

SINGLE CENTRE, OPEN-LABEL & NON RANDOMIZED CLINICAL TRIAL TESTING LMWH EFFICACY ON PERINATAL OUTCOME IN LATE SECOND TRIMESTER OLIGOHYDRAMNIOS CASES

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ABSTRACT

Objective: To find out low molecular weight heparin (LMWH) efficacy in late second trimester oligohydramnios cases.

Study Design: Quasi-experimental study.

Place and Duration of Study: Combined Military Hospital Malir, from Jan to Jun 2017.

Methodology: A total of 30 patients having amniotic fluid index (AFI) <8 on ultrasound scan during their late second trimester phase were enrolled in the study after informed consent. Exclusion criteria included congenital anomalies on U/S, PPRM, and drug-induced oligohydramnios. Personal, medical and obstetric history was obtained for age, parity and co-morbidities like hypertension, antiphospholipid syndrome, and previous oligohydramnios. Low molecular weight heparin was started at a dose of 0.5mg/kg of body weight subcutaneously for 8-12 weeks and stopped 24 hours prior to delivery. Rescan for amniotic fluid index and fetal biometry assessment was done every 2 weeks till the date of delivery. Fetal outcome in terms of maturity, mode of delivery, birth weight, APGAR score and need for NICU admission were measured.

Results: There were 28 live births and two intrauterine deaths. Twelve patients were delivered normally and 18 had elective LSCS. Of twenty-eight cases, eight were premature low birth weight (LBW) babies. Twenty-six patients showed significant improvement in amniotic fluid index. Average birth weight was 2.5kg. Neonates showed an average APGAR score of 7. Eight neonates admitted in NICU (for prematurity and/or low birth weight) and discharged within a week.

Conclusion: Low molecular weight heparin plays a significant role in treating oligohydramnios in cases with or without risk factors. However, further studies with a large sample size including a control sample are recommended to validate the results.

Keywords: Clinical trial, Oligohydramnios, Low molecular weight heparin.

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INTRODUCTION

Oligohydramnios is associated with perinatal morbidity and mortality of around 80-90%¹. Adverse fetal outcomes like intrauterine deaths and intrauterine growth retardation happen frequently if oligohydramnios cases are left untreated or do not respond to therapy². Low molecular weight heparin (LMWH) has shown promising results in oligohydramnios cases. Low molecular weight heparin fractions were first prepared by fractionation of the crude unfractionated heparin during 1970-1980³. Fractionated Heparin has been more advantageous than its unfractionated counterpart. It has a prolonged plasma half-life, easily introduced once or twice dosing daily, more predictable anticoagulant response with no need for routine laboratory monitoring. It is also associated with lesser frequencies of severe side effects like heparin-induced thrombocytopenia and osteoporosis. They do not cross the placental barrier, therefore, they are the most prescribed anticoagulant drugs during pregnancy⁴. However, it is necessary to identify variables and risk factors in cases with

oligohydramnios for the successful prolongation of pregnancy and to improve fetal outcomes in terms of maturity, birth weight and APGAR score. Risk factors are also important for the improvement of treatment strategies and prognosis⁵. Randomized trials are needed to determine whether treating oligohydramnios can successfully improve pregnancy outcomes. If oligohydramnios is not associated with any other complications or risk factors, there is very little chance to have an adverse fetal outcome⁶. Therefore, isolated oligohydramnios is usually not treated with termination of pregnancy. Antiphospholipid antibodies (APLA) are autoimmune antibodies directed against phospholipid-binding plasma proteins and have associations with both arterial and venous thrombosis as well as pregnancy morbidities like severe oligohydramnios and associated intrauterine growth retardation^{7,8}. Low molecular weight heparins are an attractive alternative to unfractionated heparin due to their logistic advantages and their association with a lower incidence of osteoporosis and thrombocytopenia.

Pregnancy is a prothrombotic state and LMWH is most commonly used for thromboprophylaxis for various indications. Safety and efficacy of LMWH is

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established already in pregnancy but there are lot of debate regarding its indications, dose and duration. LMWH is being used in antiphospholipid syndrome for quite some time. But in cases of idiopathic oligohydramnios reported in second trimester LMWH is administered and results are very encouraging. Therefore it is hypothesized that LMWH is equally effective in oligohydramnios cases in improving perinatal outcomes regardless of their etiologies and co-morbid conditions.

METHODOLOGY

This quasi-experimental study was conducted in the department of Obstetrics and Gynecology, Combined Military Hospital Malir, from January to June 2017. Study proposal was submitted to Ethics Review Board and approval was obtained vide letter number 1440/Adm/Trg/2016 dated 20 December 2016. Prior to inclusion in the study, patients had to give their consent to participate to the study. A total of thirty patients (n=30) were enrolled in this study. Both patients and physician were aware of the treatment given to them. Sampling was non-probability consecutive sampling.

