International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622

www.gynaecologyjournal.com
2020; 4(6): 151-158
Received: 22-08-2020
Accepted: 07-10-2020

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Comparison of empirical use of low dose aspirin alone and low dose aspirin plus low molecular weight heparine in the treatment of unexplained recurrent pregnancy loss

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DOI: https://doi.org/10.33545/gynae.2020.v4.i6c.747

Abstract
Background: Unexplained Recurrent Miscarriage is a major women's health problem. Recurrent pregnancy losses have commonly been defined as three or more consecutive spontaneous pregnancy losses. In 50-60% of cases of recurrent pregnancy losses, the cause remains unclear and known as unexplained/idiopathic recurrent pregnancy loss. It could be useful to use Aspirin, or Aspirin plus Heparin in women with unexplained recurrent miscarriage, which is believed to be caused by thrombosis in decidual vessels.
Objective: Objective of this study was to compare the maternal and fetal outcome in patients with unexplained recurrent pregnancy loss treated with LDA Vs LDA plus LMWH during pregnancy.
Method: An open clinical trial was conducted at the Department of Obstetrics and Gynecology at ACPM MEDICAL COLLEGE, DHULE from June 2019 to September 2020 to investigate the effects of treatment with low dose aspirin (LDA) alone versus LDA in combination with low-molecular-weight-heparin (LMWH) on patients with a history of recurrent miscarriages. We enrolled 150 women with history of three or more consecutive miscarriages in this study. Participants were randomly assigned to receive either LDA alone or a combination of LDA and LMWH. The primary outcomes were the rate of miscarriages and live births for each group.
Result: Regarding the primary outcome the two groups did not differ significantly. Four neonates in Group A and Three in group B were admitted in NICU. There were no congenital anomalies detected in either group. There was no significant difference observed in the mean birth weight of neonates born in either group.
Conclusion: Low dose Aspirin and Low dose Aspirin plus Low Molecular Weight heparin improves pregnancy outcome and increase rate of live birth without any significant differences.

Keywords: Aspirin, low molecular weight heparin, pregnancy, recurrent, unexplained

Introduction
Pregnancy loss is a frustrating and challenging problem not only for couples but also for clinicians. Pregnancy loss is often associated with guilt, embarrassment and depressive state. The emotional issue surrounding the pregnancy loss becomes magnified exponentially when pregnancy loss occurs on repetitive basis. Recurrent miscarriages are the loss of three or more consecutive pregnancies before the 24th week of gestation. It is either primary (in women without a previous live-born infant) or secondary (in women with at least one previous live-born infant) [1]. Nearly 1-2% of women suffer from recurrent miscarriages due to multifactorial causes such as uterine anomalies, endocrine disorders, immunological causes, infections, chromosomal anomalies and maternal autoimmune diseases [2, 3] In about 50-60% cases of recurrent pregnancy losses, the cause remains unclear known as Unexplained or idiopathic [4, 5].
There is evidence to suggest that successful pregnancy outcome depends on the development and maintenance of adequate utero-placental circulation, and that the hypercoagulability associated with thrombophilia might result in recurrent miscarriages [6]. Normal pregnancies lead to hemostatic changes towards a procoagulatory state, followed by an increase concentration of clotting factors and fibrinogen and decrease level of anticoagulant factors with reduced fibrinolytic activity [7]. It seems that some of RPL patients are in a permanent acquired procoagulatory state, in which fibrin deposits are found in the intervillous space of the placentas

[8].

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 [9]. According to some authors thrombophilia markers are not the only criteria for the initiation of the treatment [10]. 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. Presence or absence of antiphospholipid antibodies is not always associated with recurrent fetal loss which is proved by other pathological mechanisms that are involved leading to same outcome [11]. 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 [12].

Because of the potential involvement of thrombophilia in recurrent miscarriage, the use of antithrombotic agents has been suggested as a potential means of increasing the live birth rates in subsequent pregnancies in women with unexplained recurrent miscarriages [13, 14].

