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Original Article

The influence of blood pressure, the time of urinary protein rise, and early intervention measures on the outcomes of pregnant gestational hypertension patients: a retrospective analysis based on the 2019 ACOG classification

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Abstract: Objective: To explore the influence of blood pressure, the time of urinary protein rise, and early intervention on pregnancy outcomes by determining the changes in hemorheology, the coagulation related indexes, and the incidence of pregnancy complications in patients with gestational hypertension. Methods: The clinical data of 260 parturients of singleton pregnancy with hypertension (the research group) were analyzed retrospectively. According to the American Congress of Obstetricians and Gynecologists' (ACOG) 2019 classification of pregnancy hypertension, these parturients were placed in the pregnancy hypertension group (group A), the preeclampsia without severe manifestations group (group B), the preeclampsia with severe manifestations group (group C), the chronic hypertension group (group D), or the chronic hypertension with preeclampsia group (group E). In addition, 260 pregnant women in the third trimester of pregnancy without complications during the same period in The First Affiliated Hospital of Fujian Medical University were selected as the control group. Results: The research group had a higher rate of elderly patients (>35 years old) and overweight patients (≥24 kg/m^2) than the control group. Also, the incidences of postpartum thrombosis and postpartum hemorrhage and the proportion of gestational diabetes mellitus and the level of postpartum D-dimer in the research group were all higher than they were in the control group ($P<0.05$). Among the research groups, the age and body mass indexes (BMI) of group E were markedly higher than they were in the other groups, the fetal growth restriction (FGR) rates of groups C and D were markedly higher than they were in the other groups, and the stillbirth rate of group D was much higher than it was in the other groups ($P<0.05$). A multivariate logistic regression analysis showed that odds ratios (OR) of early-onset hypertension and early-onset proteinuria (earlier than 32 weeks) were 4.301 and 3.186. In addition, the use of antihypertensive drugs in late pregnancy increased the incidence of FGR (OR=4.297). Conclusion: The postpartum hyper-coagulable state of patients with gestational hypertension is increased, and they are prone to venous thrombosis. The early use of antihypertensive drugs in patients with gestational hypertension can improve neonatal outcomes.

Keywords: Hypertensive disorders complicating pregnancy, gestational diabetes, American congress of obstetricians and gynecologists, blood flow changes, pregnancy outcomes

Introduction

Hypertensive disorder in pregnancy (HDP) is one of the most important causes of maternal death, and the morbidity of HDP in China is about 9.40% to 10.40% [1]. HDP is commonly characterized by hypertension, edema, proteinuria, convulsions, coma, heart and kidney failure, and even maternal and infant death [2, 3]. At present, many theories about the pathogenesis of the disease have been proposed, including the immunity theory, the uterus and placenta ischemia theory, the pregnancy hypertension and plasma endothelin theory, the nitric oxide theory, and so on [4-7].

In 2019, the American Congress of Obstetricians and Gynecologists' (ACOG) clinical management guidelines for obstetricians and gynecologists for treating gestational hypertension were

proposed by ACOG's Practice Bulletin Committee [8]. This guideline comprehensively reviewed and summarized the available data on gestational hypertension and proposed evidence-based medicine suggestions for the associated clinical treatment. The new views and concepts proposed by this group are currently influencing the clinical diagnosis and management of gestational hypertension by obstetricians throughout the world. According to this guideline, HDP is divided into preeclampsia/eclampsia, chronic hypertension, chronic hypertension with preeclampsia, and pregnancy hypertension. Different types of HDP have different severities, so the corresponding clinical treatments and pregnancy outcomes are also different [9-12].

In recent years, with the increased use of blood diagnosis, some scholars have pointed out that the coagulation system and hemorheology play important roles in the development of gestational hypertension [13], and the benefits of early antihypertensive intervention are very significant [14]. Therefore, in this study, the patients in our study cohort were placed into different groups according to the 2019 ACOG classification of pregnancy hypertension. The relationship between the information of the different types of HDP patients, including their general clinical data, hemorheological changes, gestational weeks of onset, gestational weeks of intervention, gestational weeks of termination, and the severity of and their corresponding fetal prognosis and long-term blood pressure, etc. were analyzed retrospectively, aiming to provide a basis and clinic guidance for the prevention of HDP and a reduction in the incidence of adverse fetal events.

