

## Pre-Eclampsia and Intrauterine Growth Restriction (IUGR) Prevention- Is Enoxaparin an Effective Option

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### ABSTRACT

**Objective:** To determine the effectiveness of Enoxaparin in preventing pre-eclampsia and intrauterine growth restriction in women with the history of pre-eclampsia and IUGR in an earlier pregnancy.

**Study Design:** Quasi-experimental study.

**Place and Duration of Study:** Department of Obstetrics and Gynaecology, Pak Emirates Military Hospital, Rawalpindi Pakistan, from Mar to Sep 2019.

**Methodology:** In this study, a total of 186 pregnant females of age 20-40 years with  $>6 \pm 0$  and  $<16 \pm 0$  weeks gestation were included. They were divided into two groups. In the study group, injection Enoxaparin 40 mg s/c OD was started from 6 weeks to 36 weeks of gestation along with Aspirin 75 mg OD. In the control group, only Aspirin 75mg OD was given. An antenatal check-up was performed, and patients were followed for liquor volume, fetal growth and doppler ultrasound. Study outcomes were noted in terms of pre-eclampsia and intrauterine growth restriction.

**Results:** The majority of the patients 100 (53.76%), were between 20-30 years of age. The mean gravidity in the study group was  $3.84 \pm 1.20$  and in the control group was  $3.83 \pm 1.22$ . In this study, pre-eclampsia was found in 6 (6.45%) patients in the Enoxaparin group and in 17 (18.28%) patients of control group ( $p$ -value 0.014). Intrauterine growth restriction was observed in 9 (9.68%) patients of Enoxaparin group and in 28 (30.11%) patients of control group ( $p$ -value 0.001).

**Conclusion:** This study concluded that Enoxaparin effectively prevents pre-eclampsia and intrauterine growth restriction in patients with a previous history the history of pre-eclampsia and IUGR in an earlier pregnancy.

**Keywords:** Enoxaparin, Intrauterine growth restriction (IUGR), Pre-eclampsia.

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### INTRODUCTION

The commonest cause of morbidity and mortality in a pregnant women is pre-eclampsia.<sup>1</sup> 3-5% pregnancies are complicated by pre-eclampsia, and the perinatal outcome is sturdily affected by the severity of hypertension.<sup>2</sup> Severe pre-eclampsia is related to diverse degrees of fetal damage. The key influence on the fetus is under-nutrition due to vascular insufficiency between the uterus and placenta, which results in growth retardation. The direct influence is altered fetal growth, ensuing greater fetal liability. Fetal health and weight are negatively influenced, causing several degrees of fetal morbidity. This fetal impairment may be severe enough to cause fetal death.

In 2011, Gris *et al.*<sup>3</sup> reported that Enoxaparin administered early during the second pregnancy helped decrease the incidence of placental vascular complications in women with a history of past severe pre-eclampsia.

Enoxaparin was innocuous without significant side effects like thrombocytopenia or substantial bleeding event. While Haddad *et al.*<sup>4</sup> reported that antepartum prophylactic enoxaparin did not extensively reduce placenta-mediated complications in females receiving aspirin (low-dose) for past severe pre-eclampsia (PE in 18% patients in the Enoxaparin group versus 22.1% in the control group and IUGR in 12.3% in Enoxaparin group versus in 19% in the control group). Similarly, Hoorn *et al.*<sup>5</sup> reported that combined LMWH and Aspirin treatment did not show a decrease in onset of frequent hypertensive disorders in patients with anti-phospholipid antibodies. Likewise, Groom *et al.*<sup>6</sup> also reported no additional benefit for adding Enoxaparin in preventing pre-eclampsia and IUGR.

As there is still an ongoing debate whether the use of LMWH is beneficial for preventing pre-eclampsia and IUGR or not, the present study was aimed to determine the effectiveness of Enoxaparin for the prevention of pre-eclampsia IUGR in patients with a previous history.<sup>7,8</sup> The results of this study will help us to use Enoxaparin in future or not. Because Enoxaparin is

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a costly drug, if it does not provide any additional benefit, there is no need to continue its use in the patients.

