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Low Molecular Weight Heparin in Recurrent Pregnancy Loss at a Tertiary Care Centre: A Prospective Observational Study

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I. Introduction

Recurrent pregnancy loss is defined as 2 or more failed pregnancies confirmed by either sonographic or histopathologic examination (as per American Society for Reproductive Medicine, 2008). It is classically defined as 3 or more consecutive pregnancy losses at or < 20 weeks of gestational age or with a fetal weight < 500g. Approximately 1% of fertile couples have recurrent pregnancy losses. Most of these are embryonic or early fetal losses and the remainder either are anembryonic or occur after 14 weeks[1].

Recurrent pregnancy loss is associated with many putative causes, however only 3 are widely accepted (1) Parental chromosomal anomalies (2) Structural uterine anomalies (3) Antiphospholipid antibody syndrome. Although 15 percent of all clinically recognized pregnancies between 4 and 20 weeks will undergo pregnancy loss, the true loss rate is more than 50 percent, since the conception gets unrecognized before four weeks. The most common etiology during first trimester is chromosomal abnormality which could be due to the aberrations in egg or sperm cell[2].

Other etiologies of recurrent pregnancy loss include anatomic abnormalities, endocrine disorders, infections or maternal health problems, lifestyle such as smoking, drugs, malnutrition, excessive caffeine and exposure to radiation or toxic substances which can hinder the process of implantation[3].

The antiphospholipid antibody syndrome (APS) is defined by these antibodies found together with various forms of reproductive losses along with substantively increased risks for venous thromboembolism (American College of Obstetricians and Gynaecologists, 2011d,2013a). Women with recurrent spontaneous pregnancy loss have a higher frequency of these antibodies compared with normal controls (5-15% vs 2-5%) respectively.In women with high levels of aCL and especially when lupus anticoagulant is identified, there are increased risks for decidual vasculopathy, placental infarction, fetal-growth restriction, early onset preeclampsia and recurrent fetal death. According to some authors thrombophilic markers are not the only criteria for the initiation of thromboprophylactic treatment[4].

However, Other investigators suggested not to treat unexplained miscarriage with heparin or aspirin without the evidence of antiphospholipid syndrome or inherited thrombophilia, because of lack of evidence of any benefit and potential risks of therapy. The fact that thrombosis at placental level is a common finding whether antiphosholipid antibodies are present or not, suggest that other pathologic mechanisms are also involved leading to same outcome, that is the fetal loss. Although in the literature there is no consensus regarding the benefit of antithrombotic therapy even in consecutive unexplained pregnancy losses, low molecular weight heparin is widely used as prophylaxis in recurrent miscarriages in general obstetric practice. Recent trials have caused the need for heparin to be questioned in women with antibodies but no history of thrombosis (Branch, 2010). Some report that women with recurrent pregnancy loss and medium or high positive titres of antibodies may benefit from therapy. Still LMWH is widely used as prophylaxis in general obstetric practice for recurrent miscarriage. The uncertain etiology and pathogenesis of unexplained recurrent miscarriage have made the treatment empirical. Heparin is started as soon as a viable pregnancy is documented and continued till 34 weeks[5].

Enoxaparin in the dose of 20-40 mg/day subcutaneously has been used successfully in pregnancy with a live birth rate of 85-95%. The purpose of this observational study is to evaluate whether the LMWH therapy improves live birth rates in women with recurrent pregnancy loss who had their confinement in Gandhi Hospital, a tertiary care centre in Secunderabad, during the period between November 2014 – November 2016.

II. Aims And Objectives

Aim:

• To evaluate the efficacy of LMWH therapy in recurrent pregnancy loss.

Objectives of the study

• To define the role of LMWH in prevention of adverse pregnancy & fetal outcome.

• To analyse the pregnancy and fetal outcome.

PATIENTS AND METHODS

PATIENTS AND METHODS

• **PLACE OF STUDY**:GANDHI HOSPITAL,SECUNDERABAD

• **TYPE OF STUDY**: PROSPECTIVE OBSERVATIONAL STUDY

• **SAMPLE SIZE**: 50 Patients

• **STUDY DURATION**: 2 YEARS

III. Method

• The 50 patients who have met the inclusion criteria are enrolled into the study and observed.

• After taking the informed consent, patients are observed from the time of administering LMWH until the delivery.

• Perinatal outcomes in terms of IUD, birth weight, gestational age, NICU admissions, neonatal mortality, neonatal bleeding and congenital anomalies are evaluated.

INCLUSION CRITERIA:

• Pregnant women of age between 20 -35 yrs.

• Recurrent pregnancy loss [Miscarriage].

• Regularly menstruating before current pregnancy.

• Got spontaneous conception.

EXCLUSION CRITERIA:

• Women with – thrombocytopenia coagulation factor deficiency renal failure, smoking, morbid obesity threatened abortion tuberculosis chronic alcoholism, cirrhosis infectious diseases multiple pregnancy

• Uterine anomalies diagnosed by ultrasonography and hysteroscopy.

• Positive consanguinity between the two partners.

• Thyroid disorders, diabetes mellitus, chromosomal anomalies.

• Polycystic ovarian syndrome.

IV. Observation And Results

An observational study of 50 women with recurrent pregnancy loss treated with low molecular weight heparin at Gandhi hospital, secunderabad from November 2014 – November 2016. This study includes both obstetric and fetal outcome.

TABLE 1: DISTRIBUTION OF CASES AS PER THE AGE OF STUDY POPULATION

AGE (years)	No. OF CASES (50)	PECENTAGE
20 – 25	17	34%
26 – 30	29	58%
31 – 35	4	8%

The above table shows that out of 50 studied, 17 (34%) were between the age group 20 – 25 years whereas 29 (58%) were between 26 – 30 years and 4 (8%) were between 31 – 35 years.

