

Uterine fibroids increase the risk of hypertensive disorders of pregnancy: a prospective cohort study

Yequn Chen^{a,*}, Mengyue Lin^{a,b,*}, Pi Guo^{c,*}, Jiaxin Xiao^a, Xiru Huang^{a,b}, Lan Xu^d, Nianling Xiong^{a,b}, Mary Clare O'Gara^e, Michael O'Meara^f, and Xuerui Tan^a

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Objective: It is unclear whether uterine fibroids are associated with the occurrence of hypertensive disorders of pregnancy (HDP). Thus, this study aimed to evaluate the association between uterine fibroids and HDP in a prospective cohort.

Methods: Overall, 2404 pregnant women who received antenatal care were enrolled in a prospective cohort in China between 2014 and 2016; 2277 women met the inclusion criteria of this study. The clinical characteristics of participants were assessed via questionnaires and physical examinations at baseline (before the 20th week of gestation), 21st–27th, 28th–34th, and 35th–39th gestational weeks. Ultrasound examination was performed before the 20th week of pregnancy to determine the presence of uterine fibroids. Linear mixed-effect and Cox proportional hazard regression models were used to analyze the association of uterine fibroids with blood pressure and HDP.

Results: Of 2277 pregnant women, 242 (10.6%) had uterine fibroids, and 45 (2.0%) subsequently developed HDP. The incidence of HDP in women with and without uterine fibroids was 5% ($n = 12$) and 1.6% ($n = 33$), respectively. The longitudinal SBPs and DBPs were significantly higher in women with uterine fibroids than in those without. The multivariable Cox model showed that the presence of uterine fibroids was associated with increased HDP risk (adjusted hazard ratio: 2.95, 95% confidence interval: 1.35–6.44).

Conclusion: Uterine fibroids in early pregnancy were associated with an increased HDP risk. Blood pressure of women with uterine fibroids should be closely monitored, and HDP preventive measures are crucial.

Keywords: hypertensive disorders of pregnancy, leiomyoma, preeclampsia, prospective studies

Abbreviations: BP, blood pressure; CI, confidence interval; Fa, folic acid supplement intake during pregnancy; fDM, family history of diabetes mellitus; fHP, family history of hypertension; FPG, fasting plasma glucose; GDM, gestational diabetes mellitus; HDP, hypertensive disorders of pregnancy

mortality worldwide [1–4]. Compared with pregnant women without HDP, women with gestational hypertension have a 1.4-to-2.2-fold increased risk of obstetric complications during pregnancy, and the risk is higher in those with severe preeclampsia [5]. HDP can induce severe maternal complications, such as cardiocerebrovascular diseases, liver and kidney failure, disseminated intravascular coagulation, and pulmonary edema. Because of the placenta dysfunction, there is also increased risk of abortion, preterm birth, fetal growth restriction, fetal distress and stillbirth in HDP [6]. Early identification of high-risk pregnant women with HDP allows intensive monitoring and interventions to reduce the incidence of obstetric complications.

The prevalence of uterine fibroids in women of child-bearing age and in pregnant women ranges from 20 to 40% and 1 to 10%, respectively [7–9]. Studies suggest that the presence of uterine fibroids is associated with increased blood pressure (BP) level, and the prevalence of hypertension in women with uterine fibroids has been shown to be as high as 40% [10–12]. Several studies indicated that women with hypertension have a higher risk for fibroids [10,13,14]. In contrast, the risk of hypertension is greater in women with fibroids than in those without fibroids [12,15–17]. Uterine fibroids are usually asymptomatic and are often discovered during an ultrasound examination performed in early pregnancy [18]. Under rapid hormonal changes, notable fibroid growth is observed during the first trimester of pregnancy [19], leading to an increased incidence of obstetric complications [20]. However, it is unclear whether

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^aDepartment of Cardiology, First Affiliated Hospital of Shantou University Medical College, ^bShantou University Medical College, ^cDepartment of Preventive Medicine, Shantou University Medical College, ^dDepartment of Gynecology and Obstetrics, First Affiliated Hospital of Shantou University Medical College, ^eDepartment of Nursing and ^fDepartment of Information Technology, Shantou University Medical College, Shantou, China

Correspondence to Xuerui Tan, The First Affiliated Hospital of Shantou University Medical College, 57 Changping Road, Shantou, Guangdong 515041, China. Tel: +86 754 8861 1690; fax: +86 754 88259850; e-mail: doctortxr@126.com.

