Original Research

Monitoring of Pregnancy-Induced Hypertension Syndrome Combined with Ultrasound Monitoring in Early Pregnancy to Prevent Chronic Hypertension with Preeclampsia

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Abstract

Background: This study explored the guiding value of monitoring pregnancy-induced hypertension syndrome (MP) for blood hypercoagulability in combination with ultrasound monitoring of uterine artery blood flow in early pregnancy and fetal growth and development in the second and third trimesters, with the goal of preventing chronic hypertension with preeclampsia (PE) and its clinical effects. **Methods**: The medical records of 189 pregnant patients with chronic hypertension between June 2016 and June 2021 were retrospectively analyzed; among them, 98 constituted the intervention group. The intervention group received MP screening for blood hypercoagulability in combination with ultrasound monitoring of uterine artery blood flow in early pregnancy and fetal growth and development in the second and third trimesters of pregnancy. Those with abnormalities were given timely symptomatic (low-molecular-weight heparin with or without aspirin) and supportive treatment. The remaining 91 patients who did not receive timely monitoring and intervention constituted the control group. Fetal outcomes and PE rates were compared between groups. **Results**: The PE incidence in the intervention group was significantly lower than that in the control group ($p < 0.01$), and the premature delivery of low-birth-weight neonates, fetal loss and neonatal asphyxia incidences were also significantly lower in the intervention group than the control group ($p < 0.05$). **Conclusions**: MP screening for blood hypercoagulability combined with ultrasound monitoring of uterine artery blood flow can effectively prevent PE occurrence in pregnant patients with chronic hypertension and significantly improve fetal outcomes. Additionally, MP screening is noninvasive and easy to use at a low cost.

Keywords: ultrasound; uterine artery blood flow; chronic hypertension; low-molecular-weight heparin; preeclampsia

1. Introduction

The incidence of pregnancy complicated by chronic hypertension is 1%–5% worldwide [1]. As maternal age at delivery continues to rise, the incidence of pregnancy complicated by chronic hypertension will continue to increase [2,3]. In particular, the incidence of perinatal complications in pregnant women with chronic hypertension complicated by preeclampsia (PE) is high [2,4–7]. The harmful effects of chronic hypertension during pregnancy to both the mother and child have long been concerns of obstetric specialists. The adverse complications of chronic hypertension during pregnancy are attributable to uncontrolled severe hypertension with or without terminal organ damage or secondary PE and placental abruption, which are the main causes of adverse maternal and fetal outcomes [8]. Even if PE does not occur, the incidence of small-for-gestational-age (SGA) neonates among pregnant women with chronic

hypertension is much higher than that among healthy pregnant women, and this condition is associated with abnormal placental etiology [9].

To date, numerous multicenter, prospective, randomized, case–control studies have been conducted to prevent PE based on multiple parameters, such as clinical manifestations, mean arterial pressure (MAP), uterine artery pulsatility index (UtA-PI), pregnancy-associated plasma protein A (PAPP-A) and serum placental growth factor (PLGF) [10–16]. Despite their satisfactory outcomes, these studies were performed rather late in gestation (11–13 weeks +6d), and various indices were used; therefore, the methods of these studies are difficult to generalize more broadly, particularly in economically underdeveloped countries and remote areas. In addition, because scholars and researchers have not reached a consensus on the etiology and pathogenesis of PE, no breakthroughs have been achieved in the

treatment of PE, and pregnancy termination remains the most effective treatment for PE patients.

From an epidemiological perspective, chronic hypertension is a high-risk factor for PE. Based on this consensus, in 2016, our institute implemented a screening approach involving the monitoring of pregnancy-induced hypertension syndrome (MP) for blood hypercoagulability combined with ultrasound monitoring of uterine artery blood flow in early pregnancy and of fetal growth and development in the second and third trimesters of pregnancy. The purpose of this combined monitoring was to identify PE in pregnant women with chronic hypertension as early as possible to provide timely intervention, thereby bringing the rates of good fetal outcomes among these patients to or close to the rates among healthy pregnant women, in addition to dropping the incidence of PE down to a minimum. Here, we retrospectively compared the pregnancy outcomes of women with chronic hypertension who received this intervention to those of women who did not receive this intervention. The results of this study might provide a basis for improving the prognosis of pregnant women with chronic hypertension and that of their infants.

2. Materials and Methods

2.1 General Data

In this retrospective study, 98 pregnant women with chronic hypertension who received treatment at the Department of Gynaecology and Obstetrics of the Second Xiangya Hospital beginning in the early stages of pregnancy between June 2016 and June 2021 were consecutively included. At the first prenatal examination, these women received routine MP screening for blood hypercoagulability combined with ultrasound monitoring of uterine artery blood flow. During the middle and late stages of pregnancy, fetal development was monitored. Patients who presented with blood hypercoagulability due to MP or abnormal uterine artery blood flow were subjected to positive case management and received early intervention. Those without abnormalities were excluded from consideration. The patients received reviews every 1–2 weeks until the fetus was born.

In addition, 91 pregnant women with chronic hypertension were randomly recruited from three municipal hospitals during the same period. These women received standard prenatal examination but did not receive MP screening. These patients constituted the control group. The general data of the two groups, such as their maternal age, number of pregnancies, body mass index (BMI), systolic blood pressure (SBP) and diastolic blood pressure (DBP) in early pregnancy, were collected, and their PE incidences and fetal outcomes were compared with those of the intervention group.

The procedures of this study were approved by the Ethics Committee of the Second Xiangya Hospital (2020-573). Written informed consent was obtained from each participant.

2.2 Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) blood pressure $\geq$130/80 mmHg; (2) a date of the last menstrual period of $\leq$12 weeks at the time of the first examination; (3) an awareness of the purpose of this study with consent to participate; (4) satisfying the requirement for matching between the sizes of the gestational sac and uterus and the gestational week according to color ultrasound; and (5) singleton pregnancies. The diagnostic criteria for chronic hypertension complicated by PE and fetal growth restriction (FGR) were in accordance with those described in Obstetrics and Gynecology (9th version) [6].