**METHODOLOGY**

This was a quasi-experimental study conducted at the Department of Gynaecology and Obstetrics, Pak Emirates Military Hospital (PEMH) Rawalpindi, from March to September 2019) after approval by the Ethical Review Committee, PEMH Rawalpindi (ERB ltr dated 7/6/2017). A total of 186 cases were included in this study.

**Inclusion Criteria:** Pregnant women aged 20-40 years with a viable singleton pregnancy, gestational age of >6 ± 0 and <16 ± 0 weeks with a past obstetric history of pre-eclampsia and IUGR were included in this study.

**Exclusion Criteria:** Pregnant women who had any contraindication to LMWH use such as previous thrombosis, previous successful pregnancy with LMWH, known pre-existing type 1 or 2 diabetes or renal disease (with serum creatinine >150), thrombocytopenia (platelet count <80 × 10<sup>9</sup>/L) prior to randomization or a known major fetal anomaly/chromosomal abnormality were excluded from this study.

Non-probability consecutive sampling technique was used for data collection. The sample size was calculated by taking 80% power of the study and frequency of pre-eclampsia in Enoxaparin group as 5.8% and in the control group as 16.8%.<sup>2</sup> These patients were divided into two equal groups (study and control groups). In the study group, injection Enoxaparin (LMWH) 40 mg s/c was started from 6-36 weeks of gestation along with Aspirin 75 mg orally, while in the control group, only Aspirin 75 mg was given orally. Informed consent was taken from all the patients prior to inclusion in the study.

Patients visiting obstetric OPD of the hospital were assessed for eligibility criteria, and those fulfilling the criteria were considered. Demographic data were collected, detailed history was taken, and obstetrics examination was performed. Antenatal check-ups were performed, and patients were followed for liquor volume, fetal growth and Doppler ultrasound. Study outcomes were noted in terms of pre-eclampsia and IUGR.

Statistical Package for Social Sciences (SPSS) version 20 was used for the data analysis. Descriptive statistics such as mean and standard deviation were calculated for numerical variables like patient age, parity and gravidity. Frequency and percentages were

computed for previous history (pre-eclampsia and IUGR) and perinatal outcomes (pre-eclampsia, IUGR). The Chi-square test was applied to compare perinatal outcomes between the study and control groups and the *p*-value of ≤0.05 was taken as significant.

**RESULTS**

The mean age of patients in the study group was 29.11 ± 4.42 years and in the control group was 28.83 ± 4.41 years. The majority of the patients 100 (53.76%) were between 20-30 years of age. The mean gravidity in the study group was 3.84 ± 1.20 and in the control group was 3.83 ± 1.22. The mean parity in the study group was 2.43 ± 0.96 and in the control group was 2.43 ± 0.98. The distribution of patients according to the previous history of pre-eclampsia & IUGR in both groups was shown in Table-I.

**Table-I: Distribution of patients according to previous history of pre-eclampsia and Intra-uterine growth restriction (IUGR) in both groups.**

Previous History	Study Group (n=93)		Control Group (n=93)	
	No (Patients)	Age %	No (Patients)	Age%
Preeclampsia	Yes	43 46.24	40	43.01
	No	50 53.76	53	56.99
Intrauterine Growth Restriction	Yes	54 58.6	55	59.14
	No	39 41.94	38	40.86

In this study, pre-eclampsia was found in 6 (6.45%) patients of Enoxaparin group and 17 (18.28%) of the control group. IUGR was observed 9 (9.68%) of the Enoxaparin group and in 28 (30.11%) of the control group as shown in Table-II. This difference was statistically significant with the *p*-value of <0.05.

**Table-II: Comparison of pre-eclampsia and Intrauterine growth restriction (IUGR) in women with history of pre-eclampsia and IUGR in previous pregnancy.**

Outcome		Study group (n=93)	Control group (n=93)	<i>p</i> -value
Pre-eclampsia	Yes	06 (6.45%)	17 (18.28%)	0.014
	No	87 (93.55%)	76 (81.72%)	
IUGR	Yes	09 (9.68%)	28 (30.11%)	0.001
	No	84 (90.32%)	65 (69.89%)	

