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Original Article

Association between Gestational Hypertension and Preeclampsia with Spontaneous Prelabor Rupture of Membrane

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Abstract

Background: Hypertensive disorders of pregnancy constitute one of the leading causes of maternal and perinatal mortality worldwide. Prelabor (premature) rupture of membranes (PROM) occurs in 10% of all pregnancies, of which 7%–8% occur after 37–42 weeks. **Aim of the Study:** The aim of the study was to investigate the association between gestational hypertension and preeclampsia with the risk of spontaneous PROM. **Materials and Methods:** This is a case-control study; 150 pregnant women with gestational age ≥20 weeks were included in this study. Eligible women were divided into three equal groups: 50 pregnant women with preeclampsia, 50 pregnant women with gestational hypertension, and 50 normotensive pregnant women. In addition, the risk of spontaneous PROM was assessed among these groups. **Results:** This study shows that 52% was primigravida in the preeclampsia group, whereas 26% in the gestational hypertension group and 38% in the normotensive group; this was statistically significant. Regarding the gestational age, 88% were full term in the preeclampsia group, 94% in the gestational hypertension, and 94% in the normotensive; there was no significant difference among the three study groups. In the preeclampsia group, seven (14%) have PROM with no significant association, whereas in the gestational hypertension group, 19 (38%) have PROM, which was statistically significant. In the normotensive group, 18 (36%) have PROM, which is also significant. The risk of PROM between each study group was compared: there was significant difference between percentages when comparing the normotensive group with the preeclampsia group (more percentage of PROM among the normotensive) and highly significant difference when comparing the gestational hypertensive group with the preeclampsia group. **Conclusion:** In this study, we concluded that gestational hypertension is associated with the risk of PROM, and preeclampsia is not associated with the risk of PROM.

Keywords: Gestational hypertension, preeclampsia, spontaneous prelabor rupture of membrane

Introduction

Hypertensive disorders of pregnancy constitute one of the leading causes of maternal and perinatal mortality worldwide, and it is the second cause of direct maternal death worldwide. Hypertension complicates 6%–12% of all pregnancies and includes two relatively benign conditions (chronic and gestational hypertension) and the more severe conditions of preeclampsia or eclampsia. Preeclampsia complicates 3%–5% of all pregnancies.[1] Gestational hypertension is a new hypertension presenting after 20 weeks of gestation without significant proteinuria and preeclampsia is a new hypertension presenting after 20 weeks of gestation with significant proteinuria.[1] The definition of prelabor (premature) rupture of membranes (PROM) is the fetal membranes rupture at term prior to the onset of labor, but labor fails to start.[2] Preterm PROM (PPROM) defined as PROM between 24 and 37 weeks.[3] PROM occurs in 10% of all pregnancies, of which 7%–8% occur after 37 weeks. The incidence of PPROM is 2%.[3] The most significant maternal consequence of term PROM is chorioamnionitis, the risk of which increases with the duration of membrane rupture,[4] increased apoptosis or necroptosis of membrane cellular components, and greater levels of specific proteases in membranes and amniotic fluid (AF) related to PPROM.

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Gestational hypertension and preeclampsia were associated with an increased risk for PROM. Increased odds were observed for term PROM compared with PPROM.[5] Most tensile strength of the membranes provided by the amniotic extracellular matrix and interstitial amniotic collagens that produced in mesenchymal cells.[6] Thus, collagen degradation has been a focus of research. The matrix metalloproteinase (MMP) family is involved with normal tissue remodeling and particularly with collagen degradation. Tissue inhibitors of MMP in part regulate MMP activity. Several of these inhibitors found in lower concentrations in AF from women with ruptured membranes. Elevated MMP levels found at a time when protease inhibitor expression declines further support that their expression alters amniotic tensile strength.[6] With membrane rupture, thrombin activity rises, which activates MMPs and prostaglandin synthesis. Greater MMP concentrations allow collagen breakdown in the fetal membranes resulting in premature rupture.[6] The aim of the study is to investigate the association between gestational hypertension and preeclampsia with the risk of spontaneous PROM.