Aspirin is increasingly used to reduce the risk of miscarriage and improve pregnancy outcome in women who have suffered recurrent miscarriage. An important factor controlling tissue perfusion is the equilibrium between thromboxane A2 (in addition to its platelet aggregating properties, it also has a vasoconstrictor effect) and prostacyclin (has vasodilatory properties) [15]. The daily administration of LDA induces a shift in the balance away from thromboxane A2 and towards prostacyclin, leading to vasodilatation and enhanced blood flow [16].

Heparin has been shown to have potentially beneficial effects on trophoblast implantation [17, 18] and influence trophoblast apoptosis. To be beneficial, heparin may need to be given at the time of implantation. LMWHs are administered subcutaneously once a day. They have considerable theoretical benefit over unfractionated heparin (UFH) including better bioavailability, a longer plasma half-life [19], more predictable pharmacokinetics and pharmaco- dynamics [20], and less potential to cause osteoporosis [21]. LMWH is also less likely to induce thrombocytopenia [22]. LMWH inhibits factor Xa more effectively than factor IIa to produce its antithrombotic effect [23]. LMWH does not cross the placenta and is safe for the fetus [24, 25].

This study evaluated the effect of various anticoagulant treatments on the live-birth rate in women with a history of at least three continuous unexplained miscarriages. It tries to compare two methods of treatment, with LDA and LDA plus LMWH.

Methods

Women with 3 or more pregnancy losses, aged between 22-40 years, booked for antenatal care and delivery in our hospital between June 2019 to September 2020 were followed till 6 months after delivery.

- **Inclusion Criteria**

Women with a definite history of recurrent miscarriages with no obvious cause (unexplained recurrent miscarriage) were included. All patients screened negative for thrombophilia and who had normal results for parental karyotyping, FBS, RFT, serum TSH, serum prolactin and homocysteine levels were included in the study.

- **Exclusion criteria**
  - Patients who fail to give the consent
  - Documented cause of recurrent miscarriages
  - History of medical disorders such as diabetes mellitus.
  - History of chronic disorders such as renal, cardiac, or liver diseases.
  - History of thromboembolic manifestations.
  - Structural anomalies of the uterus.
  - Contraindications to the use of Anticoagulants
  - History of smoking, morbid obesity

Patients were recruited from outpatient clinics. The purpose of the study and protocols used were explained to each woman, and consent was obtained from all of them. History taking (including personal, menstrual, obstetric and family history) and examinations (general, abdominal and ultrasound) were carried out. All pregnant women underwent prenatal screening. After obtaining informed consent, socio-demographic, obstetric, and medical data were gathered from the study participants using pre-tested questionnaires. The participants were randomly assigned into two groups using computer generated numbers drawn from an envelope.

- **Group A- LDA group (75 Patients)**

Once pregnancy was confirmed and fetal heart activity was detected by ultrasound, participants started taking 75 mg of LDA once daily.

- **Group B- combination group (75 Patients)**

Once pregnancy was confirmed and fetal heart activity was detected by ultrasound, participants started taking 75 mg of LDA once daily. Also 0.4 mL/day of the LMWH Enoxaparin was self-administered by women in this group

For the prophylaxis of neural-tube defects, women were advised to take folic acid (400 μg daily), starting before conception and continuing until 10 weeks of gestation. Standard care throughout pregnancy was provided by obstetrician to all women, including structural fetal ultrasonography at 18 to 22 weeks of gestation, platelet counts were also performed at 12 and 30 weeks of gestation.

The rates of maternal thrombocytopenia (defined as a platelet count of <150,000 per cubic millimeter), bleeding episodes (i.e., bleeding from the gums or nose and the amount of vaginal blood loss at delivery), and skin reactions were assessed by telephone at 3-month intervals by us and verified on the basis of obstetrical medical reports.

Follow-up examinations were conducted in the antenatal care clinic and all participants received routine iron and folic acid supplements. 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. Participants were closely monitored until delivery, which was planned at 37 weeks of gestational age, unless otherwise indicated. Treatment was stopped at the time of miscarriage or when the pregnancy reached 34 weeks gestation.

All neonates were examined by a pediatrician after delivery

- **Primary outcome**
  - The primary outcome measure was live-birth rate.