**DISCUSSION**

We conducted this study to determine the efficacy of Enoxaparin in preventing pre-eclampsia and IUGR in females with a history of PE and IUGR in the previous pregnancy. We noted PE in 6.45% patients in the Enoxaparin group and 18.28% in the control group, while IUGR was observed in 9.68% of the Enoxaparin

group and 30.11% patients of the control group. LMWH has arisen as a prospective treatment possibility in averting high-risk pregnant females from developing these complications related to the placenta. Numerous RCTs were performed to evaluate the usefulness of LMWH in pre-eclampsia and other placenta mediated disorders' prevention.<sup>9-12</sup> These clinical experiments have diverse results in the use of LMWH.<sup>13,14</sup> Some have described the decreased incidence of pre-eclampsia and newborn weight <5<sup>th</sup> percentile, FGR, major placental abruption or fetal loss after 20 weeks gestation, while others have established no treatment effect. The inferences of systematic reviews and meta analyses are inconsistent and contradictory.<sup>15</sup>

A systemic review based on eight RCTs, Roberge *et al*, concluded that a combination of LMWH and Aspirin (low dose) decreased the prevalence of PE and in small-for-gestational-age (SGA) neonates in the females with a history of PE.<sup>8</sup> Likewise, in a study conducted by Rey *et al*, Dalteparin was found to produce a lesser percentage of pre-eclampsia (severe), low birth weight babies and abruption placentae (major) in comparison with no Dalteparin in females with a positive history in the previous pregnancies.<sup>9</sup>

Similarly, Gris *et al*, conducted a study on pregnant females with a history of abruptio placentae preceding pregnancy. They reported that in these females, Enoxaparin initiated in the early part of pregnancy was linked with a lesser rate of pre-eclampsia, abruptio placentae, low birth weight babies, and loss of foetus (post 20 weeks) in contrast to no Enoxaparin.<sup>10</sup> In another study researchers evaluated the influence of Enoxaparin in females who experienced severe pre-eclampsia in their previous pregnancy. It considerably diminished pre-eclampsia, abruptio placentae, low birth weight babies, and loss of foetus (post 20 weeks) compared to the group that received no Enoxaparin.<sup>3</sup>

The systematic reviews by Dodd *et al*,<sup>15</sup> and Rodger *et al*,<sup>16</sup> established that Heparin in high-risk females substantially diminished the relapse of pre-eclampsia and was related to the noteworthy decline in preterm birth and perinatal mortality and low birth weight infants (<10<sup>th</sup> percentile for gestational age). The dosage of LMWH revealed a superior safety profile. There were no significant adverse features like foremost bleeding incidents. Though these researches were centred on pretty small and non-homogenous trials, their deductions show that conducting a strong multi-centred study is required to measure the efficacy

of LMWH in dropping the relapsing frequency of severe pre-eclampsia.

Contrary to the studies mentioned above, many researchers have documented different results highlighting no significant benefit. In 2017, RCT conducted over three countries by Groom *et al*, reported that Enoxaparin usage with standard high-risk care did not decrease the danger of recurring PE and SGA infants following pregnancy.<sup>17</sup> Likewise, Roger *et al*, in 2016, conducted a meta analysis from eight RCTs and determined that LMWH did not lessen the threat of recurring placenta-related pregnancy complications, in comparison with no LMWH.<sup>18</sup> In 2014, Thrombophilia in Pregnancy Prophylaxis Study (TIPPS), conducted by the same group Roger *et al*,<sup>19</sup> it was documented that the antepartum prophylactic Dalteparin did not decrease the manifestation of venous thromboembolism phenomenon, loss of pregnancy, or placenta-mediated pregnancy complications with thrombophilia at high risk of these complications and was connected with an augmented risk of minor bleeding. The decisive deductions on the capacity of LMWH to avert early pre-eclampsia in females of the high-risk group are impeded by the variety of the inclusion criteria of the TIPPS trial despite the size of the study. A similar study exhibited no management effect with Nadroparin in preventing pregnancy complications, including eclampsia, pre-eclampsia, abruptio placentae, IUGR, intrauterine death and HELLP syndrome.<sup>20</sup>

