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Original Research Article

Role of Low Molecular Weight Heparin and Aspirin in Women with Recurrent Pregnancy Loss

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Abstract

Background: Recurrent miscarriage is one of them that affecting the health of the women. The term recurrent miscarriage refers to two or more consecutive pregnancy losses before 20 weeks of gestation. These kinds of issues are reported among 5% of women at reproductive age and the etiology of 68% of recurrent abortions. Enoxaparin is the most commonly used agent in the existing trials. Tinzaparin sodium is also a LMWH and, its biochemical and pharmacokinetic differences from enoxaparin may have clinically important effects. The data about the administration of tinzaparin during pregnancy is limited. However, LMWH alone throughout the pregnancy in patients with URM has not been sufficiently investigated and also, there is a lack of evidence for comparing LMWH molecules in these patients.

Aim: The study aims to analyze the role of low molecular weight heparin and aspirin in women with recurrent pregnancy loss

Method: This was a prospective observational study conducted on 100 pregnant women with history of recurrent pregnancy loss admitted to Department of Obstetrics and Gynecology at Govt Medical Center & attached Bangur Hospital, Pali, Rajasthan, during the period March 2019 to December 2021. The inclusion criteria for the study involve age- 18-40 yrs, history of unexplained spontaneous recurrent abortion (2 or more), Antiphospholipid antibody positive, current pregnancy and cardiac activity confirmed by USG report. Apart from this, exclusion criteria were involving the known case of aneuploidy, anomaly, ectopic pregnancy, multiple pregnancies. Women with Cardiovascular disease, bleeding diathesis, previous thromboembolic phenomena, diabetes mellitus and other contraindication to LMWH.

Results: For the current study, 27% of the patients belonged to 21-25 years of age group following which 37% of the patients belonged to 26-30 years of age group. 19% of the patients belonged to 31-35 years of age group while the remaining 17% of the patients belonged to 36-40 years of age group. Moreover, 96% of the patients' belonged to normal BMI range while the remaining 4% of the patients belonged to overweight BMI range. Hypertensive Disorders (i.e. BP $\geq$ 140/90). 15% of the patients were detected with Precious Pregnancy/Precious Pregnancy with CRN, 6% of the patients were detected with Fetal Distress, 3% of the patients were detected with Oligo, 5% of the patients were detected with IUGR, 8% of the patients were detected with Pre-eclampsia/Pre-eclampsia with IUGR.

Conclusion: From the study, it has been concluded that LMWH resulted in an improved live-birth rate in patient with 2 or more consecutive unexplained recurrent pregnancy loss. Nevertheless these findings need to be confirmed in larger randomized trials. Tinzaparin sodium is also a LMWH.

Keywords: Live birth rate, unexplained recurrent miscarriage, Tinzaparin

Background

There are various issues that influence the health of an individual and lead to different chronic disease. Recurrent miscarriage is one of them that affecting the health of the women. The term recurrent miscarriage refers to two or more consecutive pregnancy losses before 20 weeks of gestation [1]. These kinds of issues are reported among 5% of women at reproductive age and the etiology of 68% of recurrent abortions. The issues occur due to lack of knowledge and understanding of safe pregnancy and any therapeutic innervations [2]. According to analysis of the recurrent miscarriage, the 25% of these pregnancies results in live births [3,4]. The fact that thrombosis at placental level is a common finding whether antiphosholipid antibody are present or not, suggest that other pathologic mechanisms are also involved leading to same outcome, that is the fetal loss [5,6]. Although in the literature there is no consensus regarding the benefit of antithrombotic therapy even in consecutive unexplained pregnancy losses, low molecular weight heparine (LMWH) is widely used as prophylaxis in recurrent miscarriages in general obstetric practice. The uncertain etiology and pathogenesis of URM have meant that treatment has remained empirical [7].

