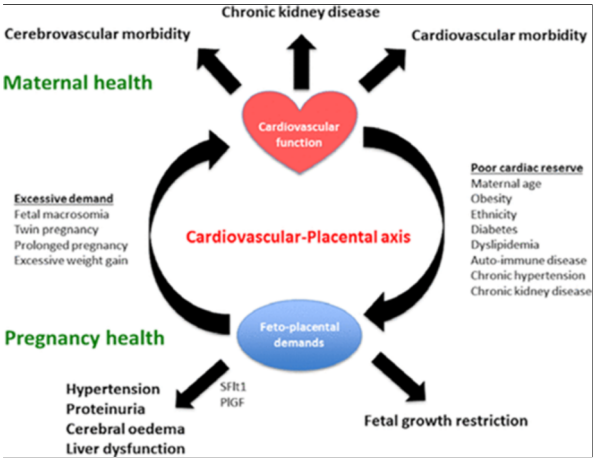


**Figure 1.** Diagram Illustrating The Interaction Between Maternal Cardiovascular Function And Placental Function, Maternal Health, And Fetal Well-being.

Placental oxidative stress or hypoxia is related to the relative balance of cardiovascular functional reserve and the cardiovascular volume/resistance load of pregnancy. The final common pathway that results in the signs and symptoms of preeclampsia involves the release of placental vasoactive substances. PIGF indicates placenta growth factor; and sFLT, soluble fms-like tyrosine kinase.

**Early Pregnancy Cardiovascular Changes Related to Preeclampsia.**
Endothelium-derived vasoconstrictors are core components of preeclampsia pathophysiology, with studies demonstrating that derangement in Ang. II (angiotensin-II), endothelin - 1, and thromboxane A2 physiology occur long before onset of signs and symptoms of preeclampsia

**Table 1: - Risk Categories And Factors In Common For Both Preeclampsia And Cardiovascular Disease.**

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| Physical | Advanced maternal age |
| | Weight (pre pregnancy and pregnancy weight gain) |
| | Ethnicity (black/afro-Caribbean or Hispanic) |
| Environmental | Smoking |
| | Sedentary lifestyle |
| | Psychological stress |
| Hormonal | Polycystic ovarian syndrome |
| | Premature ovarian failure (ovum donation pregnancy) |
| Autoimmune | Systemic lupus erythematous |
| | Antiphospholipid syndrome |
| Metabolic | Diabetes mellitus (pre pregnancy and gestational) |
| Renal | Chronic kidney disease |
| | History of acute kidney injury |
| Cardiovascular | Chronic hypertension |
| | Abnormal serum lipid profile |
| | History of placental dysfunction (preeclampsia or fetal grow restriction) |

**Statistical Analysis:**
All the analyses were done using IBM SPSS Statistics 25.0 for Windows (IBM Corporation, Armonk, NY, USA). Two sided P-values < 0.05 were considered to be notable.

**RESULT:**
Distributions of maternal characteristics by preeclampsia status for each participant's first recorded completed pregnancy. As expected, women who had preeclampsia were more likely to be nulliparous, diabetic, hypertensive, overweight or obese, and less likely to be smokers (all $P$ values <0.001). Pregnancies affected by preeclampsia were more likely to be delivered preterm (compared to those without) and had a lower mean infant birth weight. Of the included women, 86 (4.9%) had high SBP, 22 (2%) high DBP, 34 (4.3%) high MAP in early pregnancy; and 98 (4.7%) developed preeclampsia. During 12 months of follow-up, 95 (21.9%) women experienced a CVD event. Women with preeclampsia had a higher risk of developing CVD compared to women without preeclampsia (HR 1.5, 95%CI: 1.1–2.2), while risks among women with high BPs were slightly higher. In adjusted analysis, risk estimates were approximately 50% higher than that of the reference groups for all four studied exposures. Of women with later CVD, 85 (6.6%) had preeclampsia, and another 31 (5,8%) women high SBP or high MAP. Without later preeclampsia, high SBP constituted a significant risk factor (HR 1.6, 95%CI: 1.1–2.4) for CVD.

