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Anti-Coagulant Therapy in Unexplained Recurrent Pregnancy Loss – Is It Indispensible?

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Abstract

Recurrent pregnancy loss (RPL) is a heterogeneous reproductive problem with multiple aetiologies and contributing factors. It becomes quite challenging to form a work-up to detect the cause of RPL in the early months as a continuation of pregnancy involves many factors. In more than half of all recurrent miscarriage the cause still remains uncertain. Thrombophilia has been identified in about 50% of women with recurrent miscarriage and thromboprophylaxis has been suggested as an option of treatment.. In obstetric APLA Syndrome (Antiphospholipid antibody) the combination of aspirin and heparin has improved outcomes. The use of low molecular weight heparin (LMWH) has become a common practise in women with inherited thrombophilia and also those with unexplained miscarriage to help safeguard the ongoing pregnancy. To evaluate if there is any effectiveness of low molecular weight heparin (enoxaparin) in women with a history of at least two miscarriages without any apparent aetiology for recurrent pregnancy loss. A prospective randomised controlled study held at Vivekananda Institute of Medical Sciences, Kolkata from August 2015- July 2018. The study assessed the effect of anticoagulant treatment on the live-birth rate (primary outcome) in 80 antenatal women with a history of at least two miscarriages without any apparent causes. Interventions included low molecular weight heparin administration in one group and the other one was not given any anti-coagulant therapy. Similar live birth rates were observed with enoxaparin and the patients who did not receive any anti-coagulant, respectively 84% and 82% (RR 0.97, 95% CI 0.81 to 1.16). There were no significant differences in live birth weight and other pregnancy outcomes between the two groups. Therefore, there is no evidence to support any incremental benefit of adding LMWH to the treatment as a routine in unexplained cases of recurrent pregnancy loss.

Keywords: Abortion, Anti-coagulant, Enoxaparin, Live birth, Aspirin

Introduction

Recurrent pregnancy loss is a heterogeneous reproductive problem with multiple aetiologies and contributing factors. As such, evaluating and treating women with this condition is a complex task, and research in the field is a potential challenge. The definition of recurrent pregnancy loss is debated, ranging from two clinical miscarriages (not necessarily consecutive) according to the American Society for Reproductive Medicine (ASRM) to three consecutive pregnancy losses (not necessarily intrauterine) as defined by both the European Society for Human Reproduction and Embryology (ESHRE) and the Royal College of Obstetricians and Gynaecologists (RCOG). Recurrent miscarriage affects 1-2% of women (1, 2). In more than half of all recurrent miscarriage the cause still remains uncertain (2). Thrombophilia has been identified in about 50% of women with recurrent miscarriage and thromboprophylaxis has been suggested as an option of treatment (3). In obstetric APLA Syndrome (Antiphospholipid antibody) the combination of aspirin and heparin has improved outcomes (4). By analogy, the use of low molecular weight heparin (LMWH) has become commonplace in women with inherited thrombophilia and also those with unexplained miscarriage to help safeguard the pregnancy. The objective of the current study was assessment the efficacy, safety and cost-effectiveness of thromboprophylaxis with LMWH in women of unexplained recurrent miscarriage versus no treatment. Assessing the live birth rate in the study and control group being the primary outcome. Secondary outcome being late pregnancy complications as pre-eclampsia, intrauterine growth restriction (IUGR), placental abruption, drug side effects as thrombocytopenia, thrombotic episodes, antepartum, postpartum bleeding, injection site hematoma, subcutaneous bruises and allergic skin reactions.

