ASSOCIATION OF PREECLAMPSIA, PLACENTAL PATHOLOGY, AND MATERNAL-FETAL FEATURES WITH PREGNANCY-INDUCED HYPERTENSION AT DIFFERENT GESTATIONAL AGE RANGES

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ABSTRACT

AIM: This study aimed at evaluating the preeclampsia, placental pathology, and maternal and fetal features in women with pregnancy-induced hypertension (PIH) at different gestational age ranges.

METHODS: Data related to this analytical cross-sectional study was collected from 60 pregnant women recruited at Gynecology and Obstetrics Department of Hospital between 21 November 2020 and 22 May 2021. A series of maternal, fetal and placental pathology variables was evaluated and compared between the two 30-tuple groups, including pregnant women with early PIH between 20-34 weeks of gestation and those with late PIH after 34 weeks of gestation.

RESULTS: Preeclampsia was more prevalent in women with early PIH compared with those with late PIH (80% vs 20%, P:0.001), implying that preeclampsia was significantly associated with the early PIH ($p<0.05$). The rate of "syncytial knots" significantly increased with the progression of preeclampsia ($P<0.05$). A significant positive correlation existed between the early PIH and the rate of newborns admitted to NICU, the length of hospitalization, and the levels of the doppler indexes of umbilical and uterine arteries ($p<0.05$). The newborn Apgar scores were also lower in cases with early PIH than those with late PIH ($p<0.05$). The mortality rate in neonates born to mothers with early PIH was higher than neonates delivered from mothers with early PIH, but not significantly so (13.30% vs 3.30%, p:0.16).

CONCLUSION: Early PIH between 20-34 weeks of gestation might be indicative of progression to preeclampsia. Also, higher rates of pregnancy-related complications in mothers with early PIH might be indicative of different impact of PIH and preeclampsia on pregnancy outcomes depending on the gestational age. Nonetheless, further large-scale researches are needed to get a detailed picture of PIH and preeclampsia.

KEYWORDS: Pregnancy-induced hypertension, Preeclampsia, Placental pathology, Pregnancy outcomes

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INTRODUCTION

Hypertensive disorders of pregnancy are still a serious health threat for women and their offspring worldwide. Pregnancy-induced hypertension (PIH) with an overall prevalence of 5–10% of pregnancies, is a condition characterized by high blood pressure (systolic blood pressure (BP) ≥ 140 mmHg or a diastolic BP ≥ 90 mmHg) after 20 weeks of gestation without proteinuria[1, 2]. Although PIH complications are not severe, PIH can subsequently progress to preeclampsia or a severe condition after week 20 of pregnancy [3]. Preeclampsia is generally diagnosed by high BP ≥ 140/90 mmHg and proteinuria ≥ 300 mg /24 h, and or maternal organ dysfunction. Preeclampsia is prevalent in 2%–5% of pregnancies and accounted for nearly 14% of maternal death[3, 4].

The common risk factors for PIH /preeclampsia reported in many epidemiological studies are obesity, older age, stress, multiple-fetus pregnancy, first pregnancy, polycystic ovarian syndrome, diabetes, chronic kidney disease, and autoimmune disease[5, 6]. PIH may cause other fetal and maternal complications, including preterm delivery, intrauterine growth restriction, low birth weight, premature placental abruption, cardiovascular disorders, kidney and/or liver failure, HELLP syndrome, and even high risk of mortality[7, 8]. So, identifying the effects of PIH and preeclampsia on clinical pregnancy outcomes is very useful to clearly understand their pathological mechanism as well as timely prediction and management of complications.

Placenta, as the principal source of oxygen and blood supply to the fetus, can be origin of the majority of adverse pregnancy outcomes, such as fetal growth restriction (FGR) and preeclampsia resulted from the early abnormal placental development[9]. The etiology of preeclampsia is not fully understood, though it is known that the preeclampsia pathogenesis includes poor remodeling of the uteroplacental spiral arteries which lead to placenta perfusion, oxidative stress, chronic hypoxia, and thereby abnormal placentation, and other subsequent clinical disorders[10]. The evidence acknowledged that the placenta can be the source of some common maternal complications during pregnancy, such as inadequate nutrition, diabetes, obesity, and hypertension, which may also influence the infant health[9, 10].

