



# Real-World Experience of Adding Metformin in Pregnant Women with Type 1 Diabetes in a Chinese Population: A Retrospective Cohort

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## ABSTRACT

**Introduction:** Glycemic control in pregnant women with type 1 diabetes (T1D) is challenging with only insulin, and the incidence rate of adverse perinatal outcomes is high. Increasing data have indicated the safety and effect of metformin in pregnancy; however, no relevant data are available in pregnant women with T1D. We aimed to investigate glycemic control and perinatal outcomes in pregnant women with T1D in a Chinese population and explored the role of metformin in these patients.

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**Methods:** We obtained data of 38 pregnant women with T1D who received regular antenatal care and delivered at Peking Union Medical College Hospital (PUMCH) between 1 January 2006 and 31 May 2018. The perinatal outcomes of T1D patients who added metformin as adjunct treatment and those who remained on insulin-alone therapy were compared retrospectively.

**Results:** Being overweight was common (35.1%) in pregnant women with T1D. On average, the insulin dose increased by  $35.30 \pm 22.60$  unit/day during pregnancy. The cesarean delivery rate was high (65.8%), and fetal macrosomia was the main reason. The change of HbA1c in the metformin-insulin group was more prominent than in the insulin-only group ( $-1.47 \pm 1.17\%$  vs.  $-0.90 \pm 1.13\%$ ,  $p = 0.05$ ). There was no statistically significant difference in perinatal outcomes between the two groups.

**Conclusions:** The incidence of adverse perinatal outcomes in pregnant women with T1D was high. This study innovatively suggested that metformin could be safe and could contribute to improving glucose management in pregnant women with T1D.

**Keywords:** Metformin; Perinatal outcomes; Pregnancy; Type 1 diabetes

## INTRODUCTION

Pre-gestational diabetes (PGDM) is diabetes diagnosed before pregnancy, including type 1 diabetes (T1D), type 2 diabetes (T2D) or other special types of diabetes. Compared with gestational diabetes mellitus (GDM), patients with PGDM are at higher risk of adverse perinatal outcomes, which include maternal preeclampsia, babies that are large for gestational age (LGA) or have macrosomia, perinatal death, neonatal congenital malformation, neonatal hypoglycemia and hyperbilirubinemia [1, 2]. Among those with PGDM, the risk of poor perinatal outcomes in pregnancy complicated by T1D is higher than that for T2D [3]. A study from Sweden found that pregnant women with T1D had an eightfold risk of macrosomia compared with normal pregnant women [4]. However, the rate of pregnant women with T1D achieving target glycated hemoglobin (HbA1c) levels is low. In the UK, despite intensive support, only 15% of pregnant women with T1D achieve the target glycated hemoglobin (HbA1c) levels during early pregnancy, and only 40% achieve the target HbA1c levels after 24 weeks' gestation [5]. Improvement of glycemic control in pregnant women with T1D is urgently required. The incidence rate of T1D is relatively low in China, and there are few studies focused on pregnant women with T1D in the Chinese population.

It is well known that insulin resistance is prominent during pregnancy. The insulin dose can increase dramatically from pre-pregnancy to the third trimester (0.618–1.060 unit/kg) in T1D patients [6]. However, an increased insulin dose results in more maternal weight gain, which also contributes to poor perinatal outcomes [7]. In non-pregnant T1D patients, metformin significantly improved insulin sensitivity, thus reducing the insulin dose [8]. So far, there have been no reports of metformin in pregnant women with T1D, although there have been many studies on GDM or pregnant women with T2D suggesting its safety and effect [9].

Therefore, we aimed at investigating glycemic control and perinatal outcomes in pregnant women with T1D in a Chinese population

and exploring whether metformin has a role in these patients. In this study, we retrospectively analyzed the clinical data of pregnant women with T1D in Peking Union Medical College Hospital (PUMCH) in terms of blood glucose management and perinatal outcomes. Furthermore, we compared patients who added metformin as adjunct treatment with those on insulin alone.

## METHODS

We included T1D patients with singleton pregnancy who attended prenatal care and delivered in PUMCH between the 1 January 2006 and 31 May 2018. T1D was defined as patients having any one of the following criteria: (1) one or more positive islet autoantibodies; (2) insulin use only on the diagnosis date and a non-insulin glucose-lowering drug, if any, was introduced 6 months later. Pregnant women with T1D who had ever taken any dose of metformin during pregnancy were grouped as metformin plus insulin. T2D, GDM and special types of diabetes were all excluded. The study was approved by the Ethics Committee of PUMCH (approval no. ZS-1380), and the patients' written informed consents were obtained. The study was performed in accordance with the Declaration of Helsinki.

