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Fondaparinux Results in Similar Pregnancy Outcomes with Lower Adverse Reaction Rates Compared to Low Molecular Weight Heparin in Chinese Recurrent Miscarriage Women

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Fondaparinux inhibits thrombin generation by inactivating factor Xa, which has the potential to treat recurrent miscarriage (RM). However, more clinical evidence is required to support its application in Chinese women with RM. This research aimed to compare the live birth rate, gestational weeks at delivery, birth weight, Apgar score of newborns, and adverse reaction rates between fondaparinux and low molecular weight heparin (LMWH) in Chinese women with RM. Totally, 132 women with RM treated with fondaparinux or LMWH were included in this retrospective study. According to the corresponding treatment, women with RM were divided into the fondaparinux cohort (N = 45) and LMWH cohort (N = 87). The live birth rate was 68.9% in the fondaparinux cohort and 56.3% in the LMWH cohort, which was not different between the two cohorts (P = 0.161). Multivariable logistics regression analysis suggested that only previous miscarriage times (≥ 4 times vs. < 4 times) were independently related to a lower possibility of live birth in women with RM (odds ratio = 0.431, P = 0.036). It was also observed that gestational weeks at delivery (38.1 ± 1.4 vs. 37.7 ± 1.7 weeks) (P = 0.258), birth weight (2,923.7 ± 355.0 vs. 2,807.8 ± 334.0 g) (P = 0.144), and Apgar score of newborns (9.8 ± 0.5 vs. 9.6 ± 0.8) (P = 0.175) were not different between the fondaparinux cohort and LMWH cohort. Inspiringly, the total adverse reaction rate was reduced in the fondaparinux cohort vs. the LMWH cohort (20.0% vs. 37.9%) (P = 0.036). Fondaparinux results in similar pregnancy outcomes with lower adverse reaction rates compared to LMWH in Chinese women with RM.

Keywords: fondaparinux; low molecular weight heparin; pregnancy outcomes; recurrent miscarriage; safety
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Introduction

Recurrent miscarriage (RM) is an ongoing problem in women, which occurs in nearly 2.5% of women trying to conceive (Dimitriadis et al. 2020). In China, approximately 1% to 5% of women experience RM, which severely affects their mental health and places a huge economic burden (Writing Group of Chinese Expert Consensus on Diagnosis and Treatment of Spontaneous Abortion 2020; Wang et al. 2023). Thrombophilia is a common risk factor for RM with a prevalence of approximately 10% in women with RM, which refers to a state of hypercoagulability due to inherited or acquired defects in anticoagulant factors or fibrinolysis (Nahas et al. 2018; Alecsandru et al. 2021; Liu et al. 2021; Shehata et al. 2022). Without appropriate control, thrombophilia can lead to vascular thrombosis and adverse pregnancy outcomes in women with RM (Middeldorp et al. 2022). Low molecular weight heparin (LMWH) is generally recommended to treat women with RM with thrombophilia, which is effective in improving pregnancy outcomes (Schreiber et al. 2018; Coomarasamy et al. 2021). However, LMWH would unavoidably cause adverse reactions in women with RM, such as thrombocytopenia, allergic skin reactions, vaginal bleeding, and ecchymosis (Bai et

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al. 2021; Chen et al. 2022; Mu et al. 2023; Nekooghadam et al. 2023). At the same time, the option of anticoagulants apart from LMWH for women with RM is limited (McNamee et al. 2012; Coomarasamy et al. 2021). Therefore, exploring candidate anticoagulant therapies is necessary to improve pregnancy outcomes in women with RM.