Material and method

A prospective randomised controlled study held at Vivekananda Institute of Medical Sciences, Kolkata from August 2015- July 2018. The study assessed the effect of anticoagulant treatment on the live-birth rate (primary outcome) in 80 antenatal women aged between 18-40years with a history of at least two miscarriages without any apparent causes. Interventions included low molecular weight heparin administration in one group and the other one was not given any anti-coagulant therapy. Inclusion criteria were 80 women of age 18-40 yrs. with history of at least two first trimester pregnancy losses, with normal parental karyotype; normal TSH, GTT, coagulation profile, were included. We excluded patients with history of thrombophilia, renal disease, cardiovascular disease or any autoimmune disease. Data was statistically analyzed for 80 women satisfying inclusion criteria; routine antenatal investigations were done for both groups; with monitoring of platelet count and serum creatinine. Written consent form were signed by patients after explaining

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about the medication. LMWH was given from the time of confirmation of fetal cardiac activity to 37 completed weeks Outcome was assessed. Figure 1 demonstrates work plan.

Ethical consideration

The Ethical Committee of Vivekananda Institute of Medical Sciences (VIMS) has given clearance for the study on 12/06/2015. Written informed consent has been obtained from all women who participated in the study.

Statistical Analysis

Categorical variables are expressed as Number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes/ Fisher's Exact Test as appropriate. The statistical software SPSS version 20 has been used for the analysis. An alpha level of 5% has been taken, i.e. if any p value is less than 0.05 it has been considered as significant.

Results and discussion

In women with either congenital or acquired thrombophilia, LMWH plays an important role in respect to live birth rates, abortion and late obstetrical complication rates (4, 5). However, the use of LMWH to prevent recurrent miscarriages in thrombophilia remains controversial because of the small number of women treated with LMWH in the existing trials, or significant methodological problems in the study designs. On the other hand, the management of women with a history of pregnancy loss without an identified cause is unclear and the role of anticoagulants for women with unexplained recurrent miscarriage (URM) remains controversial. Previous literature have always focused on the use of thromboprophylaxis especially enoxaparin alone or others have reported that combination treatment of prednisone, aspirin, folate and progesterone might be as effective treatment as enoxaparin alone (6). A prospective randomized study conducted by Dolitsky et al., in which 40 mg enoxaparin and 100 mg oral aspirin were administered to women with URM, and as soon as fetal cardiac activity was detected (about 7-9 weeks of pregnancy),prophylaxis was started and live birth rate was 81.5% in enoxaparin group and 84% in aspirin group (7). Fawzy et al. achieved a live birth rate of 81% using enoxaparin 20 mg a day in women with ≥3 RPLwhen compared with control group with a live birth rate of 48% (6). LMWH given in first trimester and continued throughout pregnancy, has been seen to reduce early and late spontaneous abortions for women with RPL, with unexplained etiology (8). This effect might be due to the anti-inflammatory action of heparin that act on the decidua of women with recurrent miscarriage, showing necrosis, acute and chronic inflammation and vascular thrombosis compared to those of women with normal pregnancies (9). Heparin also seems to have an anti-complement effect which prevents pregnancy loss and thrombosis (10, 11). On the contrary, no effects of use of enoxaparin or nadoparin, combination of nadoparin and aspirin or only aspirin, have been reported in improving live birth rates of women with RPL (12, 13). Similarly, a multicentric randomized controlled trial of LMWH and low-dose aspirin plus intensive pregnancy surveillance resulted in a 22% miscarriage rate in women with URM versus 20% in the group receiving intensive surveillance alone, without any such medication (14). In our study there was no significant difference in both the groups with respect to live birth rate and miscarriage rate.

