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Feto-Maternal Complications of Anticoagulant Use Before and After Childbirth

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ABSTRACT

Anticoagulants prevent blood clotting, but their use in pregnancy poses challenges due to bleeding risks, particularly during delivery and postpartum. **Objectives:** To evaluate the maternal and fetal complications associated with anticoagulant use before and after childbirth, considering the safety and effectiveness of low molecular weight heparin and Warfarin. **Methods:** A cohort study was conducted at the Tertiary Care Hospital of Sindh, from August 2022 to July 2023. 266 pregnant women were chosen via consecutive sampling. Pregnant women with a gestational age of > 12 weeks, aged 18-35 years probably taking anti-coagulation therapy during pregnancy and puerperium were included in the study. While women suffering from any major systemic illness and women taking any other potential teratogenic drugs were excluded. **Results:** Maternal complications occurred in 53% of participants, with postpartum hemorrhage being the most frequent (19.9%), significantly higher in the low molecular weight heparin group ($p<0.05$). Pre-eclampsia affected 10.5% of participants, predominantly in low molecular weight heparin users ($p=0.028$). Fetal complications were reported in 59.3% of cases, with intrauterine growth restriction (13.5%) and premature birth (18.0%) being the most common. Stillbirths were more frequent among Warfarin users. Neonatal intensive care admission was required for 11.3% of infants, with low molecular weight heparin exposure showing the highest incidence. **Conclusions:** It was concluded that low molecular weight heparin was with poor maternal outcomes such as postpartum hemorrhage, wound hematoma, deep vein thrombosis, and pre-eclampsia, while fetal complications included intrauterine growth restriction, stillbirth, premature birth and low birth weight.

INTRODUCTION

Pregnancy is a hypercoagulable state due to significant alterations in maternal hemostatic mechanisms driven by hormonal changes. This hypercoagulability persists up to eight weeks postpartum, increasing the risk of thrombotic events by three to five times compared to non-pregnant women [1, 2]. Consequently, anticoagulant therapy is often administered during pregnancy and the puerperium to mitigate this risk. However, concerns remain regarding the potential risks to both the mother and fetus, and there is limited robust evidence guiding the safe and effective use of anticoagulants in pregnancy [3-5]. Warfarin, although effective and well understood, crosses the placental barrier and is associated with fetal risks, including warfarin embryopathy if used during critical periods of gestation [6]. Low Molecular Weight Heparin (LMWH) is considered a safer alternative. However, its dosing regimens during pregnancy are still not well defined, and maternal side effects such as osteoporosis and thrombocytopenia have been reported [7-9]. Despite the widespread use of anticoagulants, there is a lack of comprehensive research that defines their safety profiles during pregnancy and postpartum. This study aims to address this gap by investigating the maternal and fetal complications associated with anticoagulant therapy during these critical periods. By focusing on the clinical significance of anticoagulants, this study seeks to evaluate the maternal

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and fetal complications associated with anticoagulant use before and after childbirth, considering the safety and effectiveness of low molecular weight heparin (LMWH) and Warfarin.

METHODS

A cohort study was conducted at the Department of Gynaecology & Obstetrics with the collaboration of the Department of General Medicine & Pathology of Liaquat University of Medical & Health Sciences, from August 2022 to July 2023. The study protocol was approved by ERC of LUMHS-wide letter no. LUMHS/REC/-354. The study population consisted of 266 pregnant women, chosen via consecutive sampling who received anticoagulant therapy during the perinatal period. The sample size was calculated by taking the expected miscarriage rate of 22.2% due to the use of direct oral anticoagulants in pregnancy [10]. The margin of error was 5% with 95% of Confidence Interval. Pregnant women with a gestational age of >12 weeks, aged 18-35 years probably taking anti-coagulation therapy during pregnancy and puerperium were included in the study. Women suffering from any major systemic illness and women taking any other potential teratogenic drugs were excluded from the sample. Informed written consent was taken from each participant after debriefing her about the details of the research. All women were followed up till the end of puerperium (6 weeks' post-partum). Information regarding demographics, anticoagulant type and dosage, gestational age, mode of delivery, and maternal and fetal outcomes were gathered on pre-defined proforma. Data were analyzed using SPSS version 26.0. The Chi-square test was used to assess the association of categorical variables. p-value<0.05 was declared as statically significant.

