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RESEARCH ARTICLE

LMWH prophylaxis in pregnancy outcomes of women with suspected protein S deficiency: a retrospective case-control study

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Abstract **Given the maternal hypercoagulability during pregnancy, thrombophilia may increase the risk of adverse pregnancy outcomes (APOs). This retrospective case-control study aimed to assess whether low-molecular-weight heparin (LMWH) could improve APOs in women with protein S (PS) deficiency. We selected 35 pregnant women who were considered for potential PS deficiency, and 70 healthy pregnant women were randomly selected as the control group. Two or more consecutive miscarriages were more frequent in pregnant women with PS deficiency than in the control group (12/35 vs. 4/70, $P = 0.0001$). Ten pregnant women with PS deficiency conceived by *in vitro* fertilization-embryo transfer (IVF-ET), which was significantly higher than the number of controls who conceived by IVF-ET (4/70, $P = 0.0012$). All 20 women in the LMWH-treated group ($P = 0.001$) had live births, which were significantly higher than that in the LMWH-untreated group (8/15, 53.3%). In the subgroup aged ⩽ 32 years of age, the number of live births in both groups was 7 (7/7, 100%) and 7 (7/12, 58.3%), respectively ($P = 0.106$). In conclusion, impediments to spontaneous conception and an elevated incidence of pregnancy loss may be associated with PS deficiency. Furthermore, the elevated live birth rate might be attributable to the administration of LMWH during gestation.**

Keywords low-molecular-weight heparin; pregnancy; protein S deficiency; hereditary thrombophilia

Introduction

Given the hypercoagulable state of pregnancy, the occurrence of venous thromboembolism (VTE) is about 1–2 cases in per 1000 pregnancies, with deep vein thrombosis (DVT) accounting for 75%–80% of cases [1–3] and pulmonary embolism (PE) accounting for the remaining cases, and maternal VTE-associated mortality rates may reach 9.2% [4–6]. As compared to nonpregnant age-matched women, vulnerability to VTE during pregnancy is 15–35 times higher [7], which increases with the duration of pregnancy from the first trimester onward, and up to an 84-fold increase in the first six weeks postpartum [8–10]. In a meta-analysis, 21.9%, 33.7%, and 47.6% of pregnancy-related VTE occurred in the first, second, and third trimesters of pregnancy, respectively [11]. Nearly half of all pregnant women diagnosed with VTE have hereditary thrombophilia [12], with those who have antithrombin, protein C or protein S (PS) deficiencies having the greatest risk [13,14]. PS deficiency may contribute to the increased vulnerability to VTE because the absence of PS blocks the inactivation

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of procoagulant factors Va and VIIIa and increases the production of thrombin [15].

Hereditary thrombophilia may be associated with adverse pregnancy outcomes (APOs), e.g., recurrent pregnancy loss (RPL), preterm labor, spontaneous abortion (SA), and fetal growth restriction (FGR) [16], and the mechanisms of which may involve placental microvascular thrombosis and the inhibition of extratrophoblast and trophoblast differentiation [17]. However, the majority of available studies are small case-control studies or conducted in heterogeneous cohorts that often have conflicting results; therefore, the existence of an association between hereditary thrombophilia and APOs remains controversial [18].

Hereditary thrombophilia is a syndrome with a prevalence of only 0.02%–0.15% in the general population [19]. Previous studies focused on all or several types of hereditary thrombophilia, and reports on thromboprophylaxis during pregnancy in patients with PS deficiency are lacking. Moreover, there remains no general consensus on whether PS deficiency should be classified as "low-risk" or "high-risk" thrombophilia, nor on recommendations for thromboprophylaxis during pregnancy [20,21]; in addition, the levels of PS decrease during normal pregnancy and delivery [22,23], which has led to inconsistency in thromboprophylaxis among clinicians in clinical practice. Therefore, it is urgent to identify whether thromboprophylaxis in pregnant women with PS deficiency could improve APOs and reduce the incidence of thrombosis during pregnancy, which could contribute to better clinical care and a lower financial and emotional burdens for such pregnant women.

Methods

Study design and participants

From November 2012 to May 2024, a total of 14 850 people were tested for PS activity at Peking University People's Hospital, of whom 12 713 were female. Among the 12 713 female subjects, 1818 had protein S activity ⩽ 55%, and 35 were suspected of having PS deficiency. These participants were stratified into two groups based on anticoagulation management: (1) The LMWH-treated group comprised 20 pregnant women who received prophylactic anticoagulation with LMWH during pregnancy; (2) The LMWH-untreated group consisted of 15 women who did not receive LMWH during pregnancy. For comparative analysis, a control group of 70 healthy pregnant women was randomly selected. Given the retrospective nature of this study, the initiation timing of LMWH prophylaxis was determined according to the gestational trimester at the time of diagnosis, based on real-world clinical records. The specific screening criteria are shown in Fig. 1. This retrospective case-control study was reviewed and approved by the Peking University People's Hospital ethics committee (No. 2025PHB138-001). The study was conducted in accordance with the Declaration of Helsinki.

Eligibility criteria

Eligible patients were those highly suspected of having PS deficiency: PS activity < 55% in the nonpregnant state, < 30% in the second trimester, or < 24% in the third trimester. Furthermore, women with confirmed *PROS1* mutations were included. They had no concomitant hereditary or acquired thrombophilic disorders, such as factor V Leiden mutation, antithrombin III deficiency, protein C deficiency, antiphospholipid syndrome, systemic lupus erythematosus, or other diseases that make patients susceptible to thrombosis or miscarriage.

