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Original Research Article

Evaluation of the risk factors in pregnant females with hypertensive disorder of pregnancy

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ABSTRACT

Background: Hypertensive disorders of pregnancy (HDP) are important causes of maternal and perinatal morbidity. This study evaluated readily identifiable maternal and pregnancy-related factors associated with HDP.

Methods: This analytical cross-sectional study enrolled 211 pregnant women beyond 20 weeks of gestation at Deen Dayal Upadhyay Hospital, New Delhi, from May 2022 until completion of recruitment. Participants were categorized as HDP (n=61) or normotensive (n=150). Maternal age, body mass index (BMI), previous preeclampsia, multifetal gestation, and assisted reproductive technology (ART) conception were recorded. Categorical variables were compared using the chi-square test; $p < 0.05$ was significant.

Results: The mean age was 27.63 ± 4.93 years and mean BMI was 22.09 ± 3.08 kg/m². HDP occurred in 61 (28.9%) participants. Maternal age group was not associated with HDP ($p = 0.141$). BMI > 35 kg/m² occurred in 2/61 (3.3%) women with HDP and 0/150 normotensive women ($p = 0.026$). Previous preeclampsia was present in 8/61 (13.1%) and 2/150 (1.3%), respectively ($p = 0.0001$). Multifetal gestation occurred in 10/61 (16.4%) and 3/150 (2.0%), respectively ($p = 0.0001$). ART conception was not significantly associated with HDP ($p = 0.348$).

Conclusions: Higher BMI, previous preeclampsia, and multifetal gestation were significantly associated with HDP, whereas maternal age and ART conception were not.

Keywords: Assisted reproductive technology, Body mass index, Hypertensive disorders of pregnancy, Multifetal gestation, Preeclampsia, Risk factors

INTRODUCTION

Hypertensive disorders of pregnancy include gestational hypertension, preeclampsia, eclampsia, chronic hypertension and preeclampsia superimposed on chronic hypertension. They are a spectrum of disease that ranges from isolated elevation of blood pressure to multisystem disease that includes hepatic, renal, neurologic, hematologic, placental, and cardiovascular complications. Advice now focuses on accurate blood-pressure measurement, prompt diagnosis and evaluation for end-organ involvement as the disease can be rapid and unpredictable in development.^{1,2}

Importance of HDP is not limited to the index pregnancy. The consequences of preeclampsia and eclampsia are low

birth weight, premature birth, stillbirth, and neonatal morbidity, which are greater for the fetus when access to prenatal surveillance, emergency obstetric care, laboratory testing and critical care is limited.³⁻⁵ Mother's severe disease can result in eclampsia, HELLP syndrome, stroke, pulmonary edema, acute kidney injury, and cardiac failure.^{2,6,7}

The complex pathogenesis of preeclampsia is linked to abnormal placentation, deficient remodelling of spiral arteries, angiogenic imbalance, systemic inflammation, oxidative stress and generalized endothelial dysfunction.^{1,4} Combined first trimester screening is recommended if available, but simple clinical assessment remains important, especially in low-resource settings and high-volume public hospitals. FIGO has recommended

combined first trimester screening when it can be performed, but simple clinical assessment is relevant, particularly in low-resource settings and high-volume public hospitals.⁴

Previous preeclampsia, chronic hypertension, diabetes, renal or autoimmune disease, obesity, multifetal gestation, advanced maternal age, nulliparity, and conception achieved through assisted reproductive technology have been established clinical risk factors. Therefore, locally relevant factors must be identified to guide the provision of counselling and allocate surveillance efficiently, due to the variability of the strength of each association between them and the prevalence of coexisting risk factors between populations.⁸⁻¹⁵ The present study was aimed to evaluate selected maternal and pregnancy related risk factors associated with hypertensive disorders of pregnancy in pregnant women attending a tertiary public hospital.

METHODS

Study design and setting

This hospital-based analytical cross-sectional study was conducted in the department of obstetrics and gynaecology, Deen Dayal Upadhyay Hospital, New Delhi. Recruitment began in May 2022 and continued until the final required participant was enrolled.

Ethical considerations

The study protocol was approved by the institutional ethics committee, Deen Dayal Upadhyay Hospital (Ref. IEC-DDUH/upn118/2022-05-12/48/v1; approval dated 10 May 2022). Written informed consent was obtained from every participant before enrollment. Participant information was handled confidentially and the analysis used de-identified study data.