RESULTS

The study involved 266 participants who received anticoagulant therapy during the perinatal period. The majority of participants were aged 18-25 years (41.4%), with 34.6% aged 26-30 years and 24.0% aged 31-35 years. In terms of gestational age, 48.1% were in the second trimester (13-28 weeks), while 51.9% were in the third trimester (29-40 weeks). The predominant type of anticoagulant therapy used was Low Molecular Weight Heparin (LMWH), administered to 54.1% of the participants, followed by Warfarin (27.1%) and Aspirin (18.8%). Regarding the mode of delivery, 60.9% of deliveries were vaginal, and 39.1% were cesarean sections (Table 1).

Table 1: Demographic and Clinical Characteristics of Study Population (n=266)

Characteristic	Frequency (%)
Age (Years)	
18-25	110 (41.4%)
26-30	92 (34.6%)
31-35	64 (24.0%)
Gestational Age (weeks)	
13-28 (Second Trimester)	128 (48.1%)
29-40 (Third Trimester)	138 (51.9%)
Type of Anticoagulant Therapy	
Low Molecular Weight Heparin	144 (54.1%)
Warfarin	72 (27.1%)
Aspirin	50 (18.8%)
Mode of Delivery	
Vaginal Delivery	162 (60.9%)
Cesarean Section	104 (39.1%)

The frequency of feto-maternal complications among participants using anticoagulant therapy with 53% of mothers developed complications in the perinatal period while 59.3% of babies developed complications (Figure 1).

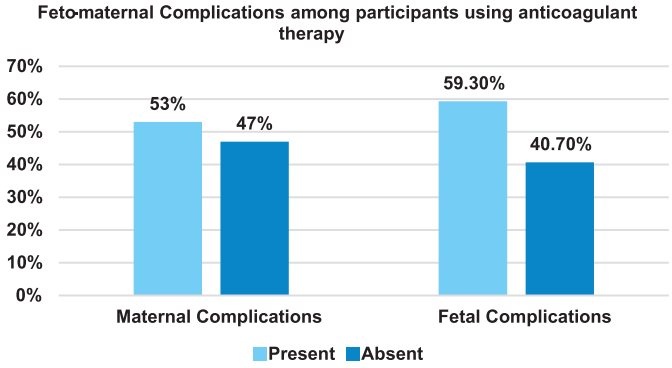

Figure 1: Frequency of Feto-Maternal Complications among Participants Using Anticoagulant Therapy

Among the maternal complications, postpartum hemorrhage was the most frequent, affecting 53 women (19.9%), with the majority (49.1%) in the LMWH group. Deep vein thrombosis and pulmonary embolism were less common, occurring in 12 (4.5%) and 4 (1.5%) participants, respectively, with LMWH users experiencing the highest rates. Wound hematoma and thromboembolic events were observed more frequently in those receiving LMWH. Pre-eclampsia was reported in 28 cases (10.5%), predominantly among LMWH users (Table 2).

Table 2: Feto-Maternal Complications Based on Anticoagulant Therapy (n=266)

Complication	LMWH (n=144)	Warfarin (n=72)	Aspirin (n=50)	Total (n=266)
Maternal Complications n=141 (53%)				
Postpartum Hemorrhage (PPH) (n=53)	26 (49.1%)	22 (41.5%)	5 (9.4%)	53 (100%)
Deep Vein Thrombosis (DVT) (n=12)	6 (50.0%)	4 (33.3%)	2 (16.7%)	12 (100%)
Pulmonary Embolism (PE) (n=4)	2 (50.0%)	1 (25.0%)	1 (25.0%)	4 (100%)
Wound Hematoma (n=24)	12 (50.0%)	10 (41.7%)	2 (8.3%)	24 (100%)
Thromboembolic Event (n=8)	4 (50.0%)	3 (37.5%)	1 (12.5%)	8 (100%)
Pre-eclampsia (N = 28)	16 (57.1%)	10 (35.7%)	2 (7.1%)	28 (100%)