*Yequn Chen, Mengyue Lin, Pi Guo contributed equally to this work.

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INTRODUCTION

Hypertensive disorder of pregnancy (HDP) affects 6–8% of pregnant women, and remains a major cause of high maternal and perinatal morbidity and

uterine fibroids are associated with the occurrence of HDP. Considering the similar pathogeneses of hypertension and HDP, we hypothesized that uterine fibroids would increase the risk of HDP.

Therefore, we examined the relationship of uterine fibroids diagnosed before the 20th week of pregnancy with a longitudinal BP pattern and the risk of HDP based on a large prospective cohort established in China between 2014 and 2016.

METHODS

This prospective cohort enrolled pregnant women who received antenatal care in the First Affiliated Hospital of Shantou University Medical College in Shantou, China. The study enrolled women aged 20–45 years who were confirmed to be pregnant via ultrasound before the 20th week of gestation. The exclusion criteria were: ectopic pregnancy, history of hypertension or diabetes, secondary hypertension, and severe mental disorders. A total of 2404 pregnant women who met the criteria were enrolled between March 2014 and June 2016. All the pregnant women were followed up at 21st–27th, 28th–34th, and 35th–39th gestational weeks. Baseline and follow-up details were collected using structural questionnaires, which included demographic data, physical and laboratory examination, and individual and family medical histories. In order to examine the causal relationship between uterine fibroids and HDP, we also excluded participants with SBP at least 140 mmHg or DBP at least 90 mmHg before the 20th week of gestation, history of HDP or gestational diabetes

mellitus, miscarriage before the 20th week of gestation, and those who had undergone in-vitro fertilization. The design framework of this study is shown in Fig. 1. The study was approved by the Ethics Committee of the First Affiliated Hospital of Shantou University Medical College and all participants provided written informed consent prior to inclusion in this study.

BP was measured thrice by trained nurses at baseline and at each follow-up, using an Omron HEM-7052 automatic BP monitor (Omron Healthcare Ltd., Dalian, China) according to the standard measurement procedure recommended by the American Heart Association [21]. An average of three BP readings was used for analysis.

Other parameters, including maternal age, baseline BP, fasting plasma glucose, monthly per capita income, educational level, nulliparity (yes or no), folic acid supplement intake during pregnancy (yes or no), family history of hypertension (yes or no), family history of diabetes mellitus (yes or no), smoking (yes or no), alcohol consumption (yes or no), weight, and height were obtained by a questionnaire. The weight and height were used to calculate BMI.

Maternal outcomes were obtained from medical records. In this study, HDP included gestational hypertension and preeclampsia. Gestational hypertension was defined as SBP at least 140 mmHg and/or DBP at least 90 mmHg without proteinuria, which develops after 20 weeks of gestation. Preeclampsia was defined as SBP at least 140 mmHg and/or DBP at least 90 mmHg after 20 weeks of gestation and proteinuria (defined as ≥ 300 mg of protein in a 24-h urine specimen or $\geq 1+$ in two random urine samples collected at least 4 h apart) [22].

