Original Research Article

Indian Journal of Obstetrics and Gynecology
Volume 7 Number 2 (Part - II), April - June 2019
DOI: http://dx.doi.org/10.21088/ijog.2321.1636.7219.29

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

Sushila Khoiwal[1], Rekha Garasiya[2], Shruti[3]

How to cite this article:
Sushila Khoiwal, Rekha Garasiya, Shruti. Role of Low Molecular Weight Heparin and Aspirin in Women With Recurrent Pregnancy Loss. Indian J Obstet Gynecol. 2019;7(2):293-301.

[1]Senior Professor and Unit Head, [2,3]Resident, Department of Obstetrics and Gynaecology, RNT Medical College, Udaipur, Rajasthan 313001, India.

Corresponding Author: Rekha Garasiya, Resident, Department of Obstetrics and Gynaecology, RNT Medical College, Udaipur, Rajasthan 313001, India.

E-mail: sbapna.1@gmail.com

Received on 03.04.2019; **Accepted on** 04.05.2019

Abstract

Introduction: It has been proved that a successful pregnancy outcome depends on the development and maintenance of adequate uteroplacental circulation and that the hypercoagulability associated with thrombophilia might result in recurrent miscarriages. Due to 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 either inherited thrombophilia or unexplained recurrent miscarriages. Thus, the main purpose of this work is to evaluate the effectiveness of LMWH and Aspirin to improve live birth rate in patients with recurrent pregnancy loss by seeing the outcome of the foetus in; Foetal weight, Mode of delivery, and Perinatal outcome.

Methodology: A prospective observational study conducted on 100 pregnant women with a history of recurrent pregnancy loss admitted to Department of Obstetrics and Gynecology at Panna Dhai Mahila Chikitsalaya, Udaipur during the period January 2017 to February 2018. Administration of LMWH (inj. enoxaparin 40 mg s.c. OD) & tab aspirin 75 mg OD from USG confirmation of early intrauterine pregnancy till 34 weeks.

Results: Patients between age 21 and 40 years were included with the mean age of 29.28 years. The mean BMI with relation to birth weight was 23.11 kg/m2. Twenty-two per cent of patients were found to be H/O IUD positive. Mode of delivery for 52% of the patients was LSCS, while for 44% of the patients it was vaginal. Two per cent 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.

Conclusion: Use of LMWH and tab aspirin daily in patients with RPL due to antiphospholipid syndrome resulted in higher live birth rates. Combination treatment with aspirin and LMWH leads to improve live birth rate among women with recurrent abortion and antiphospholipid antibodies.

Keywords: LMWH; Antiphospholipid antibodies; Recurrent Pregnancy Loss; Aspirin.

Introduction

The most beautiful feeling which a woman experiences in her life is pregnancy, also known as gestation. Normal pregnancy is the state of carrying a developing embryo with in female womb. During 1st Trimester the most important task of fetal cells is differentiation. So any harm done to the fetus during this period, is most likely to result in miscarriage. Recurrent pregnancy loss is an unfortunate, frustrating and heart wrenching experience not only

to the patient or her family but also to the obstetrician. A pregnancy loss (miscarriage) is defined as the spontaneous demise of a pregnancy before the fetus reaches viability. The term therefore includes all pregnancy losses (PLs) from the time of conception until 20 weeks of gestation [1]. Recurrent pregnancy loss (RPL) is occurrence of ≥ 3 pregnancy that ends in abortion of fetus usually before twenty weeks of gestation [1]. Newer guidelines from the American Society of Reproductive Medicine have defined RPL as the loss of two or more pregnancies. Recurrent pregnancy loss affects about 0.34% of women who become pregnant [1].

Approximately 15% of all clinically recognizable pregnancies end in pregnancy loss, with three or more losses affecting around 5% [2]. Also, women with at least two successive pregnancies range about approximately 5% [2]. Majority the reason for such loss remains unknown as only a small proportion of the reasons are identifiable, while the others remain underlying and unidentified. It has been proved 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.