Materials and Methods

A case-control study was conducted in Al-Imamain Al-Kadhmain Medical City from June 1, 2020, to December 31, 2020. The scientific council of Obstetrics and Gynecology/Iraqi Board for medical specialization and agreement of Department of Obstetrics and Gynecology of Al-Imamain Al-Kadhmain Medical City approved the study protocol. One hundred fifty pregnant

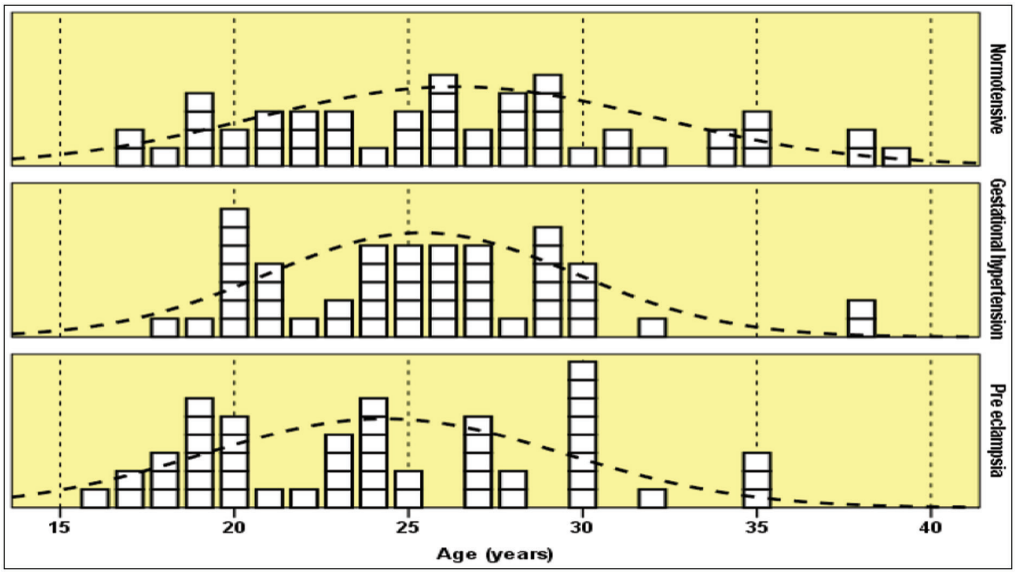

Figure 1: Distribution of patients according to age

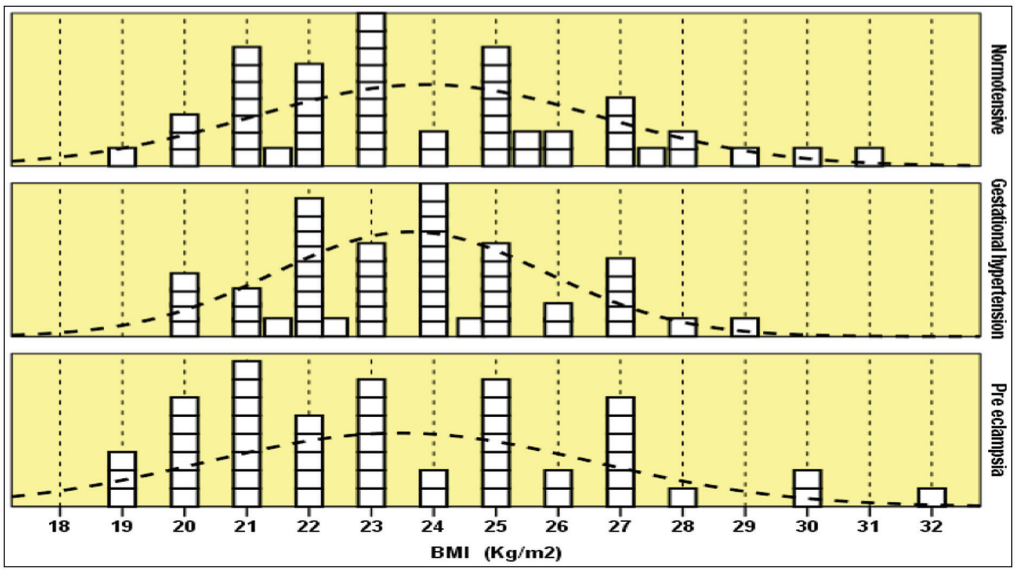

Figure 2: Distribution of patients according to BMI

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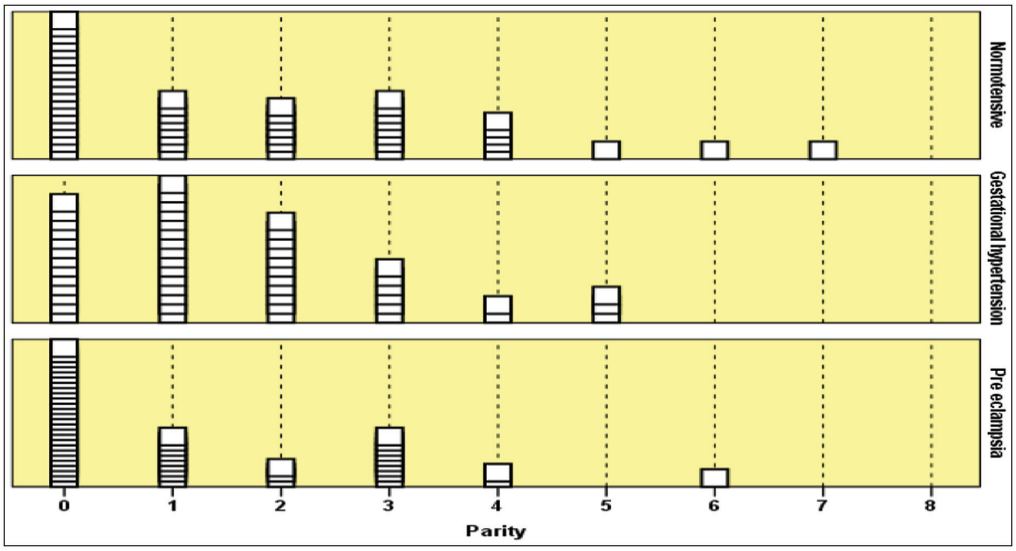