Patients who met any of the following criteria were excluded from consideration: (1) a history of a drug allergy; (2) serious dysfunction of the heart, liver, kidneys or other organs; (3) poor treatment compliance; or (4) contraindications for aspirin and low-molecular-weight heparin.

2.3 Observed Indices

The observed indices included data obtained from records of clinical parameters including blood pressure, urinary protein, term birth, premature birth, neonatal asphyxia, birth weight of the newborn, fetal or newborn loss and transfer due to newborn complications.

2.4 Methods

2.4.1 The Control Group

Patients in this group received routine pregnancy examinations but did not receive routine screening for blood hypercoagulability.

2.4.2 The Intervention Group

In addition to routine pregnancy examinations, patients in this group also received the following examinations.

(1) MP screening. An MP monitoring system was utilized to noninvasively monitor peripheral resistance (PR), vascular elasticity and blood viscosity (V), and these indices can indirectly reflect the blood hypercoagulable state. The procedures were as follows [17]. The patient laid on their left side at 45°. The probe of the monitoring system was placed at the site where the pulse of the radial artery was the strongest. When the screen displayed a pulse wave in a stable wave pattern, hemodynamic indices, such as SBP, DBP, MAP, heart rate (HR), cardiac index (CI), peripheral resistance (PR), blood viscosity (BV), mean residence time (TM) and waveform coefficient (K), were calculated by the MP monitor. Patients with SBP $\geq$130 mmHg, DBP $\geq$80 mmHg, V $\geq$4.5, vascular compliance $\leq$1.2, half-update time $\geq$23 sec, TM $\geq$33 sec, a K value $\geq$0.4 and PR $\geq$1.2 were considered to be positive and were subjected to blood hypercoagulability management.

(2) Color Doppler ultrasonography. Uterine artery blood flow during early pregnancy and fetal growth parameters during middle and late pregnancy, including fetal size,

umbilical artery blood flow and amniotic fluid conditions, were monitored using ultrasound. A GE Voluson E10 color Doppler ultrasound diagnostic instrument (General Electric Medical System Co., Ltd., Brunn am Gebirge, Austria) was used. The frequency of the convex array probe was 2.5–5.0 MHz, and that of the abdominal probe was 3.5 MHz.

The procedures of uterine artery blood flow monitoring were as follows. Bilateral uterine artery blood flow was monitored during early pregnancy (before the end of the 12th week of gestation). The patient was in the supine position with normal breathing. The gains and scanning speed of the instrument were adjusted. The ultrasonic probe was placed above the groin. Because the simultaneous display of the uterine artery and external iliac artery is required for color Doppler flow imaging, the site within 1 cm of where the uterine artery crosses the external iliac artery was chosen as the sampling site to obtain the spectrum of uterine artery blood flow. Bilateral uterine artery information was needed for each patient. The sampling volume was adjusted, and the sampling line was maintained as parallel to the blood flow direction as possible (or the included angle $<30°$) to obtain more than five blood flow spectra with a clear contour. The measurement parameters included the ratio of peak systolic velocity (S) to end diastolic velocity (D) (S/D), pulsatility index (PI) and resistance index (RI); early diastolic notches were also recorded [18]. Then, comprehensive scores were assigned according to the following uterine arterial resistance scoring (UARS) method: (1) bilateral PI >the predicted threshold (2 points), lateral PI >the predicted threshold (1 point), and bilateral PI <the predicted threshold (0 points); (2) bilateral RI >the predicted threshold (2 points); lateral RI >the predicted threshold (1 point), and bilateral RI <the predicted threshold (0 points); (3) bilateral S/D >the predicted threshold (2 points); lateral S/D >the predicted threshold (1 point); and bilateral S/D ≤the predicted threshold (0 points); (4) bilateral early diastolic notches (2 points); lateral early diastolic notches (1 point); and no early diastolic notch on either side (0 points); and (5) summing of the scores based on the four indices to obtain a total score, ranging from 0 to 8 points, with uterine arterial resistance being positively correlated with the total score [19,20]. Those patients whose total scores were >0 were subjected to positive case management. From the 20th week of gestation, fetal growth indices, such as the fetal biparietal diameter, head circumference, abdominal circumference and femoral diameter, were measured every two weeks, and fetal growth was assessed. In the meantime, fetal umbilical cord blood flow and amniotic fluid were monitored. All these measurements were performed by staff with more than 5 years of obstetric ultrasound experience.

Treatment for the intervention group is described below.

(1) Treatment method. For patients with a positive MP outcome, aspirin or low-molecular-weight heparin was administered; for those with a noticeable MP outcome, combined medication was provided [21,22]. Treatment flow charts for this group are shown in Figs. 1,2.

For patients at <12 gestational weeks, the detailed drug regimen was as follows: for a comprehensive MP score ≤60%, the patient received low-molecular-weight heparin at 5000 U (subcutaneous injection, qd); for a comprehensive MP score between 60% and 80%, the patient underwent alternating use of low-molecular-weight heparin at 5000 U (subcutaneous injection, qd) and low-molecular-weight heparin at 5000 U (subcutaneous injection, bid); and for a comprehensive MP score ≥80%, the patient received low-molecular-weight heparin at 5000 U (subcutaneous injection, bid). For patients with a noticeable hypercoagulable state, a review was performed after one week, and according to the review results, the drug dose was adjusted appropriately. For patients with uterine arterial notches and MP abnormalities, low-molecular-weight heparin at 5000 U (subcutaneous injection, bid) was given. After one week, re-examination was performed. If the treatment effect was not satisfactory, extraoral aspirin at 50 mg was given. After one week, re-examination was performed. If the treatment effect remained unsatisfactory, the dose of oral aspirin was increased (up to 100 mg). The side effects of the drugs and bleeding throughout the body were closely monitored during treatment. If bleeding was observed, drugs were reduced or terminated immediately.