Definitions

PS Deficiency

Given the strong correlation between PS activity and PS antigen reported in previous studies and the cutoff value proposed by the American College of Obstetricians and Gynecologists [24,25], in our study, patients were strongly suspected of having PS deficiency if PS levels were below 55% in the nonpregnant state or below 30% in the second and 24% in the third trimesters of pregnancy. Also, the diagnosis of PS deficiency could be confirmed if genetic testing identified the presence of *PROS1* gene mutations in the maternal case records.

Adverse pregnancy outcomes

APOs include the following events: preeclampsia, placental abruption, miscarriage, stillbirth, preterm labor, FGR, and small for gestational age (SGA), etc. [26–30].

Recurrent pregnancy loss

RPL is identified as 2 or more successive failed clinical pregnancies, including biochemical pregnancies, with the same partner documented by ultrasound or histopathology [31,32].

Clinical data assessment

All pregnant women with PS deficiency and control subjects were closely monitored, and the following clinical data were analyzed for this retrospective study: (1) historical background information: family history or a previous history of thrombosis, past pregnancy outcomes, including RPL, SA, preeclampsia, intraoperative hemorrhage and postpartum hemorrhage, and

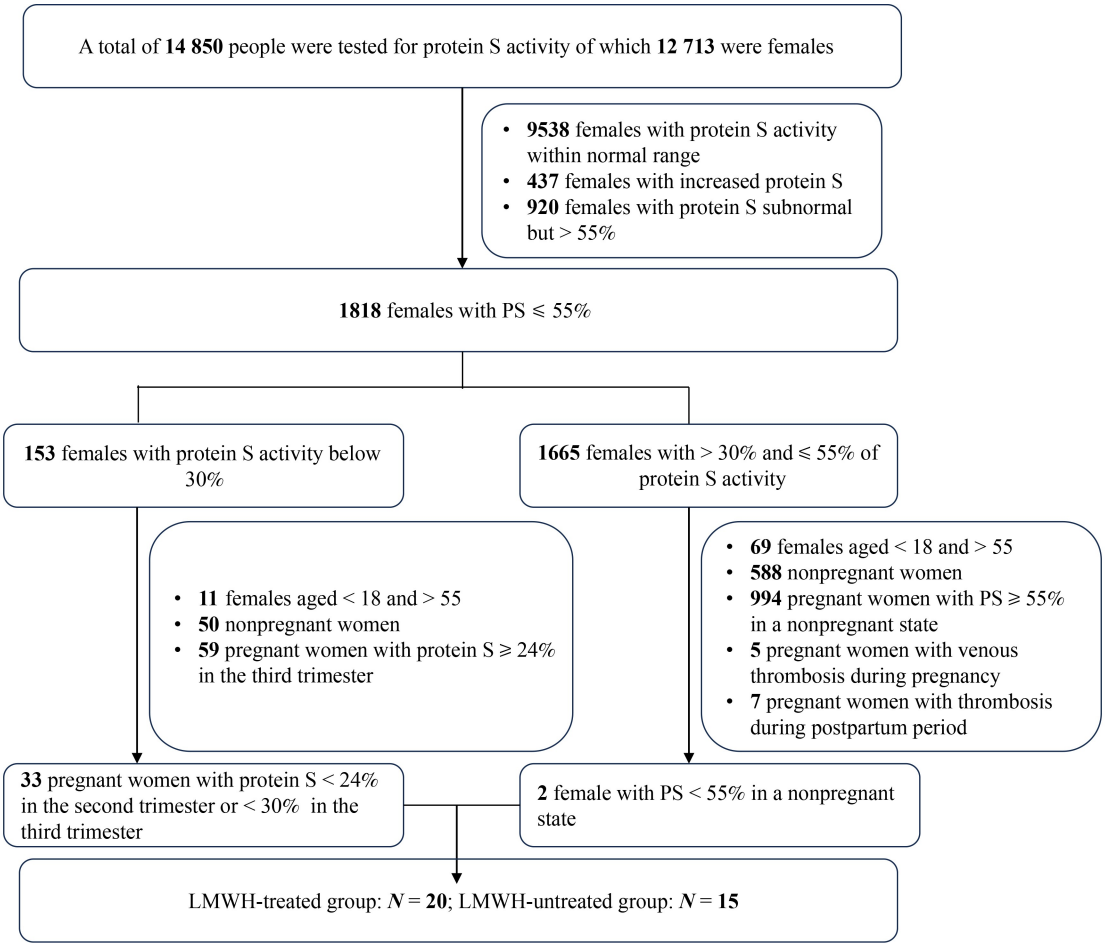

Fig. 1 Among 1818 females whose PS activity was ⩽ 55%, 35 were diagnosed with PS deficiency including 20 who used prophylactic anticoagulation with LMWH during pregnancy and 15 who did not receive LMWH or any other anticoagulation during pregnancy and only received standard care.

oligohydramnios, etc.; (2) basic maternal characteristics during the current pregnancy: age at delivery, body mass index (BMI), mode of conception and delivery, and gestational week at delivery; (3) pregnancy outcomes for the current pregnancy: thrombosis, preeclampsia, oligohydramnios, livebirth, preterm labor, intrauterine fetal death (IUFD), hemorrhage during delivery, and postpartum hemorrhage (2 h, 24 h), which were confirmed by independent obstetricians using standard criteria; (4) prophylactic anticoagulation during the current pregnancy and postpartum period; and (5) neonatal data, including sex, weight, SGA status, Apgar score, abnormalities, complications and others.

