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Original Research Article

Comparison of empirical use of low dose aspirin and enoxaparin in the treatment of unexplained recurrent pregnancy loss

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ABSTRACT

Background: Recurrent pregnancy losses have commonly been defined as three or more consecutive spontaneous pregnancy losses. About 1-2% of women suffer from recurrent miscarriages. The cause is multifactorial such as uterine anomalies, endocrine disorders, immunological causes, infections, chromosomal anomalies and maternal autoimmune diseases. In 50-60% of cases recurrent pregnancy losses, the cause remains unclear. Objective of this study was to compare the maternal and fetal outcome in patients with unexplained recurrent pregnancy loss treated with LMWH (Enoxaparin) vs Aspirin during pregnancy.

Methods: Women with 3 or more pregnancy losses, aged between 18-40 years, booked for antenatal care and delivery in our hospital between January 2012 and December 2016 were followed till 6 months after delivery.

Results: A total number of 146 women were assessed for eligibility. We had 62 women in Group A (aspirin group) and 84 women in Group E (enoxaparin group). Enoxaparin was given to all those ladies who had taken aspirin in previous pregnancies with no live outcome. Good neonatal outcome was observed with Enoxaparin.

Conclusions: Live birth rates did not show significant difference between the two study groups. But empirical use of enoxaparin in patients with no live birth who have taken low dose aspirin in previous pregnancy had shown improved results, so enoxaparin should be used empirically as a first line agent in such cases.

Keywords: Aspirin, Enoxaparin, Low molecular weight heparin, Pregnancy, Recurrent, Unexplained

INTRODUCTION

Recurrent pregnancy losses have commonly been defined as three or more consecutive spontaneous pregnancy losses.¹ Chromosomal abnormalities have been seen in 10-15% of miscarriages. About 1-2% of women suffer from recurrent miscarriages.^{2,3} The cause is multifactorial such as uterine anomalies, endocrine disorders, immunological causes, infections, chromosomal anomalies and maternal autoimmune diseases. In 50-60% of cases recurrent pregnancy losses, the cause remains unclear.^{4,5} In large meta-analysis different thrombophilia polymorphism has been identified to be associated with recurrent fetal loss. Therefore, interventions with

thromboprophylaxis for the prevention of recurrent miscarriages have been proposed.⁶ According to some authors thrombophilia markers are not the only criteria for the initiation of the treatment.⁷ Whereas other investigators suggest not to treat unexplained miscarriage without evidenced antiphospholipid syndrome or inherited thrombophilia. It is well known fact that thrombosis is common at placental level whether antiphospholipid antibodies are present or not, suggesting that other pathological mechanisms are involved leading to same outcome i.e. fetal loss.⁸ LMWH (low molecular weight heparin) and aspirin in low doses have been used empirically to prevent recurrent pregnancy losses. Though there is no consensus regarding the empirical use

of antithrombotic therapy in unexplained pregnancy losses.⁹ LMWH is widely used as prophylaxis in recurrent miscarriages in general obstetric practice.

LMWH is most commonly used agent in the existing trials. In our trial, we aimed to investigate whether the use of LMWH improves live birth rate when compared to aspirin to know which thrombolytic treatment is the best to prescribe to women with recurrent miscarriage without known cause of thrombophilia.

Objective of this study was to compare the maternal and fetal outcome in patients with unexplained recurrent pregnancy loss treated with LMWH (Enoxaparin) versus Aspirin.

METHODS

Women with 3 or more pregnancy losses, aged between 18-40 years, booked for antenatal care and delivery in our hospital between January 2012 and December 2016 were followed till 6 months after delivery.

Inclusion criteria

- All women had normal results for parental karyotyping, FBS, RFT, serum TSH, serum prolactin and homocysteine levels and all included patients had been screened negative for thrombophilia.

Exclusion criteria

- Women with cardiovascular disease, bleeding diathesis, previous thromboembolic phenomena, DM, vaginal bleeding, multiple pregnancies, smoking, morbid obesity, presence of contraindication for anticoagulants were also excluded.