Abortion

Abortion is defined as the spontaneous or induced termination of pregnancy before fetal viability, viability lies between the lines that separate abortion from pre-term birth. The National Center of Health and Statistics, the Center for Disease Control & Prevention and the World Health Organization all define abortion as Pregnancy termination before 20 weeks gestation or with a fetus born weighing < 500 grams [3]. This can happen either by choice through surgery or medication (induced abortion), or it can happen naturally (spontaneous abortion – often called a miscarriage). 75% abortion occurs before 16 weeks and of these about 75% occurs before 8 weeks of pregnancy. Most common cause is chromosomal or genetic in about 50% of cases in 1st trimester [3].

Common Causes of Abortion

A majority of the abortion occurs during the first trimester, while some of them get terminated by the second trimester. The possible reasons of abortion can be many. Following are the most identifiable causes of abortion:

Causes of First Trimester Abortion

a. Genetic factors (50%) - Chromosomal abnormalities, Multi factorial causes like ageing sperm, chromosomal aneuploidy, and spermatic Y deletion.
b. Endocrine causes (accounts for 10-15% case) - Corpus insufficiency, Hyperprolactinemia, Polycystic ovarian syndrome (PCOS), diabetes, thyroid disorder, etc.
c. Immunological causes.
    - Autoimmune- Antiphospholipid antibodies
    - Alloimmune -Increased NK cell activity.
d. Infections-Accounts for 5-10% cases.

Causes for Second Trimester Abortion

a. Anatomical abnormalities -
    - Cervical incompetence
    - Mullerian phase defect
    - Uterine synechiae
b. Chronic maternal illness such as uncontrolled diabetes, chronic renal disease.
c. Infections - syphilis, toxoplasmosis and listeriosis.
d. Unexplained causes [4].

Diagnosis of Recurrent Pregnancy Loss

Despite extensive investigations of women with three or more miscarriages, the cause of recurrent pregnancy loss remains unknown in the majority of women. On the basis of a parallel drawn with the antiphospholipid syndrome, hypotheses on thrombotic mechanism were raised in unexplained pregnancy loss. An association with some inherited thrombophilias was suggested. Women with inherited thrombophilia may also be subject to pregnancy loss [5]. The presumption is that the inherited thrombophilias, like APL, Predispose to placental vasculopathy. According to some authors thrombophilic markers are not the only criteria for the initiation of thromboprophylactic treatment. The fact that thrombosis at placental level is a common finding whether antiphospholipid antibody are present or not, suggest that other pathologic mechanism are also involved leading to same outcome, that is fetal loss. LMWH is widely used as prophylaxis in recurrent miscarriage in general obstetrics practice [6].

Antiphospholipid Syndrome

Antiphospholipid antibody syndrome (APS) is an autoimmune thrombophilic syndrome characterized by recurrent venous, arterial or small vessel thrombosis and pregnancy morbidity in the presence of antiphospholipid antibodies [7]. It was first defined as a syndrome in 1983. Consisting of a triad of manifestation involving arterial and /or venous thrombosis, recurrent fetal loss, accompanied by mild to moderate thrombocytopenia and elevated titers of antiphospholipid (apl) antibodies, lupus anticoagulant (LA) and/or anticardiolipin antibodies (aCL). APS may occur in association with other autoimmune disorders called secondary APS or may be primary in the absence of any underlying illness. Obstetric and fetal complications include early and late pregnancy losses and pre-eclampsia. Tools capable of early and reliable identification of the high-risk APS patient population would be clinically useful. Known thrombotic risk variables include a "triple-positive" aPL profile (positive for lupus anticoagulant, aCL, and anti-b2-GP1 antibodies), high mean platelet volumes as a surrogate for increased platelet activation and decreased plasminogen and elevated plasminogen activator inhibitor-1 levels. Approximately 10% to 40% of patients with systemic lupus erythematosus (SLE) and up to 20% of patients with rheumatoid arthritis have positive aPL serologies. Moreover, patients with SLE who have positive lupus anticoagulant have a 50% chance of developing venous or arterial thrombotic events within a 20-year follow-up period [8].