**DISCUSSION:**
We found significantly increased risk of CVD, comparable to that of preeclampsia, among women having the <5% highest blood pressure measurements at the first antenatal visit in early pregnancy following exclusion of women with cardiovascular medication. Furthermore, though preeclampsia was overlapping with >95th percentile blood pressures, these measurements identified additional women at a number comparable to those identified at increased risk by preeclampsia as a risk factor. Raised blood pressure at the first antenatal visit in early pregnancy without later preeclampsia was only a risk factor for CVD when SBP was separately considered, while raised MAP and DBP increased the risk of preeclampsia. The risk of raised SBP on CVD is in line with other studies [20, 21], although not entirely comparable as not performed on pregnant women. However, considering the younger age group in our study (mean age of 26 years), analyzing the risk of DBP could have resulted in congruence with a study among young (18 to 24 years old)

However, with the used cut-of, the DBP-group was the smallest in this study, and we could not find an increased risk of isolated raised DBP. The increased risk of elevated blood pressures on CVD remained after adjusting for the major non-modifiable and modifiable factors suggesting that the association with CVD is a result of both established risk factors and pregnancy-specific components. This knowledge provides a window of opportunity to identify additional women with elevated blood pressures during pregnancy without hypertensive disorders that carry the risk of CVDs later in life [23]. Our findings of preeclampsia and its association with later development of CVDs are congruent with previous *meta*-analyses [24, 25. 26]. The strength of association (relative risk) was nearly similar to what was observed in our study. However, all the studies included in the Meta analysis had a median follow-up time of <40 years. Our study affirms that the effect of preeclampsia on the risk of CVDs does not vary significantly with the increasing years of follow-up.

## CONCLUSION:

The risk factors for preeclampsia are cardiovascular in nature, cardiovascular signs and symptoms predominate in the clinical syndrome of preeclampsia, and cardiovascular morbidity persists for decades after preeclampsia. All of these make a strong case for the involvement of the maternal cardiovascular system in the pathogenesis of preeclampsia. Info graphic outlining involvement of the maternal cardiovascular system in the pathogenesis and recovery from preeclampsia (PE).

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| **Before Pregnancy**<br>PE and cardiovascular disease share many common antecedents. Factors such as age, obesity diabetes, renal disease, abnormal lipid profile, family history of myocardial infarction and previous PE pregnancy increase the risk of developing both disorders. | **Early Pregnancy Changes**<br>Increased peripheral vascular resistance (i.e. in uterine, brachial or ophthalmic arteries), higher BP and low PIGF are associated with an increased risk of developing PE in pregnancy. |
| **At Clinical onset of PE**<br>Echo findings associated with PE Early – onset PE – concentric remodeling. Diastolic/systolic dysfunction, decreased stroke volume, cardiac output, late–onset PE increased left ventricular mass impaired myocardial relaxation / contractility diastolic function | **Monitoring BP**<br>• Home monitoring of BP of appears to be clinically safe and more economical.<br>• Incidence of significant hypertension Appears lower with name monitoring.<br>• Role of hemodynamic monitoring to guide anti-hypertensive therapy deserve further evaluation. |
| **Delivery & Peripartum care**<br>Incidence of serious maternal complications with PE (such as pulmonary edema, renal dysfunction and Peripartum cardiomyopathy) occur more frequently in women with the poorest cardiovascular function. | **Postpartum Period**<br>• About 50% of women will remain hypertensive at 2-3 months postpartum<br>• About 10% of women will develop chronic hypertension within a year<br>• Non-attendance at post partum visits is common and home monitoring may be of benefit in these women |
| **Life after PE (up to 5-10 years)**<br>Increased risk of cardiovascular disease in both mother and offspring, Magnitude of risk is related to the severity of PE and by proxy severity of maternal cardiovascular dysfunction pregnancy | **Aging after PE (10+ years)**<br>Increased long-term risk of cardiovascular disease, Renal disorder, diabetes, dementia– leading to reduced life expectancy. Risk is related to Severity of PE and maternal cardiovascular dysfunction in pregnancy. |

The pathogenesis of preeclampsia has always known to be a consequence of placental damage secondary to oxidative stress or hypoxia resulting in the release in a maternal systemic anti angiogenic imbalance. Hypertensive disorders of pregnancy, including preeclampsia, have a similar pattern of increased risk across all 12 cardiovascular disorders and chronic hypertension, and the impact was evident soon after pregnancy. It should be considered as a natural screening tool for cardiovascular events.

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