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Fetal Complications n=158 (59.3%)				
Intrauterine Growth Restriction (IUGR) (n=36)	18 (50.0%)	12 (33.3%)	6 (16.7%)	36 (100%)
Premature Birth (<37 weeks) (n=48)	22 (45.8%)	20 (41.7%)	6 (12.5%)	48 (100%)
Low Birth Weight (<2.5 kg) (n=39)	18 (46.2%)	16 (41.0%)	5 (12.8%)	39 (100%)
Stillbirth (n=5)	2 (40.0%)	3 (60.0%)	0 (0.0%)	5 (100%)
Neonatal Intensive Care Admission (n=30)	14 (46.7%)	12 (40.0%)	4 (13.3%)	30 (100%)

Fetal complications included intrauterine growth restriction (IUGR) in 36 infants (13.5%), premature birth in 48 cases (18.0%), and low birth weight in 39 infants (14.7%). IUGR and low birth weight were most common among LMWH users, while premature birth also affected a significant portion of the LMWH group. Stillbirths were rare, with a higher rate observed in Warfarin users. Neonatal intensive care admission was required for 30 infants (11.3%), with the highest frequency in those exposed to LMWH (Table 3).

Table 3: Maternal and Fetal Complications Before and After Childbirth (n=266)

Complication	Before Childbirth	After Childbirth	p-value
Maternal Complications n=141 (53%)			
Postpartum Hemorrhage (PPH)	N/A	53 (37.6%)	N/A
Deep Vein Thrombosis (DVT)	8 (5.7%)	4 (2.8%)	0.182
Pulmonary Embolism (PE)	3 (2.1%)	1 (0.7%)	0.403
Wound Hematoma	N/A	24 (17.0%)	N/A
Thromboembolic Event	6 (4.3%)	2 (1.4%)	0.157
Pre-eclampsia	28 (19.9%)	N/A	N/A
Fetal Complications n=158 (59.3%)			
Intrauterine Growth Restriction (IUGR)	36 (22.8%)	N/A	N/A
Premature Birth (<37 weeks)	N/A	48 (30.4%)	N/A
Low Birth Weight (<2.5 kg)	N/A	39 (24.7%)	N/A
Stillbirth	5 (3.2%)	N/A	N/A
Neonatal Intensive Care Admission	N/A	30 (19.0%)	N/A

(Chi-square test was applied) but none of the values was of statistical significance)