Figure 3: Distribution of patients according to parity

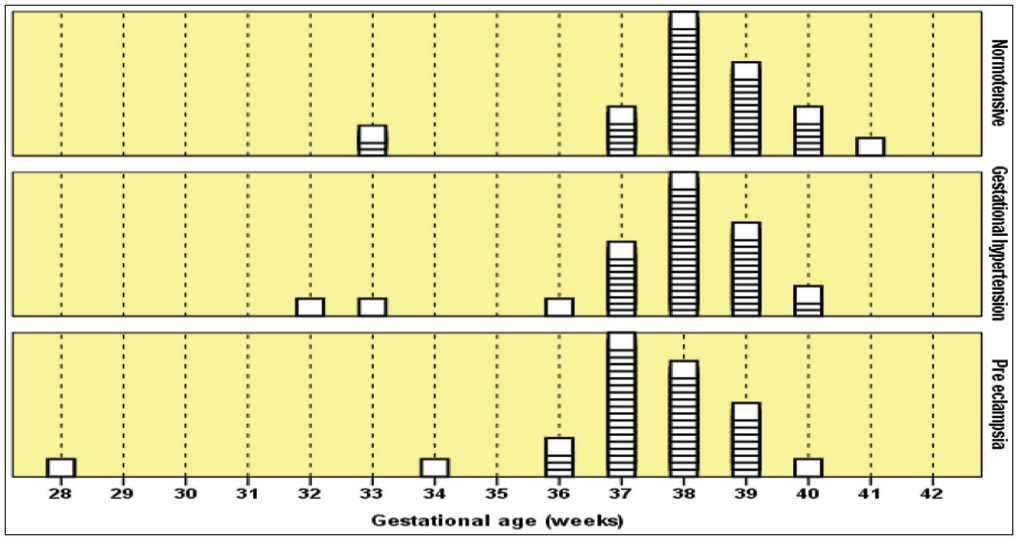

Figure 4: Distribution of patients according to gestational age (weeks)

women with gestational age ≥20 weeks were included in this study. They were informed about the nature of the study, and verbal consent was obtained from them. The data were collected by a specially designed questionnaire.

Group A: 50 pregnant women who were diagnosed with preeclampsia with gestational age ≥20 weeks.
Group B: 50 pregnant women who were diagnosed with gestational hypertension.
Group C: 50 pregnant women who were normotensive.

