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Original Article

THE EFFECT OF LOW-MOLECULAR-WEIGHT HEPARIN ON THE BIRTH WEIGHT IN 28 TO 34-WEEK PREGNANCIES COMPLICATED BY INTRAUTERINE GROWTH RESTRICTION

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Background: The use of low-molecular-weight Heparin (LMWH) in intra-uterine growth reduction (IUGR) is very common. However, its effect on the neonatal birth weight has not been studied in our context. This study aims to compare the mean birth weight of neonates receiving IUGR versus controls in females presenting with IUGR. **Methods:** This comparative cross-sectional study enrolled 100 women aged 18–40 years with parity <6, presenting at 28–34 weeks of gestation with IUGR, from the Department of Obstetrics and Gynaecology, Pakistan Institute of Medical Sciences, Islamabad. After applying the selection criteria and obtaining approval, group 1 females were given LMWH (0.2–0.4 mL by subcutaneous injection) along with parenteral nutrition, while in group 2, females received only parenteral nutrition (control group). Then, females were followed up every 15 days until delivery. At the time of delivery, the baby's birth weight was recorded. **Results:** The mean age of women in group 1 was 30.10±5.48 years, and in group 2 was 29.06±4.48 years. Mean gestational age was 30.49±1.87 weeks. The mean birth weight of infants in group 1 was 2957.20±177.76 grams, and in group 2 was 2663.7±176.32 grams, with a p<0.0001. **Conclusion:** The mean birth weight of neonates receiving LMWH is higher compared to controls in females presenting with intrauterine growth retardation.

Keywords: Intrauterine growth restriction, heparin, LMWH, birth weight.

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INTRODUCTION

A reduction in foetal growth rate that prevents an infant from reaching its full potential is known as intrauterine growth restriction (IUGR).[1] Additionally, it continues to be a major global cause of perinatal morbidity and mortality. With a reported incidence of 25%, IUGR is notably prevalent in Pakistan.[2] The main cause of IUGR is utero-placental insufficiency, although the aetiology is complex.[3] Major complications for the new-borns are linked to this condition, such as intrapartum asphyxia, hypoglycaemia, and meconium aspiration syndrome.

Management of IUGR often includes bed rest, but this increases the risk of thrombosis. Heparin, with its anticoagulant properties and its ability to inhibit complement activation on trophoblasts, has been considered an effective therapeutic agent for preventing pregnancy complications such as IUGR.[4] Theoretical advantages of LMWH over unfractionated heparin include superior bioavailability and a lower risk of complications.

Several emerging studies have begun investigating the specific efficacy of LMWH in improving outcomes in pregnancies with IUGR.[5,6] The most important study to date, that of Yu *et al,* from China, demonstrated that among females with IUGR between 28 and 34 weeks of gestation, the mean birth weight was significantly higher in those treated with LMWH compared with controls (3080±225 grams vs. 2580±304 grams).[7] This suggests further exploration; due to the lack of effective intervention for IUGR pregnancies, further research is needed to establish how effective LMWH can be as a regular treatment modality in the Pakistani context.

This study is based on the aforementioned research gap. It aimed to compare the mean birth weight of new-borns to mothers presenting with IUGR who were administered LMWH versus those who received standard care alone. The main benefit of this study is to provide concrete evidence on the role of LMWH as a therapeutic intervention to improve foetal growth and, consequently, perinatal outcomes in cases of IUGR.

MATERIALS AND METHODS

This comparative cross-sectional study was conducted at the Department of Obstetrics and Gynaecology, Pakistan Institute of Medical Sciences, Islamabad, from February 15, 2023, to April 15, 2024. With non-probability, consecutive sampling, a sample size of 100, (50) in each group was calculated with a 95% confidence interval and 5% level of significance, 80% power of the test, with a mean birth weight of 3080±225 g in the LMWH group and 2580±304 g in the control group in females presenting with intrauterine growth retardation. [7] Females of age 18–40 years of parity <6 presenting during gestational age 28-34weeks (on USG and antenatal record) presenting with IUGR (as per operational definition) were included whereas, pregnancies complicated by gestational diabetics (BSR >185mg/dL), hypertensive (BP>140/90), eclamptic, underweight (BMI <18 Kg/m^2) were excluded.