LMWH prophylactic anticoagulation

There is no consensus regarding the management of pregnant women with PS deficiency during both the antepartum and postpartum periods. The Royal College of Obstetricians and Gynaecologists (RCOG) and Gesellschaft für Thrombose und Hämostaseforschung (GTH) [1] guidelines recommend prophylactic anticoagulation throughout both the antepartum and postpartum periods, irrespective of the presence or absence of a family history of VTE. The American Society of Hematology (ASH) [33] and American College of Chest Physicians (ACCP) [21] guidelines recommend that postpartum thromboprophylaxis is restricted to patients with a family history of VTE. For those without a family history of VTE, surveillance without anticoagulation is advised during both antepartum and postpartum periods. The ACOG [34] guidelines propose that, in cases without a family history of VTE, prophylaxis should be initiated only when additional thrombotic risk factors are present (e.g., obesity (BMI ⩾ 30), prolonged immobilization, or cesarean delivery). For patients with a family history of VTE, postpartum prophylaxis is recommended, while antepartum management —either surveillance or prophylaxis —should be individualized based on comprehensive risk stratification. A flexible approach is endorsed by Scottish Obstetric and Gynaecological

Committee (SOCG) [35], allowing clinicians to choose between prophylactic anticoagulation and surveillance during antepartum and postpartum periods, irrespective of the patient's family history of VTE. In our study, a retrospective observational study, treatment decisions were clinician-dependent, reflecting real-world clinical practice patterns given the absence of international guidelines for PS deficiency management during pregnancy. We affirm that all patients received care aligned with ⩾ 1 international guidelines. The LMWH-untreated group comprised women deemed low-risk according to ASH/ACCP criteria.

Statistical analysis

The normality of continuous data was assessed by the Shapiro–Wilk test, and homogeneity of variances was verified by Levene's test. For comparisons across the three groups (LMWH-treated, LMWH-untreated, and control), one-way ANOVA with Tukey's honest significant difference (HSD) post-hoc test was applied for normally distributed data. The Kruskal–Wallis test, followed by Dunn's test with Bonferroni adjustment for multiple comparisons, was used for non-normally distributed data. Categorical variables were analyzed using the Chi-square test; when the expected frequency in any cell was less than 5, Fisher's exact test was employed instead. For the comparison between all Protein S-deficient women (n = 35) and controls (n = 70), the independent Student's t-test or Mann–Whitney U test was used for continuous data, as appropriate, and the Chi-square or Fisher's exact test for categorical data. Given the limited sample size, we utilized Firth's penalized-likelihood logistic regression to reduce bias in effect estimation. The primary model assessed the association between LMWH treatment and live birth, adjusting for clinically relevant confounders, identified a priori: maternal age, VTE risk score, IVF conception, and concomitant aspirin use. Results were reported as adjusted odds ratios (aORs) with 95% confidence intervals (CIs). To evaluate the robustness of our findings, we performed several sensitivity analyses. All analyses were performed using R version 4.4.3 and GraphPad Prism 9, with a two-sided $P < 0.05$ considered statistically significant.

Results

Historical background information of pregnant women with PS deficiency and healthy pregnant women

Pregnant women with PS levels under 55% during the non-pregnancy, 30% in the second trimester, and 24% in the third trimester are considered highly suspected of having PS deficiency. Among the pregnant women who underwent PS activity testing and delivered at the People's Hospital of Peking University from November 2012 to May 2024, 35 met the above criteria for the diagnosis of PS deficiency, 20 of whom received LMWH to prevent venous thrombosis during pregnancy by the clinicians (LMWH-treated group), and 15 of whom received only standard care throughout pregnancy, without LMWH or other anticoagulant drugs to prevent thrombosis (LMWH-untreated group). Moreover, 70 healthy pregnant women were randomly selected from the hospital case system as the control group. A previous history of ectopic pregnancy and SA was reported by 2 and 8 patients in the LMWH-treated group, 1 and 5 patients in the LMWH-untreated group, and 1 and 17 patients in the control group. Two women in the LMWH-treated group had a history of venous thrombosis including one whose mother had low PS activity, and two had a family history of thrombosis. Neither the LMWH-untreated nor the control groups had a personal or family record of thrombosis. 9 patients (9/20, 45%) in the LMWH-treated group had at least 3 pregnancies, but only one of them had a total of 3 deliveries. Excluding those with induced abortions, 9 patients had live births in all of their previous pregnancies, of whom 3 were pregnant for the first time. In the LMWH-untreated group, 5 patients had a history of at least 3 pregnancies, but all had experienced at least one miscarriage, and 6 patients had live births from previous pregnancies except those with induced abortions, 5 of whom were pregnant for the first time; 70% (49/70) of the pregnant women in the control group had no history of miscarriage. The number of pregnant women with PS deficiency who had suffered 2 or more consecutive miscarriages (RPL) was considerably higher than that of the control group (12/35 vs. 4/70) (odds ratio (OR) 8.609, 95% CI 2.65–25.71; P = 0.0001). The history of other pregnancy outcomes is shown in Table 1, and no statistically significant difference was found between the PS deficiency and the control group ($P > 0.05$).