Fondaparinux is a synthetic heparin pentasaccharide with a molecular weight of 1,728 Da, which suppresses thrombin generation by inhibiting factor Xa (Zhang et al. 2019; Zhang et al. 2022). In recent years, a few studies have reported the efficacy and safety of fondaparinux in improving pregnancy outcomes in women with RM (Winger and Reed 2009; Zhao et al. 2021). For example, a prior study observes that the pregnancy success rate is 59% and 58% in women with RM receiving fondaparinux and enoxaparin; meanwhile, fondaparinux achieves comparable safety to enoxaparin (Winger and Reed 2009). Notably, another study illustrates that the pregnancy outcomes, including stillbirth, abortion, premature delivery, full-term delivery, and live birth rate, are not different between women with RM receiving fondaparinux and those receiving LMWH (Zhao et al. 2021). Interestingly, this previous study finds that the total adverse reaction occurrence rate is lower in women with RM receiving fondaparinux (5.76%) compared with those receiving LMWH (19.12%) (Zhao et al. 2021). Given that fondaparinux has just been launched in China, more real-world clinical evidence is required to support its use in Chinese women with RM; meanwhile, there are no studies that compare the effect of fondaparinux and LMWH on the Apgar score of newborns, which is an important index to evaluate the health status of newborns.

Accordingly, this research aimed to compare the live birth rate, gestational weeks at delivery, birth weight, Apgar score of newborns, and adverse reaction rates between fondaparinux and LMWH in Chinese women with RM.

Methods

Patients

In this retrospective research, we included 132 women with RM who were treated with fondaparinux (N = 45) or LMWH (N = 87) from February 2019 to August 2022. The eligible criteria were: i) diagnosed as RM (the definition of RM was times of miscarriage ≥ 3) (Royal College of Obstericians and Gynaecologists 2011); ii) with a hypercoagulable state; iii) with singleton pregnancies; iv) treated with fondaparinux or LMWH; v) with completed clinical data for analyses. Patients with the following criteria were excluded: i) combined with hemorrhagic diseases or coagulation disorders; ii) combined with acute infective endocarditis, peptic ulcers, severe liver insufficiencies, or severe renal insufficiencies; iii) with histories of active bleeding in trauma or post-operation. Besides, this research obtained approval from the Ethics Committee of The Fourth Hospital of Shijiazhuang. All patients signed the informed consent.

Treatment

Patients treated with fondaparinux were defined as the fondaparinux cohort, while those treated with LMWH were defined as the LMWH cohort. The fondaparinux and LMWH (enoxaparin) were administrated conventionally from confirmation of pregnancy until delivery or 24 weeks of gestation at 2.5 mg/day and 40 mg/day, respectively (Winger and Reed 2009; Clark et al. 2010; Pasquier et al. 2015). The treatment was given for at least 12 weeks. The decision to prescribe fondaparinux or enoxaparin was primarily based on the patient's willingness and the physician's suggestions. Combination medications of intravenous immunoglobulin (IVIG) and tumor necrosis factor inhibitor (TNFi) were screened and collected.

Data collection

Demographics, previous miscarriage times, conception type, treatment, and study outcomes were collected. The primary outcome of this research was the live birth rate between the two cohorts. The live birth was defined as the complete expulsion or extraction of the product of fertilization from its mother, regardless of the duration of the pregnancy, with breaths or any other evidence of life after separation (Zegers-Hochschild et al. 2009). The other outcomes were gestational weeks at delivery, birth weight, Apgar score of newborns, and adverse reaction rate between the two cohorts. The Apgar score of newborns was a convenient method for reporting the status of the newborn infant, which was based on five components: color, heart rate, reflexes, muscle tone, and respiration. Each component was scored 0 to 2 (American Academy Of Pediatrics Committee On Fetus and Newborn et al. 2015).

Statistical analyses

SPSS v.26.0 (IBM, Armonk, NY, USA) was used to analyze data. The Kolmogorov-Smirnov test was used to check continuous variables for normal distribution. The comparison analyses between cohorts were conducted through the student t-test, Chi-square test, or Fisher's exact test. Factors associated with the live birth rate and total adverse reaction rate among women with RM were explored by logistics regression analyses. Anticoagulant therapy (fondaparinux vs. LMWH), age (≥ 35 years vs. < 35 years), body mass index (BMI) (≥ 24 kg/m^2 vs. < 24 kg/m^2), previous miscarriage times (≥ 4 times vs. < 4 times), conception type (assisted reproductive technology vs. spontaneous), combination: IVIG (yes vs. no), and combination: TNFi therapy (yes vs. no) were included in the univariable analysis. Of note, age ≥ 35 years was defined as advanced maternal age, and BMI ≥ 24 kg/m^2 was defined as obesity (Satpathy et al. 2008; Lean et al. 2017); therefore, we cut the age by 35 years and BMI by 24 kg/m^2. Meanwhile, the included patients had at least 3 times of miscarriage. Therefore, we cut the previous miscarriage times by < 4 and ≥ 4. The enter method was used in the subsequent multivariable analyses. A *P* value less than 0.05 indicated that