Materials and methods

We conducted a retrospective analysis of the clinical data of the 260 HDP parturients (the research group) who were hospitalized in the obstetrics department of the First Affiliated Hospital of Fujian Medical University and who terminated their pregnancies from January 2016 to December 31, 2018. Inclusion criteria: The patients met the diagnostic criteria for pregnancy hypertension [8], patients with singleton pregnancies, and patients who signed the informed consent. Exclusion criteria: Fetuses with severe birth defects or chromosomal abnormalities, multiple pregnancy, accompanied by other pregnancy complications, incomplete clinical data. In addition, 260 pregnant women in the third trimester of pregnancy without complications were selected as the control group. This study was approved by the Ethics Committee of The First Affiliated Hospital of Fujian Medical University.

According to ACOG's 2019 classification for pregnancy hypertension and preeclampsia, the parturients in the research group were placed into the pregnancy hypertension group (group A), the preeclampsia without severe manifestation group (group B), the preeclampsia with severe manifestation group (group C), the chronic hypertension group (group D) or the chronic hypertension with preeclampsia group (group E) [8].

Outcome measures

1. Analyze the general data of the control and research groups, including maternal age, height, early pregnancy weight, childbirth gestational weeks, delivery mode, incidence of pregnancy combined with disease, newborn birth weight, etc. 2. The hemorheology indexes of the control and research groups were analyzed, including hemoglobin, platelet count, prothrombin time (PT), activated partial thromboplastin time (APTT), thrombin time (TT), fibrinogen (Fib), and postpartum D-dimer. 3. The pregnancy outcome indexes of the control and research groups were analyzed, including gestational diabetes mellitus, postpartum hemorrhage, postpartum venous thrombosis, fetal growth restriction (FGR), and cesarean sections. 4. Analyze the gestational age of the blood pressure rise, the gestational age of the protein positive transfer, the gestational age of the delivery and the outcomes of the adverse pregnancies (newborn) in the control group and research group. 5. A multivariate logistic regression analysis was used to analyze the FGR risk factors in the research group.

Statistical analysis

The data was analyzed using SPSS 25.0 software. The measurement data were expressed as the mean ± standard deviation ($\bar{x}$ ± sd), and the comparisons between groups were conducted using ANOVA combined with a post analysis using LSD. The enumeration data were

Table 1. Comparison of the general data of the pregnant women in the research and control groups (n, %)

Item	Control group	Research group					P
		Group A	Group B	Group C	Group D	Group E	
Cases	260	49	82	77	17	35	
Age (years)							<0.001
>35	37 (14.23)	13 (26.53)	14 (17.17)	24 (31.17)	4 (23.53)	20 (57.14)	
<35	223 (85.77)	36 (73.47)	68 (82.93)	53 (68.83)	13 (76.47)	15 (42.86)	
BMI (kg/m^2) in early pregnancy							<0.001
>24	37 (14.23)	15 (30.61)	24 (29.27)	15 (19.48)	8 (47.06)	18 (51.43)	
<24	223 (85.77)	34 (69.39)	58 (82.52)	62 (80.25)	9 (52.94)	17 (48.57)	
Birth history							0.260
Primipara	163 (62.69)	29 (59.18)	57 (69.51)	56 (72.73)	9 (52.94)	20 (57.14)	
Multipara	97 (37.31)	20 (40.82)	25 (30.49)	21 (27.27)	8 (47.06)	15 (42.86)	
History of abortion							0.073
Yes	98 (37.69)	18 (36.73)	36 (43.90)	43 (55.84)	9 (52.94)	17 (48.57)	
No	162 (62.31)	31 (63.27)	46 (56.10)	34 (44.16)	8 (47.06)	18 (51.43)	
Degree of education							0.122
University and above	115 (44.23)	24 (48.98)	28 (34.15)	45 (58.44)	7 (41.18)	17 (48.57)	
Under university	145 (55.77)	25 (51.02)	54 (65.85)	32 (41.56)	10 (58.82)	18 (51.43)	
Unhealthy lifestyle*							0.478
Yes	5 (1.92)	2 (4.08)	4 (4.88)	1 (1.30)	1 (5.88)	2 (5.71)	
No	255 (98.08)	47 (95.92)	78 (95.12)	76 (98.70)	16 (94.12)	33 (94.29)	
Naturally conceived							0.398
Yes	6 (2.31)	0 (0.0)	4 (4.88)	3 (3.90)	0 (0.0)	0 (0.0)	
No	254 (97.7)	49 (100)	78 (95.12)	74 (96.10)	17 (100.0)	35 (100.0)	