Maternal background data

A summary of the characteristics of the current pregnancy in pregnant women with PS deficiency and healthy controls is presented in Table 2. The ages at delivery in the LMWH-treated group, LMWH-untreated group, and control group were (34.75 ± 3.51) years, (32.30 ± 3.44) years, and (32.12 ± 3.65) years, respectively. The median weeks of gestation at delivery among the women with live births in the three groups was 38.86 gestational weeks, 38.71 gestational weeks, and 39.29 gestational weeks, respectively. 14, 8, and 54 patients were overweight (BMI 25–29.9 kg/m^2) in early pregnancy in the three groups, respectively; 1 patient each was obese

Table 1 Maternal background information for pregnant women in the LMWH-treated group, LMWH-untreated group, and control group

	LMWH-treated ($N = 20$)	LMWH-untreated ($N = 15$)	Control ($N = 70$)	P (overall)	P (pairwise)	P (PS deficiency vs. control)
Previous pregnancy outcomes, *n*						
Ectopic pregnancy	2	1	1	0.173		0.0715
SA	8	5	17	0.354		0.1783
Induced abortion	2	0	6	0.4751		0.7159
Intraoperative hemorrhage	1	0	4	0.640		0.6627
Preeclampsia	0	0	1	0.7769		> 0.9999
Premature rupture of membranes	0	0	4	0.3536		0.2986
Oligohydramnios	0	1	1	0.3176		0.2986
History of thrombosis, *n*						
Thrombosis only	1	0	0	0.117		0.3333
Family history of thrombosis only	2	0	0	0.0131*	LMWH-treated vs. LMWH-untreated: 0.4958 LMWH-treated vs. control: 0.0474* LMWH-untreated vs. control: > 0.9999	0.1090
History of thrombosis and family history of low PS levels	1	0	0	0.117		0.3333
Number of pregnancies, *n*						
1	3	7	35	0.0194*	LMWH-treated vs. LMWH-untreated: 0.0619 LMWH-treated vs. control: 0.0052* LMWH-untreated vs. control: > 0.9999	0.0396*
2	8	3	20	0.4191		0.8220
⩾ 3	9	5	15	0.0998		0.0635
Number of deliveries, *n*						
0	0	5	0	< 0.0001****	LMWH-treated vs. LMWH-untreated: 0.0093** LMWH-treated vs. control: > 0.9999 LMWH-untreated vs. control: < 0.0001****	0.0034**
1	14	9	51	0.6114		0.4997
2	5	1	17	0.3042		0.4624
⩾ 3	1	0	2	0.6798		> 0.9999
Number of spontaneous abortions, *n*						
0	9	6	49	0.0258*	LMWH-treated vs. LMWH-untreated: > 0.9999 LMWH-treated vs. control: 0.0621 LMWH-untreated vs. control: 0.038*	0.0106*
1	4	4	14	0.8416		0.8010
⩾ 2 (RPL)	7	5	4	0.0006***	LMWH-treated vs. LMWH-untreated: > 0.9999 LMWH-treated vs. control: 0.0019** LMWH-untreated vs. control: 0.0074**	0.0001****

SA, spontaneous abortion; RPL, recurrent pregnancy loss. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$.

Table 2 Basic characteristics in the LMWH-treated group, LMWH-untreated group, and control group

	LMWH-treated ($N = 20$)	LMWH-untreated ($N = 15$)	Control ($N = 70$)	P (overall)	P (pairwise)	P (PS deficiency vs. control)
Age at delivery, mean ± SD, year	34.75 ± 3.51	32.30 ± 3.44	32.12 ± 3.65	0.0123*	LMWH-treated vs. LMWH-untreated: 0.0293* LMWH-treated vs. control: 0.0221* LMWH-untreated vs. control: > 0.9999	0.1468
Gestational week at delivery, median (IQR), GW	38.86 (38.5, 39.64)	38.71 (37.71, 39.25)	39.29 (38.18, 40)	0.0025**	LMWH-treated vs. LMWH-untreated: 0.0268* LMWH-treated vs. control: > 0.9999 LMWH-untreated vs. control: 0.0268**	0.0225*
Height at delivery, mean ± SD, m	1.61 ± 0.06	1.61 ± 0.05	1.63 ± 0.05	0.3846		0.2943
Weight in early pregnancy, mean ± SD, kg	57.97 ± 9.43	60.34 ± 8.43	58.91 ± 10.68	0.6734		0.5342
Weight at delivery, mean ± SD, kg	69.75 ± 11.62	72.17 ± 11.42	73.31 ± 11.42	0.5856		0.3744
BMI in early pregnancy, *n*						
< 18.5 kg/m^2	1	1	1	0.4427		0.2571
18.5–24.9 kg/m^2	14	8	54	0.1675		0.1227
25–29.9 kg/m^2	3	3	14	0.877		0.7752
⩾ 30 kg/m^2	1	0	1	0.4962		> 0.9999
No data available	1	3	0			
BMI at delivery						
< 18.5 kg/m^2	0	0	0			> 0.9999
18.5–24.9 kg/m^2	8	4	19	0.5209		0.4494
25–29.9 kg/m^2	7	3	34	0.099		0.0502
⩾ 30 kg/m^2	4	4	17	0.8886		0.8713
No data available	1	4	0			
Postpartum VTE score, median (IQR)	4 (2, 5.5)	2 (2, 3)	1 (0, 2)	< 0.0001****	LMWH-treated vs. LMWH-untreated: 0.4342 LMWH-treated vs. control: < 0.0001**** LMWH-untreated vs. control: 0.0665	< 0.0001****
Conception methods, *n*						
Spontaneous pregnancy	12	8	62	0.0011**	LMWH-treated vs. LMWH-untreated: 0.7412 LMWH-treated vs. control: 0.0066** LMWH-untreated vs. control: 0.0038**	0.0002***
IVF-ET	8	2	4	0.0004***	LMWH-treated vs. LMWH-untreated: 0.1340 LMWH-treated vs. control: 0.0005*** LMWH-untreated vs. control: 0.2851	0.0021**
Inducted ovulation	0	0	4	0.3536		0.2986
Mode of delivery, *n*						
Vaginal delivery	13	4	39	0.0627		0.4892
Planned cesarean section	3	2	19	0.3327		0.2170
Emergency cesarean section	4	2	12	0.8745		> 0.9999

BMI, body mass index; IVF-ET: *in vitro* fertilization-embryo transfer. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$.