Placental pathology can be clinically useful to perinatal diagnosis as well as explain the pathophysiology of many pregnancy-related complications, such as preterm delivery, intrauterine growth restriction, preterm labor, and preeclampsia[11, 12]. Therefore, gynecologists, pediatricians, and histologists are always looking for the histology changes of the placenta. Also, pathological findings of the placenta may indicate whether or not subsequent pregnancies should be considered at high-risk pregnancies (for example the mild infarction)[13]. Given the previous placental pathological evidences in preeclampsia [e.g., hypoplasia, placental inflammation, and vascular lesions], placental examination plays an important role in the early diagnosis and management of pregnancy and prenatal complications[12].

The current analytical cross-sectional study focuses on evaluating the preeclampsia, placental pathology, and maternal and fetal features in two groups of women with PIH between 20-34 weeks of gestation and those with PIH after 34 weeks of gestation. During the placental pathological examination, a series of variables was evaluated, including syncytial knots, fibrinoid necrosis in placenta, calcification, placental infarction, chorangioma, hyalinized villi, and stromal pathology.

METHOD

Study design

In this analytical cross-sectional study, pregnant women referred to Imam Khomeini Hospital in the city of Ahvaz, Iran, were evaluated. This research was approved by Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran with Ethical Code: IR.AJUMS.HGOLESTAN.REC.1399.099, and all participants signed the informed consent prior to enrollment.

Participants and Methods

Data of the current study was collected from 60 pregnant women recruited at Gynecology and Obstetrics Department of Hospital between 21 November 2020 and 22 May 2021. The inclusion criteria were the presence of PIH, no history of smoking, alcohol, and drug addiction. The exclusion criteria were women who had chronic blood pressure, fetal anomalies, infectious diseases, and/or a history of severe trauma during pregnancy. The participants' information was extracted from their medical records, including demographic data [i.e., age, gender, body mass index (BMI)], underlying disease, and pregnancy health history [e.g., the number of previous pregnancies, history of high BP, time of PIH, history of abortion, maternal diseases, maternal medications, type of delivery and/or pregnancy, neonatal status, birth weight, length of hospitalization in the neonatal intensive care unit (NICU), and the final status of the infant (dead or alive)].

The recruited patients were divided into two 30-tuple groups of mothers with PIH between 20-34 weeks of gestation and those with PIH after 34 weeks of gestation. The placenta samples of mothers were placed in 10% formalin and sent to the pathology laboratory for macroscopic and microscopic examination. The prepared slides were examined by a pathologist for pathological variables, such as syncytial nodule, fibrinoid necrosis in placenta, calcification, placental infarction, chorangioma, hyalinized villi, and stromal pathology (e.g., hypocellular fibrosis, spindle cell stroma, smooth muscle differentiation, edematous stroma, and adipose tissue).

Definitions:

According to National and European scientific society's guidelines, pregnancy-induced hypertension is defined as systolic BP ≥140 mmHg and diastolic BP ≥90 mmHg after the 20th week of gestation in women without previous hypertension, which measured by an oscilometric device for at least two measurements 4 h apart[14]. Preeclampsia was generally diagnosed by high BP ≥ 140/90 mmHg and proteinuria ≥ 300 mg/24 h, and or maternal organ dysfunction[15]. Systolic and diastolic BP were measured after the 20th week of gestation. Gestational age was detected using ultrasound examination.

Statistical analysis

The quantitative variables were described as mean, standard deviation, median and interquartile range while the qualitative variables were expressed as frequency (percentage). The normality of data was checked by the Shapiro-Wilk test. Also, an independent sample T-Test as well as the chi-square test were respectively used to compare the quantitative and qualitative variables between the two studied groups. $P < 0.05$ is considered as statistically significant, and the data were analyzed by SPSS version 26 (SPSS Inc., Chicago, Ill., USA).