- **Secondary outcome**
  - Miscarriage less than 28 weeks.
  - Preterm delivery less than 37 weeks.
  - Obstetric complications -pre-eclampsia, intrauterine growth restriction, placental abruption
  - Drug side effects as thrombocytopenia, thrombotic episodes, injection sites hematoma, subcutaneous bruises and allergic skin reaction.
  - Perinatal outcome in terms of birth weight, gestational week, number mortality, congenital anomalies

Statistical Analysis

Data were described in terms of range; frequencies (number of cases) and relative frequencies (percentages) as appropriate. Chi square (χ^2) test was performed for comparing the categorial data. A probability value (p value) > 0.05 was considered statistically significant. The result analysed by SPSS (Statistical Package for the Social Science) SPSS 17 version statistical program for Microsoft Windows.

Results

A total number of 150 women were assessed in this study. We had 75 women in Group A- LDA group and 75 women in Group B- combination group [LDA + LMWH**]**

Table 1: Agewise Distribution of Pregnant Women

	Group A (LDA)	Group B (LDA+LMWH)
Age		
> 25	06	05
> 25-30	37	40
> 30-35	21	20
> 35	11	10
Total	75	75

Chi-square value = 2.072, p value = 0.345.

Majority of the patients in both our study groups were between 25-30 years followed by 30-35 years (Table 1).

Table 2: Distribution of patients according to number of abortions

	Group A (LDA)	Group B (LDA+LMWH)
No. of abortions		
A3	49	52
A4	16	12
A5	5	6
A6	3	4
>A7	2	1

Chi-square value = 0.542, p value = 0.453.

All the patients enrolled in the study had more than three consecutive abortions. 16 patients in Group A AND 12 in Group B had previous 4 abortions where as 5 in Group A and 6 patients in Group B had 5 abortions. Patients with previous 6 abortions were 3 in Group A and 4 in group B. Two patients in Group A and one patient in Group B had seven or more than seven abortions (Table 2).

Table 3: Distribution of patients according to gestational age

	Group A (LDA)	Group B (LDA+LMWH)
Gestation (in weeks)		
=28	5	4
>28-32	18	22
>32-36	36	38
>36-40	16	11
Total	75	75

Chi-square value = 0.0818, p-value = 0.873.

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

Table 4: Distribution of patients according to fetal outcome

	Liveborn	Liveborn	Abortion/Stillborn	Abortion/Stillborn
POG (weeks)	**Group A**	**Group B**	**Group A**	**Group B**
< 28	0	03	05	01
28-32	16	19	02	03
32-36	14	10	03	06
36-40	33	32	02	01
Total	63	64	12	11

Liveborn chi-square value = 0.0577, p value = 0.848, stillborn chi-square value = 0.876, p value = 0.865

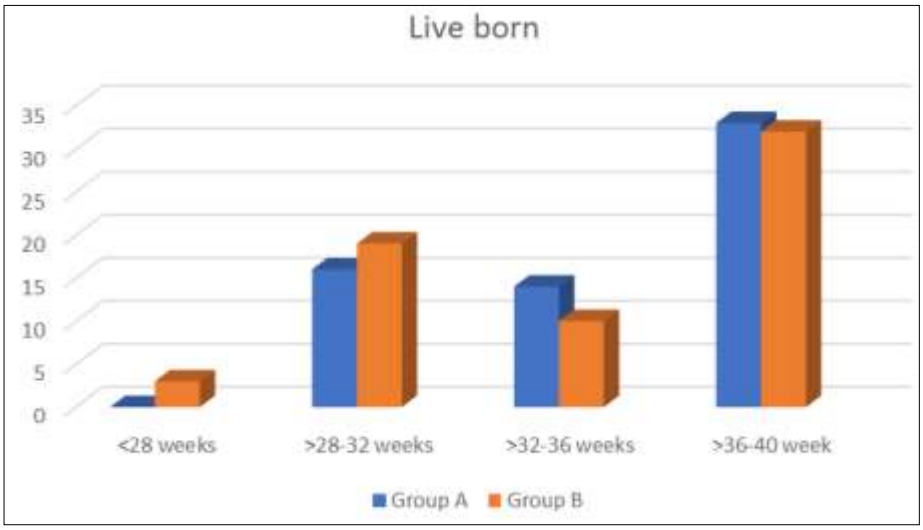
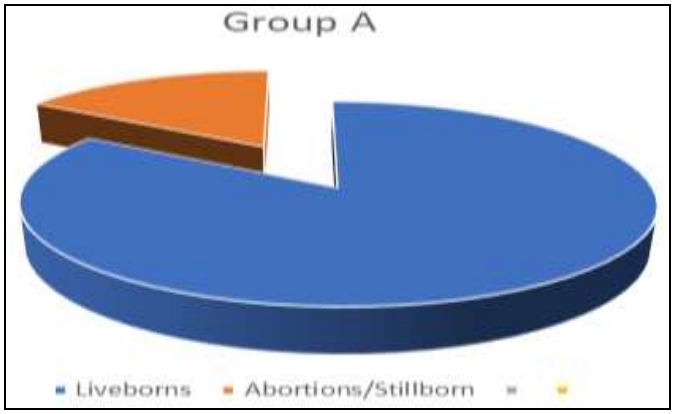