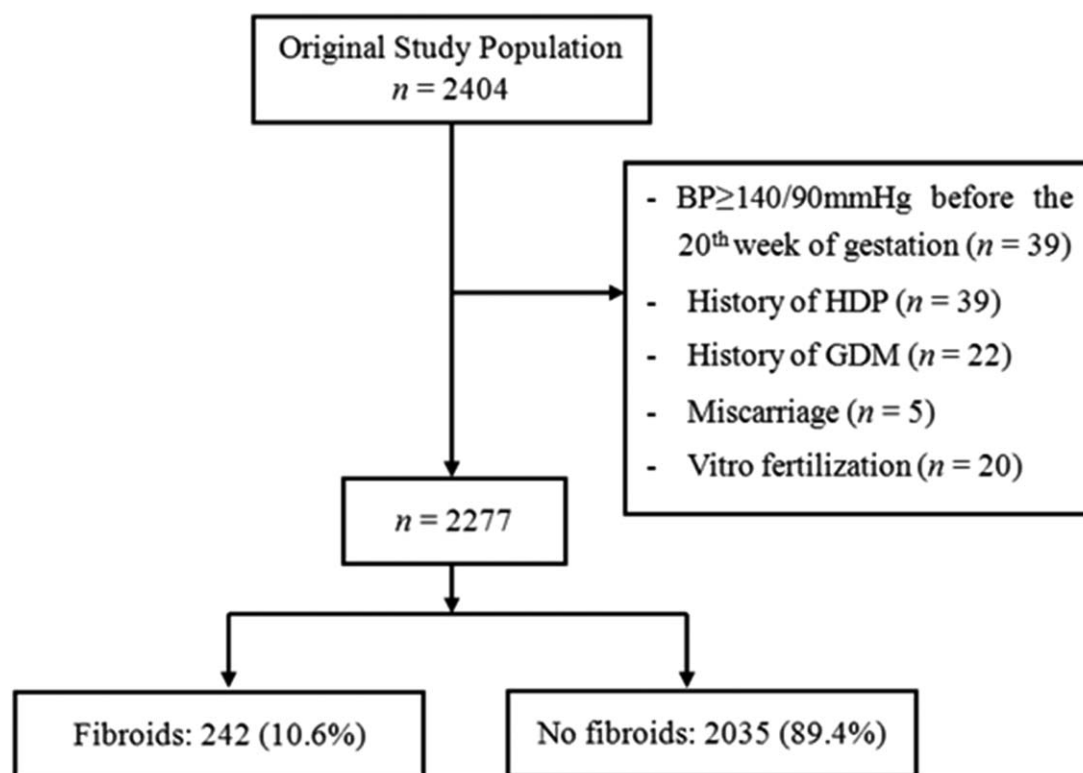


FIGURE 1 Designed framework of the study. Flow diagram showing selection of study population, sample size, and exclusions. BP, blood pressure; GDM, gestational diabetes mellitus; HDP, hypertensive disorder of pregnancy.

All ultrasound measurements were performed by an experienced operator before the 20th week of gestation. Women with uterine fibroids were defined as those for whom ultrasonography examination revealed at least one fibroid.

Continuous variables are expressed as mean \pm standard deviation, and categorical variables as absolute numbers with percentage. Chi-square tests and *t* tests were used for group comparisons. Linear mixed-effect regression models were used to evaluate the effect of uterine fibroids on the changing profile of SBP and DBP during pregnancy. This regression technique accommodates time-dependent and time-independent covariates. The variables, gestational age and gestational age squared, were included in linear mixed-effects regression models to fit the quadratic function of the association of BP with time [23]. Gestational age was treated in the models both as a random and fixed effect, whereas other covariates including maternal age, BMI, nulliparity, income, education, folic acid supplement, smoking, alcohol consumption, and family history of hypertension and diabetes were treated as fixed effects. The results are expressed as regression coefficients [95% confidence interval (CI)]. Three models adjusted for potential confounders were used to examine the association between uterine fibroids and BP pattern: model 1 was adjusted for gestational age (linear and quadratic terms). Model 2 was adjusted for gestational age, maternal age, baseline BMI, and educational level. Model 3 was further adjusted for monthly per capita income, nulliparity, folic acid supplement intake during pregnancy, smoking, alcohol consumption, family history of hypertension, and family history of diabetes. This analysis strategy provides verifications of whether the association between uterine fibroids and BP change during pregnancy is independent of other covariates. The curves of longitudinal BP change with gestational age were estimated using quadratic regression function as

the pattern of variation of SBP and DBP during pregnancy approaches a parabola [24].