For patients at >12 gestational weeks, the detailed drug regimen was as follows: for a comprehensive MP score ≤60%, the patient received aspirin at 50 mg (po, qn); for a comprehensive MP score between 60% and 70%, the patient received aspirin at 75 mg (po, qn); for a comprehensive MP score between 70% and 80%, the patient received aspirin at 100 mg (po, qn); and for a comprehensive MP score ≥80%, the patient received aspirin at 100 mg (po, qn) and low-molecular-weight heparin at 5000 U (iv, qd). For patients in a noticeable hypercoagulable state, re-examination was performed after one week, and the drug dose was adjusted according to the examination results. For patients with uterine arterial notches and MP abnormalities, low-molecular-weight heparin at 5000 U (subcutaneous injection, bid) was given. After one week, re-examination was performed. If the treatment effect was not satisfactory, extraoral aspirin at 50 mg was given. After one week, re-examination was performed. If the treatment effect was still not satisfactory, the dose of oral aspirin was increased (up to 100 mg). The side effects of the drugs and bleeding at any part of the body were closely monitored during medication. Once bleeding was observed, drugs were reduced or terminated immediately. For patients who did not present with adverse effects, the drugs were used until the 36th gestational week. The influence of aspirin on the hemostatic function of platelets can last 7–10 d. Therefore, to prevent postpartum hemorrhage, the use of aspirin was terminated once the patient presented with perinatal signs or hemor-
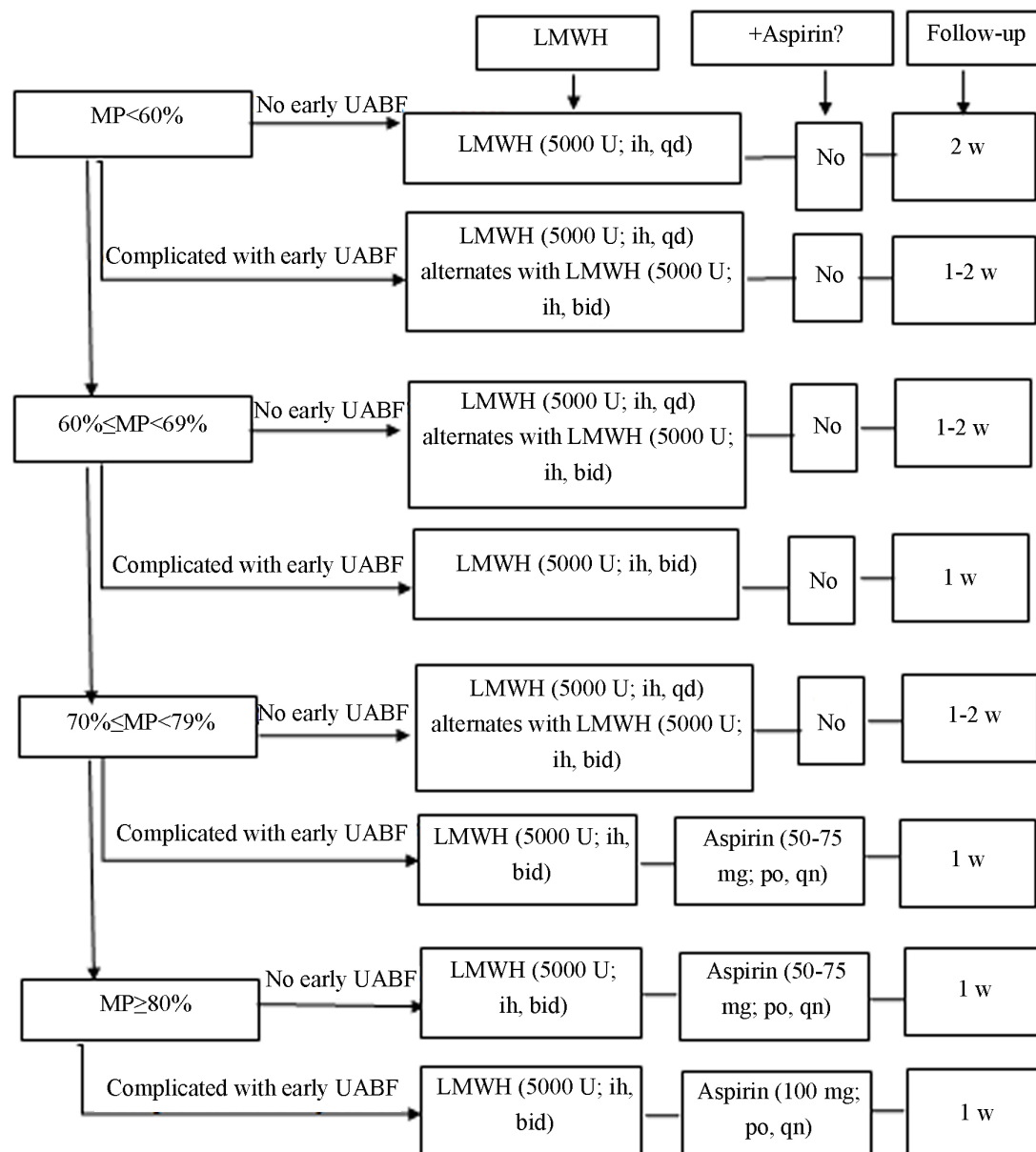
Fig. 1. Intervention flow chart for the intervention group (≤12 gestational weeks). MP and uterine artery blood flow (UABF) notch monitoring were performed. The intervention mainly involved low-molecular-weight heparin (LMWH), assisted with aspirin.

rhage from other systems. If the patient required continuous anticoagulation treatment, low-molecular-weight heparin was used.

At gestational week ≥36 weeks, aspirin was replaced with low-molecular-weight heparin, and the usage was the same as that mentioned above. At 24 h before pregnancy termination, medication was stopped.