(BMI ⩾ 30 kg/m^2) in the LMWH-treated group and the control group. At delivery, the number of obese women increased to 4 and 4 in the LMWH-treated and LMWH-untreated group, respectively, and to 17 in the control group. The postnatal VTE scores in the LMWH-treated, LMWH-untreated, and control groups were 4 (2, 5.5), 2 (2, 3), and 1 (0, 2), respectively. Most of the patients conceived spontaneously; 10 pregnant women with PS deficiency (including 8 pregnant women in the LMWH-treated group and 2 pregnant women in LMWH-untreated group) conceived via *in vitro* fertilization-embryo transfer (IVF-ET), and this proportion was significantly higher than those in the control group (5.71%, 4/70) (OR 6.6, 95% CI 1.884–20.09; P = 0.0012). Moreover, 88.57% (62/70) of women in the control group conceived spontaneously, whereas the remaining 4 (5.71%) women conceived via induced ovulation. Similarly, more than half of the deliveries were vaginal deliveries: 13/20 (65%) in the LMWH-treated group, 4/15 (26.67%) in the LMWH-untreated group, and 39/70 (55.71%) in the control group. In addition, 4 women (4/20, 20%) in the LMWH-treated group delivered by emergency cesarean section, compared with 2 women (2/15, 13.33%) in the LMWH-untreated group and 12 women (12/70, 17.14%) in the control group delivered by emergency cesarean section, and the remaining women delivered by planned cesarean section.

Current pregnancy outcomes in women with PS deficiency and healthy women

We compared baseline differences between the LMWH-treated and LMWH-untreated groups, including maternal age, pre-pregnancy BMI, personal or family history of thrombosis, prior pregnancy complications (postpartum hemorrhage, gestational diabetes, hypertension, preeclampsia), number of prior induced abortions, history of ⩾ 2 pregnancy losses (spontaneous miscarriage or biochemical pregnancy), ectopic pregnancy history, IVF-ET utilization, current pregnancy complications (gestational hypertension/preeclampsia, gestational diabetes), total number of pregnancies/deliveries, and the initiation time and dosages of LMWH and aspirin. Statistical analysis revealed a significant intergroup difference (P < 0.05) in maternal age (P = 0.008), as detailed in Table S1. To address confounding by age, we stratified patients by the overall median age (32 years) and performed Fisher's exact tests (Table 3). In the > 32-year subgroup, LMWH-treated patients achieved 100% live births (13/13), compared with 33.3% (1/3) in LMWH-untreated patients (P = 0.025). In the ⩽ 32-year subgroup, LMWH treatment similarly resulted in a 100% live birth rate (7/7), versus 58.3% (7/12) in LMWH-untreated patients (P = 0.106). These stratified outcomes align with the overall treatment effect (20/20 vs. 8/15 live births, P = 0.001), suggesting a potential age-dependent modification of LMWH efficacy, though the subgroup analyses were underpowered. Secondary outcomes (e.g., preterm birth, VTE) occurred in only 1–2 cases (Table S2), precluding formal statistical comparisons.

We utilized Firth's penalized-likelihood logistic regression, a method specifically designed for small sample sizes and perfect separation, to adjust for key baseline imbalances, including age, VTE risk score, IVF conception, and aspirin use. The primary multivariable model demonstrated a significant association between LMWH treatment and live birth (aOR 31.10, 95% CI 1.93–13766.15, P = 0.0098) (Table S3, Fig. S1). Despite adjustment for these measured confounders, we acknowledge the extreme width of the CI, reflecting substantial uncertainty inherent in the small sample size and the low events-per-variable (EPV) ratio of 5.6. To evaluate potential confounding factors and validate the robustness of our primary findings, a series of sensitivity analyses were performed using Firth's penalized-likelihood logistic regression (Table S4). In a subgroup analysis excluding patients who conceived via IVF-ET —a key potential source of confounding by indication —the point estimate for the LMWH effect remained positive, though attenuated and no longer statistically significant given the further reduced sample size (aOR = 8.26, P = 0.076). Although the effect was attenuated in the subgroup that excluded patients conceived via IVF-ET, the point estimate for LMWH effect remained positive, and the association remained robust across multiple sensitivity models accounting for key potential confounders. The wide CI likely reflects limited statistical power due to a low events-per-variable ratio (EPV = 4.8–7.0), which falls below the conventional threshold of 10. Nonetheless, these findings support a compelling hypothesis that LMWH may confer beneficial effects on pregnancy outcomes in women highly

Table 3 Differences in live births between LMWH-treated and LMWH-untreated groups compared based on age stratification

	Age > 32			Age ⩽ 32		
	LMWH-treated (N = 13)	LMWH-untreated (N = 3)	P	LMWH-treated (N = 7)	LMWH-untreated (N = 12)	P
Live births	13	1	0.025	7	7	0.106
SA/IUFD	0	2		0	5	

SA, spontaneous abortion; IUFD, intrauterine fetal death.

suspected of having PS deficiency. Large-scale, prospective randomized controlled trials are warranted to validate these preliminary findings and establish causal inference.