PIE DIAGRAM 1. DISTRIBUTION OF CASES AS PER THE AGE OF STUDY POPULATION

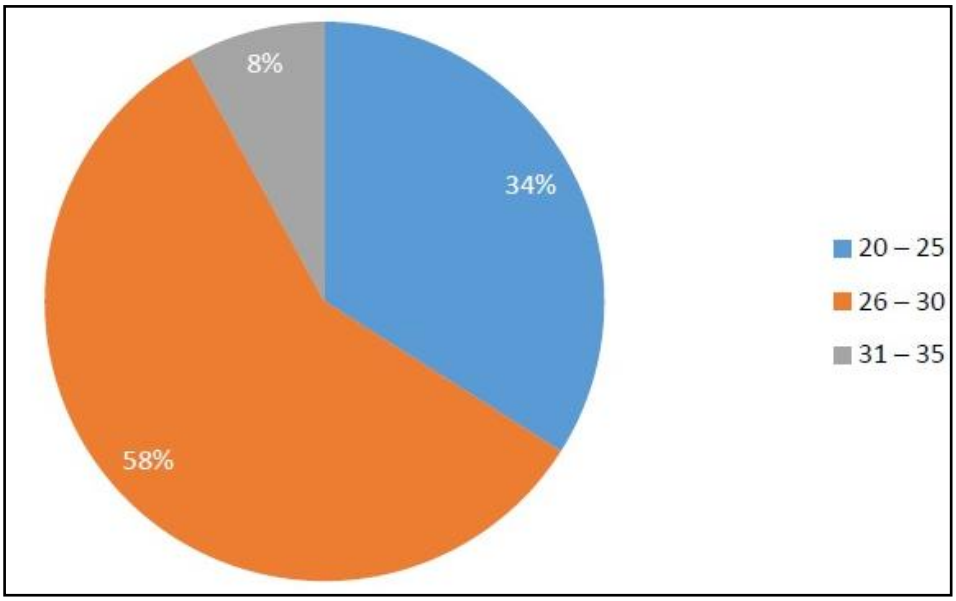


TABLE 2. DISTRIBUTION OF CASES AS PER BODY MASS INDEX (BMI)

BMI (kg/m^2)	No. OF CASES (50)	PERCENTAGE
< 18.5	3	6%
18.5 – 24.9	44	88%
25 – 29.9	3	6%

The above table shows majority of women (88%) were having normal BMI (18.5 – 24.9) and 6% were of under weight and 6% were of over weight.

PIE DIAGRAM 2. DISTRIBUTION OF CASES AS PER BODY MASS INDEX

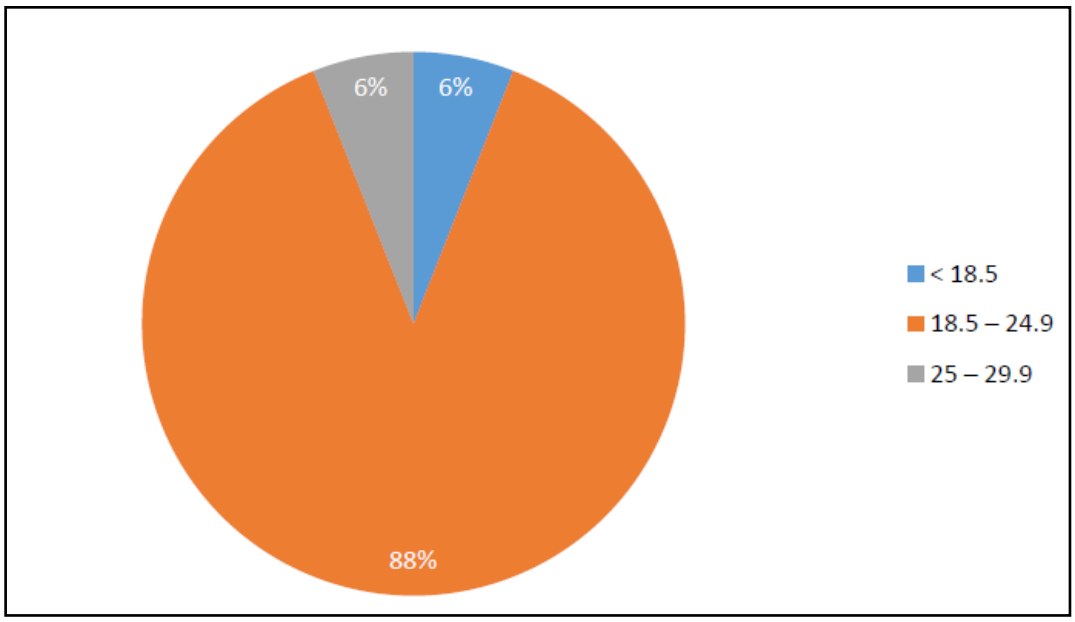
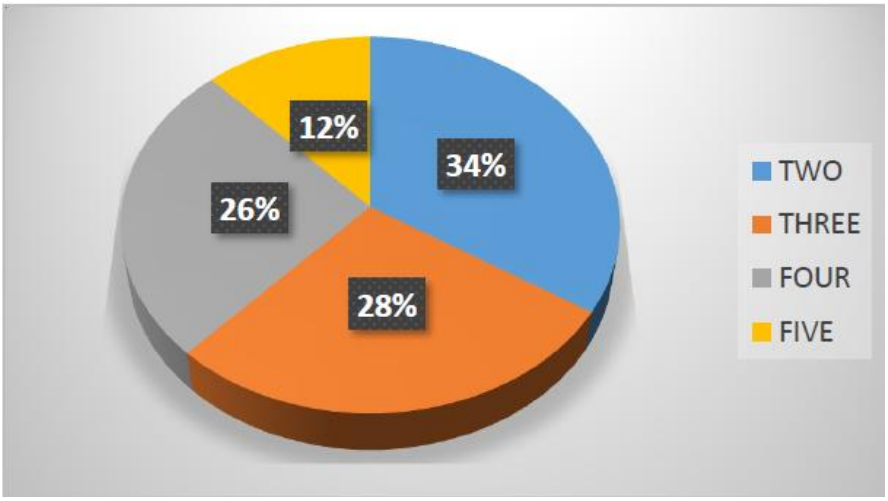