Note: *: refers to smoking, drinking, staying up late, and unhealthy eating habits. BMI: body mass index.

expressed as n (%) and analyzed using χ^2 tests. A logistic multivariate regression analysis was used to examine the relationship between BMI and age before pregnancy and pregnancy associated diseases and outcomes, all with two-sided tests. P<0.05 indicates that a difference is statistically significant.

Results

General data analysis

According to the 2019 ACOG classification of gestational hypertension, among the 260 cases of gestational hypertension, there were 49 cases of gestational hypertension, 82 cases of preeclampsia without severe manifestations, 77 cases of preeclampsia with severe manifestations, 17 cases of pregnancy with chronic hypertension, and 35 cases of pregnancy with chronic hypertension with preeclampsia.

No significant differences in terms of birth history, abortion history, education levels, bad living habits, or natural conception was found between the control group and the other groups (P>0.05). In addition, the proportions of elderly patients (>35 years old) and overweight patients (≥24 kg/m^2) in the pregnancy hypertension group were both much higher than they were in the control group (P<0.05) (as shown in **Table 1**).

Comparison of the hemorheology between the research and control groups

No significant differences in the hemoglobin, APTT, TT, or Fib levels existed among the groups. The platelet count of group C was significantly lower than the counts in the control group, group B, and group D. In addition, significant differences existed in PT and postpartum D-dimer among the groups (all P<0.05) (as shown in **Figure 1**).

Comparison of the maternal and infant outcomes in the research and control groups

The proportion of gestational diabetes mellitus, the postpartum hemorrhage rate, the fetal growth restriction (FGR) rate, and the uterine

