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Identifying Thromboprophylaxis and Aspirin Use in Pregnancy: Predictors and Maternal Outcomes—the Italian MoMs Study

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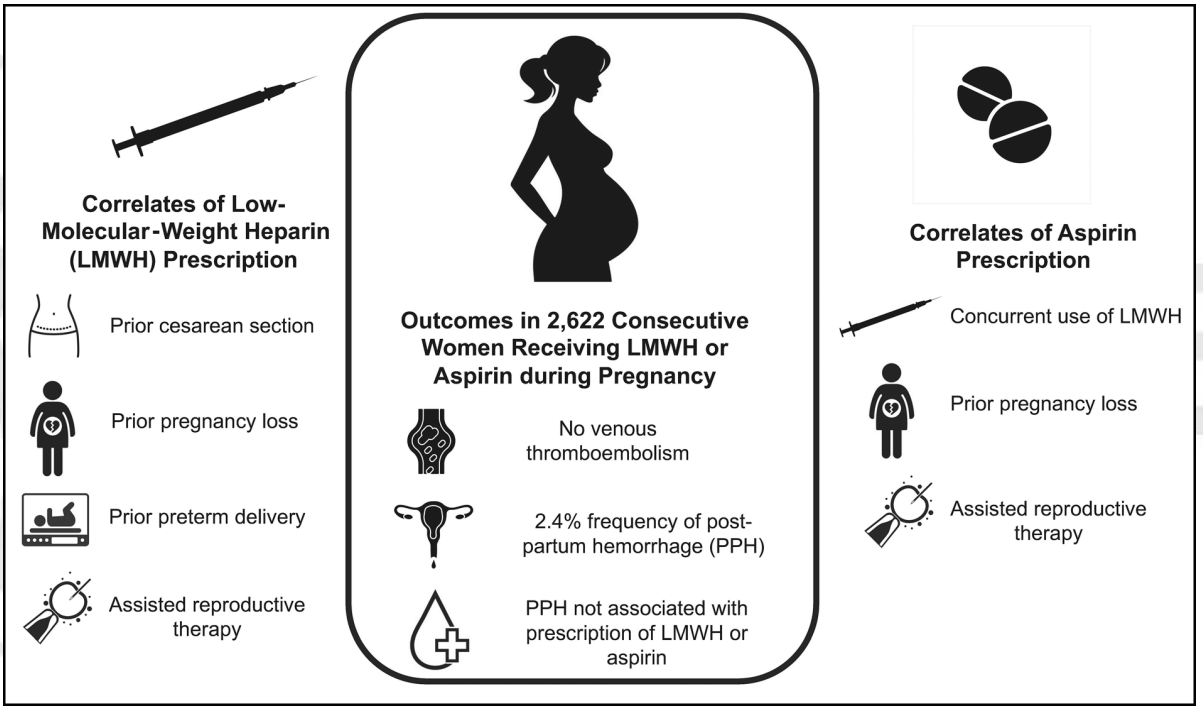
GRAPHICAL ABSTRACT



ABSTRACT

Background The use of low-molecular-weight heparin (LMWH) and aspirin during pregnancy is increasing, yet robust clinical trial evidence supporting their efficacy remains limited.

Patients and Methods In a multicenter prospectively enrolled cohort study, we evaluated the prescription patterns and associated maternal–fetal outcomes of antithrombotic therapy in 2,622 women admitted for delivery across three Italian obstetric centers between January 2022 and November 2023. Data were collected on conception methods, administration details (timing, dose, indication) of LMWH and low-dose aspirin (LDA), and maternal–fetal outcomes from admission to postpartum discharge. Data on prescription of antithrombotic drugs were available for 1,898 women.