Study population

Pregnant women beyond 20 weeks of gestation who attended the obstetric outpatient department or obstetric services were screened. Women with HDP, defined in the study protocol as blood pressure $\geq 140/90$ mmHg on two occasions at least 4 hours apart after 20 weeks of gestation in a previously normotensive woman, and gestational-age-matched normotensive pregnant women were included in the analytical cohort. The final sample consisted of 211 participants, of whom 61 had HDP and 150 did not.

Eligibility criteria

Pregnant women meeting the study screening and enrollment criteria were eligible. Women with coronary artery disease, liver disorders, a relevant history of drug intake, or autoimmune disease such as systemic lupus erythematosus or rheumatoid arthritis were excluded.

Sample-size calculation

The minimum sample size was estimated using the logistic-regression sample-size approach described in the thesis and assumptions derived from Mishra and Sreepathi.¹⁰ A reported odds ratio of 4.54, disease proportion of 15.4%, two-sided alpha of 5%, and power of 80% yielded a minimum requirement of 210.58, rounded to 211 participants. Eligible pregnant women presenting to the obstetric services during the study period were enrolled until the required sample size was achieved. Women with HDP were compared with gestational-age-matched normotensive pregnant women.

Data collection and measurements

A structured proforma was used to record demographic, obstetric, and clinical information. Medical and antenatal records were reviewed. The prespecified clinical factors included maternal age, parity, BMI, previous preeclampsia, multifetal gestation, and pregnancy conceived through ART. General examination included pulse rate and blood-pressure measurement. Weight and height were measured and BMI was calculated as weight in kilograms divided by the square of height in meters. Mean arterial pressure was recorded in the thesis dataset. Obstetric examination and review of antenatal records were performed for all participants. Measures to reduce information and measurement bias included use of a structured data-collection proforma, review of available medical and antenatal records, and standardized recording of anthropometric and blood-pressure measurements. The same prespecified definitions and exposure categories were applied to all participants.

Outcome and exposure variables

The primary outcome for the present manuscript was the presence of HDP as reported in the thesis results. Exposure categories were retained exactly as reported: age ≤ 25 , 26-30, 31-35, and >35 years; BMI ≤ 35 and >35 kg/m²; previous preeclampsia (yes/no); multifetal gestation (yes/no); and ART conception (yes/no).

Statistical analysis

Data were checked for completeness, cleaned, entered into Microsoft Excel, and analyzed using licensed SPSS software version 24.0 (IBM Corp., Chicago, Illinois, USA). Continuous variables were summarized using mean, median, standard deviation, minimum, and maximum. Categorical variables were summarized as frequency and percentage. Associations between categorical variables and HDP were evaluated with the chi-square test. A p value <0.05 was considered statistically significant. Because the thesis reported bivariate analyses, this manuscript does not present adjusted effect estimates.

RESULTS

A total of 211 pregnant women were included. The mean age was 27.63 ± 4.93 years, with a median of 28 years and a range of 18-41 years. Seventy-seven (36.5%) women were aged ≤ 25 years, 76 (36.0%) were 26-30 years, 43

(20.4%) were 31-35 years, and 15 (7.1%) were older than 35 years (Tables 1 and 2). Complete data were available for all variables included in the analyses reported in this manuscript, therefore no participants were excluded from an analysis because of missing values.

Table 1: Descriptive characteristics of the study participants (n=211).

Variables	Mean	Median	SD	Minimum	Maximum
Age (years)	27.63	28.00	4.93	18	41
Weight (kg)	58.35	58.00	8.10	48.00	105.00
Height (cm)	162.59	162.00	3.48	154.00	171.00
BMI (kg/m ²)	22.09	21.30	3.08	18.14	36.76
Pulse rate (/min)	86.80	87.00	4.81	78.00	102.00
Systolic BP (mm Hg)	126.47	120.00	17.24	100.00	174.00
Diastolic BP (mm Hg)	76.81	76.00	10.71	58.00	110.00
Mean arterial pressure (mm Hg)	93.36	90.67	12.28	74.00	131.33

BMI: body mass index; BP: blood pressure; SD: standard deviation.

Table 2: Distribution of categorical characteristics among the study participants (n=211).

Characteristics	Category	N	%
Age group (in years)	≤ 25	77	36.5
	26-30	76	36.0
	31-35	43	20.4
	> 35	15	7.1
BMI	≤ 35 kg/m ²	209	99.1
	> 35 kg/m ²	2	0.9
Previous preeclampsia	No	201	95.3
	Yes	10	4.7
Multifetal gestation	No	198	93.8
	Yes	13	6.2
ART conception	No	207	98.1
	Yes	4	1.9
Hypertensive disorder of pregnancy	Yes	61	28.9
	No	150	71.1

ART: assisted reproductive technology; BMI: body mass index.

