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# Comparative Study between the Effect of Low Molecular Weight Heparin and Sildenafil Citrate on Intrauterine Growth Restriction

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## ABSTRACT

**Background:** Fetal growth restriction (FGR) is defined as when fetal weight below the 10th percentile for gestational age or two Standard Deviation below the mean weight for gestational age.

**Aim:** To assess the impacts of low-molecular-weight heparin (LMWH) and sildenafil citrate on the flow of blood through the placenta, which affects the growth and well-being of the fetus in utero.

**Methods:** Fifty females with placentally mediated FGR were included in this randomized comparative clinical research, which was conducted between twenty-eight and thirty-five weeks of gestation. Randomly, they have been categorized into 2 groups: Group: Sildenafil (SC) Involved 25 women received Sildenafil 25 milligrams every eight hours (Silden® EIPICO Co.). Also, the LMWH group: involved 25 women who received a single daily dosage of LMWH (tinzaparin) (Innohep® LEO pharmaceutical products) subcutaneously starting at the diagnosis of fetal growth restriction until delivery at Damanhur Medical National Institute between January 2022 and January 2023.

**Results:** A statistically significant variance was observed within the examined groups according to improvement of umbilical artery PI, umbilical artery resistive index, APGAR 1, APGAR 5, birth weight (BW), prematurity, intraventricular hemorrhage, maternal headache, and maternal flushing. No significant difference was observed within the examined groups regarding assessed fetal weight, gestational age, amniotic fluid index, and abdominal circumference during diagnosis.

**Conclusion:** LMWH in fetal growth-restricted pregnancies significantly increases neonatal body weight, prolongs gestational age at delivery from randomization to delivery, and enhances fetoplacental blood flow, resulting in fewer maternal and neonatal complications.

**Keywords**: SC, FGR, LMWH.

## INTRODUCTION

Fetal growth restriction is described as when infant's weight < the 10$^{th}$ percentile of its gestational age or two Standard Deviation under the mean weight for gestational age. Tenth percentile is the weight below which lie 10% of the population at this gestational age [(1)]. Fetal growth restriction is prevalent globally, accounting for fifty to sixty percent of neonates with low birth weight. Serious obstetric complications like fetal loss, preeclampsia, and FGR are caused by placental dysfunction [(2)].

FGR complications during pregnancy can cause fetal health deterioration, necessitating a focus on underlying pathologic causes. Birth timing is crucial for balancing preterm risks against fetal mortality and organ damage. Current therapeutic interventions do not change the FGR course, but targeting faulty trophoblastic invasion into spiral arteries is the most successful [(3)].

(LMWH) may be able to decrease trophoblast apoptosis by modulating anti-apoptotic B-cell lymphoma family members, according to in vitro experiments [(4)]. Furthermore, it improves the activities of heparin-binding epidermal growth factor and matrix metalloprotease-2, as well as the cysteine-rich angiogenic inducer 61. Thus, improving the invasiveness of extravillous trophoblasts [(5)]. Additionally, as compared to gestation-matched controls who didn't receive low molecular weight heparin, in vivo usage of the drug during pregnancy had a beneficial impact on indicators of angiogenesis with a reduced soluble fms-like tyrosine kinase-1/placental growth factor (sFlt-1/PlGF) ratio and a higher concentration of placental growth factor (PlGF) in serum [(6)].

In growth-restricted ovine models, sildenafil citrate, a phosphodiesterase inhibitor, was demonstrated to rise amino acid availability and improve uterine blood flow. However, in STRIDER investigations in Australia, the UK, and New Zealand, conflicting findings have been reported, indicating that sildenafil doesn't improve pregnancy results or prolong pregnancy in severe early-onset FGR patients [(7)].

This investigation has been conducted to compare the effects of Sildenafil citrate, the most commonly prescribed therapy for FGR, against low-molecular-weight heparin. LMWH has the potential to theoretically reverse various pathological mechanisms of fetal growth restriction on placental bed blood flow, resulting in alterations in wellbeing and fetal growth in utero.

## METHODS

This randomized comparative clinical study was conducted between twenty-eight and thirty-five weeks of



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gestation, and 50 females were diagnosed with placentally mediated FGR.

At random, they have been divided into two groups: Sildenafil (SC) group: involved 25 females received Sildenafil citrate 25 milligrams every eight hr. (Silden® EIPICO Co.) and LMWH group: involved from the time that fetal growth restriction was diagnosed until delivery, 25 females were given a single daily dose of LMWH (tinzaparin) (Innohep® LEO pharmaceutical products). The doses were 20 mg for women < 50 kg, 40 milligrams for women 50 to 90 kg, and 60 milligrams for women > 90 kg [(8)].

