Aspirin versus low molecular weight heparin for secondary prevention of venous thromboembolism in pregnancy

Original Article

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ABSTRACT

Introduction: Strategies for optimal prophylaxis in pregnant women with a history of venous thromboembolism (VTE) are not currently based on high-quality evidence. Both Thromboembolism and anticoagulation treatment account for significant maternal morbidity and mortality. This study examined patients with thromboembolism associated with pregnancy and evaluated the efficiency of Aspirin against anticoagulation in secondary prophylaxis during pregnancy.

Patients and Methods: A retrospective analysis was conducted on 106 consecutive episodes of pregnancy in 89 women, with previous venous thromboembolic events. In 72 episodes, patients received 150 mg/day of Aspirin only. In the other 34 episodes, patients received prophylactic anticoagulation in the form of low molecular weight heparin. Patients were given the secondary prophylaxis medication throughout the whole period of pregnancy and followed-up for 6 weeks postpartum.

Results: The patient's mean age was 25 (±SD 3.7) years. Re-thrombosis developed in 13% of the Aspirin-only group versus 20% in the anti-coagulation group (*P=0.025*). The shorter the duration between the last episode of VTE and the new conception, the higher the re-thrombosis rate (*P value=0.0001*). The rate of re-thrombosis was higher in patients with previous unprovoked VTE compared with those with provoked events (20.8% vs. 12.2% *P value=0.049*) irrespective of the anticoagulation protocol.

Conclusion: Aspirin is not inferior to prophylactic low molecular weight heparin in 2ry prevention of VTE in pregnant females. Implementation of anticoagulation should be tailored according to risk factors rather than pregnancy. The longer the gap between VTE and subsequent pregnancy the lower the re-thrombosis rate. This emphasizes the importance of gestational regulation following VTE.

Key Words: Aspirin, heparin, pregnancy, secondary prevention, thromboembolism.

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INTRODUCTION

Pregnancy and puerperium are well-established risk factors for the development of venous thromboembolism (VTE), including both pulmonary embolism (PE) and deep venous thrombosis (DVT). VTE is more common and more difficult to diagnose in pregnant patients than in those who are not[1–5].

Both Thromboembolism and anticoagulation treatment still account for significant maternal morbidity. There is a significant gap in the current body of evidence, posing a challenging task to establish a solid protocol for VTE prophylaxis during pregnancy. The safety and side effects of different anticoagulants add to the complexity of the situation.

Pregnant women are very difficult to enroll in randomized controlled trials due to the dilemma of ethical approval of such studies, and the fact that pregnant women are more conscious of the possibility of congenital anomalies and fetal risks associated with medications[6–9].

Another crucial factor that impacted prophylaxis protocols in the past two decades, especially in developing countries was the availability and the cost of different treatment options. In the absence of publicly funded health services and drug payment schemes, extended treatment duration may significantly impact patients financially, and may also lead to discontinuation or non-compliance when the more expensive drugs are prescribed for extended durations.

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In this study, we examined pregnant ladies with a history of VTE and evaluated the efficacy of Aspirin versus prophylactic low molecular weight heparin (pLMWH) for secondary VTE prophylaxis.

PATIENTS AND METHODS:

Ethical approval for the study was acquired through the institutional committee. Patient consent was waived by the committee. A retrospective analysis of prospectively collected and maintained data was performed by retrieving data from our institutional record system including both public and private clinics. The study included all patients presented between January 2005 and December 2020.

The inclusion criteria were:

Pregnant patients, or patients planning for pregnancy, with a previous history but no active symptoms of VTE, were referred for secondary prophylaxis. Previous VTE diagnosis was confirmed only if there was radiologic evidence of VTE in the patient's records.

The exclusion criteria were:

(a) Pregnant patients presenting with active VTE episodes or currently being treated for VTE

(b) Patients with a concurrent diagnosis of the mechanical cause of VTE as pelvic tumor mass or other malignancy.

(c) Patients on life-long anti-coagulation treatment or receiving anticoagulation during the time of presentation for any other medical cause.

Treatment protocol

All patients were offered pLMWH at the first instance. Patients were offered to alternatively go on Aspirin (150 mg once daily) only if they were unable to proceed with pLMWH due to financial aspects, and after a thorough explanation of the differences between the two options with regards to efficacy and side effects according to the available evidence at the time of treatment. This discussion was documented in the patient's records.

Endpoints

The primary endpoint was a recurrence of VTE. Secondary endpoints included complications of treatment, namely bleeding, and complications of pregnancy and its outcome.