RESULTS

Preliminary data analysis showed that there were no significant differences between mothers with early PIH and those with late PIH in terms of the age, height, weight, and BMI ($p>0.05$; Table 1). Preeclampsia were more prevalent in cases with early PIH compared with those with late PIH (80% vs 20%); this indicated a significant positive correlation between preeclampsia and PIH between 20-34 weeks of gestation (p: 0.001; Table 1).

The mean level of systolic BP on admission in women with early PIH (167.17±16.95 mmHg) was partially higher than those with late PIH (160.33±12.17 mmHg), but not significantly so (p: 0.078). The mean level of diastolic BP in women with early PIH (96.17±6.65 mmHg) was significantly higher than those with late PIH (91.33±8.60 mmHg; p: 0.018). But no significant differences were found between the two groups in terms of the mean levels of systolic and/or diastolic BP during care of patients ($p>0.05$; Table 1). Moreover, there was no significant correlation between the history of underlying disease (i.e., brain, liver and or cardiac disorders) and PIH ($P <0.05$; Table 1). Anti-PIH medication use was more prevalent among women with early PIH compared to those with late PIH (46.70% vs 20%, p: 0.04). Also, no significant correlation was found between the history of abortion and PIH (p: 0.99; Table 1).

Table 1. Summary of demographic and basic gestational information of pregnant mothers

		Study Group			
	Late GH Mean±SD	Early PIH Mean±SD	P-value		
Age of Pregnant Mothers	32.13±6.84	33.80±6.80			0.38
Height	163.40±4.12	160.37±7.48			0.06
Prenatal Weight	78.47±10.10	78.70±17.07			0.95
BMI	31.25±10.30	30.68±6.36			0.79
Systolic Blood Pressure (on admission)	160.33±12.17	167.17±16.95			0.07
Diastolic Blood Pressure (on admission)	91.33±8.60	96.17±6.65			0.018
Systolic Blood Pressure (during patient care)	120±9.83	125±25.56			0.32
Diastolic Blood Pressure (during patient care)	78.67±6.81	78.67±15.92			0.99
			Total		
The presence of proteinuria, N %No	24 (80)	6 (20)	30 (50)		0.001
	Yes	6 (20)	24 (80)	30 (50)	
Anti-PIH medication use, N %	No	24 (80)	16 (53.3)	40 (66.7)	0.03
	Yes	6 (20)	14 (46.7)	20 (33.3)	
Brain Disorder, N %	does not have	25 (83.3)	21 (70)	46	0.36
	Standard	5 (16.7)	9 (30)	14 (23.3)	
Liver problems, N %	No	27 (90)	25 (83.3)	52 (86.7)	0.7
	Yes	3 (10)	5 (16.7)	8 (13.3)	
Cardiac disorders, N %	Yes	1 (3.30%)	0		
History of Abortion, N %	No	30 (100)	25 (83.3)	55 (91.7)	0.88
	Yes	0 (0) 5 (16.7)	5 (8.3)		

PIH: pregnancy-induced hypertension

A significant correlation existed between the fetal weight on ultrasound and PIH (P<0.05), of which the rate of fetuses with 10_95 fetal weight was more prevalent in cases with early PIH. Also, the mean age of fetuses as well as the mean weight of babies born to women with late PIH were significantly higher than those with early PIH (P<0.05). (Table 2)

Table 2. Summary of descriptive information about the fetal basic conditions

		Study Groups			
		Late GH	Early PIH	Total	P-value
Fetal Age – Days, Mean±SD		246.67±50.90	143.30±112.38	0.001	
Percentage of Fetal Weight on	0	0 (0)	2 (6.7)	2 (3.3)	
Ultrasound, N%	0-10	6 (20)	0 (0)	6 (10)	
	10-50	9 (30)	11 (36.7)	20 (33.3)	0.03
	50-90	15 (50)	16 (53.3)	31 (51.7)	
	90-95	0 (0)	1 (3.3)	1 (1.7)	
Percentage of Fetal Birth Weight, N%	0-5	3 (10)	2 (6.7)	5 (8.3)	
	5-10	3 (10)	4 (13.3)	7 (11.7)	0.13
	10-50	14 (46.7)	14 (46.7)	28 (46.7)	
	50-90	10 (33.3)	5 (16.7)	15 (25)	
	90-100	0 (0)	5 (16.7)	5 (8.3)	

Furthermore, no statistically significant difference in the mean weight of placenta was observed between the two studied groups (p: 0.946). But a remarkable correlation was found between the location of the placenta on ultrasound and PIH ($p<0.05$), as posterior, fundal-posterior, and lateral placenta were more prevalent in those with late PIH. Whereas, most mothers with the early PIH had the anterior placenta ($p<0.05$). (Table 3).