Obstetric morbidities in APS are thought to be secondary to placental vascular insufficiencies, with early (<10 weeks) and late (≥10 weeks) miscarriages being the most common obstetric manifestations of APS, followed by premature labor and eclampsia and intrauterine growth restriction [9].

Diagnosis of Antiphospholipid Antibody Syndrome

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met.

Clinical criteria

Vascular thrombosis:

1. One or more documented episodes of arterial, venous or small vessel thrombosis other than superficial venous thrombosis-in any tissue or organ. Thrombosis must be confirmed by objective validated criteria. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall [10].
2. Pregnancy morbidity
   a. One or more premature unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
   b. One or more premature births of a morphological normal neonate before the 34th week of gestation because of (i) eclampsia or severe pre-eclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency, or
   c. Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded [10].

Laboratory criteria

These criteria for laboratory testing are consistent with current American Congress of obstetricians and Gynecologists clinical management guidelines.

1. Lupus anticoagulant (LA) present in plasma, on two or more occasions at least 12 weeks apart, detected according to the guidelines of the International Society on Thrombosis and Haemostasis (Scientific Subcommittee on Las/phospholipid dependent syndrome) [10].
2. Anticardiolipin antibody (aCL) of lgG and/or lgM isotype in serum or plasma present in medium or higher titer (i.e. >40 GPL or MPL or > the 99th percentile), on two or more occasions at least 12 weeks apart, measured by a standardized ELISA.
3. Anti-b2-glycoprotein-I antibody of lgG and.or lgM isotype in serum or plasma (in titer > the 99th percentile), present on two or more occasions, at least 12 weeks apart, measured by a standardized ELISA, according to recommended procedures [9].

Investigators are strongly advised to classify APS patients in studies into one of the following categories more than one laboratory criteria present (any combination). IIa, LA present alone; IIc, anti-b2GPI antibody present alone [14].

Endothelial Nitric Oxide Synthase Inhibition and Thrombosis

Endothelium-derived nitric oxide (NO), produced by endothelial NO synthase (eNOS), is important for normal endothelial function and vascular health. Patients with APS have lower plasma nitrite levels and an impaired endothelium dependent vascular response, suggestive of impaired eNOS activity and reduced NO production and endothelial function [9].

Mechanism of Pregnancy Loss Associated with APS

Systemic thromboembolism is the principal manifestation of APS. APS is an autoimmune disease characterized by thrombophilia, adverse obstetric events and recurrent miscarriages, accelerated atherosclerosis, increased risk for myocardial infarction and stroke, and valvular heart disease. Morbidity and mortality in APS is strongly associated with aPL-mediated vascular endothelial cell dysfunction and complement system activation [9]. Thrombi in the placental circulation and the beneficial effect of antithrombotic therapy in APS patient suffering from recurrent pregnancy loss (RPL) suggest a central role for this mechanism in reproductive failure. The underlying basis for the hypercoagulable state in APS is complex and involves altered activity of all three major component that govern homeostasis: platelets, fibrinolysis, and the coagulation cascade. The coagulation system in APS was shown to be altered at different levels. aPL inhibit both protein C activation and the function of activated protein c(APC), thereby preventing the inactivation of activated factors V and VIII. This inhibition is conditional upon the presence of β_2–GPI which is a pre-requisite for the binding of APL to protein C [9].

Low Molecular Weight Heparin (LMWH)

LMWH is a class of anticoagulant medications. LMWH are defined as heparin salt having average molecular weight less than 8000 Dalton (Da) and for which atleast 60% of all chain have a molecular weight less than 8000 Da. They are used in prevention blood clots and treatment of venous thrombolism and myocardial infarction. Heparin is a naturally occurring polysaccharide that inhibits coagulation, the process that leads to thrombosis. Natural heparin consist of molecular chain of varying length, or molecular weight chain of varying molecular weight from 5000 to over 40,000 Da [11]. LMWH are much easier and convenient to use compared with unfractioned heparin. This is due to their long half life and few side effects. There is also no need for frequent monitoring of partial thromboplastin time. LMWH agents are - dalteparin, enoxaparin, certoparin and few other less popular preparations. ENOXAPARIN is most commonly used agent in existing trial [8].