TABLE 3 : DISTRIBUTION OF CASES AS PER PREVIOUS NUMBER OF MISCARRIAGES

PREVIOUS No. OF MISCARRIAGES	No. OF CASES (50)	PERCENTAGE
TWO	17	34%
THREE	14	28%
FOUR	13	26%
FIVE	6	12%

Out of 50 cases studied 17 (34%) were having history of two previous miscarriages,14 (28%) had three previous miscarriages, 13 (26%) had four and 6 (12%) had five previous miscarriages.

PIE DIAGRAM 3: DISTRIBUTION OF CASES AS PER PREVIOUS NUMBER OF MISCARRIAGES



OBSTETRIC OUTCOME

Obstetric outcome was analyzed in detail and 38 out of 50 (76%) pregnancies were found to be continued beyond 20 wks.
30 out of 50 (60%) were live births.
Intrauterine growth restriction was seen in 12 (24%) cases.
8 out of 50 (16%) were intrauterine deaths.
12 out of 50 (24%) were miscarriages.
4 out of 50 (8%) cases were diagnosed to have abruption and 3 (6%) were found to have pre-eclampsia.

TABLE 4. OBSTETRIC OUTCOME OF THE STUDY POPULATION

OBSTETRIC OUTCOME	No. of cases	Percentage
Pregnancy beyond 20 wks	38	76%
Live births	30	60%
Miscarriages	12	24%
IUD	8	16%
IUGR	12	24%
Abruption	4	8%
Pre-eclampsia	3	6%

TABLE 5 : DISTRIBUTION OF CASES AS PER THE STUDY OUTCOME

Outcome	Total cases - 50	Percentage
Live births	30	60%
Miscarriages	12	24%
Intrauterine deaths	8	16%

When the outcome of study population was analysed, 30 out of 50 (60%) were live births, 12 out of 50 (24%) were miscarriages and 8 out of 50 (16%) were intrauterine deaths.

PIE DIAGRAM 4. DISTRIBUTION OF CASES AS PER THE STUDY OUTCOME

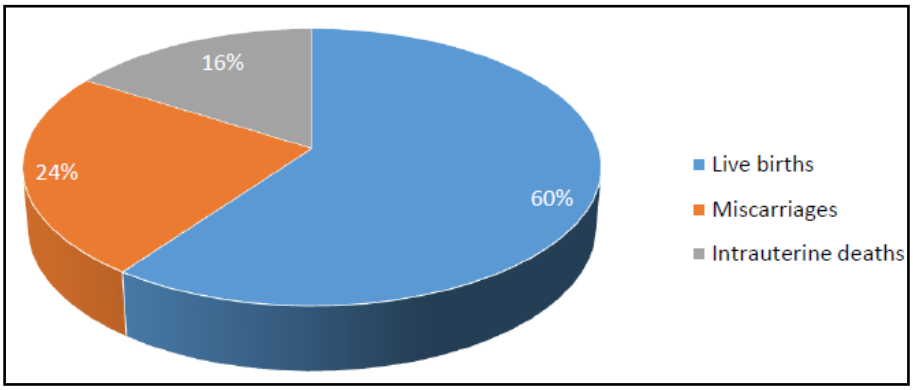


TABLE 6. No. OF LIVE BIRTHS AS PER THE GESTATIONAL AGE

Gestational age (wks)	No of live births (30)	Percentage (%)
<28 (Extremely preterm)	0	0
28 –< 32 (Very preterm)	6	20%
32 - <37 (late preterm)	21	70%
37 completed (term)	3	10%

On assessing the gestational age of different cases in the live births group, it was between 28-<32 wks in 6 cases (20%), 32-<37 wks in 21 cases (70%) and 37 wks in 3 (10%) cases.

GRAPH NO.1 NO. OF LIVE BIRTHS AS PER THE GESTATIONAL AGE

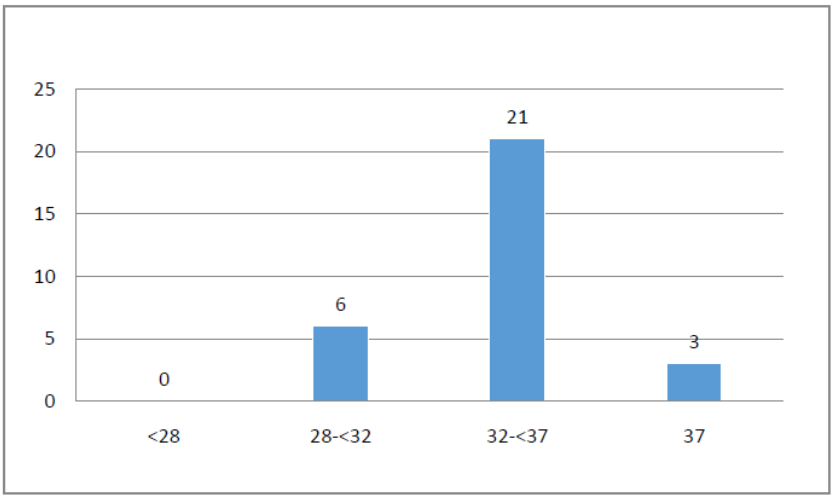
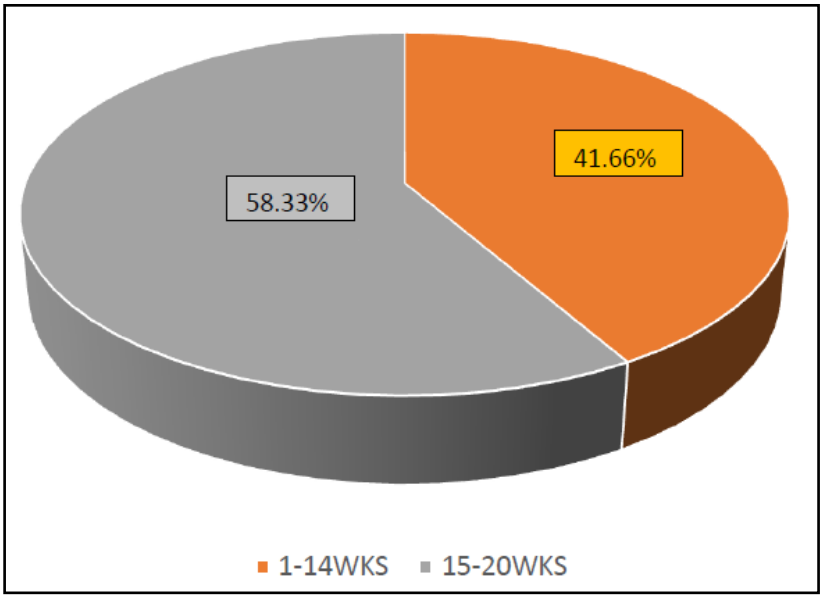