Results Among 1,898 women with available data, 157 (8.3%) received LDA (100 mg/day) and 746 (39.3%) received LMWH (49 during pregnancy and 697 in the postpartum period). Predictors of LMWH use included prior cesarean (OR 3.1, 95% CI 1.7–5.8), preterm delivery (OR 3.8, 95% CI 1.7–8.9), pregnancy loss (OR 2.7, 95% CI 1.5–4.9), and assisted conception (OR 14.6, 95% CI 2.8–76.5). LDA use was associated with pregnancy loss (OR 2.1, 95% CI 1.4–3.0), ART (OR 4.7, 95% CI 2.2–10.2), and LMWH co-administration (OR 2.5, 95% CI 1.1–5.5). Postpartum LMWH use was primarily associated with cesarean delivery. Postpartum hemorrhage occurred in 2.4% of cases, with no significant difference in those receiving LDA or LMWH.

Conclusion These findings reflect current real-world prescribing practices and highlight key maternal characteristics influencing antithrombotic therapy decisions. The study underscores the importance of evidence-based approaches in the

use of LMWH and LDA during pregnancy, particularly in high-risk populations, to improve maternal–fetal outcomes while minimizing unnecessary exposure to therapies with uncertain benefit.

Keywords pregnancy, heparin, aspirin

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Introduction

In routine clinical practice, low-molecular-weight heparin (LMWH) and low-dose aspirin (LDA) are considered key components of antithrombotic therapy during pregnancy, reflecting a growing trend in their use to improve maternal and fetal outcomes, although utilization occurs frequently without support of rigorous clinical trial data.[1–4] The high relative risk of venous thromboembolism (VTE) during pregnancy and the postpartum period—affecting approximately 2 in 1,000 women—underscores the critical need for effective strategies to prevent thrombotic complications during this vulnerable time. Accordingly, LMWH is mainly prescribed both antenatally and postpartum for primary prevention and the recurrence of VTE.[5] Women with risk factors for preeclampsia such as chronic hypertension, autoimmune, or renal disease are typically prescribed LDA during pregnancy.[6] Although LMWH and LDA are generally considered safe in pregnant women, neither are without risks. Potential complications, in particular related to LMWH, include bleeding, heparin-induced thrombocytopenia, and spinal epidural hematoma associated with neuraxial anesthesia.[7,8]

In recent years, LMWH prescription has increased for managing recurrent pregnancy loss and intrauterine fetal death, owing to its anticoagulant and anti-inflammatory properties, immunomodulatory effects, and its potential to preserve placental development.[9,10] Benefits include promoting trophoblast proliferation, protecting vascular endothelium, and improving pregnancy outcomes in cases of recurrent pregnancy loss associated with antiphospholipid syndrome or other conditions.[3,11] However, questions remain regarding its efficacy in these settings, given the lack of standardized guidelines and inconsistent findings in clinical studies.[3,12] This study aimed to use a prospectively enrolled cohort to systematically describe the use of LMWH and LDA during pregnancy and hospitalization for delivery, and to provide descriptive data on live birth rates, intrauterine fetal death and maternal outcomes, such as postpartum hemorrhage (PPH), thereby contributing to the limited real-world evidence on antithrombotic therapy in pregnancy.

Methods

This multicenter study, involving a prospectively enrolled cohort, was conducted across three obstetrics departments in the Apulia region of Italy between January 2022 and November 2023. Participating institutions included the Research Hospital "Casa Sollievo della Sofferenza," the University Hospital of Foggia, and the University Hospital of Bari. Pregnant women admitted for delivery during this period were consecutively enrolled. We included women aged ≥18 years admitted for delivery at one of the participating centers. Exclusion criteria were refusal or inability to provide informed consent, or incomplete clinical data.

The study was approved by the local Ethics Committee and all patients signed an informed consent before the enrollment. The study was compliant with the Declaration of Helsinki principles.

Data collection included demographic details, obstetric history, and clinical risk factors. Furthermore, we collected information on prior and present conception via assisted reproductive techniques (ART). The timing and use of antithrombotic prophylaxis, including LMWH and/or LDA, were recorded during pregnancy and hospitalization.

Study Outcomes

Maternal and fetal outcomes were systematically and prospectively recorded from hospital admission through postpartum discharge. Primary outcomes included fetal or neonatal death and PPH. Secondary outcomes were preterm delivery (birth before 37 weeks' gestation) and maternal VTE. Maternal and neonatal outcomes were monitored until hospital discharge.