Electronic and handwritten medical records were all reviewed, and telephone visits were made when needed information was missing from medical records. Age, duration of diabetes, body mass index (BMI) and insulin injection methods were recorded. Weight, glycated hemoglobin (HbA1c) and insulin dose requirement were compared between pre-pregnancy and the third trimester. Pre-pregnancy HbA1c was defined as the last HbA1c tested within 3 months before pregnancy. HbA1c per trimester was defined as a single or a mean level during that trimester. Insulin dose recorded at the last visit within 3 months before pregnancy was defined as the pre-pregnancy insulin dose. Insulin dose recorded at the last visit at the obstetrics clinic before delivery was defined as insulin dose in the third trimester. Perinatal outcomes were recorded, including gestational weeks of delivery,

modes of delivery, preeclampsia or eclampsia, maternal weight gain, polyhydramnios, premature rupture of membranes, laceration of the perineum or lateral episiotomy, weight retention after 6 weeks of delivery, 1-min Apgar Score, macrosomia or LGA, low birth weight (LBW) or small for gestational age (SGA), neonatal hypoglycemia, neonatal intensive care units (NICU) admission, shoulder dystocia, neonatal jaundice and congenital malformations. Perinatal outcomes were also compared between patients in the metformin-insulin group and the insulin-only group. Overweight was defined as pre-pregnant BMI  $\geq 24$  kg/m<sup>2</sup>. Macrosomia was defined as birth weight of  $> 4000$  g; LGA was defined as a weight above the 90th percentile for that gestational age of Chinese infants. LBW was defined by the World Health Organization as a infant birth weight  $\leq 2499$  g, regardless of gestational age. SGA newborns were those who were smaller than normal for the gestational age, defined as a weight below the 10th percentile for the gestational age of Chinese infants. Neonatal hypoglycemia was defined as  $< 2.2$  mmol/l within 24 h and  $< 2.8$  mmol/l after 24 h, and neonatal jaundice was defined as hospitalization for neonatal hyperbilirubinemia.

### Statistical analysis

Statistical analysis was performed using SPSS 24.0 (SPSS, Inc). Descriptive analysis results were expressed as mean  $\pm$  standard deviation (SD) and percentages (%). The chi-square test or Fisher's exact test, where appropriate, was used for categorical variables. For normally distributed continuous variables, Student's *t* test was used. The Mann-Whitney *U* test was used for nonparametric variables. One-way ANOVA was also used when the change of HbA1c was analyzed.  $p < 0.05$  was accepted as a statistically significant difference.

## RESULTS

Forty-one patients with T1D delivered in our hospital from 1 January 2006 to 31 May 2018. One patient complicated by severe thrombocytopenia was excluded. Another two patients

were excluded because they did not receive antenatal care in our hospital. Thirty-eight pregnant women with T1D (mean age  $30.39 \pm 3.48$  years, BMI  $22.35 \pm 2.96$  kg/m<sup>2</sup>) were retrospectively analyzed. The mean duration of diabetes was  $7.91 \pm 5.80$  years; 35.1% of patients were overweight. The mean HbA1c before pregnancy was  $7.16 \pm 1.32\%$ . The pre-pregnancy insulin dose was  $0.64 \pm 0.23$  unit/kg day on average. HbA1c decreased by  $1.10 \pm 1.15\%$  on average from pre-pregnancy to the third trimester, and the mean HbA1c was  $5.98 \pm 0.82\%$  in the third trimester. The average amount of insulin increased  $35.30 \pm 22.60$  unit/day during pregnancy, and the mean amount of insulin in the third trimester was  $1.11 \pm 0.44$  unit/kg day (Table 1). The cesarean delivery rate was as high as 65.8%. Indications for cesarean section included macrosomia, malposition, contracted pelvic outlet, history of previous cesarean section and poor glucose control. For vaginal deliveries, the rate of laceration of the perineum or lateral episiotomy was high (76.9%). Weight retention at 6 weeks postpartum was common (87.1%), with an average retention weight of  $4.85 \pm 4.07$  kg. The mean birth weight was  $3513.95 \pm 806.37$  g, including three cases of LBW/SGA and 16 cases of macrosomia/LGA, which was the most common neonatal complication (42.1%). Although there was no difference in pre-pregnancy BMI between mothers of babies with macrosomia/LGA and normal gestational age (NGA) ( $p = 0.713$ ), gestational weight gain in mothers of macrosomia/LGA babies was higher than for NGA ( $p = 0.033$ ). Neonatal hypoglycemia was the second most common neonatal complication (28.9%), and three newborns were admitted into the NICU because of hypoglycemia. In addition, there were 4/38 cases of neonatal malformations. Two neonatal malformations occurred in the metformin-insulin group: one with polydactyly and the other with a slightly separated pelvis. Mothers of the two newborns had been prescribed metformin in pre-pregnancy and early-pregnancy, respectively. Levels of HbA1c in pre-pregnancy were high in both mothers, with 8.1% and 7.0%, respectively. There were also two neonatal malformations in the insulin-only group. One was polydactyly