In 2020 Llurba *et al*,<sup>21</sup> conducted a multicenter RCT comparing the group receiving LMWH with the control regarding placenta-mediated complications like pre-eclampsia, IUGR, abruptio placentae and intrauterine fetal loss. They found no noteworthy differences between the two arms and concluded that the recommendation of the use of LMWH alone in females in danger of placenta related complications could not be made. In another large multicenter RCT (SPIN-Scottish Pregnancy Intervention), it was established that in females with repeated miscarriages, the use of LMWH did not produce beneficial clinical results.<sup>22</sup> Likewise, Pasquier *et al*,<sup>23</sup> and Kaandorp *et al*,<sup>24</sup> concluded that LMWH did not avert early pregnancy damage. Therefore, the opinion of many researchers remains divided. We concluded that Enoxaparin effectively prevents PE and IUGR in patients with a previous history. Therefore, we recommend that enoxaparin be used routinely in every woman with a previous history of PE and IUGR to prevent and improve the fetomaternal outcome.

**CONCLUSION**

This study concluded that Enoxaparin effectively prevents pre-eclampsia and intrauterine growth restriction in patients with a previous history the history of pre-eclampsia and IUGR in an earlier pregnancy.

**Conflict of Interest:** None.

**Authors' Contribution**

SS: Conception design final approval, SB: Collection of data data analysis & interpretation, drafting of article, BM: Drafting of article.