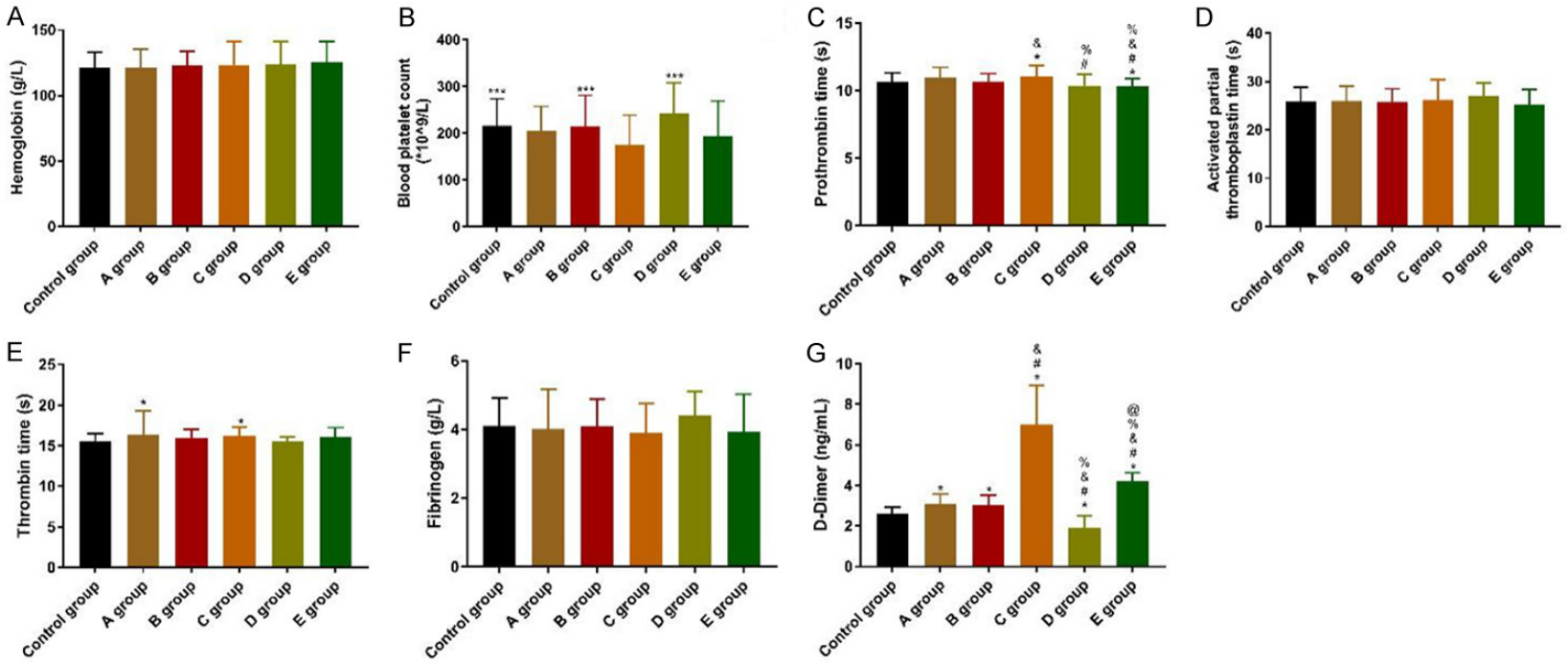

Figure 1. Comparison of the hemorheology between the research and control groups. A: Hemoglobin; B: Platelet count, compared with group C, ***P<0.001; C: Prothrombin time; D: Activated partial thromboplastin time; E: Thrombin time; F: Fibrinogen; G: Postpartum D-D dimer. C-G, compared with the control group, *P<0.05; compared with group A, #P<0.05; compared with group B, &P<0.05; compared with group C, %P<0.05; compared with group D, @P<0.05.

Table 2. Comparison of the maternal and infant outcomes between the research and control groups

Item	Control group	Research group					P
		Group A	Group B	Group C	Group D	Group E	
Cases	260	49	82	77	17	35	
Gestational diabetes mellitus	25 (9.62)	14 (28.57)	22 (26.83)	13 (16.88)	5 (28.41)	7 (15.56)	<0.001
Postpartum hemorrhage	5 (1.92)	5 (10.20)	5 (6.10)	2 (2.60)	0	3 (6.67)	<0.001
Postpartum venous thrombosis	1 (0.38)	0	2 (2.44)	2 (2.60)	1 (5.88)	3 (6.67)	<0.001
Fetal growth restriction	4 (1.54)	3 (6.12)	5 (6.10)	24 (31.17)	1 (5.88)	9 (20.00)	<0.001
Cesarean section	125 (48.08)	35 (71.43)	63 (76.83)	73 (94.81)	14 (82.35)	28 (62.22)	<0.001

Table 3. Comparison of the gestational week of blood pressure rise, protein positive transfer, delivery, and the outcomes of the adverse pregnancies (newborn) in the research group