Table 3. Comparison analysis of placental pathological indicators between the two groups.

		Study Groups			
		LLate GH	Early PIH	Total	P-value
Placental Weight, Mean±SD		524.83±91.44	527.37±178.02		0.94
The Location of the Placenta	Posterior	16 (53.3)	14 (46.7)	30 (50)	
on Ultrasound, N%	Anterior	3 (10)	9 (30)	12 (30)	
	Fundal-anterior	3 (10)	1 (3.3)	4 (6.7)	
	Fundal-posterior	4 (13.3)	0 (0)	4 (6.7)	
	Right lateral	2 (6.7)	0 (0)	2 (3.3)	
	Left lateral	2 (6.7)	0 (0)	2 (3.3)	
	left posterior lateral	0 (0)	1 (3.3)	1 (1.7)	
	Posterior midline	0 (0)	1 (3.3)	1 (1.7)	
	Anterior midline	0 (0)	1 (3.3)	1 (1.7)	
	Anterior lateral	0 (0)	3 (10)	3 (5)	
Retroplacental Hemorrhage, N%	0	26 (55.6)	20 (44.4)	46 (76.7)	0.19
	1	3 (30)	7 (70)	10 (16.7)	0.25
	2	1 (50)	1 (50)	2 (3.3)	
	3	0 (0)	2 (100)	2 (3.3)	
Syncytial Knot, N%	1	0 (0)	2 (6.7)	2 (3.4)	0.03
	2	7 (23.3)	16 (53.3)	23 (39)	0.02
	3	20 (66.7)	11 (36.7)	31 (50.8)	
	4	3 (10)	1 (3.3)	4 (6.8)	
Frequency of	0	21 (70)	17 (56.7)	38 (62.7)	0.47
Calcification, N%	1	2 (6.7)	5 (16.7)	7 (11.9)	0.58
	2	7 (23.3)	7 (23.3)	14 (23.7)	
	3	0 (0)	1 (3.3)	1 (1.7)	
Infarcted Area, N%	0	24 (80)	24 (80)	48 (79.7)	0.54
	1	3 (10)	4 (13.3)	7 (11.9)	0.77
	2	3 (10)	1 (3.3)	4 (6.8)	
	3	0 (0)	1 (3.3)	1 (1.7)	
Acute Atherosis, N%	0	26 (89.7)	26 (86.7)	52 (88.1)	0.85
	1	2 (6.9)	2 (6.7)	4 (6.8)	0.99
	2	1 (3.4)	2 (6.7)	3 (5.1)	
Fibrinoid Necrosis, N%	1	12 (40)	15 (50)	27 (44.1)	0.22
	2	8 (26.7)	11 (36.7)	19 (32.2)	0.24
	3	8 (26.7)	4 (13.3)	12 (20.3)	
	4	2 (6.6)	0 (0)	2 (3.4)	
Chorangioma, N%	0	29 (96.7)	28 (93.3)	57 (94.9)	0.61
	1	1 (3.3)	1 (3.3)	2 (3.4)	0.95
	2	0 (0)	1 (3.3)	1 (1.7)	
Hyalinised villi, N%	0	0 (0)	1 (3.3)	1 (1.7)	0.65
	1	12 (40)	15 (50)	27 (45.8)	0.8
	2	16 (53.3)	12 (40)	27 (45.8)	
	3	2 (6.7)	2 (6.7)	4 (6.7)	
Stromal Pathology, N%	0	30 (50)	30 (50)	60 (100)	