Study outcomes were locally adjudicated by physician experts using standardized definitions. Pregnancy loss was defined as a loss of an intrauterine pregnancy before 20 weeks,[13] and intrauterine fetal death was defined as a loss after 24 weeks.[14] PPH was defined as blood loss from the birth canal more than 500 mL during the first 24 hours after delivery.[15]

VTE was defined as the occurrence of a deep vein thrombosis (DVT) with or without a pulmonary embolism (PE). A DVT was considered to have occurred if it was suspected clinically and was objectively confirmed by ultrasonography. A PE diagnosis was established if clinical suspicion was present, and the diagnosis was confirmed by ventilation–perfusion lung scan, angiography, or CT.[16] The study was approved by the IRB of participating institutions. The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were followed for reporting.[17]

Statistical Analysis

For the main analysis, all deliveries recorded between January 2022 and November 2023 were considered. Maternal characteristics, obstetric history, and pregnancy outcomes were analyzed according to the use of LMWH and LDA during pregnancy. Absolute numbers, percentage, and mean (±standard

deviation [SD]) were calculated to describe variables of study groups and subpopulations of interest. Annualized incidence rates were computed as the number of events divided by the total number of live births and adjusted for the 23-month study duration, expressed as events per 1,000 live births per year.

Associations between primary and secondary outcomes and both numerical and categorical variables (age, drugs, comorbidities, medical procedures, etc.) collected during study were assessed by multivariable logistic regression. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated controlling for potential confounding variables including enrolling center, age and body mass index (BMI) (both included as continuous variables), smoking habits, total previous pregnancies, previous pregnancy loss or intrauterine fetal death, previous preterm pregnancies, previous conception by ART, previous cesarean section, conception through ART in the index pregnancy, LDA and/or LMWH, and single versus twin pregnancy. All statistical analyses were performed using SPSS version 29.0 (SPSS Inc., Chicago, IL, USA).

Assuming that the odds of PPH in untreated individuals is approximately 6%, with a 50 to 55% relative increase among women receiving LMWH or LDA,[18] we estimated that a sample of 2,034 to 2,418 women would be required to obtain prevalence estimates with a precision of approximately ± 1%.

Similarly, based on a reported prevalence of intrauterine fetal death of 1.2%,[19] we hypothesized that the odds of live births among women treated with LMWH and/or LDA might increase by 80 to 90%,[20] requiring a total sample size of between 1,762 and 2,432 women for comparably precise estimates.

These calculations were performed to ensure that the cohort size would allow reliable estimation of PPH and intrauterine fetal death rates across exposure groups. The study was observational and not designed or powered to test efficacy or safety hypotheses regarding LMWH or LDA use during pregnancy.

For the main outcomes statistical power was 80% with significance level of 0.05. The analyses were performed using G*Power software version 3.1.9.7 (Heinrich-Heine-Universität Düsseldorf, Düsseldorf).

Results

Study Population

From an initial sample of 2,673 women admitted for delivery, 2,622 were enrolled in the study (**Fig. 1**). The majority (68.7%) had experienced at least one previous pregnancy: 987 (37.6%) had delivered vaginally and 422 (16.1%) by cesarean section. A history of pregnancy loss was reported by 683 women (26%); among them, 635 (93%) had suffered one or two losses, while 48 (7%) had three or more. Two women reported a history of VTE.

Antithrombotic Therapy During Pregnancy and Postpartum

Data on prescription of LMWH and LDA were available for 1,898 women (**Table 2**).

Overall, 746 (39.3%) women received LMWH: 49 during pregnancy—including 45 who started treatment before 12 weeks' gestation—and 697 (36.7%) in the postpartum period (**Supplementary Table S1**, available in the online version only). Postpartum LMWH use was significantly higher after cesarean section (654/937, 69.8%) than vaginal delivery (44/1,630, 2.6%; $p < 0.001$). During pregnancy, 157 women (8.3%) received LDA (100 mg once daily). Among these, 66 reported a history of pregnancy loss: 44 (66.7%) had one previous loss, 12 (27.3%) had two, and 10 (15.2%) had three or more.