Fig 1: Comparison of Pregnancy outcome – Live born among two study groups

Fig 2: Comparion of Pregnancy outcome – Abortions/stillborn among two study groups



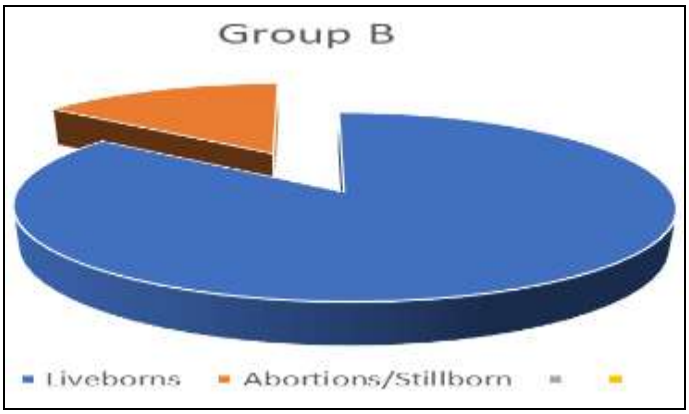


Table 5: Distribution of patients according to IUGR and NND.

	IUGR	IUGR	NND	NND
	Group A	Group B	Group A	Group B
28 weeks	0	0	0	0
> 28-32	4	4	1	1
> 32-36	7	6	1	1
> 36-40	6	5	1	0
Total	17	15	3	2

IUGR chi-square value = 0.478, p value = 0.963, NND chi-square value = 0.654, p value = 0.705.

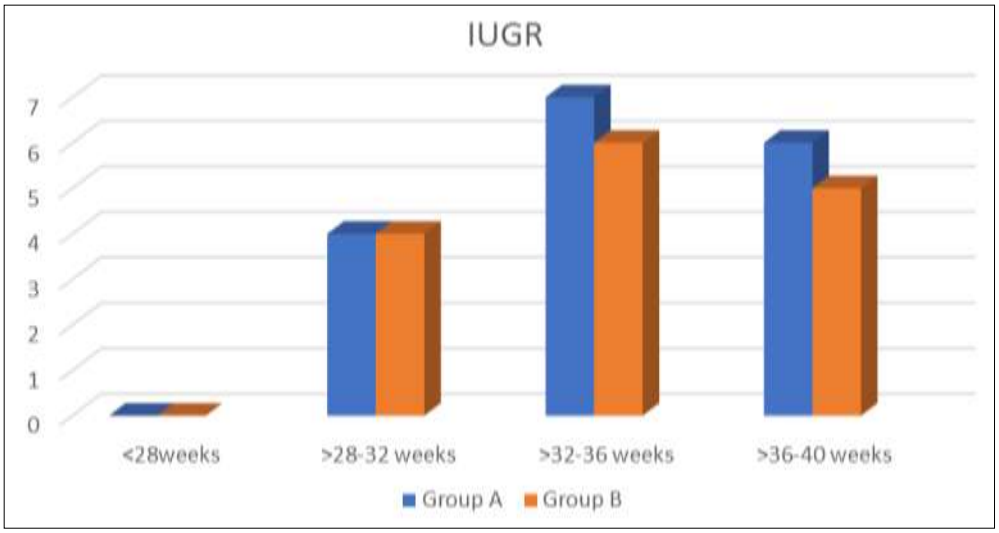


Fig 3: Comparison of Pregnancy outcome-Intrauterine growth restriction among two study groups