**Method of Randomization**

A list of random numbers that had been generated by a computer was used for randomization. A statistician randomly assigned individuals to the groups who were not involved in therapy or data collection. The opaque envelopes contained the final group assignment, with only primary investigators allowed to open them according to the women's attendance order.

This study was carried out at the Damanhur Medical National Institute between January 2022 and January 2023.

**Inclusion criteria:** Study participants were females between the ages of twenty and thirty-five years who were carrying singletons and had documented placentally mediated FGR (fetal abdominal circumference and estimated fetal weight (EFW) at or below the tenth percentile), abnormal Doppler investigations, or decreased liquor volume between twenty-eight weeks and zero days' gestation and thirty-five weeks and zero days' gestation, as confirmed by 1st-trimester ultrasound.

**Exclusion criteria:** include women who are pregnant and have suspected or known chromosomal, structural, or immediate delivery conditions; congenital infections; chronic hypertension; contraindications to sildenafil or low molecular weight heparin; cocaine use in the past month; low aspirin or anticoagulant use; thyroid disease; asthma; severe chronic anemia; chronic pulmonary disease; cyanotic congenital heart disease; sickle cell disease; inflammatory bowel disease; diabetes with vascular affection; depression; systemic lupus erythematosus; moderate to severe renal impairment; and antiphospholipid syndrome.

**Methods of randomization:** A 1:1 ratio of resources was allocated to two groups, with a list of random numbers that had been generated by a computer used for randomization. A statistician randomly assigned individuals to the groups who were not involved in therapy or data collection. The opaque envelopes contained the final group assignment, with only primary investigators allowed to open them according to the women's attendance order.

**Sample size:**

The sample size has been calculated utilzing G* power software version (3.1.9.2) and depending on earlier researches done by **Rasheedy and El Bishry** [(9)] So, with Fisher's exact test (with regard to (A priori: Compute required sample size - given α, power and effect size), α error= 0.05, power (1- β) = 0.80 generated sample size of at least 45 subjects. Adding 5 subjects (10% as drop out), so total sample size is 50 subjects divided into 25 in each group of the two groups: **Group A (LMWH):** 25 patients and **group B (Sildenafil):** 25patients.

**METHODS**

**All females have been subjected to:** history-taking to determine smoking and caffeine consumption, prior placental-mediated disease, interpregnancy interval, and attendance at antenatal visits; measurement of the symphysis-fundal height and general abdominal examination; gestational age (GA); ultrasound assessment of fetal biometry, excluding fetal abnormalities; evaluation of amniotic fluid and Doppler velocimetry;

**Following recruitment,** standard clinical monitoring on the mother and fetus, depending on the degree of growth restriction, by a sonographer that was unaware of the course of therapy. This monitoring included umbilical artery (UA) Doppler, velocimetry of the uterine arteries (Ut A), ductus venosus (DV), and middle cerebral (MCA) arteries. EFW was established by femur length (Hadlock-84), head circumference, abdominal circumference, and fetal biparietal diameter. Fetal well-being testing was conducted utilizing the amniotic fluid index (AFI), that reports decreased liquor if ≤ five centimeters. The nonstress test (NST) and biophysical profile (BPP) were also conducted. In the same vein, the conventional clinical approach was utilized to determine the subsequent delivery time [(10)].

**When the UAD flow indices were normal**, surveillance has been conducted every seven days. It involved MCA Doppler, UA Doppler (UAD), and ultrasound for (EFW, AC, and AFI), NST, and BPP two times per week. Delivery was proposed at thirty-seven weeks if there was no additional fetal compromise or at thirty-four weeks if there had been 3 weeks of stable growth.

**When end-diastolic velocities are present but decreased and UAD flow indices are abnormal** (pulsatility or resistive index >+2 SDs above mean for GA), surveillance was repeated twice weekly using UAD, MCA Doppler, weekly ultrasound for (AC, EFW, and AFI), NST, and BPP, and delivery was considered at thirty-seven weeks if there is no more fetal compromise, or at thirty-four weeks if stagnant growth for three weeks. **The surveillance has been conducted daily using the NST UAD, MCA Doppler, BPP, and DV Doppler.** In the event that the UAD revealed absent or reversed end-

diastolic frequencies prior to 32 weeks, a weekly ultrasound for AC, EFW, and AFI has been required. If there was additional fetal compromise (abnormal venous Doppler or NST) or at thirty-two weeks following steroids were administered to ensure lung maturity, the decision to deliver was made.

**A pulsatility index (PI)**: In order to define abnormal UA Doppler, abnormal DV Doppler, the 95$^{th}$ centile, or absent/reversed end-diastolic flow, the PI has been applied in the cases of abnormal uterine artery Doppler (defined as a PI > 95$^{th}$ centile) and abnormal MCA Doppler (defined as a PI less than fifth centile) [(10)]. The cerebroplacental ratio (CPR), that is a ratio of the PI of MCA to UA, was determined to be abnormal if it was less than 1.08 [(11)].