Statistical analysis

Data were processed using SPSS. Continuous variables were analyzed using the ANOVA test. Other variables were analyzed using the χ^2 test. Simple proportions of recurrence were calculated, and 95% confidence intervals (CI) were estimated using Wilson's score method. A comparison of the proportion of events between groups was done using χ^2 tests.

RESULTS:

Between January 2005 and December 2020, we recorded 106 episodes of pregnancy requiring 2ry VTE prophylaxis in 89 patients. 13 patients had two pregnancy episodes and two patients had three episodes. Patients fell into two groups; the first group (n = 72) received only antiplatelet prophylaxis in the form of Aspirin 150 mg daily. The second group (n = 34) received pLMWH. (Fig. 1).

Overall, patients were followed until 6 weeks postpartum. All patients continued to receive prophylaxis for the duration of pregnancy extended to 6 weeks after delivery.

The patient's ages ranged from 17 to 37 years (Mean 25 ±SD 3.7). None of the patients were smokers or hypertensives. 94 cases reported no co-morbidities. Three patients had previous diagnoses of Bechet's disease, 2 cases had a diagnosis of antiphospholipid syndrome, one patient was diagnosed previously with protein-c deficiency, 3 cases with rheumatoid arthritis, and one case had diabetes mellitus. None of the included patients were on life-long anticoagulation (Table 1).

Regarding the suspected causes of previous VTE, there were 48 unprovoked cases, with no evidence in patients' history or record data to suggest a provoking factor for VTE. 58 cases were provoked with a history of oral contraception (OCP) (n=3), postpartum (n=28), and previous pregnancy (n=27). The miscarriage rate was 6.6% and 8.5% in the unprovoked and provoked groups, respectively, (*P= 0.049*). (Table 2)

Ilio-femoral DVT accounted for most of the VTE incidents (N= 50). 37 patients had femoral DVT, nine had popliteal DVT, seven suffered from calf vein thrombosis and three had extensive thrombophlebitis extending into the deep system. There were no reports of PE in the study cohort.

The outcome of pregnancy related to the site of DVT is shown in (Fig. 2) The rate of miscarriage was 6.6% (n=7) in the Aspirin group, and 8.5% (n=9) in the pLMWH group respectively (*P =0.025*) (Fig. 3). Pregnancy complications were reported in 5 cases including acute kidney injury (n=1), polyhydramnios (n=1), ruptured uterus (n=1), and 2 cases of superficial thrombophlebitis of Great Saphenous vein. (Fig. 4)

Re-thrombosis developed in 13% of the Aspirin-only group versus 20% in the pLMWH group (*P=0.025*). 81 cases had their pregnancies more than a year after VTE; those included 23 cases who had a pregnancy after 1 year, 19 cases after 2 years and 39 cases after 3 years or more. 12 cases of the pregnancies ended with a miscarriage. 25 patients had become pregnant less than 1 year from their previous VTE event, and 4 of these cases ended with a miscarriage. The shorter the duration between the last episode of VTE and new conception (less than 1 year), the higher the re-thrombosis rate (*P value=0.0001*). (Table 3).

Table 1: Patients co-morbidities (pLMWH= Prophylactic low molecular weight heparin)

Comorbidities	Aspirin (*N*=72)	pLMWH (*N*=34)	Total (*N*=106)	*P* value
None	64	30	94	0.67
Bechet's syndrome	2	1	3	0.83
Anti-phospholipid antibody syndrome	1	1	2	0.79
Protein-C deficiency	0	1	1	0.66
Rheumatoid arthritis	3	0	3	0.53
Diabetic mellitus	1	0	1	0.64

Table 2: Relation between the cause of deep venous thrombosis and the outcome of pregnancy

	Outcome of pregnancy	
DVT causes	Healthy baby	Miscarriage
Unprovoked	41	7
Provoked, oral contraception pills	1	2
Provoked, postpartum	26	2
Provoked, pregnancy	22	5

Table 3: Outcome of pregnancy in relation to the timing of venous thromboembolism with multivariate analysis

	Outcome of Pregnancy		
VTE	Healthy Baby	Miscarriage	*P value*
3 years or more	38	1	
2 years	16	3	0.0001
1 year	15	8	
<1 year	21	4	