**Table 1** Characteristics of T1D patients and comparison of groups

Variables		Metformin-insulin	Insulin only	<i>p</i> value
Age (years)	30.39 ± 3.48 ( <i>n</i> = 38)	30.30 ± 4.99 ( <i>n</i> = 10)	30.43 ± 2.89 ( <i>n</i> = 28)	0.828
Duration (years)	7.91 ± 5.80 ( <i>n</i> = 38)	4.83 ± 4.33 ( <i>n</i> = 10)	9.01 ± 5.93 ( <i>n</i> = 28)	0.055
BMI (kg/m <sup>2</sup> )	22.35 ± 2.96 ( <i>n</i> = 37)	22.21 ± 3.22 ( <i>n</i> = 10)	22.40 ± 2.91 ( <i>n</i> = 27)	0.824
Overweight	35.1% ( <i>n</i> = 37)	30.0% ( <i>n</i> = 10)	37.0% ( <i>n</i> = 27)	1.000
Chronic complications of diabetes	7.9% ( <i>n</i> = 38)	0.0% ( <i>n</i> = 10)	10.7% ( <i>n</i> = 28)	0.552
CS-II	34.2% ( <i>n</i> = 38)	30.0% ( <i>n</i> = 10)	35.7% ( <i>n</i> = 28)	1.000
First parity	92.1% ( <i>n</i> = 38)	80.0% ( <i>n</i> = 10)	96.4% ( <i>n</i> = 28)	0.164
Pre-pregnancy HbA1c (%)	7.16 ± 1.32 ( <i>n</i> = 30)	7.65 ± 1.24 ( <i>n</i> = 10)	6.92 ± 1.32 ( <i>n</i> = 20)	<b>0.033</b>
Late-pregnancy HbA1c (%)	5.98 ± 0.82 ( <i>n</i> = 28)	6.09 ± 1.05 ( <i>n</i> = 9)	5.92 ± 0.71 ( <i>n</i> = 19)	0.863
Change of HbA1c (%)	− 1.10 ± 1.15 ( <i>n</i> = 25)	− 1.47 ± 1.17 ( <i>n</i> = 9)	− 0.90 ± 1.13 ( <i>n</i> = 19)	0.202
Pre-pregnancy insulin dose (U/kg·d)	0.64 ± 0.23 ( <i>n</i> = 35)	0.59 ± 0.24 ( <i>n</i> = 10)	0.66 ± 0.23 ( <i>n</i> = 25)	0.559
Late-pregnancy insulin dose (U/kg·d)	1.11 ± 0.44 ( <i>n</i> = 34)	1.01 ± 0.42 ( <i>n</i> = 10)	1.15 ± 0.45 ( <i>n</i> = 24)	0.508
Change of insulin dose (U/d)	35.30 ± 22.60 ( <i>n</i> = 31)	35.9 ± 22.44 ( <i>n</i> = 10)	35.04 ± 23.22 ( <i>n</i> = 21)	0.933
Change of weight (kg)	15.21 ± 10.38 ( <i>n</i> = 37)	13.45 ± 5.66 ( <i>n</i> = 10)	15.87 ± 11.69 ( <i>n</i> = 27)	0.706

The bold values are represents that *p* value is < 0.05

Data are shown as mean ± standard deviation (mean ± SD) or percentage (%)

BMI body mass index, HbA1c hemoglobin A1c, CS-II continuous subcutaneous insulin infusion

and the other cardiac malformation with a bright spot in the left ventricle. There were 3/38 cases of shoulder dystocia and 2/38 cases of neonatal hyperbilirubinemia in our cohort (Table 2).