Benefits of LMWH over UH

The risk of therapy appears to be significantly reduced with LMWH. Hemorrhage osteoporosis, and heparin induced thrombocytopenia in particular appear to be substantially less frequent with LMWH than UH. The increased bioavailability and longer therapeutic half life of LMWH also allow less frequent injections. Additionally, there is no overlap between the anticoagulant effect and the antithrombotic effect-hence there is no bleeding with LMWH, and little need for monitoring. During treatment with heparin we should be very careful about apTT and platelet count. Calcium and vitamin D supplementation is given to counteract osteoporosis caused by heparin [12]. It has been shown that heparin have potentially beneficial effects on trophoblast implantation and influence trophoblast apoptosis and should be given at the time of implantation to have more positive impact. LMWHs are administered subcutaneously once a day. They are considered to have more positive impacts as compared to unfractionated heparin (UFH). The benefits include better bioavailability, a longer plasma half-life, more predictable pharmacokinetics and pharmacodynamics and less potential to cause osteoporosis. LMWH is also less likely to induce thrombocytopenia. LMWH inhibits factor Xa more effectively than factor IIa to produce its antithrombotic effect. LMWH does not cross the placenta and is safe for the fetus [1].

Table 1: Dosage of LMWH [13]

LMWH	Therapeutic dose	Prophylactic dose
Dalteparin	200 units/kg once daily	5000 units SC once daily
Enoxaparin	1mg/kg every 12 hours	40 mg SC daily
Tinzaparin	175 units/kg once daily	units SC once daily

Aspirin and its Benefits

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) [2].

Benefits of Aspirin

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. Also, it has been demonstrated that women with either congenital or acquired thrombophilia might benefit from LMWH in respect to live birth rates, abortion and late obstetrical complication rates [2]. In addition, heparin and LMWH have other biological properties that could be critical for implantation and placentation. It is possible that to be beneficial, heparins may require administration at the time of the initial implantation i.e. in 5-6 weeks of gestation [14].

Dosage of LMWH and Aspirin

Aspirin plus heparin is the most efficacious regimen. Low-dose unfractionated heparin- 7500 to 10,000 units is used subcutaneously twice daily. Concurrently, low-dose aspirin – 60 to 80 mg orally once daily- is given [13].

Aspirin, given in doses of 60 to 80 mg orally daily, blocks the conversion of arachidonic acid to thromboxane A_2 while sparing prostacyclin production. This reduces synthesis of thromboxane A_2, which usually causes platelet aggregation and vasoconstriction, and simultaneously spares prostacyclin, which normally has the opposite effect. There appear to be no major side effects from low-dose aspirin other than a slight risk of small-vessel bleeding during surgical procedures. Low-dose aspirin does not appear to reduce adverse pregnancy outcomes in antiphospholipid antibody-positive women without the complete syndrome [13].

Aims and Objectives

To evaluate the effectiveness of LMWH and Aspirin to improve live birth rate in patients with recurrent pregnancy loss by seeing the outcome of foetus in: Foetal weight; Mode of delivery; Perinatal outcome.

Material and Methods

This prospective observational study was conducted on 100 pregnant women with history of recurrent pregnancy loss admitted to Department of Obstetrics and Gynecology at Panna Dhai Mahila Chikitsalaya, Udaipur during the period January 2017 to February 2018.

Inclusion Criteria

Age-18-40yrs; History of unexplained spontaneous recurrent abortion (2 or more); Antiphospholipid antibody positive; 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 40 mg 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 counts, serum calcium, kidney and liver function baseline study

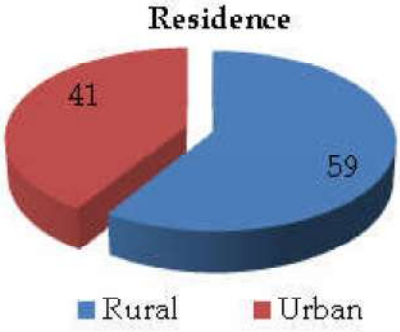
Foetal Assessment

- 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.
- At the time of delivery, details such as baby weight, APGAR score, Color of the liquor (Meconium present or absent) and NICU admissions were noted.