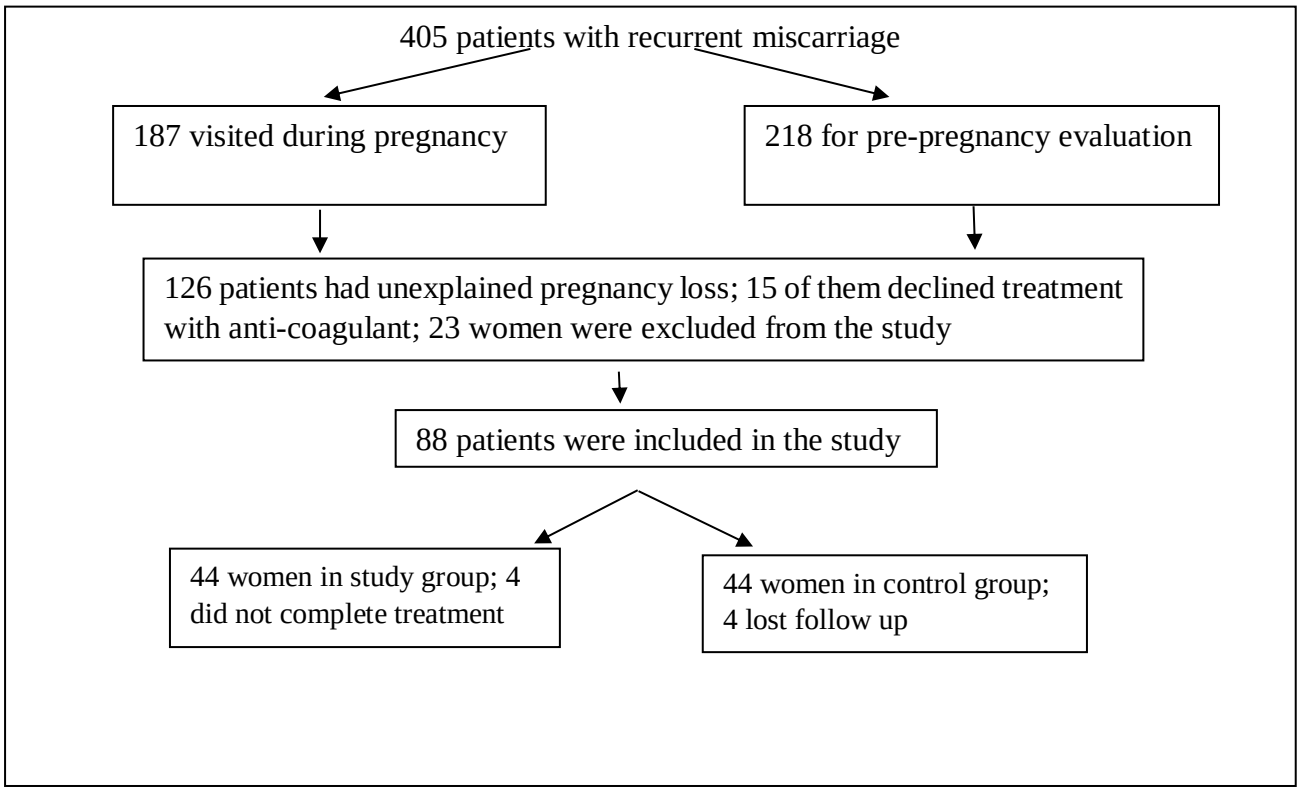

Figure 1. Study plan

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Table 1: Age, BMI, Previous miscarriage of women in control and study group

	Study group	Control group	p-value
Age (yrs); mean	28 (+ 5)	28.8 (+ 6)	0.40
BMI (Kg/m^2); mean	25.3 (+ 3)	25.7 (+ 2)	0.64
Previous abortion count; mean	3 (2-4)	2(2-5)	0.08

Table 2: Comparison of study and control groups based on maternal and foetal outcome

	Study group (n = 53)	Control group (n = 60)	p-value
Abortion rate n (%)	13(33)	15(37)	0.68
POG of miscarriage (+-sd)	9.3(+_2.4)	9.4(+_1.4)	0.85
POG of live birth(+-sd)	39.3(2.2)	38.3(2.3)	0.24
Pre-eclampsia	3(7.5)	1(2.5)	0.28
IUGR	3(7.5)	2(5)	0.36
IUD	1(2.5)	1(2.5)	1
C/s rate	17(42)	8(20)	0.06
Thromboembolic event	0(0)	1(2.5)	1