Enoxaparin is the most commonly used agent in the existing trials. Tinzaparin sodium is also a LMWH and, its biochemical and pharmacokinetic differences from enoxaparin may have clinically important effects [8]. The data about the administration of tinzaparin during pregnancy is limited. However, LMWH alone throughout the pregnancy in patients with URM has not been sufficiently investigated and also, there is a lack of evidence for comparing LMWH molecules in these patients [9]. In this observational study, we aimed to investigate whether the use of LMWH (either enoxaparin or tinzaparin) improves live birth rates when compared with control (without any thromboprophylaxis) group in women with URM [10,11]. However clinical studies have suggested not to treat unexplained miscarriage without evidenced antiphospholipid syndrome or inherited thrombophilia, with heparin or aspirin because of lack of evidence of any benefit and potential risks of therapy [12].

Aim

The study aims to analyze the role of low molecular weight heparin and aspirin in women with recurrent pregnancy loss

Method and Material

This was a prospective observational study conducted on 100 pregnant women with history of recurrent pregnancy loss admitted to Department of Obstetrics and Gynecology at Govt Medical Center & attached Bangur Hospital, Pali, Rajasthan, during the period March 2019 to December 2021.

Data Collection

Patient data was collected after informed consent from the patient.

Inclusion Criteria

1. Age- 18-40 yrs
2. History of unexplained spontaneous recurrent abortion (2 or more)
3. Antiphospholipid antibody positive
4. Current pregnancy and cardiac activity confirmed by USG report.

Exclusion Criteria

1. Known case of aneuploidy, anomaly, syndrome.
2. Ectopic pregnancy, multiple pregnancy.
3. Women with Cardiovascular disease, bleeding diathesis, previous thromboembolic phenomena, diabetes mellitus and other contraindication to LMWH.
4. Exclude the patients those who are not getting booked for delivery at PDZH, Udaipur.

Intervention

Administration of LMWH (inj. enoxaparin 60mg s.c. OD) & tab aspirin 75 mg OD from USG confirmation of early intra uterine pregnancy till 34 weeks.

Regular Maternal Assessment

Measurement of blood pressure, CBC, apTT, platelets count, serum calcium, kidney and liver function baseline study

Foetal Assessment

- Fortnightly foetal Doppler studies, AFI. Fetal biophysical profile twice a week.
- Injection betamethasone 12 mg I.M. 2 doses at 24 hrs apart will be administered to all pregnant women who have crossed 28 weeks of gestation to promote foetal lung maturity.
- Mode of termination of pregnancy was decided depending on the clinical condition of patients and the indications.

Results

For the current study, 27% of the patients belonged to 21-25 years of age group following which 37% of the patients belonged to 26-30 years of age group. 19% of the patients belonged to 31-35 years of age group while the remaining 17% of the patients belonged to 36-40 years of age group. Moreover, 96% of the patients' belonged to normal BMI range while the remaining 4% of the patients belonged to overweight BMI range. Hypertensive Disorders (i.e. BP $\geq$ 140/90). It shows that there were already 28 cases (28%) present who are diagnosed with Hypertensive Disorders. For the current analysis, 54.16% of the patients had LSCS delivery and 45.83% of the patients had vaginal delivery. Additionally, 39% of the patients had LSCS (Term) delivery followed by 35% of the patients who had Vaginal (Term). 13% of the patients had LSCS (Pre-Term) while 8% of the patients had Vaginal (Pre-Term). 4% of the patients had Spontaneous Abortion. Further, it was noticed that 1% of the patients had Vaginal (Pre-Term)-Fresh SB. Apart from this, 13% of the patients were found to be positive under H/O Preterm while the remaining 87% of the patients were found to be negative under H/O Preterm. Further, majority of patients were given LMWH at GA 8-10 weeks that is 63% followed by 22% of the patients at gestational age 10-112 weeks. 7% of the patients were given LMWH at the gestational age of between 12-14 weeks and 14-16 weeks each. Also, 1% of the patients were given LMWH at the gestational age 16-18 weeks. Further, 22% of the patients were found to be positive for H/O IUD while the remaining 78% of the patients were found to be negative for H/O IUD. Moreover, 49% of the patients were found to be positive for ACL while the remaining 51% of the patients were found to be negative for ACL. Also, 58% of the patients were found to be positive for LA while the remaining 42% of the patients were found to be negative for LA.