Ten patients were treated with metformin during pregnancy. Three of them started metformin from pre-pregnancy, four from early pregnancy and two from late pregnancy. According to the medical records, clinicians prescribed metformin mostly because satisfactory glucose control was not achieved with a high insulin dose (over 0.8 unit/kg). There were no significant differences in age, duration of diabetes, pre-pregnancy BMI and pre-pregnancy insulin dose between metformin-insulin group and insulin-only group (*p* > 0.05). Three patients in the insulin-only group were complicated by chronic diabetic complications,

while none in the metformin-insulin group. One of the three patients experienced preeclampsia and delivered a 1660-g male baby in gestational week 30. The baby was admitted to the NICU as a premature infant. Another patient delivered an LBW neonate at 37 + 2 weeks who also experienced neonate hypoglycemia and was admitted to the NICU. Rates of continuous subcutaneous insulin infusion (CS-II) were comparable in the metformin-insulin group and insulin-only group, with 30.0% and 35.7%, respectively. HbA1c in pre-pregnancy was higher in the metformin-insulin group (7.65 ± 1.24% vs. 6.92 ± 1.32%, *p* = 0.033). Although not statistically significant, the decrease of HbA1c in the metformin-insulin group was more obvious (− 1.47 ± 1.17% vs. − 0.90 ± 1.13%, *p* = 0.202). In the third trimester, the HbA1c levels in the two groups were

**Table 2** Perinatal outcomes of T1D patients and comparison of groups

Variables		Metformin-insulin	Insulin only	<i>p</i> value
1-Minute Apgar Score	9.82 ± 0.73 ( <i>n</i> = 38)	10.00 ± 0.00 ( <i>n</i> = 10)	9.75 ± 0.85 ( <i>n</i> = 28)	0.288
Preterm delivery	10.5% ( <i>n</i> = 38)	0.0% ( <i>n</i> = 10)	14.3% ( <i>n</i> = 28)	0.556
Caesarean section	65.8% ( <i>n</i> = 38)	50.0% ( <i>n</i> = 10)	71.4% ( <i>n</i> = 28)	0.263
Preeclampsia/eclampsia	7.9% ( <i>n</i> = 38)	0.0% ( <i>n</i> = 10)	10.7% ( <i>n</i> = 28)	0.552
Polyhydramnios	5.3% ( <i>n</i> = 38)	10.0% ( <i>n</i> = 10)	3.6% ( <i>n</i> = 28)	0.462
Premature rupture of membranes	10.5% ( <i>n</i> = 38)	10.0% ( <i>n</i> = 10)	10.7% ( <i>n</i> = 28)	1.000
Laceration of perineum or lateral episiotomy	76.9% ( <i>n</i> = 13)	100% ( <i>n</i> = 5)	62.5% ( <i>n</i> = 8)	0.231
Weight retention in postpartum of 6 weeks	87.1% ( <i>n</i> = 31)	88.9% ( <i>n</i> = 9)	86.4% ( <i>n</i> = 22)	1.000
Weight retention in postpartum of 6 weeks (kg)	4.85 ± 4.07 ( <i>n</i> = 26)	4.39 ± 2.22 ( <i>n</i> = 8)	5.06 ± 4.71 ( <i>n</i> = 18)	0.781
Birth height (cm)	49.08 ± 2.59 ( <i>n</i> = 37)	49.90 ± 2.47 ( <i>n</i> = 10)	48.78 ± 2.60 ( <i>n</i> = 27)	0.323
Birth weight (g)	3513.95 ± 806.37 ( <i>n</i> = 38)	3817.00 ± 910.74 ( <i>n</i> = 10)	3405.71 ± 753.93 ( <i>n</i> = 28)	0.371
LBW/SGA	7.9% ( <i>n</i> = 38)	0.0% ( <i>n</i> = 10)	10.7% ( <i>n</i> = 28)	0.552
Macrosomia/LGA	42.1% ( <i>n</i> = 38)	50.0% ( <i>n</i> = 10)	39.3% ( <i>n</i> = 28)	0.713
Neonatal hypoglycemia	28.9% ( <i>n</i> = 38)	10.0% ( <i>n</i> = 10)	35.7% ( <i>n</i> = 28)	0.225
NICU	18.4% ( <i>n</i> = 38)	10.0% ( <i>n</i> = 10)	21.4% ( <i>n</i> = 28)	0.650
Shoulder dystocia	7.9% ( <i>n</i> = 38)	10.0% ( <i>n</i> = 10)	7.1% ( <i>n</i> = 28)	1.000
Neonatal malformation	10.5% ( <i>n</i> = 38)	20.0% ( <i>n</i> = 10)	7.1% ( <i>n</i> = 28)	0.279
Neonatal hyperbilirubinemia	5.3% ( <i>n</i> = 38)	20.0% ( <i>n</i> = 10)	0.0% ( <i>n</i> = 28)	0.064