Table 3: Maternal safety outcome in control and study group

	Study group	Control group	p-value
Subcutaneous bruises	1(2.5%)	0(0)	1
Allergic reaction	2(5%)	0(0)	1
Postpartum eclampsia	0(0)	1(2.5%)	1

Table 4: Neonatal outcome in control and study group

	Study group	Control group	p-value
Birth weight (gm);mean	3283(554)	3142(537)	0.09
NICU admission	2(5)	1(2.5)	0.52
Preterm delivery			
<32 weeks	3(7.5)	2(5)	1
>32weeks	5(12.5)	8(20)	0.2

Caesarean deliveries were seen to be higher in the study group though not statistically significant (p= 0.06) One patient in the control group had deep vein thrombosis. The use of emprical LMWH in women with URM is undoubtedly unneccessary in view of the fact that supportive care alone offers a chance of upto 75% for a successful pregnancy (15). However, there is a substantial amount of patients given LMWHs without adequate evidence and the prognosis of these patients were unknown. RPL has been associated with a higher incidence of late obstetric complications (16). In Dolitzky et al. study these obstetric complications were not seen and they commented that either the obstetric complications are associated with thrombophilias or the treatment had a beneficial effect on both enoxaparin and aspirin group (7). Both enoxaparin and tinzaparin showed no statistically significant difference with respect to live birth rate and abortion rate. However, Tinzaparin

has been shown to be safe and effective anticoagulant in the management of RPL in thrombophilic disorders (7). A study comparing the antithrombotic properties of enoxaparin, tinzaparin and deltaparin revealed significant differences in anti-FXa and anti-FIIa activity between products, but the clinical relevance of these biochemical and pharmacologic differences between LMWH molecules is still questionable (17).

As per our present study, the use of LMWH in the first trimester of pregnancy appears to be safe for mother and neonate; maternal bleeding, venous/arterial thrombotic episodes or heparin induced thrombocytopenia were not observed (Table 3 and 4). Clinical evidence suggests that women with thrombophilia have an increased risk of pregnancy loss and complications such as preeclampsia, placental abruption, and IUGR (18, 19). Pregnancy complications following enoxaparin prophylaxis in women with thrombophilia and RPL is beneficial in terms of both fetal and maternal health. Previous smaller studies have reported the benefits of prophylaxis in improving pregnancy outcomes in women with RPL and thrombophilia (20, 21). Similarly in our study we did not notice any adverse maternal or fetal outcome when comparing both groups. The use of LMWH in pregnancy does not appear to have any increased risk of IUGR, IUD, pre-eclampsia or preterm deliveries as results of our study (Table 2). This correlates with the study by Brenner B. et al., where the use of enoxaparin in pregnancy has been seen to have safe considering maternal and fetal outcome (22).

Conclusion

In this randomized controlled trial study, enoxaparin given at the daily dose of 40 mg (subcutaneous) did not improve the chance of a live birth in non-thrombophilic women with unexplained recurrent miscarriage. Therefore, we can conclude that prophylactic doses of LMWH do not improve the chance of a live birth in non-thrombophilic women with unexplained recurrent miscarriage and should consequently no longer be routinely prescribed in clinical practice.

Limitations

The sample size was not determined prior at the beginning of the study to reach a proper power. The number of patients in each group was arbitrarily chosen however comparable to the previous studies. The treatment groups were also not a randomly assigned. So the potential biases were not excluded including; selection bias and close follow-up of patients who have been under the active treatment arm.

Ethical issue

Authors are aware of, and comply with, best practice in publication ethics specifically with regard to authorship (avoidance of guest authorship), dual submission, manipulation of figures, competing interests and compliance with policies on research ethics. Authors adhere to publication requirements that submitted work is original and has not been published elsewhere in any language.

Competing interests

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

Authors' contribution

All authors of this study have a complete contribution for data collection, data analyses and manuscript writing.

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