(2) Antihypertensive treatment. The use and withdrawal of antihypertensive drugs were based on several recommendations. According to the recommendations proposed by the International Society for the Study of Hypertension in Pregnancy (ISSHP) in 2018, the target blood pressure for the treatment of pregnancy complicated by chronic hypertension is (110–140)/(80–85) mmHg, and the

indication for drug withdrawal is blood pressure ≤110/80 mmHg [23]. According to the recommendations proposed by the National Institute for Health and Care Excellence (NICE), the suggested target blood pressure for the treatment of pregnancy complicated by chronic hypertension is 135/85 mmHg, and the indication for drug withdrawal is blood pressure ≤110/70 mmHg or the presence of clinical hypotensive symptoms [23]. According to the Guidelines for the Prevention and Treatment of Hypertension in China (2018), the recommended treatment target is <150/100 mmHg (blood pressure should not be reduced to a level <130/80 mmHg in case placental perfusion is affected) [24].
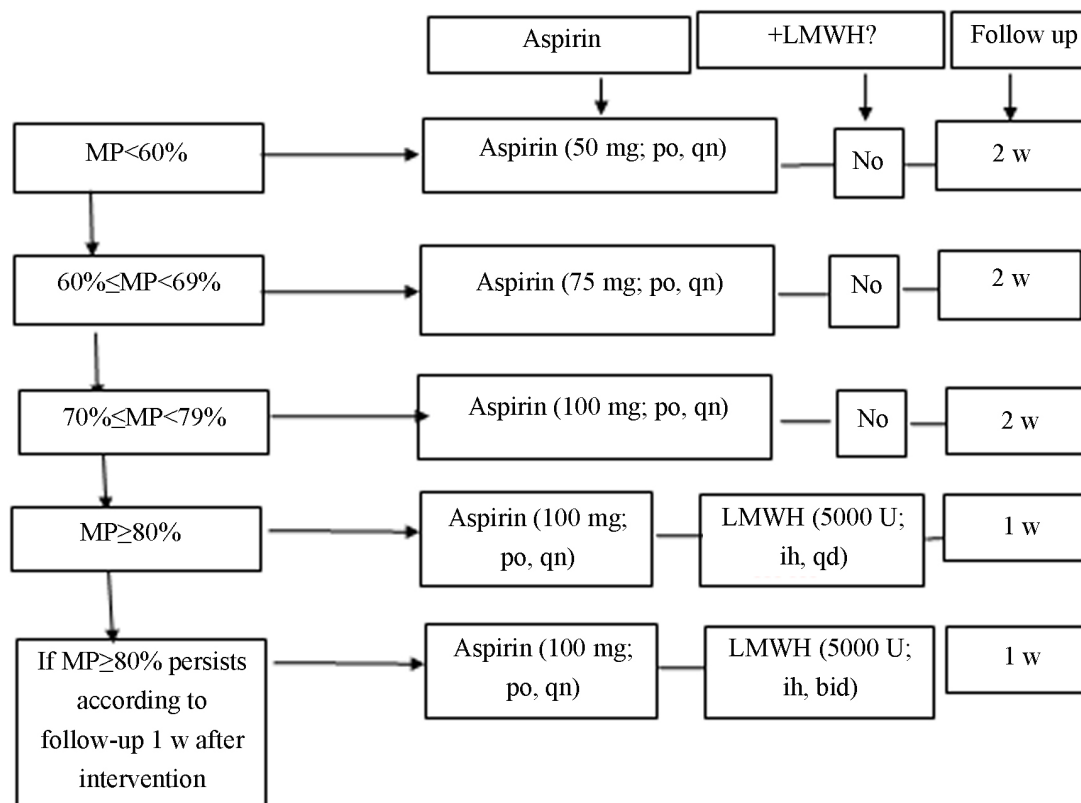
Fig. 2. Intervention flow chart for the intervention group (>12 gestational weeks). MP screening was performed. The intervention mainly involved aspirin combined with low-molecular-weight heparin (LMWH).

2.5 Observed Indices

Apart from routine pregnancy examinations, blood pressure, urinary protein and platelets were monitored. The primary observed outcomes included term births, premature births, neonatal asphyxia, the birth weight of the neonate, neonatal transfer and fetal loss.

2.6 Statistical Analysis

Data were analyzed with SPSS 22.0 (IBM Corp., Chicago, IL, USA). Measurement data are presented as the mean $\pm$ standard deviation ($\bar{x} \pm s$). The t test and Kruskal–Wallis H test were used for between-group comparisons. Count data were compared using the χ^2 test. $p < 0.05$ was considered a significant difference.

3. Results

3.1 General Data

The two groups did not show significant differences in the number of cases requiring antihypertensive drugs before pregnancy, mode of conception, maternal age, the number of pregnancies, BMI, SBP or DBP in early pregnancy ($p > 0.05$; Table 1).

3.2 PE Occurrence

In the intervention group, pregnancy termination occurred in nine patients due to fetal abnormalities and missed abortions, and in the control group, pregnancy termination occurred in eight patients. The incidence of chronic hypertension complicated by PE in the intervention group was significantly lower than that in the control group (6 *vs.* 27; $p < 0.05$; Table 2).

3.3 Fetal Outcomes

The intervention group had 81 term births and eight premature births. Among the newborns, 3 presented with mild asphyxia, but no cases of severe asphyxia occurred. The intervention group had six low-birth-weight infants, including two term-birth infants (one due to a unicornuate uterine pregnancy and one due to pregnancy after transcervical resection of adhesion (TCRA), a small placenta and a thin umbilical cord) and four prematurely born infants. Neonatal transfer occurred in seven cases. Labor was induced for four patients due to fetal abnormalities, and dilation and curettage were performed for five patients due to missed abortion during early pregnancy. No fetal losses occurred.

The control group had 53 term births and 23 premature births. Among the newborns, 12 suffered from mild asphyxia, and eight had severe asphyxia. The control group had 19 low-birth-weight infants, including eight term-birth infants and 11 (12.1%) prematurely born infants. Labor was induced for three patients due to fetal abnor-

Table 1. General data of the two groups.