TABLE 7 : No. OF MISCARRIAGES AS PER THE GESTATIONAL AGE

Gestational age (wks)	No of miscarriages(12)	Percentage (%)
1 – 14	5	41.66 %
15 – 20	7	58.33 %

The total number of miscarriages in the study population was 12, out of which 41.66% occurred in the first trimester (1-14 wks GA) and 58.33% occurred in the second trimester (15-20 wks GA).

PIE DIAGRAM 5: NO OF MISCARRIAGES AS PER THE GESTATIONAL AGE



PIE DIAGRAM 6. TEST RESULTS OF ANTIPHOSPHOLIPID ANTIBODIES (APLA) AMONG THE STUDY POPULATION

aCL was measured in all cases and 10 (20%) turned out to be positive.

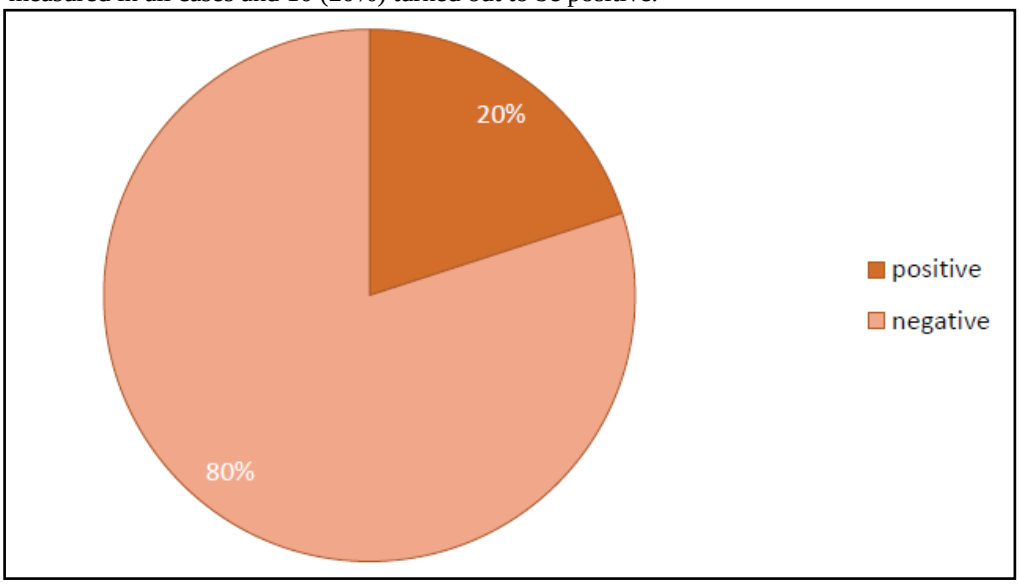


TABLE 8. DISTRIBUTION OF CASES AS PER THE MODE OF DELIVERY

Mode of delivery	No of live births (30)	Percentage (%)
Spontaneous vaginal delivery	14	46.6 %
Caesarean section	16	53.3 %

46.6 % of live births were delivered by spontaneous vaginal delivery and 53.3% were delivered by Caesarean section.