Table 1. Clinical characteristics of women with recurrent miscarriage (RM).

Characteristics	LMWH cohort (N = 87)	Fondaparinux cohort (N = 45)	*P* value
Age (years)			
Mean ± SD	33.3 ± 2.8	32.8 ± 3.0	0.389
≥ 35, n (%)	28 (32.2)	19 (42.2)	0.254
BMI (kg/m2)			
Mean ± SD	22.5 ± 2.2	23.0 ± 2.4	0.221
≥ 24, n (%)	23 (26.4)	12 (26.7)	0.977
Previous miscarriage times			
Mean ± SD	3.9 ± 1.0	3.6 ± 0.7	0.240
≥ 4, n (%)	48 (55.2)	23 (51.1)	0.657
Conception type, n (%)			0.380
Spontaneous	76 (87.4)	42 (93.3)	
Assisted reproductive technology	11 (12.6)	3 (6.7)	
Combination: IVIG, n (%)	78 (89.7)	37 (82.2)	0.227
Combination: TNFi therapy, n (%)	17 (19.5)	12 (26.7)	0.349

LMWH, low molecular weight heparin; SD, standard deviation; BMI, body mass index; IVIG, intravenous immunoglobulin; TNFi, tumor necrosis factor inhibitor.

there was a statistical significance.

Results

Clinical features of the fondaparinux cohort and the LMWH cohort

The mean age of the fondaparinux cohort and the LMWH cohort was 32.8 ± 3.0 years and 33.3 ± 2.8 years, respectively (mean ± standard deviation, SD) (P = 0.389). Meanwhile, the proportion of women aged ≥ 35 years was 42.2% and 32.2% in the fondaparinux cohort and the LMWH cohort, respectively (P = 0.254). All clinical features were not different between the two cohorts (all P > 0.05), including BMI, previous miscarriage times, and conception type. In addition, the proportion of women who received the combination of IVIG (P = 0.227) and TNFi therapy (P = 0.349) did not differ between the two cohorts, either. The specific clinical information of the two cohorts is listed in Table 1.

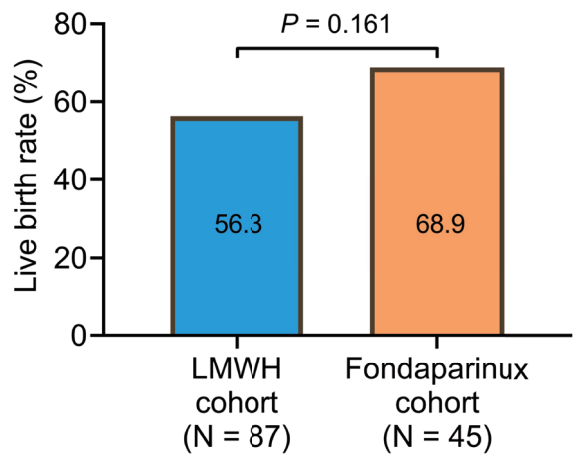

Fig. 1. Comparison of live birth rate between the fondaparinux cohort and the low molecular weight heparin (LMWH) cohort.