Index	Group		p value
	Intervention (n = 98)	Control (n = 91)	
Age (years)	36.02 ± 4.67	35.45 ± 3.97	0.591
Number of cases requiring antihypertensive drugs before pregnancy (n)	17	14	0.703
Natural/assisted conception (n/n)	88/10	83/8	0.732
Average duration of pregnancy	3.18 ± 1.62	3.24 ± 1.70	0.899
BMI	22.38 ± 2.48		0.749
SBP in early pregnancy	87.61 ± 6.43	87.43 ± 4.95	
DBP in early pregnancy	145.62 ± 7.58	145.93 ± 5.52	0.295

Table 2. Occurrence of PE in the two groups.

Index	Group		χ^2	p value
	Intervention (n = 98)	Control (n = 91)		
Actual number of pregnancies	89	83	0.020	0.888
PE	6	27	18.421	<0.001

Table 3. Fetal outcomes of the two groups.

Index	Intervention (n = 98)	Control (n = 91)	χ^2	p
ctual number of pregnancies	89	83		
Term births (n)	81	53	18.401	<0.001
Premature births (n)	8	23	12.160	0.001
Mild neonatal asphyxia (n)	3	12	7.650	0.006
Severe neonatal asphyxia (n)	0	8	9.846	0.002
Low-birth-weight infants	6	19	10.630	0.001
Neonatal transfers	7	29	22.053	<0.001
Fetal losses	0	6	7.291	0.007
Abortions due to abnormalities	4	3	0.108	0.742
Missed abortions	5	6	0.191	0.662

malities, and dilation and curettage were performed for six patients due to missed abortion during early pregnancy. In addition, six fetal losses occurred in the control group. Among the fetal losses, four were due to small for gestational age, a loss of umbilical artery blood flow and severe FGR; therefore, abortion was performed (two cases of intrauterine fetal death and two cases of rescue withdrawal because of an extremely low birth weight), and cesarean section was performed in two pregnancies due to intrauterine death (one complicated by placental abruption and one complicated by hemolysis, elevated liver enzymes and low platelet (HELLP) syndrome). Neonatal transfer occurred in 29 cases.

Except for their rates of fetal abnormalities and missed abortion ($p > 0.05$), the fetal outcomes of the intervention group were significantly better than those of the control group ($p < 0.05$). The results are summarized in Table 3.

3.4 Ultrasound Monitoring during Pregnancy of the Intervention Group

Among the patients in the intervention group, blood hypercoagulability positivity was high according to the findings of MP screening. After timely intervention, a sig-

Table 4. Blood hypercoagulability (MP) and uterine artery blood flow positivity (ultrasound) of the intervention group.

Detection method	+	−
MP	87	11
Uterine artery blood flow	34	64
χ^2	60.668	
p	<0.001	

nificant change in the positive rate of uterine artery blood flow was observed (Table 4).

In the intervention group, fetal growth was closely monitored by ultrasound every two weeks. When an increase in umbilical cord blood flow resistance was observed or the growth curve was not satisfactory, the patient was hospitalized and received symptomatic and supportive treatment (7–10 d as a treatment course). Satisfactory pregnancy outcomes were achieved.

4. Discussion

Chronic hypertension is an important risk factor for PE, and a blood hypercoagulable state serves as the pathological basis of PE [25]. Scholars have utilized MP screen-

ing to monitor the blood hypercoagulable state in pregnant women, and satisfactory prediction rates have been reported [26–29]. However, all these reported studies were performed after the 20th week of gestation. In our previous study, we found that blood hypercoagulability was detected noticeably earlier in MP screening than the presence of clinical manifestations. By monitoring changes in blood hypercoagulability in older women in early pregnancy and providing timely anticoagulant and antithrombotic intervention accordingly, namely, by providing reasonable intervention according to the blood hypercoagulable state rather than a blood pressure increase after 20 w of gestation, we significantly decreased the incidence of PE in older pregnant women as well as the incidence of the associated complications and greatly improved the prognoses of the mothers and infants, thereby achieving satisfactory results. Therefore, the effect of MP screening for blood hypercoagulability is satisfactory in early intervention for pregnant women with chronic hypertension.

By the end of the 20th week of gestation, the pathophysiological process of PE is basically completed, and some patients may present with typical clinical manifestations of PE even at this time. Therefore, normally, once abnormalities in uterine arterial blood flow and umbilical cord blood flow are observed, PE is beyond the initiation stage and has already entered the developmental stage. Vascular remodeling normally starts from the 8th gestational week and is completed by the end of the 20th gestational week [30]. That is, if attention is given to only the developmental stage of PE, namely, from the 20th gestational week onward, the optimal time for early intervention and the correction of placental and maternal vascular dysfunction, as well as for improving fetal prognosis, may be missed. Therefore, in clinical practice, early prediction or early screening should be performed during the initiation stage, when trophoblasts infiltrate the spiral arterioles of the myometrium, and intervention is provided before the completion of vascular remodeling. This strategy might be of greater clinical significance and have wider application prospects.

The blood hypercoagulable state in PE pregnant women causes insufficient placental blood flow perfusion and blocks material transportation between villous vessels, thereby affecting the intrauterine growth of the fetus [31]. FGR is associated with a low PLGF circulating level; low-molecular-weight heparin promotes the generation and release of the PLGF from placental villi and vascular endothelium *in vitro*, and monitoring of the uterine artery blood flow in early pregnancy [32] and of the growth of the fetus during middle and late pregnancy for women who are prone to a blood hypercoagulable state [33], as well as the use of aspirin at a low dose combined with low-molecular-weight heparin when necessary, can reduce the development of PE and its complications such as FGR [34]. In this study, the intervention group received MP for blood hypercoagulability combined with ultrasound monitoring of uterine

artery blood flow in the early stage of pregnancy, and when necessary, these women were given treatment with low-molecular-weight heparin and aspirin. In addition, during the second and third trimesters of pregnancy, fetal growth was closely monitored using B-ultrasound [33], and when necessary, supportive treatment promoting fetal growth and development was provided. For these reasons, satisfactory clinical effects were achieved. Our results were consistent with those reported in the literature [34]. Therefore, MP screening is well suited as an "early warning" platform for the early prediction of blood hypercoagulability. The monitoring system is easy to operate, with high accuracy and satisfactory repeatability. The monitoring system can provide early hypercoagulability parameters for the prevention of and effective intervention for PE. In addition, the combination of the MP monitoring system with ultrasound monitoring of fetal growth and development in the second and third trimesters of pregnancy significantly improved the prognoses of the fetuses.