Observations and Discussion

The age distribution of 100 patients in our study, shows that 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. The mean age of was found to be 29.28 ± 5.22 years. Similar to study by Elmahashi, et al. [14] (2014), the mean age of the patients was 26.5 years in the group with LDA alone and 27.3 in the group with LDA and LMWH, which was almost similar to that of the current study. 59% of the patients were from rural areas while the remaining 41% of the patients were from urban area.



Graph 1: Residence of the patients

Graph 2: BMI range

Ninety six percent (96%) of the patients' belonged to normal BMI range while remaining 4% of the patients belonged to overweight BMI range.

Table 1: Distribution according to Number of Previous Abortions.

No. of Previous Abortions	No. of Patients	Percent (%)
2	21	21
3	50	50
4	18	18
5	11	11

Table 1 shows that 21 cases had 2 previous abortions, 50 cases had 3 previous abortions, 18 cases had 4 previous abortions and 11 cases had 5 previous abortions. 22% of the patients had used history of IUD use previously while remaining 78% of the patients didn't had previous history of use of IUD.

Table 2: Number of positive patients for ACL and LA

	No. of Patients	Percentage
Only ACL Positive	42	42
Only LA Positive	51	51
Both ACL and LA Positive	7	7
Total	100	100

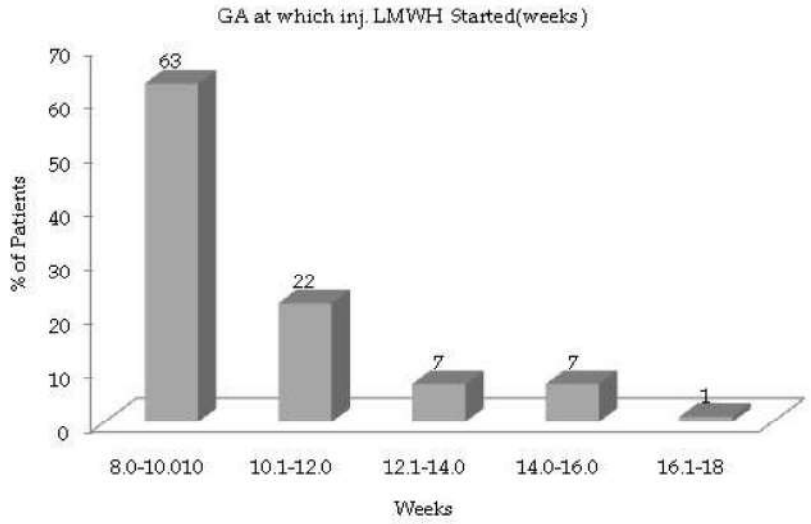
Table 2 shows that 7% patients were positive for both ACL and LA, while 51% were only LA positive and 42% were only ACL positive.

Majority of patients were given LMWH at gestational age (weeks) 8-10 weeks that is 63% followed by 22% of patients at gestational age 10-12 weeks. 7% of the patients were givben LMWH at the gestational age between 12-14 weeks and 14-16 weeks each. Also, 1% of the patients were given LMWH at the gestational age 16-18 weeks. The mean Gestational age at the time of admission was 10.00 weeks. Further, the GA at the time of admission was 8.1 weeks in group with LDA alone and 8.3 weeks in the group with LDA. Our findings were similar to findings that of Elmahashi et al. [14] (2014).

Table 3: Mode of delivery

Mode of Delivery	No. of Patients	Percentage
LSCS	52	54.16
Vaginal	44	45.83
Total	96	100

Table 3 shows that out of total 96 patients, 54.16% of the patients had LSCS delivery and



Graph 3: Distribution according to GA at which inj. LMWH Started

45.83% of the patients had vaginal delivery. As compared to the study conducted by Mohamed et al. [15] (2013) it was seen that in the LMWH + aspirin group 70% (n=30) of the patients had delivery through caesarean while 30% (n=13) of the patients had vaginal delivery. Further, in the group with aspirin alone 67% (n=10) of the patients had caesarean delivery while 33% (n=5) of the patients had vaginal delivery. These results are not comparable with the study of Mohamed et al. (2014) [15] who had 70% LSCS and 30% vaginal deliveries.