Data are shown as mean ± standard deviation (mean ± SD) or percentage (%)

*BMI* body mass index, *NICU* neonatal intensive care unit, *LBW* low birth weight, *SGA* small for gestational age, *LGA* large for gestational age

equivalent ( $6.09 \pm 1.05\%$  vs.  $5.92 \pm 0.71\%$ ,  $p = 0.863$ ). One-way ANOVA did not indicate that the levels of baseline HbA1c had an impact on the levels of HbA1c reduction (data not shown). Whether in pre-pregnancy or in the third trimester, there was no difference in the amount of insulin between the two groups. Patients in the metformin-insulin group gained less weight during pregnancy; however, no statistical difference

was reached (Table 1). In all, there was no difference in perinatal outcomes between the two groups. When patients with chronic diabetic complications were excluded, there was still no difference in perinatal events (data not shown). However, the metformin-insulin group seemed to experience a lower incidence rate than the insulin-only group in most adverse perinatal outcomes we investigated (Table 2).

## DISCUSSION

It is universally recognized that insulin resistance plays a vital role in pregnancy, as the placenta physically releases progesterone, prolactin and cortisol. Insulin resistance has also been proposed as a critical reason for suboptimal glycemic control in T1D [10], although the traditional view is still that T1D results from an autoimmune destruction of pancreatic  $\beta$ -cells, and the predominant pathophysiology is an essentially absolute insulin deficiency. Insulin resistance is associated with increased insulin dose requirements and further weight gain. Including 237 pregnancies affected by T1D, a study indicated that the daily insulin dose increased by 52 units per day on average [11]. Consistent with the previous study, in our study, the amount of insulin in pregnancy increased  $33.72 \pm 23.38$  units/day on average. Similar to other studies, obesity was more prevalent in T1D women than in non-diabetic women. In our study, 35.1% patients were overweight before pregnancy, higher than the reported non-diabetic overweight incidence (14.4%) [12]. It is reported that maternal BMI and gestational weight gain are critical risk factors for poor perinatal outcomes [13–15]. Women who seemingly achieve adequate glycemic control in pregnancy continue to experience a higher risk of excess fetal growth, leading to LGA or macrosomia [16]. In our study, the mean HbA1c was  $5.98 \pm 0.82\%$  in the third trimester. However, 16 neonates (42.1%) had macrosomia/LGA, which was the most common neonatal complication. We found that gestational weight gain might explain the high incidence rate of macrosomia/LGA.

There has been growing interest in exploring the role of metformin as an adjunct to insulin therapy in T1D, with the aim of improving insulin sensitivity and glycemic control, limiting the insulin dose and weight gain. REMOVAL was the largest multicenter, double-blind, placebo-controlled trial assessing the effect of metformin over 3 years in 428 adults (age > 40 years) with T1D. HbA1c was reduced by metformin over 3 years ( $-0.13\%$ , 95% CI