No significant association was found between retroplacental haemorrhage of placenta and PIH (p>0.05). There was a significant correlation between the rate of syncytial knots and PIH (P<0.05), as its rate significantly increased with the progression of preeclampsia. But there was no significant correlation between PIH and other placental pathological indicators, including the incidence of calcification, infarction, fibrinoid necrosis, chorangioma, and hyalinised villi (p>0.05). In this study, no evidences of stromal pathology were observed in all patients. (Table 3)

The rate of newborns admitted to NICU who born to mothers with the early PIH was higher than those with late PIH (60% vs 6.70%, p: 0.001). The mean length of NICU hospitalization (day) for newborns in the early PIH group (6.03±10.83) was significantly longer than those of the late PIH group [(0.37±1.45; P<0.05); Table 4].

The postpartum mean level of serum creatinine in mothers with the early PIH, particularly mothers with preeclampsia, was significantly higher than those with late PIH (P=0.008). Also, the postpartum mean level of platelets count in mothers with the early PIH was significantly lower than those with late PIH (P=0.034). (Table 4)

The mean levels of doppler index umbilical artery, doppler index uterine artery right, and the doppler index uterine artery left were significantly higher in cases with early PIH than those with late PIH (p<0.05). Moreover, the minimum and maximum neonatal Apgar scores in babies born to mothers with late PIH were significantly greater than those born to mothers with early PIH (p <0.05). Also, the mean weight of babies born to mothers with late PIH (3034±452.1 grams) was higher than those born to mothers with early PIH (2252.93±974.67 grams; p: 0.001). The results of the first trimester pregnancy-associated plasma protein-P (PAPP-P) test were not statistically different between the two groups (P: 0.671). (Table 4)

The mortality rate among babies born to mothers with early PIH (13.30%) was higher than those born to mothers with late PIH, but not significantly so (3.30%, p:0.161). (Table 4)

Table 4. Analysis of some indicators of newborn and postpartum mothers after delivery in two study groups

Variables		Late GH	Early PIH	P Value
NICU, N %	No	28 (93.3)	12 (40)	0.001
	Yes	2 (6.7)	18 (60)	0.001
		(Mean±SD)	(Mean±SD)	
Number of NICU Hospitalization Days		0.37±1.45	6.03±10.83	0.008
Weight of the Newborn		3034±452.1	2252.93±974.67	0.001
ALT		33.37±89.58	78.10±195.04	0.25
AST		27.40±25.18	75.80±162.83	0.11
Serum creatinine		0.70±0.09	0.80±0.18	0.008
Platelets		213133.33±65526.9	179666.67±52966.05	0.034
First Trimester PAPP-P Test		0.33±0.49	0.27±0.58	0.67
Doppler index Umbilical Artery		0.07±0.27	0.29±0.47	0.027
Doppler Index Uterine Artery Right		0.24±0.56	1.63±0.43	0.001
Doppler Index Uterine Artery Left		0.23±0.47	2.42±0.51	0.001
Minimum Apgar Score of the Baby		8.23±0.82	7.30±2.12	0.03
Maximum Apgar Score of the Baby		10.33±0.66	8.43±2.21	0.041
The Condition of the Baby, N %	Dead	1 (3.3)	4 (13.3)	0.16
	Live	29 (96.7)	26 (86.7)	0.35

Neonatal Intensive Care Unit (NICU)
Pregnancy-associated plasma protein-P (PAPP-P)

DISCUSSION

The present study showed that the preeclampsia was notably more prevalent in mothers with the early PIH before 34 weeks' gestation (80% vs 20% in the late PIH group). The main purpose of this study was to evaluate the preeclampsia, placental pathology, maternal and fetal features in women with pregnancy-induced hypertension at different gestational age ranges.