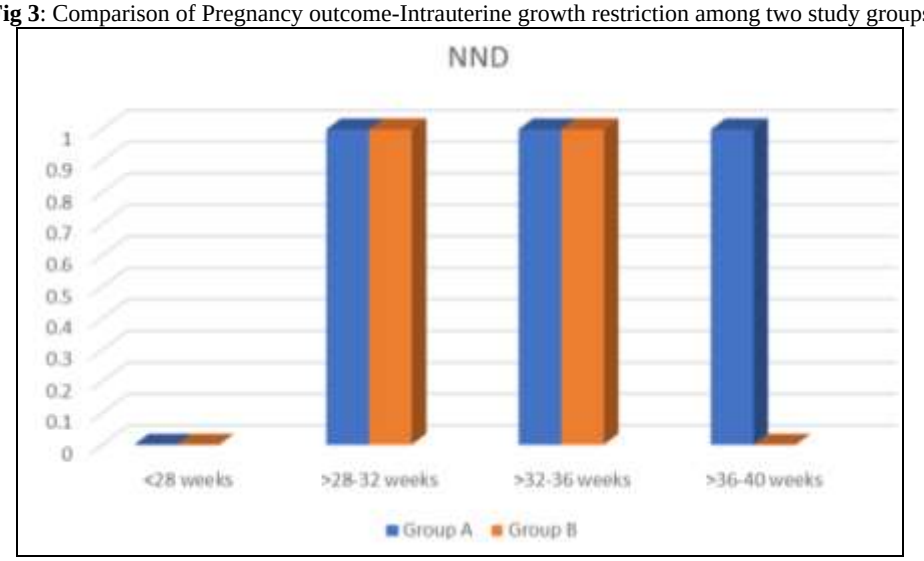


Fig 4: Comparison of Pregnancy outcome- Neonatal death among two study groups

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

	LSCS Group A	LSCS Group B	Vaginal delivery Group A	Vaginal delivery Group B
28 weeks	0	02	03	02
> 28-32	11	18	9	6
> 32-36	26	22	12	12
> 36-40	3	10	11	7
Total	40	52	35	27

LSCS chi-square value = 1.873, p value = 0.731, vaginal chi-square value = 0.682, p value = 0.801.