Medication use during pregnancy

In the LMWH-treated group, 3 patients and 8 patients started LMWH in the second trimester and third trimester, respectively; the remaining 9 patients started LMWH before IVF-ET or in early pregnancy and continued until delivery. 8 pregnant women applied LMWH in combination with aspirin (50–100 mg) for thrombo-prophylaxis. Among them, 5 pregnant women (> 32 years) initiated treatment in the first trimester, 1 pregnant woman (> 32 years) in the second trimester, 2 pregnant women (1 woman > 32 years and 1 woman ⩽ 32 years) in the third trimester. Among these 8 pregnant women, all of them used a prophylactic dose of enoxaparin except 1 pregnant woman who applied 6000 IU of enoxaparin and 1 pregnant woman who applied 4100 IU of nadroparine. 13 pregnant women (13/20, 65%) applied enoxaparin, 6 pregnant women applied nadroparine, and 1 pregnant woman applied bemiparin. In addition to the aforementioned 1 pregnant woman who applied 6000 IU of enoxaparin and 1 who was changed from a prophylactic dose to 4000 IU twice daily after 6 gestational weeks, the rest of the 18 pregnant women applied LMWH at a prophylactic dose. All pregnant women in the LMWH-treated group had no adverse events, such as epistaxis, gingival bleeding, vaginal bleeding, hematuria, or heparin-induced thrombocyto-penia. Other medications used in the LMWH-treated group included antihypertensive medication (labetalol) and dydrogesterone. Only 1 pregnant woman in the LMWH-untreated group applied aspirin at 17 weeks of gestation and delivered successfully. Other medications for pregnant women in the LMWH-untreated group included hypoglycemic drugs, oral iron, and hormone. In the control group, only 1 pregnant woman who underwent IVF-ET received LMWH. 6 pregnant women in the control group applied aspirin for preeclampsia or hypertension.

To investigate potential therapeutic interactions with aspirin, we performed comparative analyses of pregnancy outcomes across three treatment cohorts: LMWH monotherapy, LMWH-aspirin combination therapy, and LMWH-untreated controls (Table 4). In the advanced maternal age subgroup (> 32 years), both combination therapy (6/6, 100%) and LMWH monotherapy (7/7, 100%) demonstrated better efficacy in achieving live births compared with LMWH-untreated patients (1/3, 33.3%). This therapeutic advantage persisted in younger patients (⩽ 32 years), where combination therapy (2/2, 100%) and monotherapy (5/5, 100%) maintained better efficacy compared with untreated counterparts (7/12, 58.3%). Notwithstanding the modest sample sizes, particularly evident in the ⩽ 32-year combination cohort (n = 2), the consistently favorable outcomes observed across all LMWH-treated cohorts (universal live birth rates) suggest a clinically significant therapeutic effect. These preliminary findings, while requiring cautious interpretation due to inherent limitations in subgroup sample sizes, provide compelling rationale for subsequent prospective investigations to elucidate age-stratified treatment responses and refine optimal anticoagulation protocols in PS deficiency pregnant women. The observed therapeutic trends warrant further investigation through adequately powered randomized controlled trials to establish evidence-based management guidelines for this high-risk obstetric population.

Postpartum anticoagulation

In the LMWH-treated group, 4 women did not receive prophylactic anticoagulation after delivery; the remaining 16 women were treated with prophylactic doses of LMWH (enoxaparin (15/16) and nadroparin calcium (1/16)), with a median duration of prophylactic anticoagulation of 42 days (42 (9.5, 42) days). Only 4 women in the LMWH-untreated group received prophylactic anticoagulation with enoxaparin. The anticoagulation duration in 2 women was 3 days, that in 1 woman was 5 days, and that in 1 woman was 7 days. In the control group, 27 women received anticoagulation with a prophylactic dose of LMWH after delivery, and the median duration of anticoagulation was 3 days. There were no adverse events, such as hemorrhage, in any of the women who received anticoagulation therapy after delivery.

Neonatal information

There were 1, 0, and 3 women with twin pregnancies in the LMWH-treated group, LMWH-untreated group, and

Table 4 The effect of aspirin on live births based on age stratification

	Age > 32			Age ⩽ 32		
	LMWH + aspirin (N = 6)	LMWH (N = 7)	LMWH-untreated (N = 3)	LMWH + aspirin (N = 2)	LMWH (N = 5)	LMWH-untreated (N = 12)
Live births	6	7	1	2	5	7
SA/IUFD	0	0	2	0	0	5

SA, spontaneous abortion; IUFD, intrauterine fetal death.

control group, respectively; 10, 7 and 35 newborns were male, and 10, 3, and 38 newborns were female, respectively; the sex of 5 newborns in the LMWH-untreated group was unknown due to miscarriage and other reasons. The median birth weights of the neonates in the three groups were 3155 g, 3205 g, and 3240 g, respectively, and the median birth lengths were 49.5 cm, 49.5 cm, and 50 cm, respectively.