Table 3: Association of selected risk factors with hypertensive disorder of pregnancy.

Factors	Category	HDP N (%)	No HDP N (%)	P value
Age group (in years)	≤ 25	22 (36.1)	55 (36.7)	0.141
	26-30	27 (44.3)	49 (32.7)	
	31-35	11 (18.0)	32 (21.3)	
	> 35	1 (1.6)	14 (9.3)	
BMI	≤ 35 kg/m ²	59 (96.7)	150 (100.0)	0.026
	> 35 kg/m ²	2 (3.3)	0 (0.0)	
Previous preeclampsia	No	53 (86.9)	148 (98.7)	0.0001
	Yes	8 (13.1)	2 (1.3)	
Multifetal gestation	No	51 (83.6)	147 (98.0)	0.0001
	Yes	10 (16.4)	3 (2.0)	
ART conception	No	59 (96.7)	148 (98.7)	0.348
	Yes	2 (3.3)	2 (1.3)	

ART: assisted reproductive technology; BMI: body mass index; HDP: hypertensive disorder of pregnancy.

The mean weight was 58.35 ± 8.10 kg, mean height was 162.59 ± 3.48 cm, and mean BMI was 22.09 ± 3.08 kg/m². Two participants (0.9%) had BMI >35 kg/m². Mean systolic blood pressure was 126.47 ± 17.24 mmHg, mean diastolic blood pressure was 76.81 ± 10.71 mmHg, and mean arterial pressure was 93.36 ± 12.28 mmHg (Table 1).

Previous preeclampsia was reported in 10 (4.7%) participants, multifetal gestation in 13 (6.2%), and conception following ART in 4 (1.9%). HDP was present in 61 (28.9%) women and absent in 150 (71.1%) (Table 2).

Age group was not significantly associated with HDP ($p=0.141$). Among women with HDP, 22 (36.1%) were aged ≤ 25 years, 27 (44.3%) were 26-30 years, 11 (18.0%) were 31-35 years, and 1 (1.6%) was older than 35 years. The corresponding counts among women without HDP were 55 (36.7%), 49 (32.7%), 32 (21.3%), and 14 (9.3%), respectively (Table 3).

BMI >35 kg/m² was recorded in 2 (3.3%) women with HDP and in none of the normotensive group; this association was statistically significant ($p=0.026$). Previous preeclampsia was present in 8 (13.1%) women with HDP compared with 2 (1.3%) women without HDP ($p=0.0001$). Multifetal gestation was present in 10 (16.4%) women with HDP and 3 (2.0%) women without HDP ($p=0.0001$). ART conception was reported in 2 (3.3%) women with HDP and 2 (1.3%) women without HDP, with no statistically significant association ($p=0.348$) (Table 3).

DISCUSSION

This study assessed some simple clinical parameters in 211 pregnant women at a tertiary public hospital in relation to HDP. Statistically significant findings were the association of HDP with BMI >35 kg/m², previous preeclampsia, and multifetal gestation. No significant association was found between HDP and the age group of mothers and conception by ART in this cohort. The results validate the ongoing importance of meticulous history taking, anthropometry and fetal number estimation in routine antenatal care.

Those who were classified as HDP accounted for 28.9% of the participants. This is above the 6.5% reported by Ain et al and the 13.9% reported by Nath et al, and cannot be interpreted as the proportion of the population since recruitment was done in a tertiary hospital and there is an analytical comparison group.^{8,9} The representation of HDP might be due to the referral of women with high blood pressure or obstetric complications. Variation among studies may also be due to variations in diagnostic criteria, gestational age at assessment, healthcare-seeking behavior, and sampling strategy.

There was no significant correlation between maternal age and HDP ($p=0.141$). Only 15 of the participants were above 35 years of age and one woman with HDP was in this age group. The small sample size of older people

significantly restricts the capacity to identify an age relationship. However, Hinkosa et al found that women aged 35 years or older had higher odds of having HDP and Tessema et al.^{11,17} found that advanced age was an associated factor. Mishra and Sreeprathi found a relationship between both extremes of maternal age.¹⁰ As such, the lack of statistical significance in the present cohort should be viewed as a cohort-specific finding and not as a statement that age is not important.