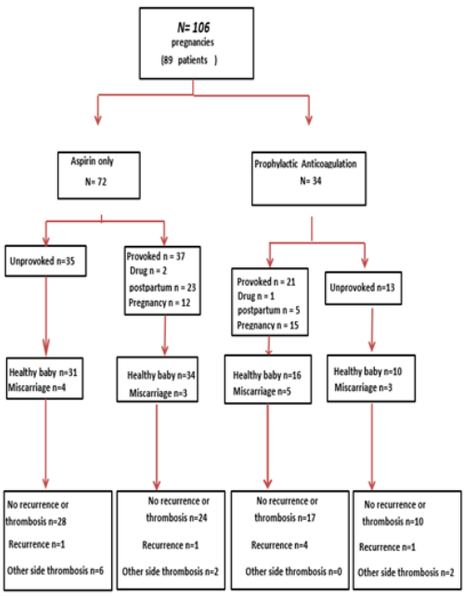

Fig. 1: Flow chart showing the categories of study participants.

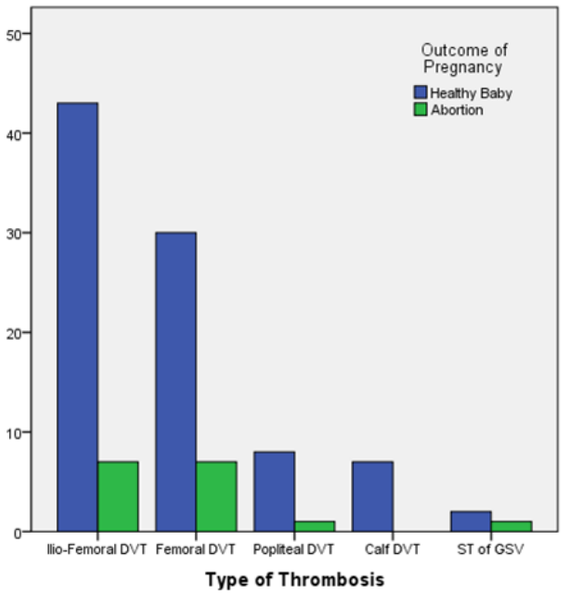

Fig. 2: Anatomical distribution of deep venous thrombosis and pregnancy outcome.

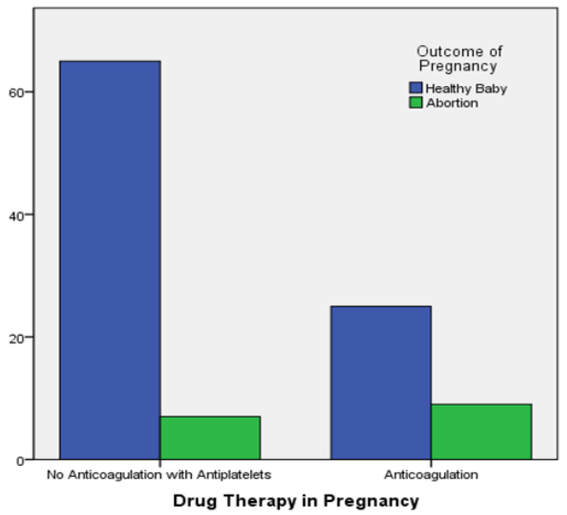

Fig. 3: Pregnancy outcome in Aspirin versus Prophylactic low molecular weight heparin groups.

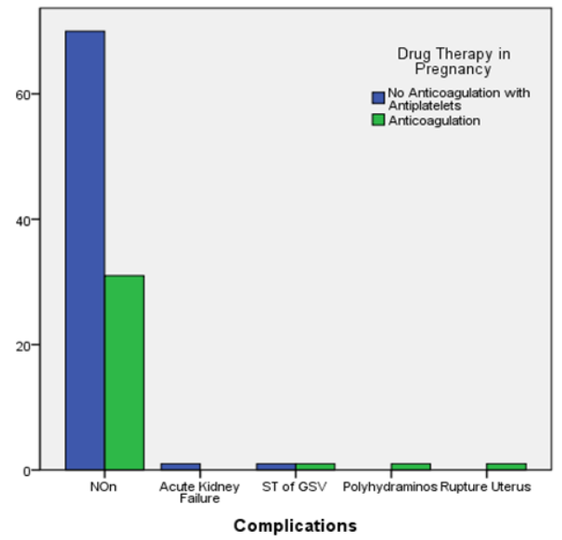

Fig. 4: Pregnancy complications in both groups.

DISCUSSION

Pregnancy predisposes to thrombosis due to the presence of all the components of Virchow's triad, including endothelial injury, blood stasis, and hypercoagulability. Both mechanical and chemical factors predispose to stasis. These include the pressure posed by the gravid uterus and the venous wall relaxation induced by active pregnancy hormones.