Apgar scores at 1 min, 5 min, and 10 min were 10 in both the LMWH-treated group and the control group. The median Apgar scores at 1 min, 5 min, and 10 min in the LMWH-untreated group were 10, 9.5, and 9.5, respectively. One neonate with severe asphyxia in the LMWH-treated group had Apgar scores of 3, 7, and 9 at 1 min, 5 min, and 10 min, respectively. Among the live-born neonates, one neonates in the LMWH-untreated group did not achieve a 1-min Apgar score of 10. The median 1-min, 5-min, and 10-min Apgar scores of the neonates in the control group were all 10. In addition, there was 1, 0, and 2 cases of SGA in the LMWH-treated, LMWH-untreated, and control group, respectively; 2, 1, and 3 neonates had FGR in the three groups, respectively. Neonatal asphyxia was observed in one neonate each in the LMWH-treated group and control group. 1 neonate in the LMWH-untreated group and 4 neonates in the control group had macrosomia, and one neonate in the LMWH-untreated group had chromosomal anomalies, with no statistical difference among the groups ($P > 0.05$) (Table 5).

Discussion

This was a retrospective observational study designed to compare the differences in pregnancy outcomes between pregnant women with PS deficiency and healthy pregnant women without bleeding or thrombotic disorders, and to investigate whether LMWH prophylaxis is associated with the pregnancy outcomes of women with PS deficiency. Compared with 5.7% (4/70) in the control group, women with PS deficiency exhibited a statistically significant 28.6% (10/35) pregnancy rate via IVF-ET. This disparity suggests an association between PS deficiency and reduced natural fecundity.

Second, in the PS deficiency cohort, the prevalence of ⩾ 2 prior miscarriages was significantly higher compared with the control group (12/35 vs. 4/70, $P = 0.0001$), implicating a potential link between PS deficiency and APOs.

We conducted stratified analyses by median age (> 32 vs. ⩽ 32 years) to evaluate the impact of LMWH thromboprophylaxis on live birth outcomes. Both age subgroups demonstrated consistent directional trends favoring LMWH intervention, with complete live birth preservation observed in all LMWH-treated pregnancies versus lower rates in LMWH-untreated counterparts (33.3% in the > 32-year subgroup; 58.3% in the ⩽ 32-year subgroup). These stratified patterns suggest potential age-related modification of LMWH therapeutic effects, particularly indicating enhanced clinical utility in older gravidae (> 32 years) with PS deficiency —a finding concordant with established epidemiological data demonstrating escalating miscarriage risks with advancing maternal age (13% at 12–19 years, 11% at 20–24 years, 12% at 25–29 years, 15% at 30–34 years, 25% at 35–39 years, 51% at 40–44 years, and 93% at ⩾ 45 years) [36]. Concomitant analysis of aspirin's therapeutic impact through age-stratified evaluation revealed no statistically significant associations. However, this null finding should be interpreted cautiously given the underpowered subgroup analyses (particularly in younger cohorts with limited aspirin-exposed cases). The observed age-dependent therapeutic gradients, while mechanistically plausible given known physiologic changes in thrombotic risk profiles and placental perfusion efficiency across reproductive aging, necessitate rigorous validation through prospective cohort studies with pre-specified age stratification and adequate power to detect potential modifier effects. These exploratory findings underscore the imperative for precision-medicine approaches in managing thrombophilic pregnancies, integrating both maternal age and thrombotic risk stratification to optimize anticoagulation protocols.

In a meta-analysis that included 10 randomized controlled trials and 12 cohort studies, the use of LMWH was reported to potentially decrease the incidence of APOs and improve live birth rates in women with hereditary thrombophilia [37]. In addition, a prospective randomized trial comparing the effects of LMWH and low-dose aspirin on the rate of live births showed that LMWH could increase the rate to 86% but only 29% in the aspirin [38]. Thromboprophylaxis is effective in reducing the risk of miscarriage in pregnant women with hereditary antithrombin, protein C, or PS deficiency (miscarriage rate: 0% vs. 45%) [39]. A meta-analysis of 36 studies suggested that all thrombophilia patients present an elevated risk of VTE and that PS deficiency represents high-risk thrombophilia, and the study recommended that thromboprophylaxis should be performed either antenatally or postnatally or both antenatally and postnatally [40].

However, in an open-label, randomized trial conducted at 36 hospitals across 5 countries [41], prenatal prophylactic use of LMWH did not reduce the incidence of VTE, miscarriage, or other APOs in pregnant patients diagnosed with hereditary thrombophilia; instead, it increased the incidence of minor bleeding. Notably, 164 and 162 patients were included in the LMWH and standard care groups, respectively. However, more than half of the patients had factor V Leiden mutations, with

Table 5 Basic neonatal characteristics and outcomes of the current pregnancy for women in the LMWH-treated group, LMWH-untreated group, and control group

	LMWH-treated ($N = 20$)	LMWH-untreated ($N = 15$)	Control ($N = 70$)	P (overall)	P (pairwise)	P (PS deficiency vs. control)
Sex, *n*						
Male	10	7	35	0.9718		0.8902
Female	10	3	38	0.0541		0.0976
Sex unknown	0	5	0	< 0.0001****	LMWH-treated vs. LMWH-untreated: 0.0093** LMWH-treated vs. control: > 0.9999 LMWH-untreated vs. control: < 0.0001****	0.0034**
Height of term newborn babies, median (IQR), cm	49.5 (48, 51)	49.5 (46.75, 50.75)	50 (49, 50.5)		0.8341	0.5935
Body weight of term newborns, median (IQR), g	3155 (2735, 3412.5)	3205 (2467.5, 3497.5)	3240 (3025, 3515)	0.6588		0.3671
Apgar score, median (IQR)						
1 min	10 (10, 10)	10 (6.5, 10)	10 (10, 10)	0.0527		0.0668
5 min	10 (10, 10)	9.5 (10, 10)	10 (10, 10)	0.0485*	LMWH-treated vs. LMWH-untreated: 0.311 LMWH-treated vs. control: > 0.9999 LMWH-untreated vs. control: 0.0435*	0.0778
10 min	10 (10, 10)	9.5 (10, 10)	10 (10, 10)	0.2379		0.1938
Macrosomia, *n*	0	1	4	0.5326		0.6627
SGA, *n*	1	0	2	0.6798		> 0.9999
Neonatal asphyxia, *n*	1	0	1	0.4962		> 0.9999
FGR, *n*	2	1	3	0.6150		0.3978
Chromosomal abnormalities in the fetus, *n*	0	1	0	0.0484*	LMWH-treated vs. LMWH-untreated: 0.4286 LMWH-treated vs. control: > 0.9999 LMWH-untreated vs. control: 0.1765	0.3333