A small subset of nine women (0.5%) received both LMWH and LDA. These women were older than those not treated (mean age 40.1 vs. 32.1 years), and the majority (88.9%) had a history of pregnancy loss—half of them reporting only one prior event (**Table 2**).

Predictors of the Use of Antithrombotic Drugs

Univariate analyses showed that LMWH use during pregnancy was significantly associated with prior cesarean section, previous preterm delivery, pregnancy loss, and ART conception, with ART showing the strongest association. LDA use correlated with previous preterm delivery and ART conception (**Table 2**), and concurrent LMWH exposure (p:0.004). These associations were confirmed in logistic regression models adjusted for age, BMI, prior pregnancy loss, previous ART conception, previous preterm delivery, ART conception in the current pregnancy, LMWH administration, and twin pregnancy (**Table 3**).

Outcomes of the Index Pregnancy

No maternal fatalities or pregnancy-associated VTE were observed. Live births were recorded in 2,505 pregnancies (97.8%) (**Table 4**).

Median birth weight did not differ significantly between infants born to mothers treated with LMWH (3,270 g; interquartile range [IQR] 2,990–3,570) and those not treated (3,270 g; IQR 2,855–3,575; Mann–Whitney U test, $p = 0.56$). In contrast, infants born to women who received LDA had a lower median birth weight (3,065 g; IQR 2,700–3,380) compared with those born to mothers not exposed to LDA (3,290 g; IQR 3,000–3,580; $p < 0.001$). Overall, adverse pregnancy outcomes were uncommon, with intrauterine fetal death reported in nine cases (0.4%) (**Table 5**). Twin pregnancies ($n = 60$) showed a higher rate of intrauterine fetal death (3.3% vs. 0.2% in singletons, $p < 0.001$), remaining strongly associated after adjustment for ART conception and use of LMWH, LDA, or both (OR 21.4, 95% CI 3.8–119).

PPH occurred in 61 women (2.4%) (**Table 5**). Of these, 4 (6.6%) had received LDA during pregnancy, none had been treated with LMWH during gestation, and 22 (36.1%) had received LMWH in the postpartum period. The prevalence of PPH did not differ significantly between women prescribed with postpartum LMWH and those not exposed (22/697 [3.2%] vs. 39/1,925 [2.0%]; $p = 0.10$). Red blood cell transfusion was required in 22 of 61 women with PPH (36.1%) compared with 44 of 2,561 (1.7%) without PPH ($p < 0.001$).

Discussion

In this multicenter, prospectively enrolled cohort study, we observed that the overall use of antithrombotic agents during pregnancy was relatively low with only 2.6% of women receiving