**Outcomes**:

**Primary outcome:** weight at birth for newborns. Neonatal outcomes encompassed neonatal necrotizing enterocolitis, intraventricular hemorrhage (IVH), respiratory distress syndrome (RDS), APGAR scores at one and five minutes, and neonatal anemia.

**Secondary outcomes:** involving growth velocity, time from randomization to delivery, GA at delivery, changes in PI of fetal MCA, CPR, and UA, UT A, one week following therapy, neonatal and fetal deaths.

**Ethical approval**

**The GOTHI research center's Ethics Committee confirmed the research protocol. The cases or their legal representatives obtained written, informed consent. Before enrollment, the lead investigator fully explained the study to potentially eligible women, including its advantages, drawbacks, and potential consequences. A formal informed consent was then obtained.** ***All women provided informed consent themselves.***

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**RESULTS**

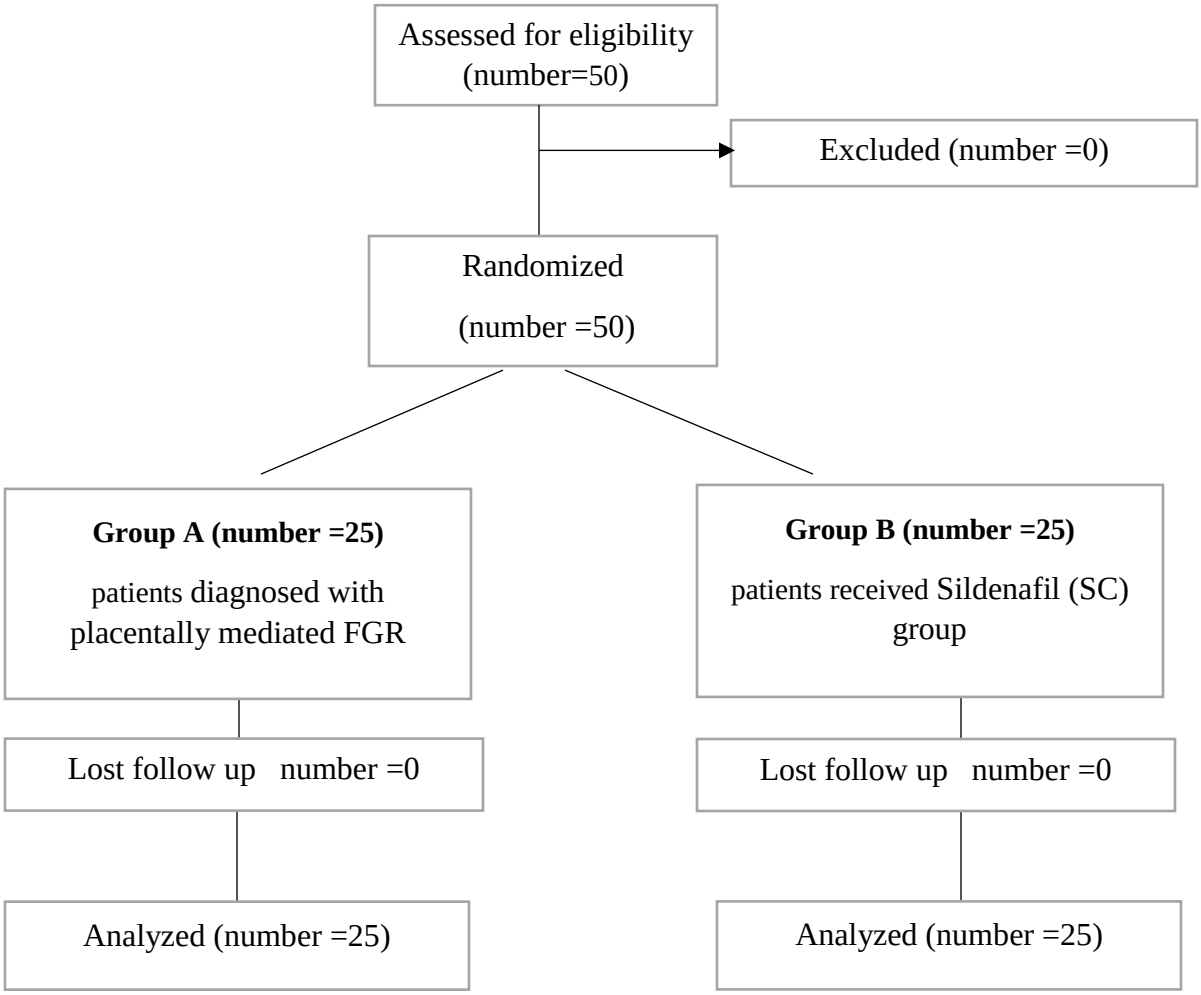


**Figure (1): Flow Chart**

There has been a statistically insignificant difference within the examined groups regarding BMI, age, weight, parity, interpregnancy interval, previous placental-mediated diseases, pregnancy by in vitro fertilization, regular antenatal care, caffeine intake >200 mg/day and smoking **(Table 1).**