Table 4: Indication of LSCS

Indication of LSCS	No. of Patients	Percentage
Precious Pregnancy/Precious Pregnancy with CRN	15	15
Fetal Distress	6	6
Oligo	3	3
IUGR	5	5
Pre-eclampsia/Pre-eclampsia with IUGR	8	8
APH (Abruptio/Placenta Previa)	5	5
Breech Presentation	3	3
Transverse Lie	2	2
Previous CS	2	2
PROM with failure of indication	2	2
Uteroplacental insufficiency	2	2
None	47	47
Total	100	100

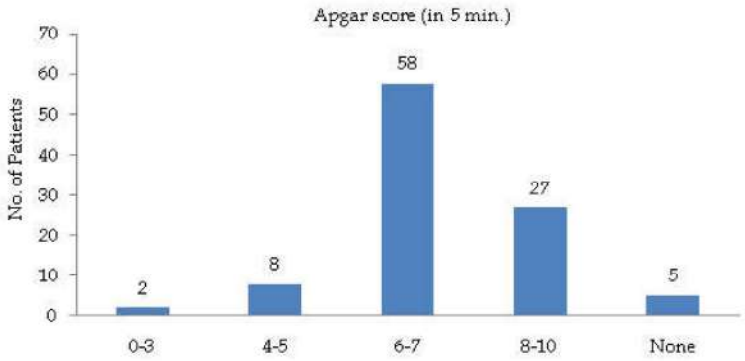
Fifteen percent (15%) of the patients were detected with Precious Pregnancy/Precious Pregnancy with CRN, 6% of the patients were detected with Fetal Distress, 3% of the patients were detected with Oligo, 5% of the patients were detected with IUGR, 8% of the patients were detected with Pre-eclampsia/Pre-eclampsia with IUGR (Table 4). IUGR cases in our study are comparable with the study performed by Swain and Singh (2017) [28] who 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 and the remaining 47% of the patients did not show any indications of LSCS.

Table 5: Complications of Child

Complications (Child)	No. of Patients	Percentage
Blood stained liquor	3	3
Liquor thick meconium stained	7	7
None	90	90
Total	100	100

Table 5 shows that out of total 100 patients, 3% of the patients had Blood stained liquor, 7% of the patients had Liquor meconium stained, while the remaining 90% of the patients did not have any complications.

Graph 4 shows that 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



Graph 4: APGAR Score (in 5 min)

Graph 5: Birth weight of Newborn baby

remaining 5% of the patients did not belong to any of the APGAR score category. Graph 5 shows that 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. The mean weight was found to be 2.51 kg with a standard deviation of 0.45. Similar results were found in the study conducted by Elmahashi, et al. [14] (2014), where the mean weight of neonatal birth among the patients given LMWH mixed with Low Dose Aspirin was found to be 3.05 kg. It was similar to that of the current study. In another study by Mohamad and Sadd (2014) [15], the authors reported mean birth weight of 3.25 Kg, which is not comparable to our study.

Table 6: Duration of stay in NICU

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

Table 6 show that the NICU stay for 5% of the neonates was between 0-3 days, the NICU stay for 12% of the neonates of was 4-6 days, the NICU stay for 4% of the neonates was 7-9 days and the NICU stay for 5% of the neonates was 10 days and above. The remaining 76% of the neonates did not stay in the NICU at all.

Table 7: Perinatal Outcome

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

Table 7 shows that 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., [16] (2011) where the spontaneous abortion was administered in only one of the woman, but in the current study it was found out that 4 women had spontaneous abortion.

Similar results were found in the study of Yuksel, et al. [17] (2014)¸ 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. Moreover, study performed by Mohamad and Saad (2014) [15] have similar results that of current study. Their study found live birth rate of 91% which is similar to our outcome. Similar results (91.5%) were obtained by Abbas and Ali (2014) [18].