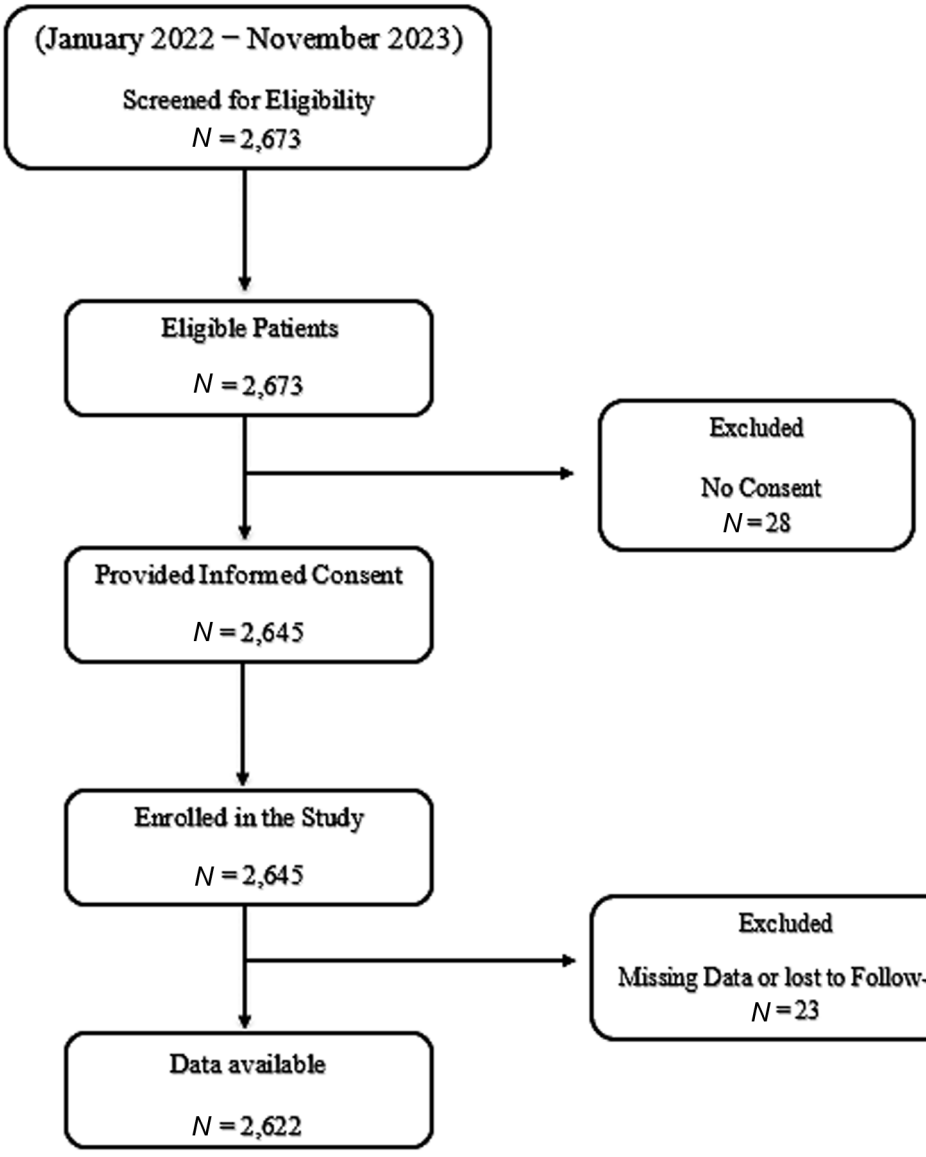

Fig. 1 Flowchart illustrating study enrollment.

LMWH and 8.3% receiving LDA. Antithrombotic therapy was most commonly prescribed in pregnancies perceived to be high risk. LMWH use was significantly associated with a history of pregnancy loss, preterm birth conception via ART, and prior cesarean delivery. Similarly, LDA use was linked to pregnancy loss, ART conception, and concurrent LMWH administration. There was no evidence of a significant increase in PPH risk related to the use of either LMWH or LDA. Postpartum LMWH administration was strongly associated with cesarean delivery.

A central finding of this study is that LMWH and LDA were primarily prescribed to women perceived to be at elevated obstetric risk, reflecting current clinical prescribing patterns. Although overall use was low, prescriptions were concentrated among women with pregnancy loss, ART conception, prior cesarean delivery, or twin pregnancies, aligning with clinician concerns about increased thrombotic risk in these scenarios. This pattern is consistent with prior data from the Netherlands, in which use of antithrombotic agents increased among similar populations between 2013 and 2019. Specifically, LMWH prescriptions rose to 0.9%, while antiplatelet drug use increased to 4.8% of the pregnant population, indicating that exposure to antithrombotic drugs during pregnancy is common.[21] Antithrombotic drugs during pregnancy are indicated for the prevention and treatment of VTE, antiphospholipid syndrome, and prevention of placenta-mediated complications such as preeclampsia or recurrent pregnancy loss.[5,6,11,14] However, the administration of these medications frequently extended beyond evidence-based indications.