PIE DIAGRAM 7. DISTRIBUTION OF CASES AS PER THE MODE OF DELIVERY

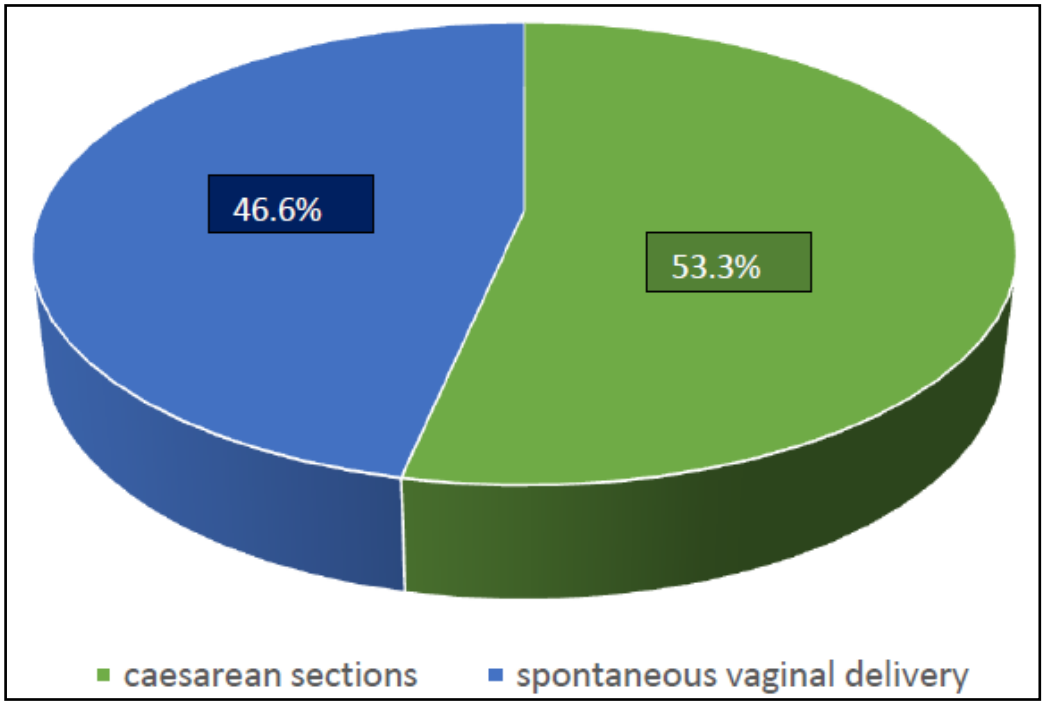


TABLE 9: No.OF LSCS AS PER THE GESTATIONAL AGE

Gestational age (wks)	LSCS (16)	
<34	2,	12.5%
34 - <37	11,	68.7%
37 completed	3,	18.7%

Out of 30 live births 16 were born by caesarean section of which majority(68.7%) were done at 34- <37 weeks of gestational age.

GRAPH 2. No. OF LSCS AS PER THE GESTATIONAL AGE

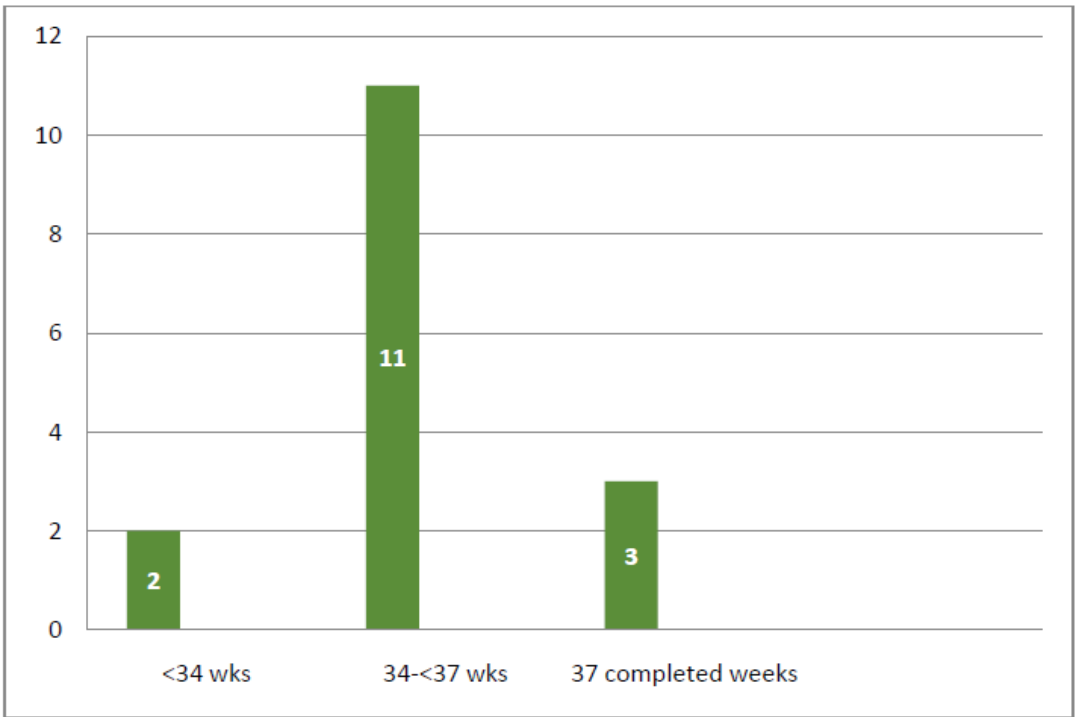


TABLE 10. No. OF INTRAUTERINE FETAL DEATHS AS PER THE GESTATIONAL AGE

Gestational age (wks)	No of IUFD (8)	Percentage
<28	2	25%
28 - <32	6	75%
32 - <37	0	0
37 completed	0	0

Out of 8 intrauterine fetal deaths, 75% occurred between 28- <32 weeks gestational age and 25% below 28 weeks of gestational age.

TABLE 11. No. OF INTRAUTERINE GROWTH RESTRICTION CASES ASPER THE GESTATIONAL AGE

Gestational age (wks)	IUGR (12)	Percentage
<28	0	0
28 - <32	2	16.6%
32 - <37	8	66.6%
37 completed	2	16.6%

Out of 12 IUGR cases 8 (66.67%) were found to have IUGR between the gestational age of 32- <37 weeks.