Patients were divided into two groups, Group A received aspirin and Group E patients received LMWH (Enoxaparin). Group A (62 patients) and Group E with (84 patients), who had unexplained RPL were included in the study. Total 146 patients were followed throughout their pregnancy and delivered in our hospital. As soon as pregnancy was confirmed, Enoxaparin was given as 1mg/kg/day as subcutaneous injection in all those patients who had taken aspirin in previous pregnancy and outcome was not good and aspirin as 75 mg once a day orally in those patients who had not taken aspirin in previous pregnancy. All pregnant women underwent prenatal screening. Adherence of treatment was confirmed during follow up of patients. Patients were called every 2-3 weeks till 28 weeks, then every 2 weekly between 28-34 weeks, then weekly until delivery to assess fetal growth, fetal well-being and drug side effects. LMWH (enoxaparin) was stopped 12 hours before delivery. In preterm patients, aspirin was stopped with the onset of labour and was continued in patients who reached 36 weeks. Outcomes were listed as live birth

rate, abortion rate, number of women with pre-eclampsia, IUGR, placental abruptions and drug side effects as thrombocytopenia thrombotic episodes, injection sites hematoma, subcutaneous bruises and allergic skin reaction.

All infants were examined by a paediatrician after delivery. Perinatal outcome in terms of birth weight, gestational week, number mortality, congenital anomalies were evaluated.

Data were described in terms of range; frequencies (number of cases) and relative frequencies (percentages) as appropriate. For comparing categorical data, Chi square (χ^2) test was performed and exact test was used when the expected frequency is less than 5. A probability value (p value) less than 0.05 was considered statistically significant. All statistical calculations were done using SPSS (Statistical Package for the Social Science) SPSS 17 version statistical program for Microsoft Windows.

RESULTS

A total number of 146 women were assessed for eligibility. We had 62 women in Group A (aspirin group) and 84 women in Group E (enoxaparin group).

Table 1: distribution of patients according to age of pregnant women.

	Group A (Aspirin)	Group E (Enoxaparin)
Age		
= 25	03	04
> 25-30	32	45
> 30-35	21	20
> 35	06	15
Total	62	84

Chi-square value = 2.972, p value = 0.396.

During this five-year period (January 2012 to December 2016), total number of deliveries were 5853 out of which 3626 were caesarean sections and 2227 were vaginal deliveries. In both our study groups, majority of the patients were between 25-30 years followed by 30-35 years (Table 1).

Table 2: Distribution of patients according to number of abortions.

	Group A	Group E
A3	43	53
A4-A6	15	24
> A7	04	07

Chi-square value = 0.636, p value = 0.727.

All the patients enrolled in the study had more than three consecutive abortions. Fifteen patients in Group A and 24 patients in Group E had 4-6 abortions. Four patients in

Group A and seven patients in Group E had seven or more than seven abortions (Table 2).

Table 3: Distribution of patients according to gestational age.

Gestation (in weeks)	Group A	Group E
= 28	03	04
> 28-32	18	26
> 32-36	28	36
> 36-40	13	18
Total	62	84

Chi-square value = 0.0908, p-value = 0.993.

Majority of the patients in both the groups delivered between 32-36 weeks gestation (Table 3) with maximum number of live births (Table 4).

Maximum number of IUGR babies were born between 32-36 weeks gestation in both the groups. There were four neonatal deaths, three in Group A and one in Group E (Table 5). More number of patients delivered vaginally in Group A as compared to Group E though the difference was not statistically significant (Table 6). Placenta previa, placental abruption, PIH (pregnancy induced hypertension), and PPH (postpartum hemorrhage) incidence was comparable in both the groups (Table 7).

Table 4: Distribution of patients according to fetal outcome.