Live birth rate in the fondaparinux cohort and the LMWH cohort

Live birth rate was 68.9% in the fondaparinux cohort and 56.3% in the LMWH cohort, respectively. Although live birth rate was slightly higher in the fondaparinux cohort compared to the LMWH cohort, it did not achieve statistical significance (P = 0.161) (Fig. 1). According to univariable logistics regression analysis, anticoagulant therapy (fondaparinux vs. LMWH) [odds ratio (OR) = 1.717, P = 0.163] was not correlated with live birth. Age (≥ 35 years vs. < 35 years) (OR = 0.471, P = 0.043) and previous miscarriage times (≥ 4 times vs. < 4 times) (OR = 0.397, P = 0.013) were related to a lower possibility of live birth. After adjustment, only previous miscarriage times (≥ 4 times vs. < 4 times) independently estimated a lower possibility of live birth (OR = 0.431, P = 0.036) (Table 2).

Gestational weeks at delivery, birth weight, and Apgar score of newborns in the fondaparinux cohort and the LMWH cohort

Gestational weeks at delivery were 38.1 ± 1.4 weeks in the fondaparinux cohort, and 37.7 ± 1.7 weeks in the LMWH cohort, which were not different between the two cohorts (P = 0.258) (Fig. 2A). Birth weight was 2,923.7 ± 355.0 g and 2,807.8 ± 334.0 g in the fondaparinux cohort and the LMWH cohort, respectively, which did not differ between the two cohorts (P = 0.144) (Fig. 2B). Apgar score of newborns was 9.8 ± 0.5 and 9.6 ± 0.8 in the fondaparinux cohort and the LMWH cohort, respectively, which was not different between the two cohorts (P = 0.175) (Fig. 2C).

Table 2. Logistics regression analyses of live birth among women with recurrent miscarriage (RM).

Factors	Univariable analysis		Multivariable analysis	
	P value	OR (95% CI)	*P* value	OR (95% CI)
Anticoagulant therapy, fondaparinux vs. LMWH	0.163	1.717 (0.803-3.672)	0.133	1.898 (0.824-4.372)
Age, ≥ 35 years vs. < 35 years	0.043	0.471 (0.227-0.976)	0.058	0.434 (0.183-1.027)
BMI, ≥ 24 kg/m^2 vs. < 24 kg/m^2	0.625	0.822 (0.375-1.802)	0.446	0.713 (0.299-1.700)
Previous miscarriage times, ≥ 4 times vs. < 4 times	0.013	0.397 (0.192-0.823)	0.036	0.431 (0.196-0.948)
Conception type, assisted reproductive technology vs. spontaneous	0.158	0.446 (0.145-1.370)	0.560	0.684 (0.190-2.456)
Combination: IVIG, yes vs. no	0.086	2.483 (0.880-7.009)	0.096	2.611 (0.843-8.085)
Combination: TNFi therapy, yes vs. no	0.145	1.958 (0.793-4.830)	0.055	2.691 (0.978-7.405)

OR, odds ratio; CI, confidence interval; LMWH, low molecular weight heparin; BMI, body mass index; IVIG, intravenous immunoglobulin; TNFi, tumor necrosis factor inhibitor.

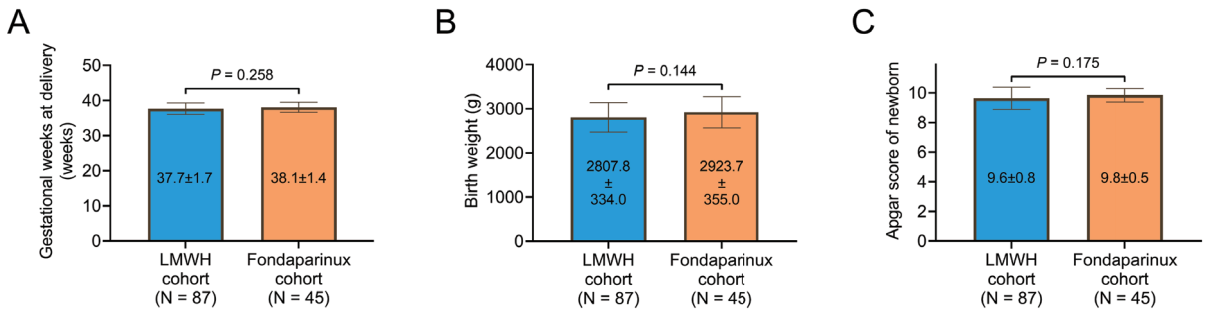

Fig. 2. Comparison of gestational weeks at delivery, birth weight, and Apgar score of newborns between the fondaparinux cohort and the low molecular weight heparin (LMWH) cohort.
Gestational weeks at delivery (A), birth weight (B), and Apgar score of newborns (C) were not different between the fondaparinux cohort and the LMWH cohort. Data are shown as mean ± SD.