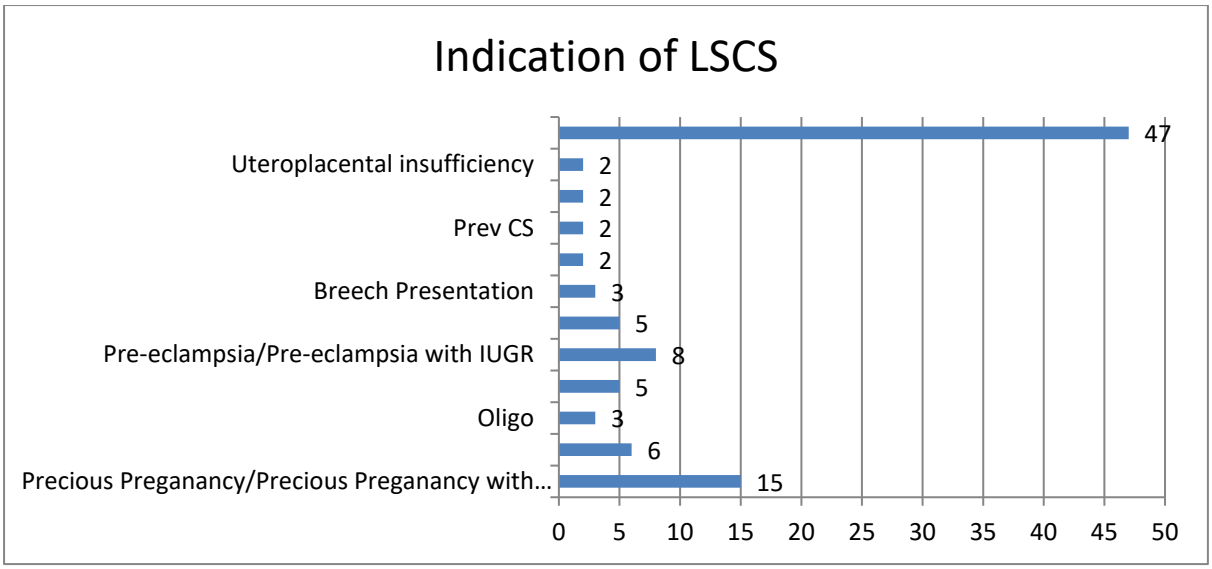

Figure 1: Indication of LSCS

15% of the patients were detected with Precious Pregnancy/Precious Pregnancy with CRN, 6% of the patients were detected with Fetal Distress, 3% of the patients were detected with Oligo, 5% of the patients were detected with IUGR, 8% of the patients were detected with Pre-eclampsia/Pre-eclampsia with IUGR. Further, 94% of the patients did not have any complications, while 3% had Abruption Placenta and remaining 3% had Atonic PPH managed conservatively. Also, 3% of the patients had Blood stained liqour, 7% of the patients had Liqour meconium stained, while the remaining 90% of the patients did not have complications. Furthermore, 2% of the patients belonged to the 0-3 APGAR score, 8% of the patients belonged to the 4-5 APGAR score, 58% of the patients belonged to 6-7 APGAR Score, 27% of the patients belonged to 8-10 APGAR score while the remaining 5% of the patients did not belong to any of the APGAR score category.

Table 1: Birth Weight

Birth Weight	No. of Patients	Percentage
0-1 kg	5	4
1.01-1.99 kg	13	9
2.01-2.99 kg	64	30
3.0 kg & above	18	6
Total	**100**	**100**

According to analysis, 5% of the children weighed between 0-1 kg, 13% of the children weighed between 1.01-1.99 kg, 64% of the children weighed between 2.01-2.99 kg and the remaining 18% of the children weighed 3.0 kg and above.

