Evaluation of Different Treatment strategies of Early Pregnancy Deep Venous Thrombosis

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Abstract

Purpose: *The aim of this study is to assess the maternal outcomes and complications of deep venous thrombosis (DVT) encountered in early pregnancy, mainly regarding recurrence using different regimens of fondaparinux treatment periods, rather than mentioned in different studies and recommended by the royal and American Colleges of Obstetricians and Gynecologists, but with close surveillance program and frequent follow up visits and duplex US follow up of different patients groups.* ***Methods****: the study was conducted on 60 women with DVT presented during the 1st trimester of pregnancy in zagazig university hospitals; patients received fondaparinux therapeutic dose, until full clinical improvement and duplex complete recanalization, then the patients were randomly divided into 2 groups the 1st continued on a prophylactic dose of fondaparinux till the end of pregnancy and the other kept on aspirin 75 mg daily till beginning of 9th month where they received a prophylactic dose of fondaparinux till the end of pregnancy. After delivery all patients will be on warfarin for six weeks with target INR between two and three. All patients will be followed up for 24 weeks after labour with outcomes assessment of complications specifically recurrence.* ***Results****: the study was carried out during the period between June 2015 to June 2017; the mean age of the patients was 25.33±1.17 and 24.4±5.07 for both groups respectively. Level of DVT, maternal outcome including; DVT recanalization and complications such as recurrence (DVT and or PE) and post thrombotic syndrome (PTS) were compared between both groups.* ***Conclusion:*** *the low rate of recurrence in our study challenged the belief that all pregnant females with recanalized DVT should receive LMWH prophylaxis all throughout pregnancy; therefore we recommend fondaparinux prophylaxis from the beginning of the 9th month of pregnancy stopped 24 hours before labour and return to full therapeutic dose in the postpartum period with oral anticoagulant therapy (warfarin) till target INR is achieved, where fondaparinux is stopped and continue with warfarin for at least 6 weeks.*

Key words*: deep venous thrombosis - pregnancy- fondaparinux*

INTRODUCTION

Antithrombotic treatments should never be used unwisely in pregnancy, and its applications should be restricted to defined clinical settings after a careful consideration of pros and cons[1]

Anti-phospholipid syndrome is the major example of thrombophilia encountered during pregnancy. Anti-phospholipid antibodies as a laboratory marker plus one clinical manifestation indicate the presence of the disease. The disease carry the increase the incidence of unfavourable outcome and increase the chance of VTE, in one series, the risk of recurrent thrombosis during pregnancy was five percent, despite treatment with low or intermediate dose low-molecular-weight heparin [2]

Bleeding complications due to anticoagulation treatment in pregnant females were recorded to reach 2%[3].

Pregnancy related thromboprophylaxis is a debatable issue because it entails continuous LMWH or unfractionated heparin (UFH) injection. Both are costly, troublesome, unpleasant to use and are accompanied by hazards of bleeding, heparin induced thrombocytopenia (HIT) and osteoporosis, although these complications are rare with LMWH yet there still burdens [4,5].

On the other hand PTS may complicate in a large number of cases up to 60% of patients after acute DVT extended in the ileo-femoral venous tree [6].

Objective:

The aim of this study is to assess the maternal outcomes and complications of deep venous thrombosis (DVT) in encountered in early pregnancy, mainly as regard recurrence using different regiments of fondaparinux treatment periods, rather than mentioned in different studies

and recommended by the royal and American Colleges of Obstetricians and Gynecologists, but with close surveillance program of frequent follow up visits and duplex US follow up of different patients groups.

PATIENTS AND METHODS

Clinical evaluation was conducted to every patient, including a comprehensive history with special attention to maternal age, anticoagulation treatment, and obstetric history. By history taking all women were asked for any previous attacks of calve pain and swelling, dyspnoea and chest pain or anti-coagulation treatment or miscarriage. Investigations included duplex scan performed every 4 weeks, complete blood picture, serum creatinine, random blood sugar, also all patients included in the study underwent thrombophilia screening, including fibrinogen, anti-thrombin activity, lupus anticoagulant, anti-cardiolipin antibodies protein C and protein S activity.