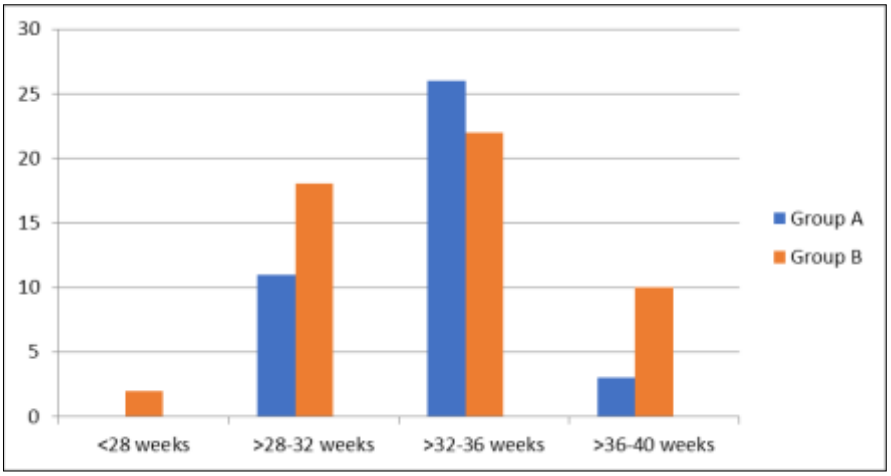


Fig 5: Comparison of mode of delivery-LSCS among two study groups

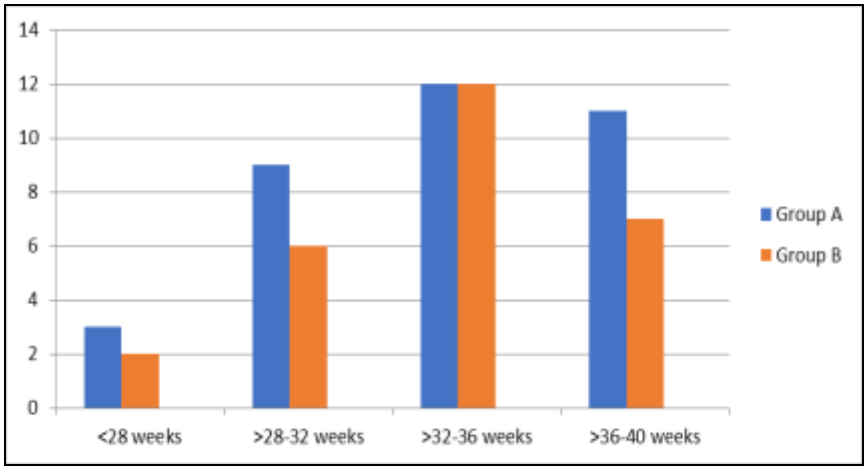


Fig 6: Comparison of mode of delivery-Vaginal Delivery among two study groups

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

	Group A	Group B
Placental previa	12	14
Placental abruption	04	03
PPH	03	02
PIH	07	10

Placenta previa chi-square value = 1.822, p value = 0.684, placental abruption chi-square value = 1.673, p value = 0 .431, PPH chi- square value = 1.344, p value = 0.298, PIH chi-square value = 0.071, p value = 0.095.

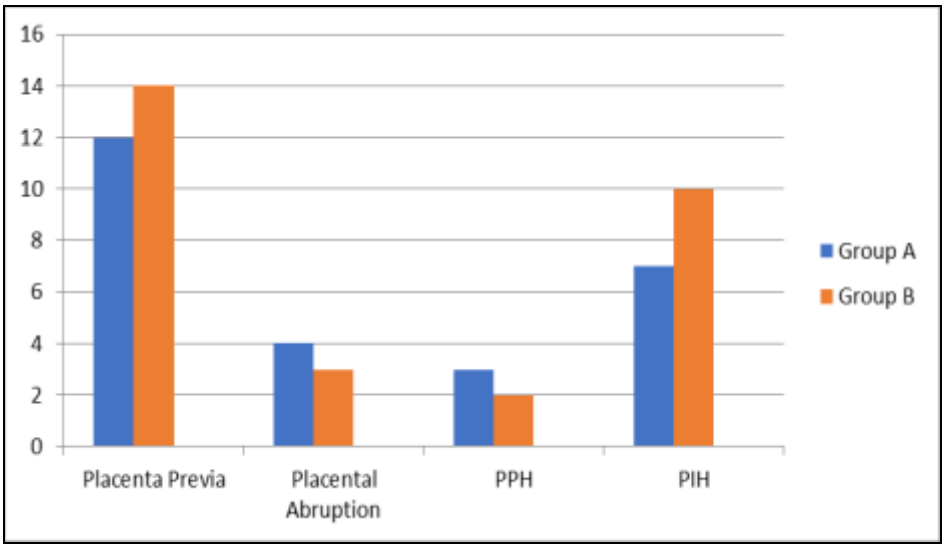
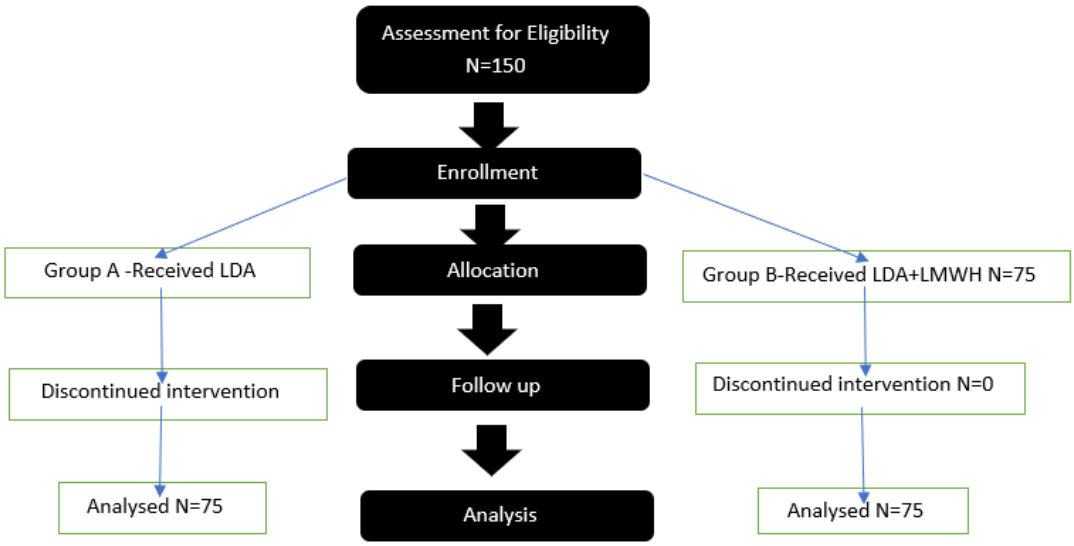