Parity, chronic disease, vascular health, BMI, and socioeconomic factors are likely to modify the relationship between age and HDP. In the current study, the mean age was 27.63 years with almost three-quarters of all participants being 30 years or less, while in the study by Nath et al, the risk was found to be higher in women aged over 28 years.⁹ The relative youth of a study population and the small number of individuals at the extremes of age may mask relationships which are apparent in larger and more representative populations. Clinical risk assessment should therefore continue to consider age together with the complete obstetric and medical history.

BMI >35 kg/m² was statistically associated with HDP ($p=0.026$), as both the women with BMI >35 kg/m² were in the HDP group. This finding is in the same direction as the vast amount of literature that has been published on overweight/obesity and gestational hypertension and preeclampsia. A systematic review and meta-analysis conducted by Motedayen et al revealed that women with preeclampsia had higher BMI.¹³ Similarly, women with high BMI also had a higher risk of hypertensive disorders, according to Kahsay et al and Tesfa et al.^{12,14} In large clinical cohorts, maternal obesity has been linked to poor pregnancy outcomes, too.²⁰

There are multiple mechanisms that may account for the relationship between adiposity and HDP. Insulin resistance, chronic low-grade inflammation, oxidative stress, dyslipidemia and disturbed adipokine signalling are hallmarks of obesity. These abnormalities can exacerbate endothelial dysfunction and disrupt adaptation of the vasculature to pregnancy. This may be compounded by increased sympathetic activity, sodium retention and metabolic vulnerability. Biological plausibility of this association is high, but the current finding is observed in just two subjects with BMI >35 kg/m². The p value should therefore be used with care as a sparse cell may lead to an unstable estimate and does not reflect the size of risk and/or its accuracy.

The BMI threshold used in the thesis was >35 kg/m² while many studies consider overweight as ≥ 25 kg/m² or obesity as ≥ 30 kg/m². In the current cohort, the mean BMI was 22.09 kg/m² and 99.1% of participants had BMI of ≤ 35 kg/m². A more granular analysis across standard BMI categories would probably have provided greater clinical information and statistical power. However, the trend noted in the direction supports preconception counselling on healthy weight and healthy weight gain during

pregnancy. Both pre-pregnancy obesity and high GWT were linked to hypertension in pregnancy, with Kazemian et al reporting the link.¹⁸ This makes weight optimization a potentially modifiable factor in prevention.

Having had a previous preeclampsia was strongly associated with HDP in the current pregnancy. Women with HDP had a history in 13.1%, and 1.3% of women without HDP ($p=0.0001$). This has clinical relevance as it is readily apparent at booking and consistently acknowledged as a key risk factor in international guidance.¹⁻⁴ Tesfa et al reported significantly higher odds among those with previous preeclampsia and this finding has been replicated in settings.¹²

Recurrence could be due to ongoing maternal vulnerability such as genetic predisposition, cardiometabolic risk, vascular dysfunction, and common environmental risk. Previously, the risk of recurrence is also dependent on gestational age at the time of the previous episode and severity of the previous episode, length of time between pregnancies, chronic hypertension, diabetes, renal disease and BMI. Previous preeclampsia was expressed as a binary variable in the present study, and therefore did not allow the exploration of these clinically relevant gradients. However, this clear distinction between the groups suggests that early identification, counselling and consideration of aspirin prophylaxis (if considered appropriate following the guidelines) and close antenatal monitoring should be considered.^{1,2,4}

There was a statistically significant association between HDP and multifetal gestation (16.4% versus 2.0%). This is consistent with case-control and meta-analytic studies demonstrating an increased risk in twin and higher order pregnancies, which may be due to larger placental mass, higher angiogenic/antiangiogenic signalling, greater maternal cardiovascular demand, and higher rates of placental dysfunction.^{11,12,19} Multiple pregnancies often coexist with ART conception and advanced maternal age making interpretation difficult if not done within a context of multivariable analysis.

This overall rate of multifetal gestation was 6.2%, a higher rate than is found in an unselected obstetric population. This could be due to tertiary centre referral or local case mix or to include pregnancies with greater need for closer supervision. The discovery has immediate clinical implications: multifetal pregnancy women should be monitored for blood pressure, taught what to look for and receive proper fetal monitoring. Bivariate analysis was reported, with no attempt to calculate adjusted estimates to account for the effects of plurality on correlated factors.