Exclusion criteria:

Patients with renal insufficiency, patients with onset of DVT after the 1st trimester and patients with thrombophilia or a history of VTE.

All steps of the treatment were discussed carefully with all patients and the study was approved by the Institutional Review Board.

All patients received fondaparinux 7.5mg for patients' weight 50- 100kg S.C. once daily injection and 10 mg once daily for more than 100kg in weight, which was selected according to previous studies supporting its use during pregnancy [7,8]. Then patients will be randomly divided into two groups 30 patients in each one, both groups treated by therapeutic dose of fondaparinux till full clinical improvement and duplex recanalization, then the 1st group will continue on prophylactic dose the till 24 hours before delivery and the 2nd group stopped fondaparinux after duplex recanalization and clinical improvement (subsidence of leg swelling, tightness, and pain, typically disappeared) and kept on and aspirin 75 mg daily and close follow up every two weeks till the beginning of 9th month of pregnancy, when they stopped aspirin and received prophylactic daily dose of fondaparinux(2.5 mg S.C.) stopped 24 hours before expected date of labour.

Graduated compression stockings were prescribed after 2 weeks from beginning fondaparinux treatment, patients were committed to use even after clinical improvement.

Both groups began warfarin on the 2nd day after labour, warfarin was compatible with breast-feeding and continued therapeutic dose of fondaparinux till reaching target INR (2-3), then continued warfarin only for at least 6 weeks after labour. All patients were followed up 24 weeks after labour to for detection of any manifestation of PTS, with follow up DUS every 12 week.

When pulmonary embolism (PE) was suspected, a chest x-ray was performed firstly before the decision for further imaging studies (ventilation perfusion scan or pulmonary computed tomography angiography CTA). Chest radiography which exposed the foetus to 0.1 m Gray, those exposures were below thresholds associated with teratogenesis[9], could rule out other pathologies such as pneumonia or pneumothorax that may mimic the symptoms of PE, then when the case was suspicious of PE ventilation perfusion scan was performed during antenatal period and pulmonary CTA was performed during postnatal period.

Obstetric complications included mainly postpartum hemorrhage (during vaginal delivery >500 ml and during cesarean delivery >1000 ml blood loss, or requiring transfusion).

Statistical analysis

Continuous data were presented as means± standard deviations (SDs), categorical data as counts and percentages. Statistical differences among groups were evaluated by independent sample t test or Mann–Whitney U test for continuous data, and by Fisher exact test for categorical data. P-value of less than 0.05 was considered statistically significant

RESULTS

The study was carried out in vascular surgery department at zagazig university hospitals during the period between June 2015 to June 2017 and included 60 pregnant females with DVT on anticoagulant therapy

Patient demographics: it was summarized in table (1) without statistically significant results between both groups, where the age of the patients ranged between 18 and 41 for the 1st group and 19 and 39 years old for the 2nd group with a mean 25.33±1.17, 24.4±5.07 for both groups respectively. 28 (46.6%) patients were

seen as inpatients, and 32(53.4%) patients followed outpatients. There were inter-disciplinary consultations between vascular, obstetrics and gynaecology departments. Follow-up was 24 weeks after labour.

Table (1): Demographic criteria in both groups

	Group A N=30	**Group B N=30**	**P value**
Age	25.33±7.08	24.4±5.07	0.101
Body weight	79.6±8.2	77.4±6.7	0.154
Blood cell count			
Hb (mean)	11.1±1.47	10.7±1.38	0.796
Platelet count (mean)	159.7±40.9	146.7±39.4	0.669
Duration of pregnancy enrolment (mean in weeks)	9.96± 1.4	10.36±1.3	0.878
Rt lower limb	17	12	0.862
Lt lower limb	13	18	0.369