Table 2: Stay in NICU (Days)

Stay in NICU (Days)	No. of Patients	Percentage
0-3	5	5
4-6	12	12
7-9	4	4
10 & above	5	5
None	76	76
Total	**100**	**100**

As per the analysis of above table, the hospital stay for 5% of the patients was between 0-3 days, the hospital stay for 12% of the patients of was 4-6 days, the hospital stay for 4% of the patients was 7-9 days and the hospital stay for 5% of the patients was 10 days and above. The remaining 76% of the patients did not stay in the hospital at all.

Table 3: Neonatal Death

Neonatal Death	No. of Patients	Percentage
Yes	2	2
No	98	98
Total	**100**	**100**

As per the outcome total 100 patients who gave birth, 2% of them resulted in neonatal deaths.

Table 4: Success rate

Success rate	No. of Patients	Percentage
Neonatal Death	2	2
(Spontaneous) Abortion	4	4
Fresh Still Birth	1	1
Survival to hospital discharge	93	93
Total	**100**	**100**

According to analysis, 2% of the births resulted in neonatal deaths, 4% of the pregnancies resulted in spontaneous abortion, 1% of the deliveries resulted in fresh still birth and the remaining 93% of the births resulted in survival to hospital discharge. In addition to this, 58% of the patients were found to be positive for LA while the remaining 42% of the patients were found to be negative for LA. Apart from this, 94% of the patients did not have any complications, while 3% had Abruption Placenta and remaining 3% had Atonic PPH managed conservatively.

Discussion

According to analysis of the recurrent miscarriage, the 25% of these pregnancies results in live births. The fact that thrombosis at placental level is a common finding whether antiphospholipid antibody are present or not, suggest that other pathologic mechanisms are also involved leading to same outcome, that is the fetal loss. Enoxaparin is the most commonly used agent in the existing trials. Tinzaparin sodium is also a LMWH and, its biochemical and pharmacokinetic differences from enoxaparin may have clinically important effects. The data about the administration of tinzaparin during pregnancy is limited. As per the outcome of the current study, Hypertensive Disorders (i.e. BP ≥ 140/90). It shows that there were already 28 cases (28%) present who are diagnosed with Hypertensive Disorders. For the current analysis, 54.16% of the patients had LSCS delivery and 45.83% of the patients had vaginal delivery. Apart from this, 13% of the patients were found to be positive under H/O Preterm while the remaining 87% of the patients were found to be negative under H/O Preterm. Wang, et al. (2019) [13] ¸ LMWHs are found to be effective in improving live birth rate that turned out to be 85% with LMWH. In addition, heparin has an anti-complement effect which is absolutely required to prevent pregnancy loss and thrombosis.

According to the outcome of the current study, 2% of the births resulted in neonatal deaths, 4% of the pregnancies resulted in spontaneous abortion, 1% of the deliveries resulted in fresh still birth and the remaining 93% of the births resulted in survival to hospital discharge. As per the study of Ruffatti et al, (2011) [14] where the spontaneous abortion was administered in only one of the women, but in the

current study it was found out that 4 women had spontaneous abortion. In addition to this, Swain and Singh (2017) [15] study had 15% IUGR cases. Five percent of the patients were detected with APH (Abruptio/Placenta Previa), 3% of the patients were detected with Breech Presentation, 2% of the patients were detected with Transverse Lie, 2% of the patients were detected with Prev CS, 2% of the patients were detected with PROM with failure of indication, 2% of the patients were detected with Uteroplacental insufficiency. [16]

Conclusion

From the study, it has been concluded that LMWH resulted in an improved live-birth rate in patient with 2 or more consecutive unexplained recurrent pregnancy loss. Nevertheless, these findings need to be confirmed in larger randomized trials. Tinzaparin sodium is also a LMWH and, its biochemical and pharmacokinetic differences from enoxaparin may have clinically important effects. Heparin has an anti-complement effect which is absolutely required to prevent pregnancy loss and thrombosis.

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