Fig 7: Comparison of Incidences of Pregnancy related complications among two study groups

Maximum number of IUGR babies were born between 32-36 weeks gestation in both the groups. There were five neonatal deaths, three in Group A and two in Group B (Table 5). More number of patients delivered vaginally in Group A as compared to Group B 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). None of the women in either group developed a thromboembolic complications during pregnancy.

There were no congenital malformation detected in either group. Four neonates in Group A and Three in Group B were admitted in NICU. Birth weight did not significantly differ between the two groups, with a mean birth weight of 2850.4 +/-370g for Group A and 2910+/-279g for GroupB. Very few incidences of injection sites hematoma, subcutaneous bruises and allergic skin reaction noted with Group B.

Consort Flow Diagram:



Discussion

Recurrent miscarriage (RM) is defined as three or more consecutive miscarriages occurring before 24 weeks post-menstruation. Around 1% of fertile couples will experience recurrent early pregnancy losses [26]. The risk of recurrence increases with the maternal age and number of successive losses. Parental chromosomal abnormalities, maternal thrombophilic disorders and structural uterine anomalies are known to have direct association with recurrent miscarriages. Maternal immune dysfunction and endocrine abnormalities have also been postulated in recurrent pregnancy losses [9].

The majority of cases of recurrent pregnancy losses following investigation are classified as idiopathic, when there is no identifiable cause 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 focused at theories related with defects in implantation, trophoblast invasion and placentation, as well as various embryopathic factors [15].

The hypothesis that women with unexplained recurrent miscarriage might benefit from aspirin, heparin, or both was based on a presumption that this condition might be caused by thrombosis in decidual vessels [27, 28]. In one study, levels of circulating procoagulant microparticles were higher in women with recurrent miscarriage than in control subjects [29]. However, the concept that recurrent miscarriage can be attributed routinely to thrombosis is probably an oversimplification.

Aspirin inhibits the action of the enzyme cyclo-oxygenase and thereby suppresses the production of TXA2 in platelets. In vascular cell walls, cyclo-oxygenase is also responsible for the conversion of arachidonic acid to prostacyclin (PGI2). TXA2 induces platelet aggregation and vasoconstriction, whilst PGI2 inhibits platelet aggregation and induces vasodilation. Women with a history of recurrent early miscarriage in weeks 4–7 of gestation have an excess of TXA2 production and between weeks 8-11 they are relatively PG12 deficient compared with women with no previous history of pregnancy loss. These changes are greatest among those which pregnancies end in miscarriage. The shift in the TXA2:PG12 ratio in favor of TXA2, may lead to vasospasm and platelet aggregation in the trophoblast, causing development of microthrombi and placental necrosis [30].

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 [31]. Also heparin has an anti-complement effect which is absolutely required to prevent pregnancy loss and thrombosis [32, 33].

Conclusion

From our study we conclude that Low Dose Aspirin alone Versus combination of Low Dose Aspirin and Low molecular weight Heparin have equal results in terms of improved pregnancy outcome and increase in the rate of live births in patients with history of unexplained recurrent pregnancy loss.

Recommendations

Initiation of Low Dose Aspirin therapy [75mg] as soon as pregnancy is confirmed and fetal heart activity detected by ultrasound in patients with unexplained recurrent miscarriages should be practiced as it is cheap, has better compliance with the patient and has lesser side effects.

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