It is notable that in our cohort, most women with a history of pregnancy loss had experienced only one or two losses (18/25, 72%), which does not meet the threshold typically required to justify LMWH use according to RCT data.[12,22] A meta-analysis of RCTs demonstrated that LMWH reduces miscarriage rates in women with three or more losses but not in those with fewer losses.[23] In the subgroup of ART pregnancies, LMWH was prescribed in 13.2%, LDA

Table 1 General clinical characteristics of the entire sample

Clinical characteristics	All patients $n = 2,622$
Age, mean (SD)	32.1 (6.0)
BMI, mean (SD)	24.6 (4.9)
First pregnancy	742/2,369 (31.3)
One or more previous pregnancies	1,627/2,369 (68.7)
Previous CS	421 (16.1)
Previous VD	986 (37.6)
Previous pregnancy loss	683 (26)
Previous preterm delivery	90 (3.4)
Previous ART conception	43 (2.2)
Present ART conception	43 (1.6)
LMWH in pregnancy[a]	49 (2.6)
LDA in pregnancy[a]	157 (8.3)
LMWH + LDA in pregnancy	9 (0.5)
LMWH during hospitalization (after delivery)[a]	697 (36.7)

Abbreviations: ART, assisted reproductive technique; BMI, body mass index; CS, cesarean section; LDA, low-dose aspirin; LMWH, low -molecular-weight heparin; SD, standard deviation; VD, vaginal delivery.
Notes: Variables are expressed as numbers (%) if not otherwise specified.
[a]Information not available for the whole cohort.

in 6.4%, and LMWH with LDA in 11.1%. This was observed despite robust evidence from RCTs and meta-analyses indicating that LMWH and LDA do not improve live birth rates or pregnancy outcomes in low-risk women undergoing ART.[24,25]

These findings highlight a persistent gap between clinical practice and evidence-based guideline. The present findings also confirm the association between twin pregnancies and intrauterine fetal death.[26] In the setting featured in our cohort study, these conditions are more likely to be managed with LMWH, LDA, or both (OR: 21.4; 95% CI: 3.8–119), highlighting the increased likelihood of intervention for high-risk pregnancies.

Our study found no significant increase in the odds of PPH with either LMWH or LDA use. Among the 61 cases of PPH, we observed that only 4 involved the use of LDA, none were associated with antepartum LMWH, and 22 had received LMWH postpartum. These findings are reassuring but must be interpreted cautiously due to the limited number of bleeding events and the observational nature of the study. Moreover, the underutilization of tranexamic acid in PPH management highlights a missed opportunity for protocol adherence (**Table 4**).

The association between postpartum LMWH use and cesarean delivery (93.4%) aligns with findings from a recent multicenter study of 21,114 women, in which cesarean section emerged as the strongest predictor of thromboprophylaxis,[27] as well as with European guidelines—such as those from the Royal College of Obstetricians and Gynaecologists (RCOG)—which recommend

Table 2 Women's characteristics according to use of LMWH and LDA in the index pregnancy[a]

	LMWH $n = 49$	No LMWH $n = 1,849$	*p* value
Age, mean (SD)	34.9 ± 6.9	31.8 ± 6	<0.001
Nulliparity	15 (30.6)	897 (48.5)	0.017
Previous CS	20 (40.8)	284 (15.4)	<0.001
Previous VD	14 (28.6)	691 (37.4)	0.18
Previous pregnancy loss	25 (51.0)	449 (24.3)	<0.001
Previous preterm delivery	8 (16.3)	61 (3.3)	<0.001
Previous ART conception	2 (4.1)	7 (0.4)	0.02
Present ART conception[b]	5 (13.2)	33 (1.8)	0.003
	LDA $n = 157$	**No LDA** $n = 1,774$	*p*
Age, mean (SD)	34.7 ± 7	31.7 ± 6	<0.001
Nulliparity	66 (42.0)	847 (47.7)	0.08
Previous cesarean section	37 (23.6)	120 (6.8)	0.008
Previous vaginal delivery	36 (22.9)	676 (38.1)	<0.001
Previous pregnancy loss	66 (42)	423 (23.8)	<0.001
Previous preterm delivery	84 (53.5)	6 (0.3)	<0.001
Previous ART conception	5 (3.2)	7 (0.4)	0.002
Present ART conception[b]	10 (6.4)	28 (1.6)	<0.001
	LMWH + LDA $n = 9$	**No LMWH + LDA** $n = 1,889$	
Age, mean (SD)	40.1 ± 4.4	32.1 ± 5.9	<0.001
Nulliparity	5 (55.5)	1,248 (66.1)	0.44
Previous cesarean section	1 (11.1)	420 (22.2)	0.6
Previous vaginal delivery	3 (33.3)	983 (52.0)	0.5