In this study, the intervention group received early MP screening, and if abnormalities were observed, anticoagulant drugs were administered. Our results showed that the maternal and fetal outcomes of the intervention group were significantly better than those of the control group. This finding is consistent with that reported by Rolnik *et al*. [16]. In their randomized, case–control study, a total of 1620 patients from multiple centers were involved; the results showed that the use of aspirin (150 mg/d) for high-risk pregnant women at gestational ages of 11–14 weeks decreased the incidence of PE by 82% [16]. Aspirin is an antiplatelet drug that has antipyretic, analgesic and anti-inflammatory functions. The main mechanism of action of aspirin is that it reduces endothelial cell injury and inhibits platelet aggregation and thrombosis, thereby having antihypertensive and anticoagulant effects [35,36]. Aspirin at a low dose does not increase the incidence of maternal thrombocytopenia, maternal postpartum hemorrhage, or prenatal and postpartum hemorrhage, nor does it increase the bleeding tendency and neonatal disease rate of the newborns; therefore, oral administration of low-dose aspirin during pregnancy is relatively safe for mothers and infants [37–39].

Low-molecular-weight heparin is the heparin fragment of unfractionated heparin (UFH) obtained after chemical decomposition or enzymatic cleavage, with a molecular mass ranging from 4000 U to 6500 U. It is an antithrombin-dependent thrombin inhibitor and has a stable dose effect *in vivo*. As low-molecular-weight heparin has a rather large molecular mass, it does not penetrate through the placenta and therefore has no teratogenic effect on the fetus. Apart from the anticoagulant and platelet aggregation-inhibiting effect, low-molecular-weight heparin also has anti-inflammatory, anti-apoptotic, antithrombotic and vascular endothelial cell-protecting effects; it can reduce blood V, improve placental function, increase the blood supply to the fetus, improve fetal intrauterine reserve capacity and

promote fetal growth [40]. Low-molecular-weight heparin treatment was reported to have a positive effect on PE as early as the 1960s [41]. Low-molecular-weight heparin plays an important role in the infiltration and proliferation of early trophoblasts [42] and improves the pathogenesis of "superficial placental implantation" in PE. Low-molecular-weight heparin has satisfactory safety during pregnancy, and side effects are seldom reported [43].

The occurrence of PE is associated with the immune system [44]. Fetal loss is associated with a decrease in Treg cells, and Treg cell deficiency can lead to embryo implantation failure [45]. In PE, the number of peripheral and decidual Treg cells decreases [46]. Both low-molecular-weight heparin and aspirin influence the function of T lymphocytes [47]. Low-molecular-weight heparin and aspirin also improve the blood hypercoagulable state and regulate the functions of T lymphocytes. Therefore, the incidence of PE is reduced, and satisfactory pregnancy outcomes are achieved. The underlying mechanism may be that low-molecular-weight heparin and aspirin reduce the development of PE by regulating peripheral and decidual Treg cells. However, to validate this presumption, further studies are needed.

This study has some limitations. The sample size was small, and most of the patients enrolled in the control group were from different hospitals (some came to visit our department once the pathological condition became severe). These factors might lead to bias in the observed results of this study. To overcome these limitations, multicenter, randomized, case–control trials with a larger sample size need to be conducted in the future.

5. Conclusions

Our previous study used the MP monitoring system to screen the blood hypercoagulability state of older pregnant women beginning in early pregnancy and guided early clinical intervention according to the screening results. In that study, we achieved satisfactory clinical results in the prevention of PE. In this study, to analyze another PE high-risk factor, chronic hypertension, the simple MP monitoring system was also used to screen the blood hypercoagulability state and initiate interventions in a timely manner. At the same time, ultrasound was used to monitor the growth and development of the fetus and provide symptomatic and supportive treatment in a timely manner, resulting in the achievement of ideal maternal and infant outcomes. It is reasonable to believe that for all pregnant women with PE high-risk factors, blood hypercoagulability can be monitored before pregnancy or in early pregnancy, and according to the screening results, timely and effective intervention can be administered and expected to achieve the same satisfactory effects. The use of this method, especially for pregnant women in economically underdeveloped and remote areas, may have notable societal benefits.

Availability of Data and Materials

All data analyzed in this study are available from the corresponding author on reasonable request.

Author Contributions

MP and SYX devised the study plan, MP and SYX led the writing of the article, MP, JYL, BL, LingY, YLDeng, WZ, YTN and WSL collected the data. MP, HYL, YZ, LiY, YW and BZ sorted the data and conducted the analysis, MP, YHZ and LYX validated the data, MP and YLDing were responsible for visualization, and MP attained the funding and supervised the whole process. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The procedures of this study were approved by the Ethics Committee of the Second Xiangya Hospital (2020-573). Written informed consent was obtained from each participant.

Acknowledgment

Not applicable.

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Nzelu D, Dumitrascu-Biris D, Kay P, Nicolaides KH, Kametas NA. Severe hypertension, preeclampsia and small for gestational age in women with chronic hypertension diagnosed before and during pregnancy. Pregnancy Hypertension. 2018; 14: 200–204.