Previously (2014), Nelson et al assessed the placental pathology of 1210 women with preeclampsia at various gestational ages. Their findings showed that the placental hypoplasia was considerably associated with early preeclampsia in the third trimester, and the placental vascular lesions was notably increased at gestational ages of 240/67 to 336/7 weeks (53%) compared with 340/7 (34%) to 366/7 (26%) and 37 weeks or longer, respectively (P <0.001) [16]. Our results were in consistent with Nelson et al.'s reports and indicated a significant positive correlation between the percentage of syncytial knots with high hypertension before 34 weeks' gestation and preeclampsia. Also, based on our findings, there was no significant correlation between PIH and other placental pathological indicators, including the incidence of calcification, infarction, fibrinoid necrosis, chorangioma, and hyalinised villi. In this regard, Ezeigwe et al reported that there were no statistically significant differences in placental calcifications, stromal edema, obstructive fibrosis, and nodules. The degree of placental infarction was related to fetal birth weight, and the association between fetal birth weight and placental involvement was more than 10% [17]. The anatomopathological features of early onset preeclampsia are significantly different from late onset preeclampsia, as cases with early onset preeclampsia are characterized with hypoxia, villous infarctions, and hypoplasia[18].

Previous scientific evidence reported that overweight (excess BMI) is significantly associated with an increased risk of preeclampsia and can predict the preeclampsia[19]. By contrast, our analysis showed that neither age and nor BMI can predict PIH and preeclampsia, except for weight of fetus during pregnancy. Also, our findings showed no evidence of a significant correlation between the history of underlying disease and PIH.

Recently, Awuah et al (2020) conducted a prospective case-control study in Ghana to assess the placenta growth, and perinatal outcomes of 84 hypertensive women. Their findings showed that 52%, 33.30%, 7.10%, 4.80%, and 2.40% of the hypertensive women had respectively preeclampsia, PIH, eclampsia, chronic hypertension, and preeclampsia superimposed on chronic hypertension. Also, they indicated a significant positive correlation between PIH and the incidence of placental infarction, placental calcification, and placental haematoma (p= 0.001). The mean weight of placental, placental diameter, placental volume, and placental thickness of the hypertensive women were significantly lower than those of the normotensive women (p<0.05). Moreover, the number of babies born to hypertensive women was considerably more than those born to normotensive women (p= 0.001)[20]. The present study did not evaluate the normotensive women. Nevertheless, the percentage of newborns admitted to NICU who were arisen from mothers with the early PIH was significantly more than those delivered by the late PIH mothers (60% vs 6.70%). The mean length of NICU hospitalization (day) for babies born to mothers with early PIH was significantly longer than those born to the those with late PIH.

Our findings showed no correlation between the fetal birth weight and PIH, yet the mean weight of the babies born to the mothers with a late PIH was notably higher than those delivered by mothers with early PIH. Maybe, the higher incidence rate of preeclampsia in mothers with early PIH led to a reduction in the mean weight of their newborns.

Based on the prior clinical evidences, the placental histological findings can differentiate hypertensive women from normotensive. However, placental pathology was almost similar between high hypertensive mothers and those with mild to severe preeclampsia[17, 20]. Accordingly, differentiation between the early and late PIH in clinical practice can

be useful in the early predicting of the preeclampsia as well as explaining its pathophysiology. Our study is one of the rare studies in this field and has succeeded in identifying a series of maternal risk factors of PIH and preeclampsia. Moreover, this study indicated that maternal-fetal features and pregnancy outcomes may significantly affected by PIH or preeclampsia depending on the gestational age.

In this study, the prevalence of preeclampsia was higher in mothers with early PIH. So, a series of changes in the early PIH group compared with the late PIH group are clinically predictable and logical [e.g., a more frequent use of PIH drug, a more percentage of fetal admitted into NICU, the longer length of NICU hospitalization, the lower weight of newborns, and the higher level of serum creatinine]. In this regard, the mean levels of the umbilical and uterine artery doppler indices were also remarkably higher in the early PIH group than in the late PIH group, which is consistent with the results of Adekanmi et al.'s study[21].

CONCLUSION

This comparative analysis showed that the early PIH between 20-34 weeks of gestation might be indicative of progression to preeclampsia. Placentas from women with early PIH significantly differ from those with late PIH histopathologically (i.e., syncytial node and placental location on ultrasound). Higher rates of maternal and fetal pregnancy-related complications in mothers with early PIH may be indicative of different impact of PIH and preeclampsia on pregnancy outcomes depending on the gestational age. Nonetheless, further comprehensive and large-scale researches are needed to get a detailed picture of PIH and preeclampsia.

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