Conclusion

LMWH (inj. enoxaparin 40 mg s.c. OD) & tab aspirin 75 mg OD from USG confirmation of early intra uterine pregnancy till 34 weeks daily in patients with RPL due to antiphospholipid syndrome resulted in higher live birth rates. Combination treatment with aspirin and LMWH leads to improved live birth rate among women with recurrent abortion and antiphospholipid antibodies.

References

1. Kling C. et al. Two-year outcome after recurrent first trimester miscarriages: prognostic value of the past obstetric history. 2016;293:1113-23.
2. Ford HB. and Schust DJ. Recurrent Pregnancy Loss: Etiology, Diagnosis, and Therapy. Rev Obstet Gynecol. 2009;2(2):76-83.
3. The Practice Committee of the American Society for Reproductive Medicine. Definition of infertility and recurrent pregnancy loss. Fertil Steril. 2008;89:1603.
4. This Day. Causes of Abortion in First Trimester of Pregnancy [Internet]. Nigeria; 2017 [cited on 2019, January 18]. Available from: https://www.thisdaylive.com/index.php/2017/11/11/causes-of-abortion-in-first-trimester-of-pregnancy/.
5. Edmos DK, Lindsay KS, Miller JF, et al. Early Embryonic mortality in women. Fertil Steril. 1982;38:447-53.
6. North Dakota Department of Health. Information About Pregnancy and Abortion [Internet]. Bismarck: Division of Family Health; 2016 [cited on 2018, December 20]. Available from: http://www.ndhealth.gov/familyhealth/preg_abortion_booklet_final.pdf.
7. Dhir V. and Pinto B. Antiphospholipid syndrome: A review. J. Mahatma Gandhi Insti of Medical Sciences. 2014;19(1):20-27.
8. Shen MC. Low-molecular-weight-heparin can benefit women with recurrent pregnancy loss and sole protein S deficiency: a historical control cohort study from Taiwan. Thromb J. 2016;14:44.
9. Corban et al. Antiphospholipid Syndrome Role of Vascular Endothelial Cells and Implications for Risk Stratification and Targeted Therapeutics. J Am Coll Cardiol. 2017;69:2317-30.
10. Miyakis S, Lockshin MD, Atsumi T, et al. International consensus statement on on update of the classification criteria for Thromb Haemost. 2006;4:295-306.
11. Durrani OM, Gordon C, Murray PI. Primary anti-phospholipid antibody syndrome (APS): current concepts. Surv Ophthalmol. 2002;47(3):215-338.
12. Alberman E. The epidemiology of repeated abortion. In beard RW, Sharp F, eds: early pregnancy loss: Mechanism and Treatment. London, RCOG Press.1988;9-17.
13. Girardi G, Redecha P, Salmon JE. Heparin prevents antiphospholipid antibody-induced fetal loss by inhibiting complement activation. Nat Med. 2004;10 (11):1222-6.
14. Elmahashi MO. et al. Low dose aspirin and low-molecular-weight heparin in the treatment of pregnant Libyan women with recurrent miscarriage. BBMC Res Notes. 2014;7(23).
15. Mohamad AAK and Saad SA. Enoxaparin and aspirin therapy for recurrent pregnancy loss due to anti-phospholipid syndrome (APS). Middle East Fertility 7 Society Journal. 2014;19(3):176-182.
16. Ruffatti A, Gervasi MT, Favaro M, Ruffatti AT, Hoxha A, Punzi L. Adjusted prophylactic doses of nadroparin plus low dose aspirin therapy in obstetric antiphospholipid syndrome. A prospective cohort management study. Clin Exp Rheumatol. 2011;29(3): 551-4.
17. Yuksel H. et al. Low molecular weight heparin use in unexplained recurrent miscarriage. Pak J Med Sci. 2014;30(6):1232-37.
18. Abbas, RT and Ali, SO. Enoxaparin plus aspirin versus aspirin alone in the management of recurrent miscarriage due to anti-phospholipid syndrome. AAMJ, 2014 April;12(4):135-147.