Inclusion criteria was Amniotic fluid index (AFI) <8 on ultrasound scan during their late second trimester phase. Patients having multiple pregnancy, structural fetal defect, PPRM (pre-labour premature rupture of membranes) and drug causing oligohydramnios were excluded. Demographic data, relevant history, physical examination and baseline investigations done (CBC, Urine analysis, BSR, Viral markers Band C, Serum Uric acid, coagulation profile, RFTs, LFTs and thrombophilia screening).

Amount of liquor was assessed by measuring AFI on ultrasonography. The method of calculating AFI is by dividing mother abdomen into four quadrants and then measuring the largest vertical pool in all four and then adding them. Oligohydramnios was defined when the maximum vertical pool is <2cm or AFI <8. Patients participating in the study were informed about the drug protocol and its effects reported in the literature. The patients were given subcutaneous LMWH at dose of 0.5 mg/kg of body weight. Rescan for fetal biometry and AFI done every two weeks till delivery or atleast 8 weeks. All women were given trial of labor if there was no obstetrical contraindication. LMW Heparin stopped 24 hours prior to delivery or cesarean section.

Mode and time of delivery and fetal outcome including fetal weight and APGAR score at birth and

NICU admission were outcome measures. Outcome of the this study were compared with the previous studies⁹⁻¹³.

RESULTS

A total of 30 patients were enrolled for the clinical trial. All patients were consented voluntarily for the study. They were also provided with informed consent in black and white. Of the 30 patients included in the study, almost 14 (50%) were in the range of 26-30 years. Minimum age was 20 years (n=2) and maximum age was 1 (40) years (table-I). Obstetric history of the patients showed 12 (40%) patients were primigravida.

Table-I: Personal, medical and obstetric variables studied in the patients of the present study.

Age Range (years)	No. of Patients
20-25	8
26-30	14
31-35	5
36-40	3
Parity	
Primigravida	12
1-2	8
3-4	7
>4	3
Co Morbid / Risk factor	
Hypertension	8
Previous History of Oligohydramnios	8
Antiphospholipid syndrome	2
None	12
Anti Fluid Index	
7	11
3-4	17
<2	2

Three co-morbid or associated factors were identified i.e. hypertension, previous oligohydramnios history that increases the risk for subsequent pregnancies, and antiphospholipid syndrome. None of the patient showed diabetes or kidney or liver diseases.

Amniotic Fluid Index (AFI) is considered normal if it is in the range of 7-25. Below which patient is diagnosed as oligohydramnios and above which as polyhydramnios. Of the 30 patients of the present study eleven can be considered at the threshold level i.e. 7 and rest were below the threshold level.

Table-II showed the improvement in AFI of the patients treated with LMWH. Only three patients did not respond to the treatment satisfactorily and their AFI remained below 4. Before treatment there were 19 patients who showed AFI at 4 or below 4. Eight babies were LBW and shifted to NICU to deal with the consequences of prematurity and LBW. Fortunately all were

discharged within the first week of their admission without developing complications. Two pregnancies were terminated into intra-uterine death (IUD). These patients did not respond to LMWH and AFI remained low. Therefore cause of their death may be attributed to scanty fluid in amniotic sac.

Table-II: Fetal Outcomes in LMWH treated cases of oligohydramnios.

AFI (in cm)	>7	12
	4-7	15
	<4	3
Mode of delivery	SVD	12
	LSCS	18
Fetal outcome	Intrauterine death (IUD)	2
	Premature and low birth weight	8
	Alive and healthy	20
Apgar score	More than 7	17
	Less than 7	13

Table-III showed a comparison of the present study with the previous three studies.

Percentage of live birth reported in the present study (93.33%) is only second to Badaway *et al*¹⁰ who reported live birth percentage as 94.7. Although the number of patients in the present study is small, however, it does not undermine the results significance. Nevertheless large sample can validate the results in this study.

Table-III: Comparison of the live birth ratio and percentage of present study with previous studies⁹⁻¹².

References	Live Births Ratio (Live Births / Total Number of Participants)		Percentage of Live Births (Live Births / Total Number of Participants) *100	
	Cases	Control	Cases	Control
Present Study	28/30	-	93.33	-
Dolitzky <i>et al</i> , 2006 ⁹	44/54	42/50	81.48	84
Badawy <i>et al</i> 2008 ¹⁰	161/170	151/170	94.70	88.82353
Fawzy <i>et al</i> , 2008 ¹¹	46/57	24/50	80.70	48
Laskin <i>et al</i> , 2009 ¹²	35/45	34/43	77.77	79.06977

Figure shows that growth retardation is the most common effect of oligohydramnios. Even when oligohydramnios was treated with LMWH growth retardation is more common than healthy cases. Percentage of elective C sections were common in oligohydramnios cases. May be the surgeons wanted to avoid fetal distress that may occur in growth retardation cases and as soon as the baby was mature enough to survive extra uterine life, surgeon decided to perform C-section. Percentage of cases with APGAR score of <7 is highest in the present study. APGAR score of the this study was taken during the first minute after the birth of baby. While in Kakhhaie *et al* 5-minute APGAR score

was reported. Difference in time after birth may be the reason for the variation seen in figure.