$-0.22$  to  $-0.04$ ,  $p = 0.006$ ), which was primarily accounted for by a reduction at 3 months ( $-0.24\%$ , 95% CI  $-0.34$  to  $-0.13$ ,  $p < 0.0001$ ). REMOVAL also demonstrated a favorable effect of metformin on body weight, insulin dose requirement and lipids, similar to previous meta-analysis of smaller studies. However, as metformin can go across the placenta, clinicians are concerned about the safety of metformin during pregnancy. Recently, increasing evidence has supported the safety of metformin during pregnancy [17]. A meta-analysis including five RCTs revealed less weight gain and fewer hypertension disorders in the metformin group [18]. A systematic review published in the British Medical Journal (BMJ) in 2015 found a significant downward trend in the risk of hypoglycemia in the metformin group [19]. Metformin may further reduce NICU admission and cesarean delivery rates [20]. Compared with insulin alone, metformin as adjunct therapy in T2D pregnant women with insulin resistance was valuable; it could reduce hypoglycemia, hospital stay days and respiratory distress syndrome [21]. We retrospectively compared glucose management and perinatal outcomes between pregnant women with T1D on metformin plus insulin and those on insulin only. As we mentioned before, metformin was usually prescribed in cases of poor glucose control with high-dose insulin in our study, resulting in higher baseline HbA1c levels in the metformin-insulin group. Our study suggested that although there was a higher HbA1c level in the metformin-insulin group in pre-pregnancy, the HbA1c decreased more pronouncedly in the metformin-insulin group without increasing the insulin dosage. It indicated that adjunct metformin in pregnant women with T1D with poor glycemic control may be valuable. Although no perinatal outcomes achieved statistical significance, maternal weight gain, neonatal hypoglycemia and NICU admission, neonatal hypoglycemia and NICU admission presented a declining trend, which is consistent with studies of pregnant women with T2D [21]. Since three patients in the insulin-alone group had chronic diabetic complications and two of them experienced adverse perinatal outcomes, which might bias the results, we likewise carried out statistical

analysis excluding these three patients, and the results corresponded with the previous ones. The metformin-insulin group seemed to experience more neonatal malformation, neonatal hyperbilirubinemia and macrosomia, but no statistically significant differences were reached. In summary, we discovered no increased adverse perinatal events with metformin therapy.

This pioneering study fills in the knowledge gap concerning metformin in T1D patients during pregnancy, providing a justification for further prospective and large-scale studies. Nevertheless, there are some limitations to our study. First, T1D prevalence is much lower in China than in Caucasian populations [22]. Moreover, a nationwide cohort study in Taiwan recently reported that T1D greatly impairs female fertility [23]. As a result, although all pregnant women with T1D who gave birth between 1 January 2006 and 31 May 2018 were included, the sample size of the study was relatively small. The statistical power was insufficient for limited subject numbers, especially in evaluating the perinatal outcomes. It is appropriate to consider this as a pioneering study, and definite conclusions should be drawn with caution. Second, levels of pre-pregnancy HbA1c were higher in the metformin-insulin group. Generally, the higher the baseline HbA1c, the greater the HbA1c reduction that might be seen after intervention; that the patients in this group might be more motivated could be one of the reasons. Further prospective studies are needed in patients with equivalent baseline HbA1c levels. Third, as a retrospective study, it was impractical to thoroughly investigate the adverse drug reactions to metformin, such as gastrointestinal discomfort. Fourth, previous studies indicated that metformin helps to reduce oxidative stress and may have a direct beneficial effect on insulin secretion impaired by oxidative stress in animal models and non-pregnant diabetic patients [24, 25]; we propose that the benefits of metformin beyond glycemic control itself makes it a promising adjunct treatment in pregnant type 1 diabetes patients. However, as a retrospective study, we were unable to measure cytokines in these patients.

## CONCLUSIONS

It is vital to explore whether oral anti-diabetic medication has its place in pregnant women with T1D, as insulin resistance plays an important role and glucose management was usually unsatisfactory for patients solely on insulin. This research fills the knowledge gap in the field of metformin use in pregnant women with T1D, suggesting that metformin might be safe and effective in these patients. Larger and prospective studies are needed to confirm this.

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**Disclosures.** Fan Ping: a physician at the Department of Endocrinology in PUMCH, who focuses on the management of diabetic pregnancy. Mingqun Deng: postgraduate student at PUMCH. Xiao Zhai: postgraduate student at PUMCH. Yingna Song: an obstetrician in the Department of Gynaecology and Obstetrics at PUMCH. Xinhua Xiao: a professor in the Department of Endocrinology at PUMCH; he has focused on investigating the role of the intrauterine environment in glucose

metabolism for many years. The authors have no other relevant disclosures.

**Compliance with Ethics Guidelines.** This retrospective study was approved by the Ethics Committee of PUMCH (approval no. ZS-1380), and written informed consent was obtained from all patients. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of PUMCH and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Data Availability.** The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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