Subgroup analyses for live birth, gestational weeks at delivery, birth weight, and Apgar score of newborns

In women aged ≥ 35 years (84.2% vs. 25.0%) (P < 0.001), with a BMI ≥ 24 kg/m^2 (83.3% vs. 43.5%) (P = 0.024), and receiving a combination with IVIG (78.4% vs. 56.4%) (P = 0.022), live birth rates were increased in the fondaparinux cohort compared to the LMWH cohort. In patients with other clinical features, including previous miscarriage times, conception type, and combination with TNFi therapy, live birth rates were not different between the two cohorts (all P > 0.05) (Supplementary Table S1).

In patients with previous miscarriage times < 4 or ≥ 4, gestational weeks at delivery, bright weight, and Apgar score of newborn were not different between the fondaparinux cohort and the LMWH cohort (all P > 0.05) (Supplementary Table S2).

Adverse reaction rate in the fondaparinux cohort and the LMWH cohort

The total adverse reaction rate was decreased in the fondaparinux cohort vs. the LMWH cohort (20.0% vs. 37.9%) (P = 0.036). Notably, vaginal bleeding (8.9% vs. 16.1%) (P = 0.253), rash (4.4% vs. 12.6%) (P = 0.217), ecchymosis (2.2% vs. 10.3%) (P = 0.163), elevated transaminase (4.4% vs. 6.9%) (P = 0.715), thrombocytopenia (2.2% vs. 5.7%) (P = 0.663), and gastrointestinal reaction (2.2% vs. 4.6%) (P = 0.661) were not different between the two cohorts (Table 3). According to multivariate logistics regression analyses, only anticoagulant therapy (fondaparinux vs. LMWH) was independently related to a lower risk of total adverse reaction (OR = 0.337, P = 0.018) (Supplementary Table S3).

Discussion

Both fondaparinux and LMWH are anticoagulant drugs, which are predominantly applied in preventing thrombosis and thromboembolic diseases (Mastroiacovo et al. 2016; Sayar et al. 2021; Parvizi et al. 2022; Wang et al. 2022). Regarding their application during pregnancy, a few studies have indicated that fondaparinux has a similar effect on improving pregnancy outcomes compared to LMWH in women with RM (Winger and Reed 2009; Zhao et al. 2021). Nevertheless, relevant evidence in Chinese women with RM is still limited. In the current study, we observed that the fondaparinux achieved a live birth rate of 68.9%, and LMWH achieved a live birth rate of 56.3% in women with RM. The live birth rate was slightly higher in RM who were treated with fondaparinux compared with those who were treated with LMWH but did not achieve statistical significance. This finding was consistent with a previous study (Zhao et al. 2021). The possible explanations might be that fondaparinux could bind to antithrombin and

Table 3. Comparison of adverse reaction rate between cohorts.

Adverse reaction, n (%)	LMWH cohort (N = 87)	Fondaparinux cohort (N = 45)	*P* value
Total adverse reaction	33 (37.9)	9 (20.0)	0.036
Vaginal bleeding	14 (16.1)	4 (8.9)	0.253
Rash	11 (12.6)	2 (4.4)	0.217
Ecchymosis	9 (10.3)	1 (2.2)	0.163
Elevated transaminase	6 (6.9)	2 (4.4)	0.715
Thrombocytopenia	5 (5.7)	1 (2.2)	0.663
Gastrointestinal reaction	4 (4.6)	1 (2.2)	0.661

LMWH, low molecular weight heparin.