GRAPH 3: No. OF INTRAUTERINE GROWTH RESTRICTION CASES AS PER THE GESTATIONAL AGE

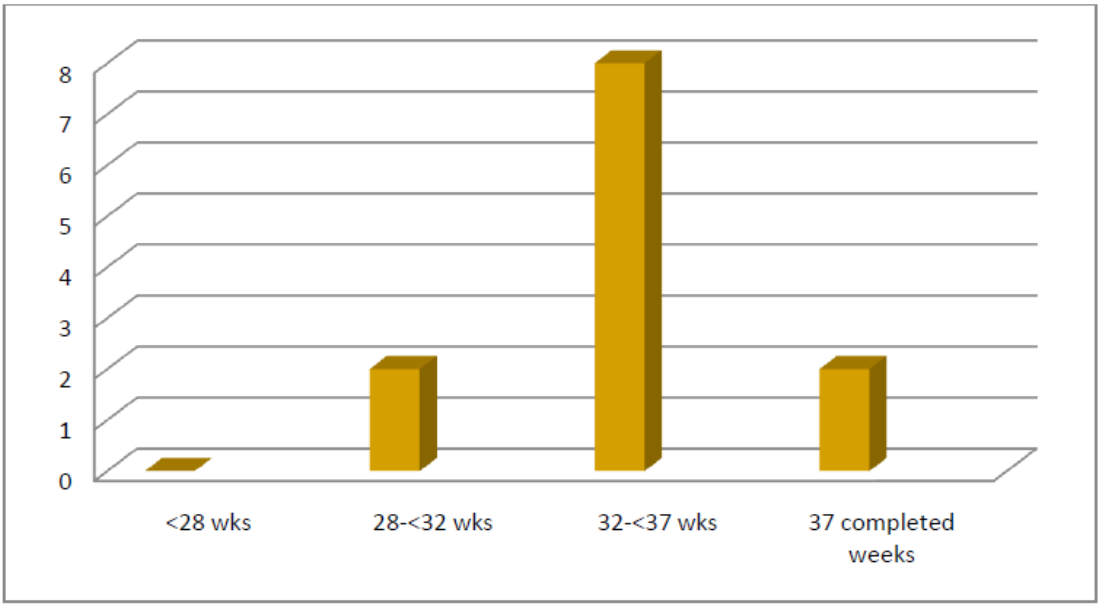


TABLE 12. FETAL OUTCOME

Fetal outcome	No of cases
Pre term	27, 90%
Term	3, 10%
NICU admissions	15, 50%
Neonatal deaths	5, 16.67%
Discharged healthy with and without NICU admission	25, 83.33%

Fetal outcome:
Out of 30 live births, 27 (90%) were preterm, 3 (10%) were term. Fifteen (50%) were discharged healthy and 15(50%) were admitted into NICU, out of which 10 were discharged healthy from NICU and 5 (16.67%) were neonatal deaths.

TABLE 13. No. OF LIVE BIRTHS AS PER THE BIRTH WEIGHT

BIRTH WEIGHT	No. OF LIVE BIRTHS	PERCENTAGE
Normal birth weight(> or =2.5kgs)	7	23.33%
Low birth weight (<2.5kgs)	22	73.33%
Very low birth weight (<1.5kgs)	1	3.33%

Birth weight was assessed in all live births. 7 (23.3%) out of 30 live births had normal birth weight, 22 (73.3%) had Low birth weight (LBW) and 1 (3.3%) had Very low birth weight (VLBW).

GRAPH 4: DISTRIBUTION OF LIVE BIRTHS AS PER THE BIRTH WEIGHT

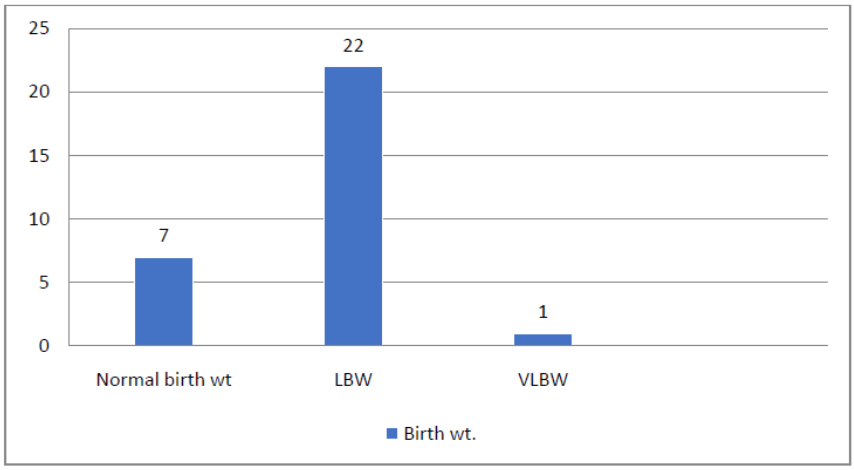


TABLE 14. No. OF NICU ADMISSIONS AS PER THE GESTATIONAL AGE

Gestational age (wks)	NICU admissions(15)	Percentage
<28	0	0
28 - <32	0	0
32 - <37	14	93.3%
37 completed	1	6.66%

Out of 15 live births admitted into NICU, 14 (93.3%) were preterm and 1 (6.66%) was of term GA.

TABLE 15. INDICATIONS FOR NICU ADMISSION

Indication	No of NICU admissions (15)
Respiratory distress	11, 73.33%
Low birth weight	14, 93.33%
Prematurity	14, 93.33%

Indications for NICU admissions were analyzed and found that in few cases there was more than one indication. Following were the over all indications for admission into NICU. Respiratory distress – 11 (73.3%), Low birth weight – 14 (93.3%), Prematurity – 14 (3.3%).

GRAPH 5 : INDICATIONS FOR NICU ADMISSION

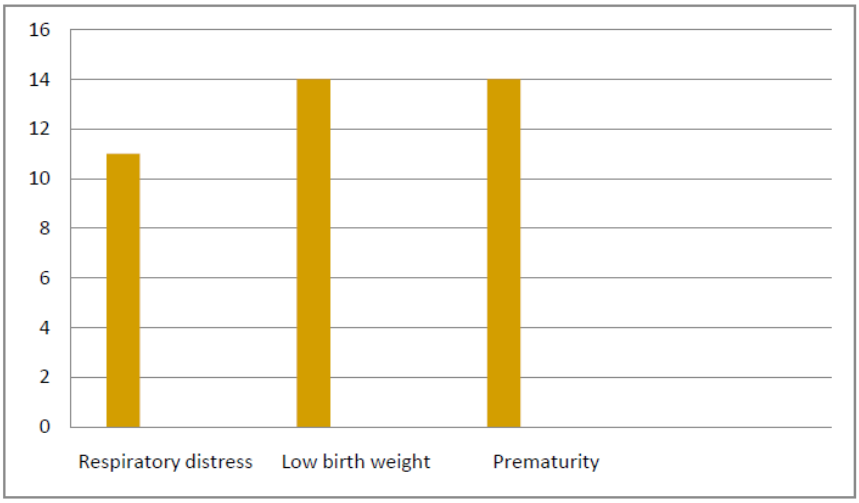


TABLE 16. No OF LIVE BIRTHS WITH ONE OR MORE OBSTETRIC COMPLICATIONS AND MODE OF DELIVERY

Complication	No of live births (30)	Caesarean section (16)	Spontaneous vaginal delivery (14)
IUGR	10	7	3
Preecclampsia	1	-	1
Abruption	3	2	1