The cumulative incidence of HDP was estimated using the Kaplan–Meier method and compared using the log-rank test. Three Cox proportional hazards regression models were constructed to determine the independent predictive value of uterine fibroids for HDP. Model 1 was unadjusted, whereas model 2 was adjusted for maternal age, baseline BMI and educational level, family history of hypertension, family history of diabetes, and baseline SBP and DBP. Model 3 was further adjusted for folic acid supplement intake during pregnancy, nulliparity, monthly per capita income, smoking, alcohol consumption, and fasting plasma glucose. Furthermore, to assess the relationship of uterine fibroids with the severity of HDP, we classified women with HDP into gestational hypertension or preeclampsia group, and performed ordinal logistic regression using the fully adjusted model. Statistical analyses were performed with SPSS version 20.0 (SPSS Inc., Chicago, Illinois, USA). Two-tailed *P* values less than 0.05 were considered statistically significant.

RESULTS

After exclusion, 2277 participants were analyzed. The baseline characteristics of this study are shown in Table 1. The mean gestational week of enrollment and ultrasound examination was 13.4 ± 3.4 and 10.4 ± 3.6 , respectively. The mean maternal age and baseline BMI were 30.5 ± 4.5 years and 20.5 ± 3.0 kg/m², respectively. Of these 2277 pregnant women, 242 (10.6%) were identified with uterine fibroids before the 20th week of gestation. Forty-five (2.0%) pregnant women subsequently developed HDP during follow-up. The incidence of HDP in women with uterine fibroids and without uterine fibroids was 5.0% (*n* = 12) and 1.6% (*n* = 33), respectively.

TABLE 1. Characteristics of participants according to fibroid status, from 2014 to 2016, China

Characteristics	Total (<i>n</i> = 2277)	No fibroid (<i>n</i> = 2035)	Fibroid (<i>n</i> = 242)	<i>P</i> value
Maternal age (years)	30.5 \pm 4.5	30.3 \pm 4.4	32.3 \pm 5.0	<0.001
BMI (kg/m ²)	20.5 \pm 3.0	20.4 \pm 3.0	21.5 \pm 3.1	<0.001
Monthly per capita income (yuan)				
<3000	934 (41.0)	840 (41.3)	94 (38.8)	0.628
3000–5000	722 (31.7)	646 (31.7)	76 (31.4)	
>5000	621 (27.3)	549 (27.0)	72 (29.8)	
Educational level				
Below high school	488 (21.4)	451 (22.2)	37 (15.3)	0.031
High school	520 (22.8)	466 (22.9)	54 (22.3)	
Beyond high school	1269 (55.7)	1118 (54.9)	151 (62.4)	
Nulliparity	1022 (44.9)	927 (45.6)	95 (39.3)	0.063
Folic acid supplement	1592 (69.9)	1419 (69.7)	173 (71.5)	0.573
Family history of hypertension	424 (18.6)	371 (18.2)	53 (21.9)	0.166
Family history of diabetes mellitus	300 (13.2)	259 (12.7)	41 (16.9)	0.067
SH-smoking	1169 (51.3)	1032 (50.7)	137 (56.6)	0.083
Smoking	47 (2.1)	42 (2.1)	5 (2.1)	0.998
Alcohol	609 (26.7)	549 (27.0)	60 (24.8)	0.468
SBP	109.5 \pm 10.2	109.3 \pm 10.0	111.3 \pm 11.0	0.004
DBP	68.8 \pm 8.1	68.7 \pm 8.1	69.7 \pm 8.3	0.061
FPG	4.3 \pm 1.3	4.3 \pm 1.3	4.3 \pm 1.3	0.625

Data are presented as means \pm standard deviation or number (percentage). FPG, fasting plasma glucose; HDP, hypertensive disorders of pregnancy; SH-smoking, second hand smoking during pregnancy.