After obtaining approval from the hospital's ethics committee and informed consent, 100 females meeting the selection criteria were enrolled in the study from the OPD. Demographic information (name, age, weight, height, gestational age, parity, and contact information) was obtained. Then, the females were randomly divided into two groups by using the lottery method. Both groups were given parenteral nutrition. In group 1, females received LMWH (0.2-0.4 mL by subcutaneous injection) along with parenteral nutrition, while in group 2, females received only parenteral nutrition (control group). Then, females were followed up every 15 days until delivery. At the time of delivery, the baby's birth weight was recorded. All this information was collected through a pre-designed proforma.

Considering the data to be normally distributed, descriptive statistics and the sample *t*-test were used to analyse the data in SPSS IBM software. $p \leq 0.05$ was taken as significant

RESULTS

A total of 100 participants with an age range of 18 to 40 had a mean age of 29.78±5.0 years (group 1 was 30.10±5.48 years, and group 2 was 29.06±4.48 years). The age in years and gestational age in weeks, and parity of both groups are shown in Table-1. The Mean birth weight of group 1, i.e., 2957.2±177.76, with a $p = 0.0001$, is shown in Figure-1.

The stratification of age, gestational age, and parity is shown in Table-2 with a significant *p*-value.

Table-1: Age distribution for both groups (n=100)

		Group I (n=50)		Group II (n=50)		Total (n=100)	
		n	%	n	%	n	%
Age (years)	18–30	26	52.0	33	66.0	59	59.0
	31–40	24	48.0	17	34.0	41	41.0
	Mean±SD	30.10±5.48		29.06±4.48		29.78±5.07	
GA (weeks)	28–30	27	54.0	27	54.0	54	54.0
	31–34	23	46.0	23	46.0	46	46.0
	Mean±SD	30.56±1.94		30.46±1.86		30.49±1.87	
Parity	0–2	11	22.0	15	30.0	26	26.0
	3–5	39	78.0	35	70.0	74	74.0

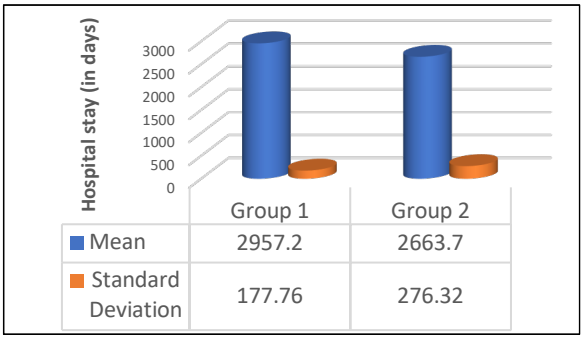

Figure-1: Mean birth weight of neonates in both groups

Table-2: Stratification of birth weight of neonates with respect to different variables

Dichotomous variables		Group 1 (n=50) Birth weight of neonates Mean±SD	Group 2 (n=50) Birth weight of neonates Mean±SD	*P*
Age of patients (years)	18–30	2985.70±164.70	2681.20±284.35	0.0001
	31–40	2926.33±189.54	2629.80±265.07	0.0001
GA (weeks)	28–30	2959.10±173.17	2767.33±262.17	0.0001
	31–34	2955.03±186.90	2542.13±245.33	0.0001
Parity	0–2	3008.55±161.80	2597.12±293.98	0.0001
	3–5	2942.74±181.33	2692.39±267.69	0.0001

$p = 0.0001$, which is statistically significant

DISCUSSION

The main aim of this study was to compare the mean birth weight of neonates born to mothers with IUGR who were given LMWH against those who received only standard care. Our results indicate a statistically significant increase in mean birth weight in the LMWH group (2957.20±177.76 g) compared with the control group (2663.7±176.32 g; $p=0.0001$). This finding strongly supports that administration of LMWH enhances fetal growth parameters in pregnancies complicated by IUGR.