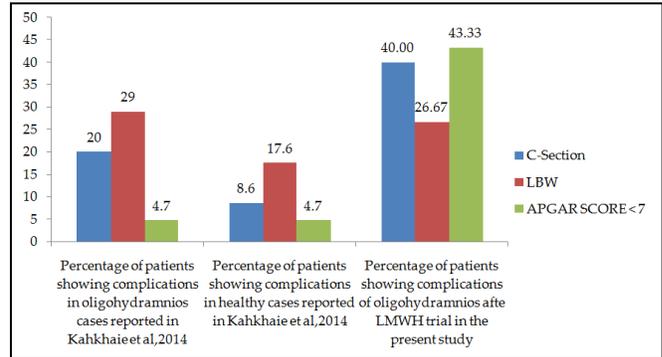


Figure: Comparison of pregnancy complications in oligohydramnios with and without treatment with LMWH and healthy cases.

DISCUSSION

Oligohydramnios is associated with poor prenatal outcome especially if it occurs in mid-trimester. Oligohydramnios complicates around 0.8-5.5% of pregnancies. Amniotic fluid has various functions in fetal growth and development. Severe oligohydramnios can lead to limb contractures, hypo plastic lungs and cord compression can lead to uteroplacental insufficiency. So far different strategies adopted to overcome this issue including maternal hydration¹⁴, amnioinfusion¹⁵ and heparin¹⁶.

Heparin can promote blood circulation and improve placental function by decreasing platelet aggregation. It inhibits fibrin formation and deposition which results in decreasing thrombosis. Chu *et al* reported that expression of heparinase is stronger in these placentae that is why there is role of exogenous heparin¹.

The role of LMWH is well established in APS and is quite successful. Its safety and efficacy for various indications in obstetrics is already established³. Groom *et al*¹⁸ suggested role of heparin in patients who are at risk of developing pre-eclampsia. Many times we do not find the cause of oligohydramnios still we gave trial of LMWH and results are encouraging.

In this study 12 patients had no risk factor or cause/s associated with oligohydramnios but their response to LMWH shows that there is role of LMWH in unexplained cases of oligohydramnios. The study by Al-Assady *et al*¹⁸ to establish the role of LMWH in unexplained IUGR and early onset oligohydramnios showed 75% live birth rate in patients given thromboprophylaxis as compared to only 37% in controls. On the contrary, Ahmed *et al*¹⁹ mentioned in her study of perinatal outcome in isolated cases of oligohydramnios had significantly lower birth weight babies and were delivered at earlier gestational age but NICU admissions were similar in both groups. A study by Akhter *et al*² in 2015 had strongly recommended role of LMWH in cases of oligohydramnios other than APS to improve the obstetrical outcome.

Data on safety and efficacy of LMWH is available but not substantial for Pakistani populations. Many studies found LMWH found it a safe and effective alternative to un-fractionated heparin for obstetric thromboprophylaxis in high-risk women²⁰.

Although randomized clinical trials (RCTs) are given more validity in research, nevertheless, many clinical situations does not fulfill the criteria set for RCTs. Some of the reasons for conducting non randomized clinical trial include less number of patients enrolled for the trial, cost of larger sample size is too much, and sometimes longer period of RCT may give rise some ethical issues which are difficult to address. In the present study we had a smaller sample size and randomization was not possible that's why we opted for non-randomized trial. However, smaller sample size reported in this study does not undermine its significance as there are latest examples of non-randomized clinical trials conducted in sample size as smaller as only twenty patients¹¹.

LIMITATION OF STUDY

It is an uncontrolled study based on smaller number of cases. Another major limitation is the heterogeneity of indications for LMWH therapy in the patients included in the study. It is not possible to comment upon the exact effect of LMWH therapy on maternal and fetal outcomes for various indications, and hence randomized, controlled trials are indicated.

CONCLUSION

Low molecular weight heparin is a safe and efficacious in pregnancy and show promising results in reducing complications of oligohydramnios and improving fetal outcomes. However larger sample size and

multicentre studies are needed to validate the efficacy of LMWH.

CONFLICT OF INTEREST

This study has no conflict of interest to be declared by any author.

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