[2] American College of Obstetricians and Gynecologists. ACOG Practice Bulletin No. 125: Chronic hypertension in pregnancy. Obstetrics and Gynecology. 2012; 119: 396–407.

[3] Moussa HN, Arian SE, Sibai BM. Management of Hypertensive Disorders in Pregnancy. Women'S Health. 2014; 10: 385–404.

[4] Nzelu D, Dumitrascu-Biris D, Nicolaides KH, Kametas NA. Chronic hypertension: first trimester blood pressure control and likelihood of severe hypertension, preeclampsia and small for gestational age. American Journal of Obstetrics and Gynecology. 2018; 218: 337.e1–337.e7.

[5] Yadav S, Singh N, Jain S, Pradhan M. Identification and management of rare causes of chronic hypertension in pregnancy in a tertiary referral centre of North India. Pregnancy Hypertension. 2019; 17: 249–252.

[6] Becker DA, Machemehl HC, Biggio JR, Siegel AM, Tita AT, Harper LM. Pregnancy Outcomes of Exacerbated Chronic Hypertension Compared with Superimposed Preeclampsia. American Journal of Perinatology. 2019; 36: 872–878.

[7] Novotny S, Lee-Plenty N, Wallace K, Kassahun-Yimer W, Jayaram A, Bofill JA, et al. Acute kidney injury associated with preeclampsia or hemolysis, elevated liver enzymes, and low platelets syndrome. Pregnancy Hypertension. 2020; 19: 94–99.

[8] Sibai BM, Koch MA, Freire S, Pinto e Silva JL, Rudge MV, Martins-Costa S, et al. The impact of prior preeclampsia on the risk of superimposed preeclampsia and other adverse pregnancy outcomes on patients with chronic hypertension. American Journal of Obstetrics and Gynecology. 2011; 204: 345.e1–345.e6.

[9] Catov JM, Nohr EA, Olsen J, Ness RB. Chronic Hypertension Related to Risk for Preterm and Term Small for Gestational Age Births. Obstetrics and Gynecology. 2008; 112: 290–296.

[10] Chaemsaithong P, Pooh RK, Zheng M, Ma R, Chaiyasit N, Tokunaka M, et al. Prospective evaluation of screening performance of first-trimester prediction models for preterm preeclampsia in an Asian population. American Journal of Obstetrics and Gynecology. 2019; 221: 650.e1–650.e16.

[11] O'Gorman N, Wright D, Poon LC, Rolnik DL, Syngelaki A, de Alvarado M, et al. Multicenter screening for pre-eclampsia by maternal factors and biomarkers at 11–13 weeks' gestation: comparison with NICE guidelines and ACOG recommendations. Ultrasound in Obstetrics and Gynecology. 2017; 49: 756–760.

[12] Tan MY, Wright D, Syngelaki A, Akolekar R, Cicero S, Janga D, et al. Comparison of diagnostic accuracy of early screening for pre-eclampsia by NICE guidelines and a method combining maternal factors and biomarkers: results of SPREE. Ultrasound in Obstetrics & Gynecology. 2018; 51: 743–750.

[13] Sonek J, Krantz D, Carmichael J, Downing C, Jessup K, Haidar Z, et al. First-trimester screening for early and late preeclampsia using maternal characteristics, biomarkers, and estimated placental volume. American Journal of Obstetrics and Gynecology. 2018; 218: 126.e1–126.e13.

[14] O'Gorman N, Wright D, Syngelaki A, Akolekar R, Wright A, Poon LC, et al. Competing risks model in screening for preeclampsia by maternal factors and biomarkers at 11-13 weeks gestation. American Journal of Obstetrics and Gynecology. 2016; 214: 103.e1–103.e12.

[15] Krantz DA, Hallahan TW. Incorporating the probability of competing event(s) into the preeclampsia competing risk algorithm. American Journal of Obstetrics and Gynecology. 2019; 221: 533–534.

[16] Rolnik DL, Wright D, Poon LC, O'Gorman N, Syngelaki A, de Paco Matallana C, et al. Aspirin versus Placebo in Pregnancies at High Risk for Preterm Preeclampsia. The New England Journal of Medicine. 2017; 377: 613–622.

[17] Cong KJ, Wang TT, Liu GR, Zhang S, Yang YM, Luo ZC. A study on the hemodynamics and microcirculation in patients with pregnancy induced hypertension. Chinese Journal of Practical Gynecology and Obstetrics. 1997; 13: 29–31. (In Chinese)

[18] Li BL, Hou LY, Wang T, Wang R. Study on the diagnostic value of uterine artery spectrum for hypertensive disorders of pregnancy complicated with fetal growth restriction. Maternal & Child Health Care of China. 2020; 35: 4599–4602. (In Chinese)

[19] Wang TT, Cheng L, Yu HL, Ke HR, Chen J. Predictive study of maternal uterine artery spectrum in early pregnancy for preeclampsia. China Modern Medicine. 2021; 28: 126–129. (In Chinese)

[20] Liu W, Lin QD, Xia JG. Scoring of uterine arterial resistance for prediction of pregnancy induced hypertension syndrome. Progresos en Obstetricia y Ginecologia. 2004; 13: 266–269. (In Chinese)

[21] Group of Hypertension in Pregnancy, Branch of Obstetrics and Gynecology, Chinese Medical Association. Guidelines for diagnosis and treatment of hypertensive disorder complicating pregnancy (2020). Chinese Journal of Obstetrics and Gynecology. 2020; 55: 227–238. (In Chinese)

[22] Zhang HJ, Yang Z. Review and prospect of the application of low molecular weight heparin in preeclampsia. Zhongguo Shiyong Fuke Yu Chanke Zazhi. 2017; 33: 755–759. (In Chinese)

[23] Webster K, Fishburn S, Maresh M, Findlay SC, Chappell LC. Diagnosis and management of hypertension in pregnancy: summary of updated NICE guidance. British Medical Journal. 2019; 366: l5119.