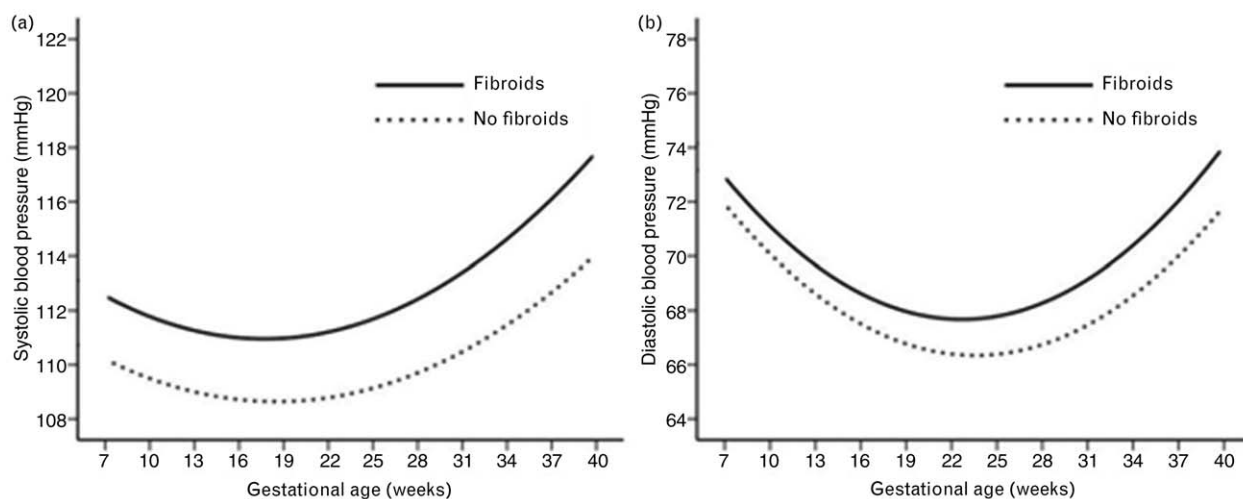


FIGURE 2 Longitudinal trend of blood pressure changes during pregnancy. Longitudinal trend of SBP (a) and DBP (b) change with gestational age versus uterine fibroids ($n=242$ in fibroid group and $n=2035$ in non fibroid group).

TABLE 2. Longitudinal Associations of SBP and DBP levels during pregnancy with uterine fibroids

Model	Covariates in model	SBP			DBP		
		β for fibroid	95% CI	P value	β for fibroid	95% CI	P value
1	Gestational age	2.66	1.42–3.90	<0.001	1.51	0.55–2.48	0.002
2	Gestational age, age, BMI, education	1.97	0.73–3.21	0.002	1.03	0.07–2.00	0.036
3	Gestational age, age, BMI, income, education, Fa, Nullip, Smoking, Alcohol, fHP, fDM	1.89	0.66–3.12	0.003	0.98	0.02–1.94	0.047

Values were based on linear mixed-effects regression models and reflect the difference in maternal BP between the uterine fibroids group and the reference group. Results were regression coefficients (95% confidence interval), and it indicates that its of statistical significant when 95% CI does not contain 0. β , regression coefficient; CI, confidence interval; education, educational level; Fa, folic acid supplement intake during pregnancy; fDM, family history of diabetes mellitus; fHP, family history of hypertension; income, monthly per capita income; Nullip, nulliparous; alcohol, alcohol consumption.

Figure 2 shows the longitudinal patterns of SBP and DBP change during pregnancy according to the status of uterine fibroids. During pregnancy, both SBP and DBP began to decline in early pregnancy; a trough occurred in mid-pregnancy and then increased until delivery. Women with

fibroids had higher SBP and DBP than those without fibroids. The distribution of maternal BP throughout pregnancy is shown in Figure S1, <http://links.lww.com/HJH/B512>. Table 2 shows the longitudinal association of fibroids with SBP and DBP change during pregnancy, before and after controlling for potential confounding factors. Fully adjusted models suggested that there was a significantly higher longitudinal SBP (regression coefficient: 1.89; 95% CI: 0.66–3.12; $P=0.003$) and DBP (regression coefficient: 0.98; 95% CI: 0.02–1.94; $P=0.047$) in uterine fibroids group.