inhibit factor Xa activation, which further suppressed thrombin formation and thrombus enlargement, thus restoring fetal blood oxygen supply (De Carolis et al. 2015; Bauersachs 2023). In terms of LMWH, it had a slightly different anticoagulant mechanism to fondaparinux, but their anticoagulant effects were similar (James 2007; Knol et al. 2010; Mu et al. 2023). Therefore, live birth rate was not different between women with RM who were treated with fondaparinux and those who were treated with LMWH. Our multivariable analysis suggested that previous miscarriage times ≥ 4 times independently estimated a lower possibility of live birth in women with RM. This finding was partly in line with previous studies (Lund et al. 2012; Hansen et al. 2016). A potential reason might be that increased times of miscarriage would lead to blocked fallopian tubes, cervical adhesions, and endometriosis, which could ultimately result in lower live birth rates (Brown et al. 2008).

Other pregnancy outcomes, such as gestational weeks at delivery, birth weight, and Apgar score of newborns, are also major concerns in women with RM (Giannubilo and Tranquilli 2012). According to a previous study, no differences are found in birth weight and gestational age at delivery between women with RM receiving fondaparinux and those receiving enoxaparin (Winger and Reed 2009). In this study, it was observed that the gestational weeks at delivery (38.1 ± 1.4 vs. 37.7 ± 1.7 weeks) and birth weight (2,923.7 ± 355.0 vs. 2,807.8 ± 334.0 g) were not different between women with RM who were treated with fondaparinux and those who were treated with LMWH. Our finding was in accordance with a previous study (Winger and Reed 2009). Apart from these two discoveries, we also found that Apgar score was 9.8 ± 0.5 and 9.6 ± 0.8 in women with RM who were treated with fondaparinux and those who were treated with LMWH, which did not achieve statistical significance. A possible reason would be that fondaparinux and LMWH might not cross the placenta; therefore, they could barely affect newborns (Lagrange et al. 2002; Giannubilo and Tranquilli 2012). Hence, the Apgar score of newborns was not affected by fondaparinux or LMWH.

A previous study has compared the safety between fondaparinux and LMWH in women with RM, which discloses that the total incidence of adverse reactions is lower in women with RM receiving fondaparinux compared to those receiving LMWH (Zhao et al. 2021). In line with this previous study (Zhao et al. 2021), we also discovered that the total adverse reaction rate was decreased in women with RM treated with fondaparinux vs. those treated with LMWH. The reasons behind this would be that: (1) Fondaparinux did not inhibit thrombin activity, leading to a lower possibility of inducing adverse reactions (Zhang et al. 2019). (2) Fondaparinux was metabolized by the kidneys and could barely affect liver functions, leading to a higher safety in women with RM (Lieu et al. 2002). Therefore, fondaparinux reduced the incidence of adverse reactions compared to LMWH in women with RM. Considering that fondaparinux was less likely to cause adverse reactions in women with RM compared to LMWH and had a small impact on the fetus, the benefits of fondaparinux should outweigh LMWH in women with RM. Our study also discovered that the most common adverse reactions were vaginal bleeding (8.9%), rash (4.4%), and elevated transaminase (4.4%) in women with RM who were treated with fondaparinux, and they were vaginal bleeding (16.1%), rash (12.6%), and ecchymosis (10.3%) in those who were treated with LMWH. These findings were partly in line with a previous study (Zhao et al. 2021). Our discoveries suggested that fondaparinux had superior safety profiles compared to LMWH in women with RM.

Some limitations should be mentioned. (1) This was a retrospective study; thus, information and selection bias might be hard to eliminate. (2) The number of women with RM in fondaparinux cohort and LMWH cohort was unmatched, which might affect the results of this study. (3) This was a nonintervention study; thus, our findings should be validated by further randomized, controlled trials.

In summary, fondaparinux possesses the comparable ability to enhance pregnancy outcomes as LMWH, with lower adverse reaction rates in Chinese women with RM. Clinically, fondaparinux may have the potential to serve as a candidate for LMWH in women with RM.

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Conflict of Interest

The authors declare no conflict of interest.

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Supplementary Files

Please find supplementary file(s);
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