DISCUSSION

Globally, LMWH is regarded as the first-line anticoagulant for pregnant women due to its safety profile, especially its minimal placental transfer and reduced risk of teratogenicity compared to Warfarin. Feto-maternal complications were a significant area of investigation in this study, with postpartum hemorrhage (19.9%) being the most common complication. This aligns with the global concern about hemorrhagic complications in anticoagulated pregnancies, particularly those using LMWH, which is known to pose a risk for bleeding complications, especially during delivery. Bannow et al., highlighted that while LMWH is effective in reducing thromboembolic events, it increases the likelihood of hemorrhagic events, including postpartum hemorrhage [4]. In contrast, our study did not find Warfarin or Aspirin to be associated with as high a frequency of hemorrhagic complications, although these agents are also known to increase bleeding risks in general. The incidence of deep vein thrombosis (DVT) (4.5%) and pulmonary embolism (PE) (1.5%) in our cohort mirrors the lower rates of thromboembolism seen in LMWH users in other international studies, such as that by Rodger et al., who demonstrated that LMWH effectively reduces DVT and PE risks during pregnancy [11]. However, our study's slightly higher rates of thromboembolic events in LMWH users (compared to Warfarin or Aspirin) may reflect a population with higher baseline thrombotic risk, necessitating LMWH use. Pre-eclampsia was reported in 10.5% of participants, predominantly in the LMWH group. This is consistent with other international studies showing an increased incidence of hypertensive disorders in pregnancies requiring anticoagulation. The use of LMWH in such cases is often multifactorial, aimed at preventing not just thromboembolic events but also placenta-mediated complications, as suggested by the work of McLintock C et al., [12]. One key contrast between our findings and those from international literature is the lower overall incidence of cesarean sections (39.1%). In studies from higher-income countries, cesarean delivery rates tend to be higher in anticoagulated pregnancies, likely due to concerns about the risk of hemorrhage during vaginal delivery. This may be reflective of differences in local clinical practices, with a preference for vaginal delivery in our cohort, even among women on anticoagulants [2]. Additionally, while postpartum hemorrhage was the most common complication in our cohort, the overall rate of feto-maternal complications appears somewhat lower than in some international studies. This could be due to variations in healthcare systems, anticoagulation protocols, and the baseline health status of the study populations [13, 14]. The analysis of maternal and fetal complications among women receiving anticoagulant therapy during the perinatal period revealed significant findings. Postpartum hemorrhage (PPH) was the most common maternal complication, affecting 37.6% of women, with the highest occurrence among Low Molecular Weight Heparin (LMWH) users (49.1%). This aligns with international studies of McLintock C & Riley LE highlighting PPH as a frequent complication in anticoagulated pregnancies, although our overall rate appears lower compared to some reports from higher-income settings, where PPH rates can exceed 30% in similar cohorts [12, 13].

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Deep vein thrombosis (DVT) and pulmonary embolism (PE) were less frequent, with 5.7% of DVT cases occurring before childbirth and 2.8% afterwards, predominantly in the LMWH group. These rates are consistent with findings that LMWH effectively reduces the risk of thromboembolic events, though these complications still occur at a notable rate [14]. Fetal complications were also prevalent, with intrauterine growth restriction (IUGR) reported in 13.5% of pregnancies and premature births in 18.0%. Premature birth was most frequent among LMWH users (45.8%), aligning with a study by Abd et al., identifying anticoagulation therapy as a risk factor for preterm labour due to its association with placental insufficiency [15]. However, the rates of low birth weight (14.7%) and neonatal intensive care admission (11.3%) were comparable to international reports of Meng et al., underscoring the risks of fetal complications associated with anticoagulant use during pregnancy [16]. Interestingly, stillbirths were rare but more common in Warfarin users (60.0%), highlighting the increased risk of fetal demise linked to this specific anticoagulant as expressed by Lo [17]. In comparison to global data, the relatively low incidence of severe maternal thromboembolic events and fetal complications in our cohort may reflect differences in healthcare settings, anticoagulation protocols, and maternal characteristics. Studies by Lafalla and Kearsley from high-income countries often report higher rates of cesarean sections and maternal complications due to concerns over bleeding risks during vaginal delivery [18, 19]. However, in our population, the preference for vaginal delivery (60.9%) among anticoagulated women suggests more conservative management strategies, possibly contributing to the lower rates of severe maternal and fetal outcomes [20]. This study was limited by its single-center design, which may reduce the generalizability of the findings. The use of consecutive sampling could introduce selection bias too. Additionally, the study did not account for potential confounding factors such as socioeconomic status or access to healthcare, which may influence maternal and fetal outcomes.

CONCLUSIONS

It was concluded that anticoagulant therapy, particularly LMWH, significantly influences both maternal and fetal outcomes. Before childbirth, LMWH use is linked with higher rates of deep vein thrombosis and pre-eclampsia, alongside a notable prevalence of intrauterine growth restriction and stillbirth. After delivery, LMWH is associated with increased risks of postpartum hemorrhage, wound hematoma, and adverse fetal outcomes such as premature birth, low birth weight, and the need for neonatal intensive care.

Authors Contribution

Conceptualization: SK
Methodology: SK, RP, SF, MAM, PK
Formal analysis: FL, UJK
Writing review and editing: RP, SF, MAM

All authors have read and agreed to the published version of the manuscript

Conflicts of Interest

All the authors declare no conflict of interest.

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