The three major factors identified during the thesis in terms of the service delivery side have different ways of use. Multifetal gestation and previous preeclampsia can be determined from the history and early ultrasound and thus may affect care prior to the onset of hypertension. BMI can be measured at booking but did not pick up the two women

in the study using the threshold in the study. All of these observations support the idea of a structured antenatal risk checklist, and not just waiting for one particular characteristic. If women have 1 or more of the major factors they can be reviewed at a more frequent interval for blood pressure, counselled about the issues of headache, visual symptoms, epigastric pain, sudden oedema and reduced fetal movements, and evaluated promptly if symptoms arise.

The identification of risk factors should be used in conjunction with, not in place of, repeated clinical assessment. Many women with HDP do not have an obvious high-risk feature and many women with a known risk factor do not have HDP. International recommendations therefore incorporate history, accurate blood-pressure measurement and assessment of proteinuria or maternal organ dysfunction in the presence of suspected hypertension, and where these tests are unavailable, consistent use of readily available clinical information can still minimise preventable opportunities and ensure timely referral.^{1,2,4}

Very few participants (4) conceived while in ART. It did not seem to have significant association with HDP ($p=0.348$). This is not significant, given the tiny amount of exposed group. ART pregnancies are also heterogeneous: Risk can vary depending on fresh or frozen embryo transfer, oocytes from donors, underlying infertility, hormonal preparation, maternal age and multi-fetal pregnancies. This relationship was confusing in Ali et al, who found a lower incidence of preeclampsia in an ART population with progesterone supplementation compared to spontaneous pregnancies.¹⁶ Presently available data are not sufficient to rule out a clinically significant relationship.

Results also impact on preconception and interpregnancy care. Women with a history of preeclampsia should be counselled for the next pregnancy about the risk of recurrence, weight management, the management of any chronic medical conditions and early booking. For severely obese women, healthy and non-stigmatising weight-management prior to conception may be helpful. In multifetal gestation, early assessment of chorionicity and appropriate maternal-fetal monitoring are important as both maternal and fetal complications occur more commonly than in a singleton pregnancy. Such interventions need to be continuous from primary care to obstetric outpatient service, ultrasonography, referral facility.

There are several strengths to this study. It applied a predetermined protocol and was approved by institutional ethics review boards, with written informed consent and standardized demographic, anthropometric, obstetric and blood-pressure measurements. A normotensive comparison group was included to allow direct assessment of clinical factors reported. The sample size was as planned and the results are about factors that can be

evaluated without an expensive laboratory or biomarker test.

Significant caveats should also be noted. The study has been carried out in a single tertiary hospital, which may affect the generalizability. Association but not temporal causation is shown by the cross-sectional design. The following exposure groups had very few subjects, and thus p values were potentially affected by sparse data: BMI>35 kg/m² and ART conception. The analysis was bivariate and no attempt was made to adjust for confounding or interaction. However, the following information was not included in the final tables of the thesis: Standard BMI categories, detailed parity, family history, chronic hypertension, diabetes, renal disease, socioeconomic variables, and pregnancy outcomes. No long term follow up was performed on the mother or infant. These limitations should be considered when interpreting the results and designing future multicenter studies.

Future studies should include larger and more diverse populations, standardized definitions and BMI categories, complete parity and medical comorbidities reporting, and multivariate analysis models. Future research may help to understand the relationship between the factors found to the severity, age of gestation at onset, maternal complications, fetal growth, prematurity and neonatal outcomes. However, in practical clinical situations, the new results provide a pragmatic message: vigilance should be raised from first antenatal contact in women with a history of preeclampsia, severe obesity, and multifetal gestation.

Another key goal is data quality enhancements. Future protocols should also document the time and technique of each BP measurement, antihypertensive therapy, proteinuria, laboratory findings of organ dysfunction and type of HDP diagnosis. Absolute numbers, together with effect estimates and confidence intervals, would be more informative than p values only, because it would make the clinical significance of associations more obvious. Exposure categories should be considered sparse and exploratory from confirmatory findings should be addressed in the prespecified analysis plan. These methodological changes would enhance the comparability between Indian centres and facilitate the creation of locally derived risk-prediction pathways. They would also allow for potentially valid subgroup analyses based on gestational age at onset, severity of disease, and singleton or multifetal pregnancy in future studies.

CONCLUSION

BMI>35 kg/m², history of preeclampsia and multifetal gestation were found to be statistically significant factors associated with hypertensive disorders of pregnancy in this study. In the sample analyzed, there was no significant association between maternal age group and ART conception. Small numbers in each exposure category should be interpreted with caution. A targeted pre-natal

evaluation of maternal weight, prior history of hypertension in pregnancy and number of fetuses can help to stratify risk and monitor more closely, especially if more sophisticated screening tests are not readily available.

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