Item	Research group					P
	Group A	Group B	Group C	Group D	Group E	
Cases	49	82	77	17	45	
Age (year)	32.27±4.80	30.46±4.69	31.77±5.19	32.41±4.66	34.71±5.15	<0.001
BMI in early pregnancy	23.09±3.00	22.46±4.19	22.28±3.10	24.42±2.53	25.61±3.93	<0.001
History of hypertension in pregnancy						
Yes				5 (29.41)	11 (31.43)	0.883
No				12 (70.59)	24 (69.57)	
Gestational week of delivery (week)	38.59±1.69	38.21±2.07*	34.51±3.66*,#	35.17±5.84*,#	33.30±4.98*,#	<0.001
Gestational week of blood pressure rise						<0.05
Before 32 weeks	10 (20.41)	14 (17.07)	34 (44.16)	6 (35.29)	31 (88.57)	
After 32 weeks	39 (79.59)	68 (82.93)	43 (55.84)	11 (64.71)	4 (11.43)	
Urinary protein positive at 32 weeks of gestation						<0.001
Yes		4 (4.88)	26 (33.77)		18 (51.43)	
No		78 (95.12)	51 (66.23)		17 (48.57)	
Time to start antihypertensive						<0.001
No intervention	49 (100)	70 (85.37)	45 (58.44)	10 (58.82)	13 (37.14)	
<14 weeks	0	0 (0)	2 (2.60)	2 (11.76)	9 (25.71)	
>14 weeks	0	0 (0)	6 (7.79)	2 (11.76)	7 (20.00)	
>28 weeks	0	12 (14.63)	24 (31.17)	3 (17.65)	6 (17.14)	
Stillbirth	1 (2.04)	0 (0)	8 (10.39)	2 (11.76)	7 (20.00)	<0.001
FGR	3 (6.12)	5 (6.1)	24 (31.17)	1 (5.88)	9 (25.71)	<0.001
Developed into hypertension after one year follow-up	3 (6.12)	12 (14.63)	16 (20.78)			0.079

Note: BMI: body mass index; FGR: fetal growth restriction. Compared with group A, *P<0.05; compared with group B, #P<0.05.

rate in the gestational hypertension group were much higher than they were in the control group, with significant differences (P<0.05). Among the research groups, groups C and E had higher FGR rates than the other groups (as shown in **Table 2**).

Comparison of the gestational week of blood pressure rise, the gestational age of protein positive transfer, the gestational age of delivery, and the outcomes of the adverse pregnancies (newborns) in the research group

In the research group, the age and body mass index of group E were much higher than they were in groups B and C (P<0.05). No significant difference in the proportion of pregnant women with hypertension was found between groups D and E (P=0.350). Group E had the lowest pregnancy week of delivery among the groups, but it had the highest positive rate of urine protein and the highest intervention rate without antihypertensive drugs among these groups (P< 0.05). Group E had the highest stillbirth rate. The FGR rates (including low birthweight) were similar in groups C and E and were higher in these two groups than in the other groups. The follow-up results showed no significant differences in the incidences of hypertension among groups A, B, and C (as shown in **Table 3**).

Table 4. Multiple factor analysis of the FGR incidences in the pregnancy hypertension group

	OR (95% CL)	P
Time of blood pressure rise		
32 weeks or more	1.0	
Earlier than 32 weeks	4.301 (1.91-9.68)	0.001
Time of urinary protein rise		
32 weeks or more	1.0	
Earlier than 32 weeks	3.186 (1.01-10.68)	0.05
Time to start antihypertensive		
Early pregnancy	1.0	
Middle pregnancy	1.819 (0.38-8.69)	0.453
Late pregnancy or before delivery	4.297 (1.70-10.86)	0.002
Age	1.030 (0.95-1.12)	0.461
BMI in early pregnancy	0.940 (0.84-1.06)	0.293

Note: OR: odds ratio; BMI: body mass index; FGR: fetal growth restriction.

Multiple factor analysis of the FGR incidences in the research group

A multivariate logistic regression analysis showed that the ORs of positive early-onset hypertension and early-onset urinary protein were 4.301 and 3.186, respectively. The ORs of using antihypertensive drugs only in late pregnancy increased the FGR rate in patients with gestational hypertension to 4.297. In addition, age and body mass index had no promoting effect on the incidence of FGR in neonates (as shown in **Table 4**).