By weeks 25–29 of pregnancy there is an ~50% reduction of venous flow velocity in the legs. This persists until nearly 6 weeks after labor, at which time normal venous flow is restored[10,11]. The left lower limb is the most common site affected by DVT (82%). It is hypothesized that anatomic causes play a major role in this process. The main factor is the compression of the left common iliac vein by the right common iliac artery, which is accentuated by the enlarging uterus[6].

There is also an endothelial injury in pelvic veins that can take place at the time of labor or as a result of increased venous pressure during pregnancy[2]. Pelvic vein thrombosis is rare outside of pregnancy, but it accounts for 6–11% of DVT in pregnant patients[6].

A hypercoagulable state is acquired during normal pregnancy. This is the most pivotal risk factor associated with VTE during pregnancy. Not only Fibrin production is increased, but also, the fibrinolytic system is suppressed, and the levels of coagulation factors II, VII, VIII, and X all rise exponentially[2,12]. There is a progressive decline in protein S levels and an acquired resistance to activated protein C[2,12]. All of these physiologic changes are meant to aid the hemostasis required during the time of delivery[1,12].

Despite the significant risk for thrombosis during pregnancy and the postpartum period, it's not normally indicated to initiate antithrombotic prophylaxis in all pregnant females. In these situations, the risks of anticoagulation are considered to overweight its benefits. The risk of bleeding complications with anticoagulation, as reported in the literature, could be as high as 2%[13].

Thromboprophylaxis during pregnancy is not a straightforward plan because it involves long-term parenteral LMWH or unfractionated heparin (UFH). Both of these options are costly, inconvenient for the patients, and not pain-free. They also pose quite significant risks of bleeding, osteoporosis, and heparin-induced thrombocytopenia[14,15]. Considering its benefits over UFH, LMWH is the preferred option for prophylaxis and treatment of VTE during pregnancy[14,15]. UFH is opted for in case of renal insufficiency. LMWH's main excretion is done by the kidneys. Thus it may accumulate in patients with renal failure[15].

Warfarin crosses the placental membrane and is considered to be teratogenic. It is a US FDA category D drug. Warfarin is associated with a 14–56% risk of miscarriage during the first trimester and carries up to 30% risk for congenital anomalies if taken during the critical phase of organogenesis (4th–8th week after conception)[16–19]. Placental crossing of warfarin in late pregnancy is linked to the risk of fetal bleeding[20] and stillbirth[16–19]. Long-term complications include a 14% risk of neurologic abnormalities and a 4% risk of lowered intelligence quotient (IQ)[21].

Studies on the use of selective factor Xa inhibitor (Fondaparinux) during pregnancy using models did

not show significant crossing through the placental barrier, but these studies are very scarce[20]. On the other hand, other studies confirmed that it crosses the placenta in some pregnant patients who received it due to heparin allergy[22]. Up until now, there is no convincing evidence to support the safety of the use of Fondaparinux for the prevention of VTE during pregnancy. It should be considered only for patients with severe allergies to heparin or heparin-induced thrombocytopenia. Small case series and case reports showed it to be safe[22–24] but it is important to recognize that most of these involve exposure after the first trimester. Other new anti-coagulants (e.g., dabigatran, rivaroxaban, apixaban, edoxaban) are believed to cross the placental barrier, and because of that, their risk during pregnancy is unknown[15].

Deciding which pregnant patients need to be on thromboprophylaxis was always a difficult one. The threshold for prescribing prophylaxis postpartum is lower than for prophylaxis during pregnancy, as it is for a shorter duration (6 weeks), has a higher relative risk of DVT, and the relative safety of warfarin during this period, even for breastfeeding mothers as it is not excreted in breast milk[14]. The relatively even distribution of DVT throughout all trimesters justifies the start of prophylaxis as early as possible[2,4,6,8].

The current literature suggests that women with a history of previous attacks of VTE have a higher risk of re-thrombosis during pregnancy. This risk is estimated to be between 2 and 10%. No large clinical trials were conducted to look at the role of VTE prophylaxis in pregnant patients with a history of VTE. There is an ongoing multinational randomized controlled prospective trial, the Highlow study, which recruits pregnant females with a previous history of VTE. It looks at the true risk of recurrence of VTE, the optimal dose, and the safety of LMWH for prophylaxis. The Netherlands, Ireland, Belgium, France, and Norway are participating, with an expected sample size approaching 1,000 women[25,26]. Many studies tried to look into the relationship between congenital thrombophilias and VTE. However, limitations in their methodology made it very difficult to come up with accurate assumptions of their risk. Deficiencies of endogenous anticoagulants such as antithrombin, protein C, and protein S were linked to a moderate risk of VTE with pregnancy[14].