Table (2): Distribution of the level of DVT in both groups

Level of DVT	**No. of limbs**		**P value**
	Group A (N=30)	**Group B (N=30)**	
Isolated calve DVT	6(20%)	4(13.3%)	0.527
Femoro-popliteal DVT	9(30%)	12(40%)	0.513
Ileofemoral DVT	15(50%)	14(46.7%)	0.853

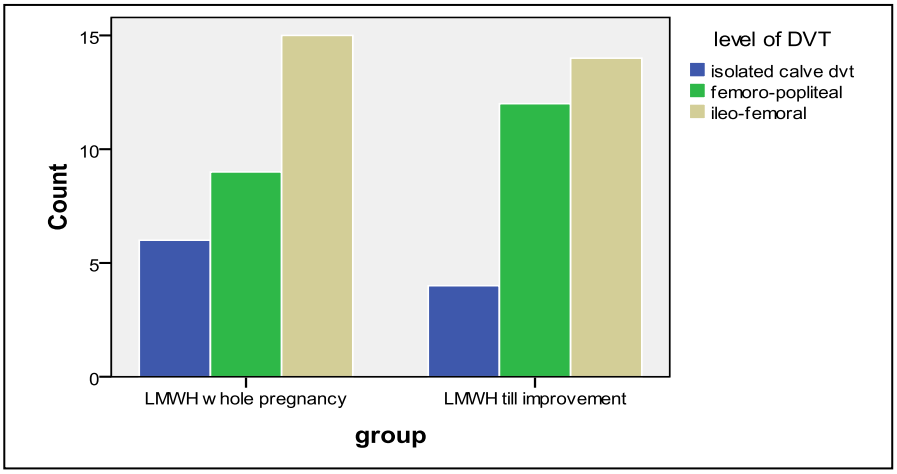


Figure (1): Distribution of the level of DVT in both groups

The level of deep venous system involvement in both groups was discussed in table (2) and figure (1) 2 patients from the 1st group and one patient from the 2nd group continued with full dose LMWH due to persistent symptoms

Maternal outcome:

The duration of fondaparinux therapeutic dose ranged between 8-16 weeks in 1st group and 8-18 weeks in the 2nd group as shown in table (3)

Table (3): Duplex criteria during all follow up visits in both groups

Venous duplex criteria	**Patients groups**	
	Group A	**Group B**
Duplex results at 4 weeks		
Resolved	0	0
Persisted	26(86.7%)	23(76.7%)
Propagated	4(13.3%)	7(23.3%)
recurrent	0	0
Duplex results at 8 weeks		
Resolved	7(23.3%)	5(16.7%)
Persisted	22(73.3%)	25(83.3%)
Propagated	1 (3.3%)	0
recurrent	0	0
Duplex results at 12 weeks		
Resolved	23(76.7%)	25(83.3%)
Persisted	6(20%)	4(13.3%)
Propagated	1(3.3%)	1(3.3%)
recurrent	0	0
Duplex results at 16 weeks		
Resolved	29(96.7%)	26(86.7%)
Persisted	1(3.3%)	2(6.65%)
Propagated	0	0
recurrent	0	2(6.65%)
Duplex results after delivery		
Resolved	28(93.35%)	27(90%)
Persisted	0	1(3.3%)
Propagated	0	0
recurrent	2(6.65%)	2(6.65)

Duplex follow up criteria in both treatment groups as regard resolution, persistence, propagation and recurrence, was summarized in table (3)