Kaplan–Meier curve analysis showed that the cumulative incidence of HDP was significantly higher in women with uterine fibroids (Fig. 3). To clarify the association between uterine fibroids and the risk of HDP, Cox proportional hazards models were constructed (Table 3). An unadjusted model revealed that women with uterine fibroids had a 2.57-fold increased risk of HDP compared with women without uterine fibroids (hazard ratio: 3.57; 95% CI: 1.83–6.94; $P<0.001$) (model 1). After adjustment for maternal age, baseline BMI, educational level, family history of hypertension and diabetes, and baseline SBP and DBP, the presence of uterine fibroids was still associated with high risk of HDP (hazard ratio: 3.12; 95% CI: 1.55–6.27; $P=0.001$) (model 2). Finally, a fully adjusted model including all variables yielded similar results (hazard ratio: 2.95; 95% CI: 1.35–6.44; $P=0.007$) (model 3). Additionally, ordinal logistic regression model showed that compared

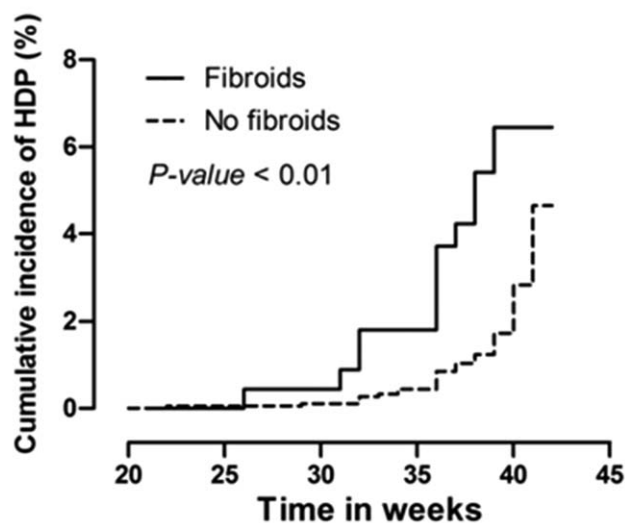


FIGURE 3 Kaplan–Meier curve of cumulative incidence of hypertensive disorder of pregnancy. Kaplan–Meier curve for hypertensive disorders of pregnancy (HDP) women by the status of uterine fibroids. P value was generated based on the log-rank test ($n=242$ in fibroid group and $n=2035$ in non fibroid group).

TABLE 3. Associations of the risk of hypertensive disorders of pregnancy with uterine fibroids

Model	Covariates in model	HR for fibroid	95% CI	P-value
1	Null	3.57	1.83–6.94	<0.001
2	Age, BMI, Education, fHP, fDM, SBP, DBP	3.12	1.55–6.27	0.001
3	Model 2 + Fa, Nullip, Income, Smoking, Alcohol, FPG	2.95	1.35–6.44	0.007

Results were showed as hazards ratio (95% confidence interval) derived from Cox proportional-hazards model. alcohol, alcohol consumption; HR, hazards ratio; CI, confidence interval; Fa, folic acid supplement intake during pregnancy; fHP, family history of hypertension; fDM, family history of diabetes mellitus; FPG, fasting plasma glucose; income, monthly per capita income; Nullip, nulliparous.

with no fibroids, women with fibroids were 2.4 times more likely to have at least one grade increase in HDP severity (Table 4).

DISCUSSION

HDP is a risk factor for severe pregnancy outcomes, and it is beneficial to identify pregnant women with a high risk of HDP. In this large prospective cohort study, we found that the presence of uterine fibroids was associated with increased longitudinal SBP and DBP in pregnant women. Compared with those without fibroids, women with uterine fibroids diagnosed before the 20th week of gestation had a higher risk for HDP during pregnancy. These results may contribute to early detection of women who are at high risk for HDP.

Previous studies showed that the prevalence of uterine fibroids increased with increasing premenopausal age [25]. One possible mechanism is related to the hormonal changes associated with increasing age [26]. Increased BMI may increase the risk of uterine fibroids through inflammatory mechanisms [27,28]. Additionally, central obesity, insulin resistance and hyperlipidemia, which were related to BMI, were all associated with a higher risk of uterine fibroids [29]. As expected, participants in the fibroids group were older and present a statistically higher BMI in our study. However, the association between uterine fibroids and the increased risk of HDP remained significant after adjusting for age, BMI, and other confounders.