[24] China Hypertension Prevention and Treatment Guidelines Revision Committee, Hypertension Alliance (China), Chinese Society of Cardiology, Hypertension Branch of China Association for the Promotion of International Exchanges in health care, Hypertension Branch of China Geriatric Society. Guidelines for prevention and treatment of hypertension in China. Chinese Journal of Cardiovascular Medicine. 2019; 24: 24–56. (In Chinese).

[25] Baptista FS, Bortolotto M, Bianchini F, Krebs V, Zugaib M, Francisco R. Can thrombophilia worsen maternal and perinatal outcomes of severe pre-eclampsia. Pregnancy Hypertension. 2018; 11: 81–86.

[26] Liu HC, Xiao L, Xu ZL, Tan JX, Li MY, Li R, et al. Effects of gestational hypertension on arterial elasticity and vascular endothelial function in pregnant women. Chinese Journal of Hypertension. 2019; 27: 372–375. (In Chinese)

[27] Wang JL, Yang Z. Monitoring and treatment of coagulation mechanism disorder in preeclampsia. Chinese Journal of Practical Gynecology and Obstetrics. 2011; 27: 886–890. (In Chinese)

[28] Wang HQ, Wang CY, Wu SM. Predictive effect of MP pregnancy induced hypertension monitoring system on pregnancy induced hypertension. Journal of Datong Medical College. 2004; 4: 11, 14. (In Chinese)

[29] Bao LY, Liang FL, Huang YJ. Predictive effect of MP pregnancy induced hypertension. Guangxi Journal of Preventive Medicine. 2001; 31: 165–166. (In Chinese)

[30] Xu JJ. Study on the mechanism of extravillous trophoblast in the remodeling of spiral artery of pregnant uterus [PhD dissertation]. Huazhong University of science and technology. 2010.

[31] Lumell NO, Nylund L. Uteroplacental blood flow. Clinical Obstetrics and Gynecology. 2012; 35: 108–118

[32] Gardosi J. Intrauterine growth restriction: new standards for assessing adverse outcome. Best Practice and Research Clinical Obstetrics and Gynaecology. 2009; 23: 741–749.

[33] Ferrazzi E, Zullino S, Stampalija T, Vener C, Cavoretto P, Gervasi MT, et al. Bedside diagnosis of two major clinical phenotypes of hypertensive disorders of pregnancy. Ultrasound in Obstetrics & Gynecology. 2016; 48: 224–231.

[34] McLaughlin K, Hobson SR, Chandran AR, Agrawal S, Windrim RC, Parks WT, et al. Circulating maternal placental growth factor responses to low-molecular-weight heparin in pregnant patients at risk of placental dysfunction. American Journal of Obstetrics and Gynecology. 2022; 226: S1145–S1156.e1.

[35] Van Doorn R, Mukhtarova N, Flyke IP, Lasarev M, Kim K, Hennekens CH, et al. Dose of aspirin to prevent preterm preeclampsia in women with moderate or high-risk factors: A systematic review and meta-analysis. PLoS ONE. 2021; 16: e0247782.

[36] Hoffman MK, Goudar SS, Kodkany BS, Metgud M, Somannavar M, Okitawutshu J, et al. Low-dose aspirin for the prevention of preterm delivery in nulliparous women with a singleton pregnancy: A randomised multicountry placebo controlled trial. Lancet. 2020; 395: 285–293.

[37] Askie LM, Duley L, Henderson-Smart DJ, Stewart LA. Antiplatelet agents for prevention of pre-eclampsia: a meta-analysis of individual patient data. The Lancet. 2007; 369: 1791–1798.

[38] Huang J, Chen X, Xing H, Chen L, Xie Z, He S, et al. Aspirin and heparin for the prevention of pre-eclampsia: protocol for a systematic review and network meta-analysis. BMJ Open. 2019; 9: e026920.

[39] Mone F, Mulcahy C, McParland P, Breathnach F, Downey P, McCormack D, *et al*. Trial of feasibility and acceptability of routine low-dose aspirin versus Early Screening Test indicated aspirin for pre-eclampsia prevention (TEST study): a multicentre randomised controlled trial. BMJ Open. 2018; 8: e022056.

[40] Katz L, de Amorim MMR, Figueiroa JN, e Silva JLP. Postpartum dexamethasone for women with hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome: a double-blind, placebo-controlled, randomized clinical trial. American Journal of Obstetrics and Gynecology. 2008; 198: 283.e1–283.e8.

[41] Baker LR, Brain MC. Heparin treatment of haemolytic anaemia and thrombocytopenia in pre-eclampsia. Proceedings of the Royal Society of Medicine. 1967; 60: 477–479.

[42] Wu XX, Chen Y, Tan JP, Liu ML, Zhang JP. Modulation of low molecular weight heparin and heparin-binding epidermal growth factor on biological functions of human first trimester trophoblast. Chinese Journal of Obstetrics and Gynecology. 2013; 48: 107–112.

[43] Wat JM, Hawrylyshyn K, Baczyk D, Greig IR, Kingdom JC. Effects of glycol-split low molecular weight heparin on placental, endothelial, and anti-inflammatory pathways relevant to preeclampsia. Biology of Reproduction. 2018; 99: 1082–1090.

[44] Jena MK, Sharma NR, Petitt M, Maulik D, Nayak NR. Pathogenesis of preeclampsia and therapeutic approaches targeting the placenta. Biomolecules. 2020; 10: 953.

[45] Nancy P, Erlebacher A. T cell behavior at the maternal-fetal interface. The International Journal of Developmental Biology. 2014; 58: 189–198.

[46] Figueiredo AS, Schumacher A. The T helper type 17/regulatory T cell paradigm in pregnancy. Immunology. 2016; 148: 13–21.

[47] Mondal S, Jana M, Dasarathi S, Roy A, Pahan K. Aspirin ameliorates experimental autoimmune encephalomyelitis through interleukin-11–mediated protection of regulatory T cells. Science Signaling. 2018; 11: eaar8278.