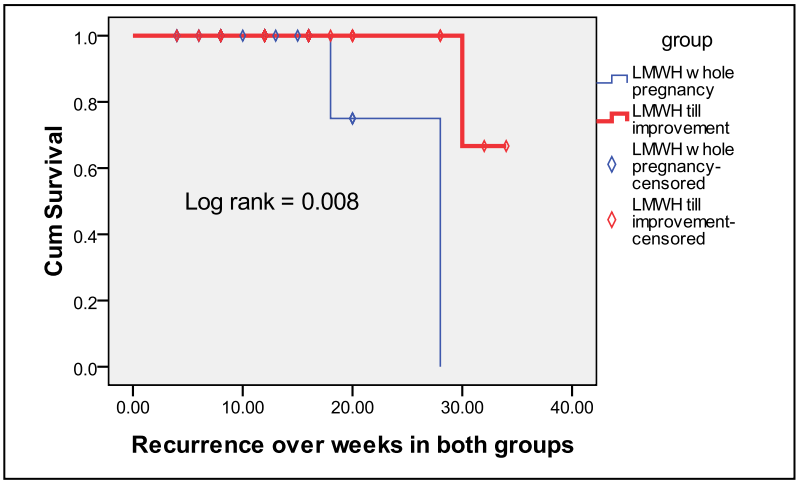
Complications

Table (4): Distribution of maternal complications in both groups

Maternal complications	**Patient groups**	
	Group A	**Group B**
Pulmonary embolism	1(3.3%)	2(6.6%)
PROM	2(6.6%)	3(9.9%)
Eclampsia-Preeclampsia	5(16.7%)	2(6.6%)
PPH	1(3.3%)	3(9.9%)
Recurrent DVT	2(6.6%)	4(13.3%)

*PPH: post partum haemorrhage

Recurrence occurred in 2 cases in the 1st group one after18 weeks after the beginning of treatment (2 weeks after taking prophylactic dose of fondaparinux) in the ipsilateral limb and the other in the contralateral lower limb 2 weeks after labour and occurred in 4 cases in the 2nd group; 2 cases at 16 and18 weeks after the onset of 1st attack, one case one week after labour and one case 3 weeks after labour and all 4 cases were in the ipsilateral lower limb with a p value 0.393 in between groups



Figure(2): Kaplan meier analysis of recurrent DVT in both groups

Table (5): Criteria of post thrombotic syndrome among both groups

Post thrombotic syndrome Criteria	**1st group**	**2nd group**	**P value**
Villalta severity category[a]			
Mild (score 5–9)	5(16.7%)	6(20%)	0.763
Moderate (score 10–14)	1(3.3%)	2(6.6%)	0564
Severe (score >14)	0	1(3.3%)	-
Iliofemoral patency[b]	29(96.6%)	27(93%)	0.305
Femoropopliteal reflux[b]	6(20%)	9(30%)	0.375

a: Qui square

b: Mann-Whitney Test

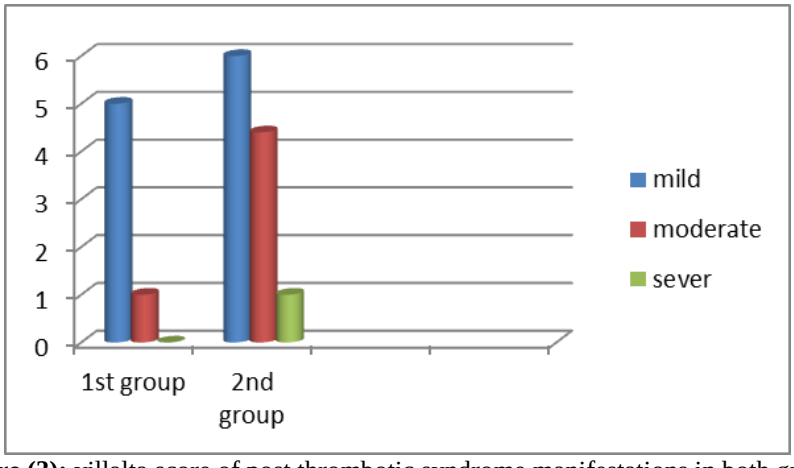


Figure (3): villalta score of post thrombotic syndrome manifestations in both groups

DISCUSSION

The debate in our issue was to compare the burden of treatment by daily self-injection by LMWH and high cost of LMWH injections for 9 months, versus the risk of recurrent VTE in pregnancy.