POG (weeks)	Liveborn	Liveborn	Abortion/stillborn	Abortion/stillborn
	Group A	Group E	Group A	Group E
< 28	0	03	3	1
28-32	15	24	3	2
32-36	24	35	4	1
36-40	12	18	1	0
Total	51	80	11	4

Liveborn chi-square value = 0.0407, p value = 0.938, stillborn chi-square value = 0.938, p value = 0.816

Table 5: Distribution of patients according to IUGR and NND.

	IUGR	IUGR	NND	NND
	Group A	Group E	Group A	Group E
28 weeks	0	0	0	0
> 28-32	3	4	2	1
> 32-36	8	6	1	0
> 36-40	4	4	0	0
Total	15	14	3	1

IUGR chi-square value = 0.395, p value = 0.821, NND chi-square value = 0.444, p value = 0.505.

Table 6: Distribution of patients according to mode of delivery.

	LSCS	LSCS	Vaginal delivery	Vaginal delivery
	Group A	Group E	Group A	Group E
28 weeks	0	02	03	02
> 28-32	9	20	8	6
> 32-36	14	24	12	12
> 36-40	2	10	11	7
Total	25	56	34	27

LSCS chi-square value = 1.726, p value = 0.631, vaginal chi-square value = 0.579, p value = 0.901.

Table 7: Distribution of patients according to APH, PPH and PIH.

	Group A	Group E
Placental previa	13	12
Placental abruption	03	01
PPH	04	02
PIH	09	11

Placenta previa chi-square value = 1.122, p value = 0.284, placental abruption chi-square value = 1.437, p value = 0.231, PPH chi-square value = 1.124, p value = 0.288, PIH chi-square value = 0.061, p value = 0.085.

DISCUSSION

Recurrent miscarriage (RM) is defined as three or more consecutive miscarriages occurring before 20 weeks post-menstruation.¹⁰ Around 1% of fertile couples will experience recurrent early pregnancy losses.¹¹ The risk of recurrence increases with the maternal age and number of successive losses.¹² Recurrent miscarriage has been directly associated with parental chromosomal abnormalities, maternal thrombophilic disorders and structural uterine anomalies.^{13,14} Maternal immune dysfunction and endocrine abnormalities have also been postulated in recurrent pregnancy losses.¹⁴

The majority of cases of recurrent pregnancy losses following investigation are classified as idiopathic, that is, no identifiable cause is identified in either partner. It is generally accepted that within the idiopathic group there is considerable heterogeneity and it is unlikely that one single pathological mechanism can be attributed to their recurrent miscarriage history.¹⁰ Current research is directed at theories on defects in nature's quality control related to implantation, trophoblast invasion and placentation, as well as factors, which may be embryopathic.¹⁵

High-quality data on the management of RPL (recurrent pregnancy loss) are limited and reported studies on the aetiology, evaluation and management of RPL are mostly observational. For these reasons, therapeutic recommendations are largely based on clinical experience and data from these observational studies.¹⁶

Acetylsalicylic acid

Low-dose aspirin is an antiplatelet agent which irreversibly inhibits platelet cyclo-oxygenase and thereby decreases the production of thromboxane A₂ (TXA₂), a potent vasoconstrictor and platelet activator. The hypothesis of an impaired placental circulation due to microthrombosis as a cause of RPL is the background for treatment with ASA.¹⁷

LMWHs have been found to be effective in improving live birth rate even in the absence of demonstrated etiologic factors. Many properties of heparin have been used for this purpose. Besides anticoagulant activity, heparin has an anti-inflammatory effect that decidua's from women with recurrent miscarriages show common pathology that necrosis, acute and chronic inflammation and vascular thrombosis compared with those of women with normal pregnancies.¹⁸ Also heparin has an anti-complement effect which is absolutely required to prevent pregnancy loss and thrombosis.^{19,20}

CONCLUSION

Live birth rates did not show significant difference between the two study groups. but empirical use of enoxaparin in patients with no live birth who had taken

ecospirin in previous pregnancy showed improved results, so Enoxaparin should be used empirically as a first line agent in patients with recurrent pregnancy loss.

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