The demographics of the study population mirror those of a general obstetric population typically seen in tertiary care. The mean age of participants was 29.78±5.07 years. As in the general obstetric population, most women (59.0%, n=59) were younger, aged 18–30 years. Our population also had very high maternal parity, with 74.0% (n=74) of women having a parity of 3–5. The anticipated benefits of LMWH observed in our population align with its pleiotropic effects, which are thought to complement its anticoagulant properties with anti-inflammatory and pro-angiogenic effects, thereby mitigating placental dysfunction.[4]

The observed statistically significant increases in birth weight observed in this study further contribute to the ongoing discussion surrounding the clinical utility of LMWH, as evidenced by substantial variations in global guideline recommendations regarding postpartum venous Thromboembolism prophylaxis.[8] Finally, and in consideration of the clinical application of our results, it

must be emphasised that, in terms of weighing benefit to risk, we need to acknowledge and recognise that bleeding events have been shown to occur in this population even though they are infrequent.[9]

The positive impact was consistent across all gestational ages. Neonates in the LMWH group had higher birth weights, whether the treatment began at 28–30 weeks (2959.10 vs. 2767.33 g) or 31–34 weeks (2955.03 vs. 2542.13 g). The larger difference in the latter group is noteworthy, suggesting that while LMWH is effective after diagnosis, foetal issues may be more severe in later-presenting cases, and the treatment helps mitigate this. A 2024 study supports this, noting that placental issues are often more severe in late-onset IUGR, and treatments that improve placental blood flow could be very helpful.[10] Lastly, the study showed that LMWH was beneficial for both low-parity (0–2) and high-parity (3–5) women (p=0.0001). This demonstrates the positive effects of LMWH in IUGR cases, regardless of the mother's disease history, including parity.

Our result, though not directly, is supported by the literature. Cruz-Lemini M *et al,* in their systematic review, concluded that the use of LMWH in high-risk pregnancies has significantly (OR= 0.61) reduced the prevalence of small-for-gestational-age new-borns.[11] This supports our study, indicating a more protective role in IUGR, as observed in our non-interventional group. Another meta-analysis by Chen J *et al*, studying the synergistic effect of LMWH with low-dose aspirin on high-risk pregnancies without thrombophilia, resulted in the prevention of foetal growth restriction.[12] Although the current study only included LMWH, it reinforces the potential therapeutic effect of LMWH in IUGR. This appears to improve the placental insufficiency, and hence the IUGR.

Studies suggest that, in addition to its role in anticoagulation, LMWH enhances placental function through various mechanisms. Through binding to cytokines like IL-6 and IFN-γ, it inhibits inflammatory pathways and reduces inflammation, playing a key role in IUGR placental issues.[13] Moreover, by inhibiting heparinise and boosting nitric oxide, it also protects the endothelial cells, resulting in improved blood flow in the placenta. Newer studies even suggest a promising role for LMWH in placental repair by enhancing the function of mesenchymal stem cells. Collectively, these factors, reducing inflammation, repairing cellular structure, and protecting vessels, seem favourable for increasing foetal weight gain, thus reducing IUGR incidence. [14]

Despite the beneficial effects of LMWH in IUGR pregnancies, conflicting studies also exist. For example, in a larger trial, TIPPS mentioned that LMWH use in high-risk pregnancies is not beneficial in reducing IUGR.[11] Such a difference can arise from variation in the study participants and the study setup. Our study included LMWH as a treatment modality for IUGR in pregnancies between 28 and 34 weeks. On the other hand, larger trials used LMWH as a preventive measure in high-risk pregnancies.[12] This appears to be a key difference because the use of LMWH in a struggling placenta might be beneficial than preventing other health issues in an already healthy placenta. Furthermore, the gestational age also matters. As in Cruz-Lemini *et al,* LMWH has a beneficial effect in preeclampsia when used before the 16th gestational week.[11,15] However, our study indicated a promising effect when treatment was initiated at the 28th gestational age, suggesting that late treatment in pregnancies with IUGR may be more effective. LMWH is generally safe during pregnancy, as shown in a 2024 review.[4] Bleeding is a known risk, but its predictable behaviour makes it the preferred option. It can be beneficial in difficult situations, such as IUGR, because the benefits to the baby's growth likely outweigh the risks.

LIMITATIONS AND FUTURE DIRECTIONS

The study's small size and single-centre design limit the generalizability of the results. The gestational range, i.e., 28–34 weeks, and limited to one condition of placental insufficiency, i.e., IUGR, is too specific and can show variable results in other placental conditions and gestational age. Future studies

CONCLUSION

The LMWH use in otherwise healthy pregnant women between gestational ages of 28-34 weeks increases the average birthweight of IUGR infants. This further supports the notion that LMWH improves placental sufficiency through various mechanisms, thereby enhancing blood flow and increasing nutrient availability to the fetus, making it a suitable treatment option for IUGR pregnancies.

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