Discussion

TT (thrombin time) refers to the time of blood coagulation after adding standardized thrombin into plasma. Thrombin formation is the final stage of coagulation is, through which fibrinogen changes into fibrin. The process of coagulation is commonly indicated by TT [15]. TT shortening is always accompanied by a hypercoagulable state and thrombotic diseases [16]. Some researchers have pointed out that the TT and PT times during pregnancy in patients with gestational hypertension are shorter than they were in the normal group, so we speculated that there might be a hypercoagulable state [17], which is inconsistent with our present study. In our study, patients with gestational hypertension had much longer TT than patients in the control group, but there was no significant difference in the clotting time. By analyzing the causes of the differences, we believe that TT prolongation can be seen in the condition of heparin increasing or the presence of heparinoid anticoagulants, such as systemic lupus erythematosus, liver disease, kidney disease, low (no) fibrinogenemia, abnormal fibrinogenemia, FDP increase, etc. [18]. In this study, many patients with gestational hypertension, especially those with preeclampsia and concurrent preeclampsia, often used of aspirin and heparin sodium continuously from early pregnancy to pre delivery, which could affect the TT results. In addition, patients with chronic hypertension and preeclampsia or severe preeclampsia also often have impaired liver function and decreased coagulation factors, which also affect the TT results.

Patients with gestational hypertension usually suffer from obstetric complications such as gestational diabetes [19]. In this study, we also found that the incidence of gestational diabetes mellitus, postpartum hemorrhage and lower extremity venous thrombosis are largely increased in patients with gestational hypertension. Postpartum hemorrhage may be related to a hypoproteinemia-induced reduction of the edema and the contraction ability of uterine myometrium [20], or it may be related to the use of antispasmodic magnesium sulfate in the treatment of gestational hypertension [21]. The high coagulation state of blood in the perioperative period and the perinatal period, or the high coagulation mechanism induced by the increase of the bleeding rate, are both reasons for the high incidence of postpartum venous thrombosis, so the anticoagulation treatment in the perinatal period is particularly important in patients with gestational hypertension [22].

In recent years, urine protein was internationally regarded as an unnecessary factor for the diagnosis of preeclampsia [23], especially if the diagnostic basis grade of the urine protein was elevated from + to ++ according to the 2019 ACOG classification [8], so some doctors in the clinic will relax the supervision of urine protein. However, in our study, positive early-onset urinary protein (before 32 weeks of gestation) was found to be associated with intrauterine growth

retardation/full-term low-weight infants. Therefore, the early detection of positive urinary protein and the corresponding effective intervention reduce the incidence of adverse neonatal outcomes.

In addition, we also found that early-onset hypertension (at less than 32 weeks) also increased the incidence of fetal growth retardation/full term low birth weight. What is more, the incidence of low birth weight or fetal growth retardation is increased in patients who only use antihypertensive drugs in late pregnancy, especially in the perinatal period. The First Affiliated Hospital of Fujian Medical University is a provincial-level comprehensive hospital, so we often receive patients with pregnancy hypertension who are transferred from some regional hospitals. These patients often have no standard management of their pregnancy blood pressure because of subjective or objective factors, and some pregnant patients even do not take antihypertensive drugs or do not insist on taking antihypertensive drugs subjectively or objectively. Hu et al. found that it was very important to strengthen the pre-pregnancy management for pregnant women with chronic hypertension, and to standardize the management of blood pressure for pregnant women with pregnancy hypertension, so as to reduce the incidence of serious complications [24]. Zhang et al. found that early intervention can reduce obstetric complications caused by gestational hypertension, can help to improve pregnancy outcomes and can reduce the morbidity of perinatal mother and child, so it is worthy of clinical promotion [25]. These above previous results are all consistent with our present study, further verifying the importance of reasonable blood pressure reduction during pregnancy.

Pregnancy hypertension is a common obstetric disease, and it often involves multiple organ damage and endangers the life of the mother and baby. Paying attention to the early measurement and management of blood pressure and urinary protein during pregnancy will largely reduce the occurrence of adverse maternal and infant outcomes. However, our present paper is a single center retrospective study, so multi-center studies and large-sample prospective studies are needed to further verify the conclusions of this paper.

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Disclosure of conflict of interest

None.

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