Consistent with the study by Farias *et al.* [24] that included 199 healthy pregnant women, our large sample analysis shows that during pregnancy, both SBP and DBP notably decrease from early pregnancy to mid-pregnancy but subsequently increase until delivery. A case-control study showed that the level of BP was higher in the uterine fibroid group than in the control group [17], and we demonstrated a similar result in pregnant women. Previous studies have suggested a relationship between uterine fibroids and hypertension [12–17]. Findings from cross-sectional and case-control studies indicate that women with hypertension are at higher risk of developing fibroids [10,13,14]. Moreover, a prospective study by Boynton–

Jarrett *et al.* found that for every 10 mmHg increase in DBP, the fibroid risk would be increased by approximately 10% [11]. In contrast, several studies have indicated that the risk of hypertension is greater in women with fibroids than in those without fibroids [15–17]. In a recent case-control study, Haan *et al.* [12] reported a notably high risk of hypertension in women with fibroids after adjusting for several cardiovascular disease risk factors. Regarding the association of uterine fibroids with HDP in pregnant women, our research could make a significant contribution to this field. Our study was based on a large prospective cohort and suggested a causal relationship between uterine fibroids and the risk of HDP. According to our study, pregnant women with uterine fibroids should be classified as high-risk for HDP. Thus, closer BP monitoring and HDP preventive measures, such as those recommended by LeFevre *et al.* [30], become necessary.

The incidence of HDP was lower in our cohort than in cohorts of other studies [3,6]. The reason for this could be the exclusion of some risk factors for HDP in our cohort, such as a history of hypertension, history of diabetes, and an elevated BP level before the 20th week of pregnancy. This strategy, combined with adjusting for several known risk factors, aimed to better explain the causal relationship between uterine fibroids and HDP. It is still unclear how uterine fibroids induce HDP. Poorly perfused placenta in early pregnancy is an important stage in the development of HDP [31]. Therefore, it is reasonable to speculate that the expansion of fibroids in early pregnancy may cause poor placental perfusion by compressing uterine blood vessels, leading to an increased risk of HDP. Combined with these effect, several molecules secreted from fibroids, such as thromboxane A2 and endothelin-1 [32,33], which are associated with endothelial dysfunction by inducing inflammation and oxidative stress response, may be other risk factors for HDP [34]. These suggest that the mechanism of HDP induction by uterine fibroids requires further study.

This study had some limitations that warrant discussion. First, in this pregnancy cohort, we did not have prepregnancy measurements, such as BMI and BP, and the history of hypertension or diabetes was based on self-reporting. However, the participants included in this study were aged 20–45 years without severe mental disorders, and had normal communication, expression, and cognition abilities, so the recall bias for the history of hypertension and diabetes should be relatively small. Second, a dose-response analysis based on the size, type, and number of uterine fibroids was not performed owing to the relatively small sample of HDP cases available. Third, since the design was observational, we can only speculate on the possible pathogenesis of HDP caused by uterine fibroids where the

TABLE 4. The relationship of uterine fibroid with the severity of hypertensive disorders of pregnancy

Fibroid	OR	95% CI	P value
No fibroid	Reference	Reference	Reference
Fibroid	2.43	1.09, 5.42	0.029

Results were showed as odds ratio (95% confidence interval) derived from Ordinal logistic regression (fully adjusted model).

precise molecular mechanisms still remain unclear. However, our study contributes to the literature as it provides new evidence on the causal relationship between uterine fibroids and the occurrence of HDP. To our knowledge, this is the first study to evaluate the association of uterine fibroids with HDP in a large prospective cohort.

In conclusion, this prospective study of pregnant women suggests that women with uterine fibroids identified during early pregnancy have a high risk of HDP, even after adjusting for multiple confounding factors. Considering the adverse effects of HDP on pregnancy, pregnant women with uterine fibroids should have their BP closely monitored, and the preventive measures for HDP are necessary.

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The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Conflicts of interest

There are no conflicts of interest.

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