All women underwent a full history-taking including age, parity, miscarriage, and the gestational age of the current pregnancy obtained by calculating the last menstrual period and early documented ultrasound. A history of sudden gush of fluid or continued leakage of fluid or feeling wet, the duration of fluid leakage, and if there was a history of lower abdominal pain or vaginal bleeding, and

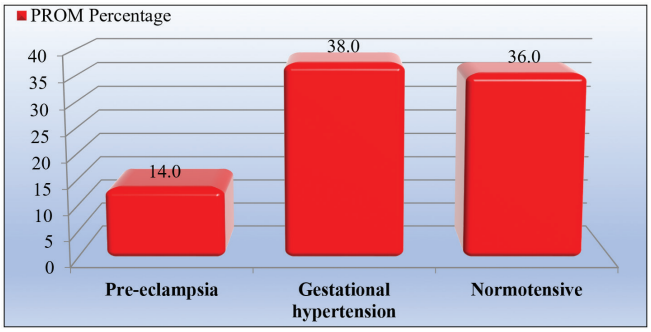

Figure 5: The association of study groups with the risk of spontaneous PROM

a history of previous premature rupture of membrane, social history, past medical history, and family history were noted. All participants have undergone thorough physical examination with blood pressure measurement

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in a sitting position with a mercury sphygmomanometer and the Korotkov sound technique using an appropriate sized cuff depending on mid-arm circumference. After rest for 5 min, blood pressure was measured in both arms; body mass index (BMI) was calculated; and abdominal examination to assess symphysio fundal height, fetal heart rate, and uterine contractions was done. Full blood count, urine for protein, renal function test, liver function test, random blood sugar, and C. reactive protein were examined.

A sterile speculum examination was also done to confirm AF pooling from the cervix. Positive results considered as confirmed PROM group. Obstetric ultrasound was done to all patients to confirm viability, AF index, gestational age, to exclude multiple pregnancy, and to determine fetal sex.

Inclusion criteria

Following are the inclusion criteria:

1. Women with a singleton pregnancy,
2. Gestational age of 24–41 weeks,
3. Age of 16–39 years,
4. BMI of 20–32,
5. Parity of 1–7.

Exclusion criteria

The patients with the following criteria were excluded:

1. Uterine over distention (multiple pregnancy and polyhydramnios),
2. Chorioamnionitis,
3. Urinary tract infection,
4. Vaginal spotting/bleeding,
5. Presence of regular uterine contractions,
6. Medical condition (e.g., diabetes mellitus, chronic hypertension, chronic kidney disease, and cardiovascular disease),
7. Uterine congenital anomalies,
8. Smokers.

Statistical analysis

The analysis of data was carried out using the available statistical package of SPSS 27 (Statistical Packages for Social Sciences, version 27). Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum–maximum values). The significance of difference of different means (quantitative data) was tested using Students *t* test for difference between two independent means or the difference among the three different means (quantitative data) using ANOVA *t* test. The significance of difference of different percentages (qualitative data) was tested using Pearson chi-square test (χ^2 test) with application of Yate's correction or Fisher exact test whenever applicable. Statistical significance was considered whenever the *P* value was equal to or less than 0.05.

Ethical consideration

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients verbal and analytical approval before sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 123 dated 04/01/2020 to get this approval.

Results

There was no statistical difference between three groups regarding mean maternal age, BMI, parity, and gestational age, as in Table 1and Figures 1-5.

Comparison of age, BMI among the three study groups

The mean maternal age of patients in the three groups was 24.3 ± 5.2 for those with preeclampsia, 25.4 ± 4.4 for those with gestational hypertension, and 26.4 ± 5.8 for normotensive group; there was no significant difference among the three study groups (*P* = 0.139). However, for those aged less than 20 years, there are more patients in the preeclampsia group (*n* = 12, 24% of total group) than in the other groups (*P* = 0.024). The mean maternal BMI was 23.5 ± 3.1 for preeclampsia group, 23.6 ± 2.2 for gestational hypertension group, and 23.9 ± 2.8 for normotensive group, with no significant difference among the three groups (*P* = 0.742).

Regarding the parity, the mean parity for the preeclampsia group was 1.1 ± 1.5, 1.6 ± 1.4 for the gestational hypertension group, and 1.7 ± 1.8 for the normotensive group. There was no significant difference among the three

Table 1: Demographic characteristics of the patients

	Preeclampsia	Gestational hypertension	Normotensive	*P* value
Age (years)	24.3 ± 5.2 (16–35)	25.4 ± 4.4 (18–34)	26.4 ± 5.8 (17–39)	0.139
BMI (kg/m^2)	23.5 ± 3.1 (19–32)	23.6 ± 2.2 (20–29)	23.9 ± 2.8 (19–31)	0.742
Parity	1.1 ± 1.5 (0–6)	1.6 ± 1.4 (0–5)	1.7 ± 1.8 (0–7)	0.175
Gestational age (weeks)	37.4 ± 1.8 (28–40)	37.9 ± 1.4 (32–40)	38.1 ± 1.6 (33–41)	0.061