Out of 12 IUGR cases, 10 were live births out of which 7 underwent caesarean section and 3 were delivered vaginally.
1 out of 3 preecclampsia cases was delivered vaginally and born alive.
Abruption was found in 4 cases out of which 3 women had live births of which
2 were delivered by caesarean section and 1 by vaginal delivery.

V. Discussion

The management of women with a history of pregnancy loss without an identifiable cause is unclear and the role of anticoagulants for women with unexplained recurrent miscarriage remains uncertain. It has been demonstrated that women with either congenital or acquired thrombophilia might benefit from LMWH with respect to live birth rates, abortion and late obstetrical complication rates[6]. Various treatment strategies have been tested. Most have focused on the use of thromboprophylaxis especially with enoxaparin alone[7]. Others have reported that combination treatment of prednisone, aspirin, folate and progesterone might be as effective treatment as enoxaparin alone. In the current study, LMWH is found to be effective in improving live birth rate even in the absence of demonstrated etiologic factors. This effect might be due to the properties of heparin other than its anticoagulant activity. Examination of deciduas from women with recurrent miscarriages show common pathology like necrosis, acute and chronic inflammation and vascular thrombosis compared with those of women with normal pregnancies. Also heparin has an anti-complement effect which is absolutely required to prevent pregnancy loss and thrombosis. Recurrent pregnancy loss has been associated with a higher incidence of late obstetric complications. Percentage of live births in Brenner B et al study11 in 2000 was 75% where 61 women were treated with enoxaparin 40mg, whereas 70.2% of live births were seen in Carp H et al study in 2003 which are comparable to the present study. But in both the studies, enoxaparin was given to women with recurrent pregnancy loss following the diagnosis of thrombophilia.

Nobel LS et al[8] in 2005 had got 84% of live births. Similarly with Fouda M et al where the percentage of live births was 80%. It might be due to samples of almost equal size (n= 25, n=24 respectively). The higher percentage of live births in Gris JC et al study (86.2%) in 2004 and Yuksel H et al study[9] (85%) in 2014 could be due to larger sample sizes (n=80, n= 100 respectively).

In the present study 12 (24%) out of 50 women miscarried. The percentage of miscarriage was found to be 15% in Yuksel H et al study in 2014 and 16% in Nobel LS et al study in 2005 which were of similar percentage. Carp H et al in 2003 reported 44.7% of miscarriages, whereas 7.2% was reported in the study done by Singh N et al .in 2003 in Indian population. The percentage of IUGR in the present study is 24% which is due to more prevalence of anaemia, poverty and non compliance of women under study. This is comparable to Tzafettal J et al study (26%) conducted in 2002 on 38 greek women. IUGR percentage was 5.5% in Dolitzky M et al study48 in Israel population which was increased to 28% in Kupfermic M et al, a study conducted in

Israel in 2011 which is slightly higher among the above mentioned studies. Nilanchali Singh et al in 2013 had showed 10.9 % of IUGR in their study on Indian population. A recent study conducted on pakisthan women by Yuksel H et al in 2014 showed the percentage of IUGR as 2% which is significantly lower than the other studies. The percentage of abruption was found to be 8% which is nearer to the percentage obtained in the study conducted by Tzafettas J et al in 2002. Kupfermic M et al in 2011 found 22% of abruption in Israel population, whereas 1.8% was found in Singh N et al study on indian population in 2013. Preecclampsia was found in 3 women (6%) out of which 1 developed at 32 weeks of gestational age and was continued upto 34 weeks, which later set into labour spontaneously and delivered vaginally. The other two ended up with IUFD at 27 and 29 weeks gestational age due to early onset of preecclampsia before reaching viability of foetus. It was 13% in Yuksel H et al study and 31 % and 21% in Kupfermic M et al and Tzafettas J et al studies respectively. None of the women in the study population developed preecclampsia as reported by Nobel LS et al in 2005. According to the study of Festin et al.in 1997[10], the percentage of anticardiolipin antibodies was 15% among

patients with previous fetal loss of unexplained origin. Zolghadri J et al in 2004 reported percentage of antiphospholipid antibodies among women with recurrent pregnancy loss as 11.6% in their study.