**REFERENCES**

1. Rodger MA, Langlois NJ, de Vries JI, Rey É, Gris JC, Martinelli I, et al. Low- molecular-weight heparin for prevention of placenta-mediated pregnancy complications: protocol for a systematic review and individual patient data meta- analysis (AFFIRM). *Syst Rev* 2014; 3(1): 69.
2. Duffett L, Rodger M. LMWH to prevent placenta-mediated pregnancy complications: an update. *Brit J Haematol* 2015; 168(5): 619-638.
3. Gris JC, Chauleur C, Molinari N, Mares P, Fabbro-peray P, Quere I, et al. Addition of enoxaparin to aspirin for secondary prevention of placental vascular complications in women with severe pre-eclampsia. *Thromb Haemost* 2011; 105(6): 1053-1062.
4. Haddad B, Winer N, Chitrit Y, Houfflin-Debarge V, Chauleur C, Bages K, et al. Enoxaparin and aspirin compared with aspirin alone to prevent placenta-mediated pregnancy complications: a randomized controlled trial. *Heparin-preeclampsia (HEPEPE) trial investigators. Obstet Gynecol* 2016; 128(5): 1053-1063.
5. Van Hoorn ME, Hague WM, van Pampus MG, Bezemer D, de Vries JI. Low molecular weight heparin and aspirin in the prevention of recurrent early onset pre-eclampsia in women with antiphospholipid antibodies: the FRUIT-RCT. *Eur J Obstet Gynecol Reprod Biol* 2016; 197(1): 168-173.
6. Groom KM, McCowan LM, Stone PR, Chamley LC, McLintock C. Enoxaparin for the prevention of preeclampsia and intra-uterine growth restriction in women with a prior history—an open-label randomised trial (the EPPI trial): study protocol. *BMC Pregnancy and Childbirth* 2016; 16(1): 367.
7. Kutteh WH. Antiphospholipid antibody-associated recurrent pregnancy loss: treatment with heparin and low-dose aspirin is superior to low-dose aspirin alone. *Am J Obstet Gynecol* 1996; 174(5): 1584-1589.
8. Roberge S, Demers S, Nicolaides KH, Bureau M, Cote S, Bujold E. Prevention of pre-eclampsia by low molecular weight heparin in addition to aspirin: a meta-analysis. *Ultrasound Obstet Gynecol* 2016; 47(5): 548-553.
9. Rey E, Garneau P, David M, Gauthier R, Leduc L, Michon N, et al. Dalteparin for the prevention of recurrence of placental-mediated complications of pregnancy in women without thrombophilia: a pilot randomized controlled trial. *J Thromb Haemost* 2009; 7(1): 58-64.
10. Gris JC, Chauleur C, Faillie JL, Baer G, Mares P. Enoxaparin for the secondary prevention of placental vascular complications in women with abruptio placentae. The pilot randomised controlled NOH-AP trial. *Thromb Haemost* 2010; 104(1): 771-779.
11. Wang X, Gao H. Prevention of preeclampsia in high-risk patients with low-molecular-weight heparin: a meta-analysis. *J Matern Fetal Neonatal Med* 2020; 33(13): 2202-2208.
12. McLaughlin K, Baczyk D, Potts A, Hladunewich M, Parker JD, Kingdom JC. Low molecular weight heparin improves endothelial function in pregnant women at high risk of preeclampsia. *Hypertension* 2017; 69(1): 180-188.
13. Rahnamaei FA, Fashami MA, Abdi F, Abbasi M. Factors effective in the prevention of preeclampsia: A systematic review. *Taiwanese J Obstet Gynecol* 2020; 59(2): 173-182.
14. Kupferminc M, Rimon E, Many A, Maslovitz S, Lessing JB, Gamzu R. Low molecular weight heparin versus no treatment in women with previous severe pregnancy complications and placental findings without thrombophilia. *Blood Coagul Fibrinol* 2011; 22(1): 123-126.
15. Dodd JM, McLeod A, Windrim RC, Kingdom J. Antithrombotic therapy for improving maternal or infant health outcomes in women considered at risk of placental dysfunction. *Cochrane Database Syst Rev* 2013; 7(1): CD006780.
16. Rodger MA, Carrier M, Le Gal G, Martinelli I, Perna A, Rey E, et al. Low-molecular-weight heparin for placenta-mediated pregnancy complications study group. meta-analysis of low-molecular-weight heparin to prevent recurrent placenta-mediated pregnancy complications. *Blood* 2014; 123(1): 822-828.
17. Groom KM, McCowan LM, Mackay LK, Lee AC, Said JM, Kane SC, et al. Enoxaparin for prevention of preeclampsia and intra-uterine growth restriction trial investigator group. enoxaparin for the prevention of preeclampsia and intrauterine growth restriction in women with a history: a randomized trial. *Am J Obstet Gynecol* 2017; 216(3): 296.
18. Rodger MA, Gris JC, de Vries JI, Martinelli I, Rey E, Schleussner E, et al Low-molecular weight heparin and recurrent placenta mediated pregnancy complications: a meta analysis of individual patient data from randomised controlled trials. *Lancet* 2016; 388(2): 2629-2641.
19. Rodger MA, Hague WM, Kingdom J, Kahn SR, Karovitch A, Sermer M, et al Antepartum dalteparin versus no antepartum dalteparin for the prevention of pregnancy complications in pregnant women with thrombophilia (TIPPS): a multinational open-label randomised trial. *Lancet (London, England)* 2014; 384(2): 1673-1683.
20. Martinelli I, Ruggerenti P, Cetin I, Pardi G, Perna A, Vergani P, et al, HAPPY Study Group. Heparin in pregnant women with previous placenta-mediated pregnancy complications: a prospective, randomized, multicenter, controlled clinical trial. *Blood* 2012; 119(14): 3269-3275.
21. Llorba E, Bella M, Burgos J, Mazarico E, Gómez-Roig MD, De Diego R, et al. Early prophylactic enoxaparin for the prevention of preeclampsia and intrauterine growth restriction: a randomized trial. *Fetal Diagn Ther* 2020; 47(11): 824-833.
22. Clark P, Walker ID, Langhorne P, Crichton L, Thomson A, Greaves M, et al. Scottish pregnancy intervention study (spin) collaborators. SPIN (Scottish pregnancy intervention) study: a multicenter, randomized controlled trial of low- molecular-weight heparin and low-dose aspirin in women with recurrent miscarriage. *Blood* 2010; 115(1): 4162-4167.
23. Pasquier E, de Saint Martin L, Bohec C, Chauleur C, Bretelle F, Marhic G, et al. Enoxaparin for prevention of unexplained recurrent miscarriage: a multicenter randomized double-blind placebo-controlled trial. *Blood* 2015; 125(1): 2200-2205.
24. Kaandorp SP, Goddijn M, van der Post JA, Hutten BA, Verhoeve HR, Hamulyák K, et al. Aspirin plus heparin or aspirin alone in women with recurrent miscarriage. *N Engl J Med* 2010; 362(2): 1586-1596.