The American College of Chest Physicians and The American College of Gynecologists recommend prophylaxis with LMWH for all pregnant females with a previous history of VTE and a diagnosis of thrombophilia, as well as for those with a history of more than two episodes of VTE[14,15]. There is no agreement on what the ideal dose should be. For those with a history of only one attack of VTE but no thrombophilia, the current recommendation is for close clinical follow-up during pregnancy, and to start prophylaxis only postpartum[14,15]. For pregnant patients with thrombophilia but no previous attacks of VTE, the recommendation of the American College of Chest Physicians is to carry out an individual risk assessment for each patient; however, it recommends postpartum anticoagulation[14].

In the present study, re-thrombosis developed in 13% of the Aspirin-only group versus 20% of the anti-coagulation group. These findings suggest that a strategy of Aspirin only is superior to anticoagulation prophylaxis in pregnant women with prior DVT, especially if the DVT-pregnancy period is equal to, or more than one year.

To the best of our knowledge, four randomized controlled trials addressed antenatal prophylaxis. Two of these studies compared either enoxaparin[27] or unfractionated heparin (UFH)[28] versus no prophylaxis in pregnant patients with high risk for VTE, including a history of previous attacks of VTE. Combined, both studies enrolled only 56 pregnant females and both concluded that there was no difference in the number of symptomatic VTE episodes. These studies were largely underpowered to detect any significant clinical difference between both modalities.

A third study randomized 117 pregnant women over 7 years to enoxaparin or UFH. The primary endpoint was changes in bone density. In this study, patients received enoxaparin or Tinzaparin, or even UFH but only VKAs were used in the second or third trimester. The last study compared Dalteparin to UFH in 105 patients with a high risk for thrombotic recurrence[29]. Finally, a prospective study of 125 pregnant women estimated a recurrent VTE rate of 2.4% (95% CI: 0.2–6.9) during pregnancy without prophylaxis[30].

The cohort of this study did not show any high incidence of underlying inherent thrombophilic risk factors. This might be related to the under-reporting bias inherent in retrospective studies extending for long periods. It also could be explained by the lack of awareness and screening for thrombophilia in pregnant females with a single attack of VTE in the past decade.

Oral contraception remains a significant cause of VTE in females of childbearing age. This is clearly demonstrated in our results. Patient-tailored prescriptions of alternative contraceptive methods should be considered by general practitioners and gynecologists after a thorough assessment of individual patient's risk factors for VTE.

Aspirin, although prescribed mostly due to financial considerations in developing countries, showed

superior results in terms of both increased efficacy and lowered complication rates in comparison to pLMWH. This is equally relevant in developed countries where expenditure on health services has become a major concern, allowing for the diversion of available funds to more pressing health issues and emergency services justified by cost-effectiveness.

Our results show that miscarriage, although not the most common, is still the most devastating complication associated with VTE and pregnancy. Gestational regulation after an episode of VTE remains of paramount importance to lower the risk of recurrent VTE and miscarriage. This risk seems to be the highest if pregnancy takes place within the first year after a VTE episode. Underlying thrombophilia and other systemic risk factors for VTE other than pregnancy must be thoroughly examined and screened for in pregnant females to avoid such unpleasant surprises, to say the least.

The main limitation of our study is its retrospective observational design, with its inherent possibility of selection bias. However, all patients were followed until the 6th postpartum week, thus decreasing the possibility of missing recurrent events after delivery. Another important limitation of our study is the lack of blindly reported outcome events. In trying to overcome this, two authors independently reviewed the outcomes to reduce bias and confirm the occurrence of the outcome.

While not a randomized trial, our study is one of the few addressing the issue of VTE-associated pregnancies and secondary prevention.

CONCLUSION

Aspirin is not inferior to pLMWH in the secondary prevention of VTE in pregnant females. Considering the lower complications risk associated with Aspirin compared with LMWH, we recommend it to be a viable option for secondary VTE prevention during pregnancy. Anticoagulation implementation should be tailored to additive risk factors rather than pregnancy.

The longer the gap between a VTE attack and subsequent pregnancy the lower the re-thrombosis rate, an observation that emphasizes the importance of gestational regulation following VTE.

Acknowledgments

Data availability statement: The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

CONFLICT OF INTEREST

There are no conflicts of interest.

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