(*Continued*)

Table 2 (*Continued*)

Previous pregnancy loss	8 (88.9)	675 (35.7)	<0.001
Previous preterm delivery	2 (22.2)	88 (4.7)	0.04
Previous ART conception	0	13 (0.7)	0.95
Present ART conception[b]	1(11.1)	42 (2.2)	0.18

Abbreviations: ART, assisted reproductive technique; CS, cesarean section; LDA, low-dose aspirin; LMWH, low-molecular-weight heparin; SD, standard deviation; VD, vaginal delivery.
Notes: Variables are expressed as numbers (%) if not otherwise specified.
[a]Information not available for the whole cohort.
[b]Data available for 38 women: 1 of them received LMWH + ASA.

Table 3 Predictors of receiving antithrombotic therapy during the index pregnancy

Use of LMWH		
	Adjusted OR	**95%CI**
Previous CS	3.1	1.7–5.8
Previous preterm delivery	3.8	1.7–8.9
Previous pregnancy loss	2.7	1.5–4.9
Previous ART conception	14.6	2.8–76.5
Use of LDA		
	Adjusted OR	**95%CI**
Previous pregnancy loss	2.1	1.4–3.0
Use of LMWH	2.5	1.1–5.5
Present ART conception	4.7	2.2–10.2

Abbreviations: ART, assisted reproductive technique; CI, confidence interval; CS, cesarean section; LDA, low-dose aspirin; LMWH, low-molecular-weight heparin; OR, odds ratio.

Table 4 Maternal and fetal outcomes of the index pregnancy

Clinical outcomes	**Overall *n* = 2,562**
Live births	2,505
Birth weight, grams, median (IQR)	3,250 (2,980–3,550)
Newborn sex, male	1,318 (51.4)
Vaginal delivery	1,630 (63.6)
Episiotomy	365/1,630 (22.4)
Cesarean section, total	937 (36.6)
Emergent cesarean section	260/937 (27.7)
Use of tranexamic acid	40 (1.6)
VTE	0 (0.0)

Abbreviations: IQR, interquartile range; VTE, venous thromboembolism.
Note: Variables are expressed as numbers (%) if not otherwise specified.

Table 5 Annualized incidence of outcomes

Outcomes	***n* (%)**	**Annual incidence per 1,000 live births**
Intrauterine fetal death	9 (0.4)	1.9
Neonatal death	3 (0.1)	0.6
Preterm delivery	238 (9.3)	49.5
Postpartum hemorrhage	61 (2.4)	12.7
Transfusion	66 (2.6)	13.7

postpartum prophylaxis for women with additional VTE risk factors, including obesity, age over 35, ART conception, and twin pregnancies.[28,29]

Several limitations must be acknowledged. The relatively small proportion of women receiving LMWH or LDA may reduce statistical power, limiting the ability to detect small differences in outcomes. The lack of standardized criteria for initiating antithrombotic therapy introduces variability, potentially affecting the interpretation of results. The study's observational design precludes causal inferences and permits residual confounding, including confounding by indication—where women perceived to be at higher risk are more likely to receive treatment—potentially biasing observed associations. For example, LMWH use was more common among women with ART conception or prior adverse pregnancy outcomes, in line with clinical practice, although it remains unclear whether these prescriptions were based on evidence-based indications or physician perception of risk. Similarly, the observed association between LDA and lower birth weight may reflect underlying maternal or pregnancy risk factors rather than a treatment effect. Although no apparent increase in PPH was observed with LMWH or LDA use, this finding should be interpreted cautiously given the study's descriptive design and limited sample size, which do not allow definitive conclusions regarding safety or efficacy.