Brill-Edwards et al. [10] stated that the chance of a new attack of VTE in pregnant females with a history of VTE is low; hence the routine antenatal prophylaxis with heparin is not justified.

We excluded females with onset of acute DVT at mid pregnancy (from 16th to 27th week of pregnancy), and late pregnancy (28th week of pregnancy or later) and included only cases with early onset acute DVT for proper study of the effect of fondaparinux on maternal outcome from the 1st trimester onwards, which was considered as a limitation in our study because the results were not generalized to pregnant females with prior thrombotic episode or a very recent insult.

When delivery is predictable, as for elective induction or planned caesarean, LMWH was discontinued 24 hours before delivery [11,12] For high-risk patients, such as those with mechanical heart valves or recent VTE, the American College of Obstetricians and Gynecologists (ACOG) recommended switching to intravenous heparin at the onset of labour. The short half-life of intravenous UFH allows stopping 4-6 hours before the anticipated time of delivery [12]. In our study we preferred to stop prophylactic dose of fondaparinux 24 hours before time of delivery.

The ACOG and the American Society of Regional Anaesthesia advised for avoiding spinal anaesthesia for 24 hours after the last LMWH dose for females on therapeutic daily doses, to minimize spinal and epidural hematoma risk, and for avoiding 12 hours after the last dose of LMWH for women receiving daily prophylactic dosing [13].

This risk of recurrent VTE is 10 times higher during the postpartum period [14,15] , therefore we selected warfarin with overlapping foundaparinox bridge in the present study until target INR was achieved for immediate postpartum prophylaxis for 6 weeks in the post-partum period or to continue treatment until full recanalization in recurrent cases because warfarin is safe during this time, whatever mother is breastfeeding or not [4].

In our study, we did not do regular monitoring to platelet count during fondaparinux treatment periods, and there were no cases with heparin induced thrombocytopenia (HIT), also Greer et al reported that regular platelet checking is not important due to extremely low incidences of HIT in women which were treated exclusively with LMWH [16].

According to the Italian pregnancy healthcare program[17] which included 22 risk factors for pregnancy-related VTE, patients with a low risk of VTE undergo clinical observation only, those with a moderate risk receive above-knee compression stockings, which was applied in our study in the 2nd group till the beginning of the 9th month of pregnancy after exclusion of high risk patients from the start. And according to Saint-Etienne study conducted by Chauleur et al[18] who developed a scoring system for VTE risk in pregnant women mainly included cases of thrombophilia and previous history of VTE which were excluded from the start from our study, each score being associated with a specific treatment and recommended aspirin which we used in the 2nd treatment group throughout pregnancy for at risk patients except 9th month.

Although there was statistically significant difference in between both treatment groups as regard recurrent cases with a log rank test 0.008, both groups had equal number of recurrent patients during the whole antenatal periods, and the significant difference was due to cases in the postnatal period with the same line of treatment in both groups.

One of the undesired consequences of proximal DVT is the establishment of several degrees of PTS. It has been suggested that PTS is due to inadequate recanalization or long lasting damage to the venous valves resulting in high degree of reflux[19]. In our study there was no statistically significant difference between both treatment groups as regard severity score of PTS and most cases (11/60) representing 18.3% had mild Villalta severity score while (3/60) representing only 5% had moderate Villalta score and only one case in the 2nd group had sever Villalta score and was an ipsilateral recurrent case. Chang and his colleagues also looked at long term outcomes in pregnancy related DVT, they found that 42% of women with DVT in pregnancy were complicated with PTS, which was severe in 7% of cases[20].

In summary, the low rate of recurrence in our study challenged the belief that all pregnant females with recanalized DVT should receive LMWH prophylaxis all throughout pregnancy; therefore we recommend fondaparinux prophylaxis from the beginning of the 9th month of pregnancy stopped 24 hours before labour and return to full therapeutic dose in the postpartum period with oral anticoagulant therapy (warfarin) till target INR is achieved, where fondaparinux is stopped and continue with warfarin for at least 6 weeks.

No conflict of in interest.

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