These antibodies were believed to cause thrombosis in the maternal circulation leading to events that resulted in fetal loss. Reports from other investigators showed that the prevalence of antiphopholipid antibodies in the normal obstetrical population is 5.3% among 7278 women, while in patients with recurrent pregnancy loss this number was 20% among 2226 women (Kutten WH etal) which is comparable to the present study. Another report by Charles et al. from the lupus unit in London showed a figure between 7% and 25% of antiphospholipid syndrome among British patients with recurrent fetal loss. Yetman DL in 1996[11] conducted retrospective data analysis of test results from an antiphospholipid antibody panel which included 866 women with a history of recurrent pregnancy loss and 288 parous women without a history of reproductive problems and concluded that anticardiolipin antibodies were detected in 17.3% of patients with recurrent pregnancy loss compared with only 4% in the control population. On the other hand, some investigators do not agree with this relationship. As in reports by Vila et al, among 552 normal French blood donors, IgG anticardiolipin was found in 6.5%, and IgM anticardiolipin in 9.4%. Also in 1998 reports from Simpson et al. showed the lack of association between antiphospholipid antibody and first trimester spontaneous abortion. The variation in the prevalence of these antibodies in different studies may be due to the different types of fetal wastage included, different types of antiphospholipid studied & the different localities in which studies were performed Further studies are needed to test for the exact role of anticardiolipin antibodies in the pathogenesis of recurrent miscarriage. Antiphospholipid antibodies are associated with intrauterine fetal growth retardation and fetal distress leading to premature birth or fetal death. These complications are caused by uteroplacental insufficiency as a result of multiple placental thromboses, infarcts, and spiral artery vasculopathy, which are almost certainly provoked by the hypercoagulable state induced by aPL antibodies.

Available data indicate that the thrombogenic function of aPL antibodies involves their general effect on platelets, endothelial cells, anticoagulant mechanisms and fibrinolytic pathways as well as their local effect on trophoblasts and villi cells, leading to reduction of annexin V (placental anticoagulant protein-I) production and inhibition of its anticoagulant function. Out of 17 women with history of 2 previous miscarriages, 9 (52.9%) women had live births whereas 8 (57.1%) out of 14 women with history of 3 previous miscarriages had live births, 8 (61.5%) out of 13 women with history of 4 previous miscarriages and 5 (83.3%) out of 6 women with history of 5 previous miscarriages had live births. In the present study the caesarean section percentage was found to be 53.3% which is very much higher than the general population (18.9%). Most of the caesarean sections were done between the gestational age of 34 - <37 weeks. Due to the high risk nature of the population under study, the iatrogenic intervention has led to higher percentage of caesarean sections. In the present study the preterm delivery rate was found to be higher, and most of them were of late preterm (32- <37 weeks).This could be due to early iatrogenic intervention in an attempt to prevent perinatal mortality and morbidity as the population under study was at high risk. 10 out of 30 live births had IUGR out of which 7 were delivered by caesarean section and 3 by spontaneous vaginal delivery. 3 women had preecclampsia out of which 2 ended up with IUD at 27 and 29 weeks of gestational age, whereas one pregnancy was continued till 34 weeks and had undergone spontaneous vaginal delivery. Out of 3 women who had abruption, 2 women underwent caesarean section and 1 had normal vaginal delivery. LMWH is the preferred agent for anticoagulation in pregnancy as there is no transplacental transfer due to their high molecular weight, hence, the incidence of fetal hemorrhage or teratogenicity is not increased. There is a trend for increased live births with LWMH usage in preventing recurrent pregnancy loss. Recurrent pregnancy loss due to thrombotic conditions during pregnancy is an important topic of discussion due to high rates of morbidity and mortality. Not only are these conditions dangerous for the mother, but also for the fetus. Several studies have been conducted to assess how to treat these serious conditions in pregnancy. Greer and Nelson-Piercy reviewed 64 studies and 2777 pregnancies and found LMWH to be effective for prophylaxis and treatment of women with RPL (85.4%) due to its decreased side effects of bleeding and heparininduced thrombocytopenia. No maternal deaths were reported. As per the 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. Currently, there is insufficient evidence to support the routine use of LWMH to improve pregnancy outcomes in women with a history of pregnancy loss. Not only are additional studies necessary but standardized criteria for trials evaluating the benefit of an intervention in recurrent pregnancy loss should be established.

VI. Summary

Majority of women (88%) were having normal BMI (18.5 – 24.9) and 6% were of under weight and 6% were of over weight. The number of live births were 30 out of 50 (60%), most of which were of preterm babies. 76% of pregnancies were found to be continued beyond 20 weeks of gestational age. Intrauterine deaths were seen in 16% of study population. 24% of women were found to have miscarriages. Abruption and preecclampsia account for 8% and 6% respectively. IUGR accounts for 24% among study population. APLA

was found to be positive in 20% of women. Out of 50 cases studied 17 (34%) were having history of two previous miscarriages, 14 (28%) had three previous miscarriages, 13 (26%) had four and 6 (12%) had five previous miscarriages. The caesarean section percentage was 53.3%, most of which were done between 34- <37 weeks of gestational age. The preterm delivery rate was found to be 90% of which 70% falls between gestational age of 32- <37 weeks. Out of 15 live births admitted into NICU, 14 were preterm and 1 was of term gestational age. Indications for admission into NICU were respiratory distress in 36.6%, low birth weight in 46.6% and Prematurity in 46.6% cases. 7 (23.3%) out of 30 live births had normal birth weight, 22 (73.3%) had Low birth weight (LBW) and 1 (3.3%) had Very low birth weight (VLBW). Out of 30 live births, 7 (23.3%) women who had live births were found to have APLA positive and 23 (76.6%) women who had live births were negative for APLA. Out of 17 women with history of 2 previous miscarriages, 9 (52.9%) women had live births whereas 8 (57.1%) out of 14 women with history of 3 previous miscarriages had live births, 8 (61.5%) out of 13 women with history of 4 previous miscarriages and 5 (83.3%) out of 6 women with history of 5 previous miscarriages had live births.

VII. Conclusion

In conclusion, with a limited number of participants, the present data demonstrates that in women with recurrent pregnancy loss, thromboprophylaxis with LMWH is effective in achieving live births. The poor obstetric outcome in women with a history of recurrent miscarriage in association with antiphospholipid antibodies may be improved with LMWH. LMWH may also promote successful embryonic implantation in the early stages of pregnancy and protect against thrombosis of the uteroplacental vasculature after successful placentation. However, the use of LMWH to prevent recurrent miscarriages remains controversial because of small sample size and lack of control arms in the present study. Hence, Large and well-designed randomized trials are needed.

References

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