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Table 2: Comparison of age and BMI among the three study groups

		Preeclampsia		Gestational hypertension		Normotensive		*P* value
		No	%	No	%	No	%	
Age (years)	<20	12	24.0	2	4.0	7	14.0	0.024*
	20–34	35	70.0	46	92.0	37	74.0	
	≥35	3	6.0	2	4.0	6	12.0	
	Mean ± SD (range)	24.3 ± 5.2 (16–35)		25.4 ± 4.4 (18–34)		26.4 ± 5.8 (17–39)		0.139
BMI (kg/m^2)	Normal (18.5–24.9)	31	62.0	35	70.0	29	58.0	
	Overweight (25–29.9)	16	32.0	15	30.0	19	38.0	
	Obese (≥30)	3	6.0	-	-	2	4.0	
	Mean ± SD (range)	23.5 ± 3.1 (19–32)		23.6 ± 2.2 (20–29)		23.9 ± 2.8 (19–31)		0.742

No = number, SD = standard deviation

*Significant difference between percentages using Pearson chi-square test (χ^2 test) at 0.05 level

Table 3: Comparison of parity and gestational age (weeks) among the three study groups

		Preeclampsia		Gestational hypertension		Normotensive		*P* value
		No	%	No	%	No	%	
Parity	Primi	26	52.0	13	26.0	19	38.0	0.028*
	Para 1 and more	24	48.0	37	74.0	31	62.0	
	Mean ± SD (range)	1.1 ± 1.5 (0–6)		1.6 ± 1.4 (0–5)		1.7 ± 1.8 (0–7)		0.175
Gestational age (weeks)	Preterm (≤37)	6	12.0	3	6.0	3	6.0	
	Full term (>37)	44	88.0	47	94.0	47	94.0	
	Mean ± SD (range)	37.4 ± 1.8 (28–40)		37.9 ± 1.4 (32–40)		38.1 ± 1.6 (33–41)		0.061

No = number, SD = standard deviation

*Significant difference between percentages using Pearson chi-square test (χ^2 test) at 0.05 level

Table 4: Comparison of the risk of spontaneous PROM among the study groups

		Preeclampsia		Gestational hypertension		Normotensive		*P* value
		No	%	No	%	No	%	
PROM	Yes	7	14.0	19#	38.0	18##	36.0	0.014*
	No	43	86.0	31	62.0	32	64.0	

No = number

*Significant difference between percentages using Pearson chi-square test (χ^2 test) at 0.05 level

#Two of them were PPROM

##Three of them were PPROM

Table 5: The risk of spontaneous PROM in each study group

		Preeclampsia		Gestational hypertension		Normotensive	
		No	%	No	%	No	%
PROM	Yes	7	14	19	38	18	36
	No	43	86	31	62	32	64
	P value	0.292		0.015*		0.017*	

No = number

*Significant difference between percentages using Pearson chi-square test (χ^2 test) at 0.05 level

Table 6: Comparison among different study groups with the risk of spontaneous PROM

	ALL PET × GHT × No	PET × No	GHT × No	PET × GHT
Term PROM	0.014*	0.011*	0.836	0.006*

No = number

*Significant difference between percentages using Pearson chi-square test (χ^2 test) at 0.05 level

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study groups ($P = 0.175$). 52% of the preeclampsia group was primigravida, compared with 26% in the gestational hypertension group, and 38% in the normotensive. This was statistically significant ($P = 0.028$).

Regarding the gestational age, 88% of the preeclampsia group was full term, 94% for the gestational hypertension group, and 94% for the normotensive group. There was no significant difference among the three study groups ($P = 0.061$).

Seven patients (14%) of the preeclampsia group have PROM, 19 patients (38%) of the gestational hypertension have PROM (two of them were preterm), and 18 patients (36%) of the normotensive patient have PROM; three of them were preterm. Significant difference were noted ($P = 0.014$) when comparing among the three study groups.

Among the preeclampsia group, seven (14%) of 50 patients have PROM with no significant association ($P = 0.292$), whereas in the gestational hypertension group, 19 (38%) of 50 patients have PROM, which was statistically significant ($P = 0.015$); in the normotensive group, 18 (36%) of 50 patients have PROM, which was also significant ($P = 0.017$).