Although PPH did not appear to be more frequent among women taking LMWH or LDA, inappropriate use of these medications may predispose to bleeding, entail additional costs, and affect patient comfort. Finally, generalizability may be limited in low-resource settings where access to antithrombotic prophylaxis, emergency obstetric care, or cesarean delivery is restricted, and aspirin's potential influence on birth weight may differ in populations with higher rates of maternal malnutrition.

These findings emphasize the importance of reserving LMWH for truly high-risk pregnancies, as its routine use in low-risk cases does not improve live birth rates or birth weight. LMWH should be reserved for high-risk pregnancies, such as those with recurrent pregnancy losses (three or more unexplained or two losses with euploid karyotypes) or those at higher risk of VTE, including those with prior events. These results further strengthen the importance of evidence-based protocols for guiding postpartum

thromboprophylaxis. Furthermore, factors such as advanced maternal age, ART conception, and twin pregnancies should prompt careful evaluation and individualized management plans to mitigate risks effectively.

The strengths of this study include its prospective multicenter design, and the inclusion of detailed demographic and clinical data, which allowed for comprehensive statistical analyses, adjusting for confounders such as BMI, age, and obstetric history. Additionally, outcomes were locally adjudicated by physician experts using validated definitions to enhance accuracy and consistency.

Future efforts should focus on improving risk stratification to ensure that antithrombotic therapy is reserved for women who are most likely to benefit. The advent of wearables for continuous, autonomous monitoring of DVT[30] will enable earlier identification of women at higher risk of VTE who may benefit from antithrombotic prophylaxis, allowing for more tailored treatment. Routine use of LMWH in low-risk pregnancies does not seem to provide measurable benefits. Present findings highlight the need for clearer guidelines and provider and patient education to ensure that antithrombotic therapy is prescribed based on evidence rather than perception.

In conclusion, this study provides valuable real-world insights into the use of LMWH and LDA in pregnancy. Although antithrombotic prophylaxis remains essential for clearly defined high-risk cases, our findings highlight a tendency toward overtreatment in lower-risk pregnancies—particularly following ART or mild obstetric complications—despite limited supporting evidence. This discrepancy between clinical guidelines and prescribing practices underscores the need for clearer decision-making protocols and more precise assessment of maternal risk factors.

What is known about this topic?

- Use of low-molecular-weight heparin (LMWH) and Low-dose aspirin (LDA) during pregnancy is increasing, particularly in high-risk pregnancies.
- There is limited robust clinical trial evidence supporting the efficacy of LMWH and LDA for improving maternal–fetal outcomes.
- Antithrombotic therapies are often prescribed based on clinical judgment rather than standardized, evidence-based guidelines.

What does this paper add?

- It provides real-world data on prescribing patterns and predictors of LMWH and LDA use in a large, multicenter Italian obstetric cohort ($n = 2{,}622$).
- The study identifies key maternal characteristics—such as prior cesarean, pregnancy loss, ART, and twin pregnancies—associated with the use of antithrombotic therapies.
- It highlights the need for cautious, evidence-based use of LMWH and LDA during pregnancy, given the uncertain benefit and the lack of association with adverse maternal–fetal outcomes like postpartum hemorrhage.

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Statements and Additional Information

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Data Availability Statement The data that support the findings are available on request from the corresponding author (E.G.).

Contributors’ Statement E.G., M.Mar., and M.Mas contributed to study concept and design; F.G., F.S., A.V., E.C., A.O., S.B., L.B., G.C., L.M., P.V., T.P., L.La., L.Lo., D.C., B.B., E. K., and A.d.L. contributed to the acquisition, analysis or interpretation of data; M.Mas. and M.Mar. contributed to statistical analysis; E.G., G.P., and M.Mar. drafted the manuscript. All the authors approved final version of the manuscript.

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Supplementary Material is available at https://doi.org/10.1055/a-2755-2565.

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