SGA, small for gestational age; FGR, fetal growth restriction. *$P < 0.05$, **$P < 0.01$, ****$P < 0.0001$.

only 14% and 13% of patients in the two groups had PS deficiency, respectively,. The results may not suggest whether LMWH could reduce live births in pregnant women with PS deficiency.

Because of the low prevalence of such disorder, the published studies that reported the effects of hereditary thrombophilia on pregnancy outcomes have included a variety of hereditary thrombophilia types, but each type has its own specific risk of thrombophilia, which may have different impacts on pregnancy outcomes. Our study, which focused on PS deficiency, suggests that prophylactic anticoagulation during pregnancy for pregnant women with PS deficiency improves the live birth rate. In addition, PS activity may decrease by more than 50% during pregnancy under normal physiological conditions [42], which is relatively common in clinical practice. Whether some interventions are necessary for pregnant women with PS deficiency is an unanswered clinical question. This study, targeting pregnant women with PS activity < 55% at preternal period, < 30% in the second trimester, or < 24% in the third trimester, is the first to investigate the effects of LMWH on pregnancy outcomes in women with PS deficiency and it avoids the need to perform *PROS*1 genetic testing, which alleviates the economic burden on patients to some extent.

However, there are several limitations to this study. First, most of pregnant women did not undergo the *PROS1* gene test, even though it was the gold standard in diagnosis. Based on PS activity alone, it is not possible to determine whether it is a PS deficiency, although it has a high sensitivity (> 90%) for detecting all clinically relevant hereditary defects (including qualitative and quantitative deficiencies) [43,44]. Lupus anticoagulants may falsely elevate PS activity in partial thromboplastin time (PTT)-based assays, while elevated factor VIII levels can reduce measured PS activity. Additionally, the *factor V Leiden* mutation is associated with spuriously low PS values in certain activity assays. However, on the basis of the decreased degree of PS in the pregnant women included in this study, a predisposition to PS deficiency is highly suspected, which is instructive as to whether anticoagulant interventions should be performed in such patients in the clinical setting. In addition, the control group in this study included a random sample of healthy pregnant women, and those with coagulation-related disorders were excluded; nevertheless, the control group data might not necessarily reflect the average delivery data of women with normal pregnancies. Third, the current study inadequately addressed the potential confounding effects of aspirin use and heterogeneous LMWH initiation timelines. While our data demonstrated 100% live birth rates with LMWH initiation across all trimesters, the small sizes preclude conclusive analysis of optimal timing. This critical question —whether earlier initiation further improves outcomes (e.g., reducing early pregnancy loss or placental complications) —requires prospective investigation in larger cohorts. Future investigations require cohort expansion with balanced enrollment across distinct treatment initiation intervals to elucidate both the temporal efficacy variations of LMWH therapy and the impact of aspirin on pregnancy outcomes in patients with PS deficiency through methodologically rigorous analyses. Finally, the study is single-centered, with a relatively small sample size (N = 35 with PS deficiency), which may limit its broader applicability. Larger-scale, multi-center prospective studies involving multi-ethnic cohorts are urgently warranted to validate these findings and specifically evaluate the impact of LMWH plus aspirin versus LMWH monotherapy on pregnancy outcomes in women with PS deficiency, in order to explore the incremental benefit of aspirin. Despite these limitations, our results provide internally consistent data that may serve as a benchmark for comparative analyses in larger studies.

Conclusions

Our findings indicate an association between PS deficiency and challenges in spontaneous conception, as well as an elevated miscarriage risk. Prophylactic LMWH anticoagulation appears to enhance live birth rates in these pregnancies. However, larger, multicenter prospective studies are required to confirm the independent impact of LMWH on improving live birth outcomes in pregnant women with PS deficiency.

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Compliance with ethics guidelines

Conflicts of interest Mengtong Zang, Zhuoyu An, Yuxiu Chen, Menglin Li, Jianying Zhou, Mengyu Xiao, Lulu Wang, Qiuyu Guo, Chencong Wang, Haixia Fu, Yun He, Qian Jiang, Hao Jiang, Jin Lu, Xiangyu Zhao, Yingjun Chang, Yu Wang, Xue Xu, Guoli Liu, Xiuli Sun, Xiaohong Zhang, Meiying Liang, Wentao Yue, Xiaowei Liu, Jianliu Wang, Xiaojun Huang, and Xiaohui Zhang declare that they have no conflict of interest.

This study (2025PHB138-001) has been approved by the Ethics Committee of Peking University People's Hospital, in accordance with the Declaration of Helsinki. All patient data was dissociated and anonymized; informed consent was waived by our Institutional Review Board because of the retrospective nature of our study and

because the results did not affect the clinical management of patients.

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