The risk of PROM between each study group was compared: there was no significant difference (0.011) between percentages when comparing the normotensive group with the preeclampsia group (more percentage of PROM among the normotensive).

There was no significant difference ($P = 0.836$) between the gestational hypertension group and normotensive group, but there was highly significant difference ($P = 0.006$) when the gestational hypertensive group was compared with the preeclampsia group as shown in Tables 2-6.

Discussion

Hypertensive disorders of pregnancy constitute one of the leading causes of maternal and perinatal mortality worldwide.[1] PROM occurs in 10% of all pregnancies, of which 7%–8% occur after 37 weeks. The incidence of PPROM is 2%.[3] In this study, we ascertained the risk of PROM for hypertensive disorders of pregnancy (preeclampsia and gestational hypertension) in comparing with normotensive patients after excluding any potential confounders like previous history of PROM, uterine over distention. In the current study, the mean maternal age of patients was not significantly different among the three study groups. But for those aged less than 20 years, there are more patients in the preeclampsia group ($n = 7$, 24% of total group) than in the other groups. The study by Tebeu *et al.* (2011)[7] and Adeyinka *et al.* (2010)[8] concluded that hypertensive disorders of pregnancy (including preeclampsia) have higher incidence rate in younger patients, although it is known that advance maternal age (35 years or older) is associated with an increased risk of preeclampsia. 52% of preeclampsia group was primigravida, compared with 26% in the gestational hypertension group and 38% in the normotensive; this reflects the fact that nulliparous women are at an increased risk of preeclampsia.[9,10]

In the current study, indicating that gestational hypertension associated with PROM when comparing with preeclampsia. This also was observed in the study by Liu *et al.* (2019)[5]; in that study, gestational hypertension was associated with an increase in the odds of PROM of 4.21 times (95% confidence interval: 3.77–4.70) and the risk of PROM also increased in preeclampsia, which was different from our study where no significant risk is observed. This might be explained by the fact that preeclampsia patients (especially with severe features) more likely to develop complications (eclampsia, HELLP syndrome, placental abruption, and preterm birth) and need interventions, whereas more patients with gestational hypertension can be expectantly managed with continued observation.[11]

In this study, the majority of PROM patients was at term; this is due to the number of women at term far exceeded the number with the preterm. In the study by Liu *et al.* (2019),[5] hypertensive disorders of pregnancy were associated with a higher risk of term PROM than PPROM. In gestational hypertension, the rise of blood pressure is due to the constriction of blood vessels, and angiogenesis was impaired, which leads to hypoxia and hyperplasia of trophoblastic cells, which causes an increased production of placental hormone as mentioned in a study by Tranquilli *et al.* (2014).[12] At term, the expression of the relaxin gene is enhanced, which increases MMP-3 and MMP-9 activities in the fetal membrane, resulting in the degradation of collagen and the ruptures of membrane.[13]

In the current study, there was a highly significant difference when the gestational hypertensive group was compared with the preeclampsia group; this result was consistent with the study by Ananth (1997).[14] A longitudinal study in Nova Scotia concluded that preeclampsia has a strong association with medically induced preterm birth, but not with PPROM, but this finding is not consistent with the study by Liu *et al.* (2019)[5] where a higher risk of PROM in preeclampsia is compared with normotensive women.

In this study, in the gestational hypertension group, 19 (38%) of 50 patients have PROM, which was statistically significant; the risk is higher in the gestational hypertension group, which is consistent with the study by Liu *et al.* (2019),[5] in which the incidence of PROM was 17.7% with gestational hypertension compared with 5.9% in the normotensive group. The mechanism that explains the association of gestational hypertension with PROM is not well known and unclear. Hypertension keeps the

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body in a low-grade inflammatory state via the activation of oxidative stress and upregulation of cytokines, chemokines, and molecules.[15]

The risk of abruption is strongly associated with chronic hypertension, PROM, and especially abruption in a prior pregnancy and somewhat more modestly with preeclampsia. The criteria for the diagnosis of placental abruption, hypertensive disorders, and PROM may have introduced variability among the results of these studies.[16]

Conclusion

In this study, we concluded that gestational hypertension is associated with the risk of PROM, and preeclampsia is not associated with the risk of PROM.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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