**Table 1: Demographic and basic clinical data between the examined groups**

| **Variables** | | **LMWH (N = 25)** | | **Sildenafil (N = 25)** | **P-value** |
|---|---|---|---|---|---|
| Age (years) | Mean ± standard deviation | **27.6 ± 2.6** | | 28.7 ± 2.7 | 0.1* |
| Weight (kilogram) | Mean ± standard deviation | **73.7 ± 6.1** | | 72.9 ± 4.3 | 0.237* |
| BMI (kg/m²) | Mean ± standard deviation | **26.7 ± 0.1** | | 26.4 ± 2.0 | 0.159* |
| Parity (N, %) | Primigravida | **7 (28.0%)** | | 9 (36.0%) | 0.54# |
| | Multigravida | **18 (72.0%)** | | 16 (64.0%) | |
| Interpregnancy interval (months) | Mean ± standard deviation | **16.3 ± 5.7** | | 16.7 ± 3.4 | 0.7* |
| Prior placental-mediated diseases | Fetal growth restriction | **4 (16.0%)** | | 5 (20.0%) | 0.71# |
| | Previous intrauterine fetal death | **3 (12.0%)** | | 2 (8.0%) | 0.63# |
| | Preeclampsia | **3 (12.0%)** | | 1 (4.0%) | 0.29# |
| | Unexplained antepartum hemorrhage | **2 (8.0%)** | | 1 (4.0%) | 0.55# |
| Pregnancy by in vitro fertilization | | **0 (0.0%)** | | 1 (4.0%) | 0.31$ |
| Regular antenatal care | | **5 (20.0%)** | | 7 (28.0%) | 0.5# |
| Caffeine intake >200 mg/day | | **14 (56.0%)** | | 12 (48.0%) | 0.57# |
| Smoking | **None** | **21 (84.0%)** | | 20 (80.0%) | 0.71# |
| | **Secondhand smoke exposure** | **5 (20.0%)** | | 6 (24.0%) | 0.73# |
| | **Active** | **1 (4.0%)** | | 2 (8.0%) | 0.55$ |

*: **Independent samples t-test**
**#: Chi-square test**
**$ = Fisher's exact test**

There has been a statistically insignificant difference between the examined groups according to EFW, AFI, gestational age, and abdominal circumference during diagnosis. While there has been a statistically significant difference according to gestational age, EFW, AFI, and abdominal circumference at delivery time, there has been a significant elevation in EFW, AFI, gestational age, and abdominal circumference throughout follow-up in the low molecular weight heparin group and in EFW, AFI and gestational age, within the sildenafil group **(Table 2).**

**Table 2: Basic ultrasound alterations between the examined groups**

| Parameter | | LMWH (N=25) | Sildenafil (N=25) | P value(between groups) |
|---|---|---|---|---|
| **Estimated fetal weight (g)** | At the time of diagnosis | 1260.2 ± 250 | 1245.1 ± 230.4 | 0.82* |
| | At delivery time | 1630.7 ± 191 | 1429.2 ± 235 | <0.001* |
| | P value (pre vs post) | <0.001** | 0.007** | |
| **Gestational age (weeks)** | At the time of diagnosis | 30.8 ± 2.5 | 30.2 ± 1.5 | 0.30* |
| | At delivery time | 34.0 ± 1.0 | 32.2 ± 1.5 | <0.001* |
| | P value (pre vs post) | <0.001** | <0.001** | |
| **Abdominal circumference (cm)** | At the time of diagnosis | 24.9 ± 3.3 | 24.4 ± 3.1 | 0.58* |
| | At delivery time | 28.9 ± 2.5 | 25.7 ± 3.1 | <0.001* |
| | P value (pre vs post) | <0.001** | 0.14** | |
| **Amniotic fluid index (cm)** | At the time of diagnosis | 3.6 ± 1.5 | 3.8 ± 1.6 | 0.65* |
| | At delivery time | 6.1 ± 1.5 | 5.1 ± 1.7 | 0.03* |
| | P value (pre vs post) | <0.001** | 0.007** | |

*: **Independent samples t-test**

****: paired t-test (pre vs post within the same group)**

There has been a statistically significant *variance* between the examined groups regarding the enhancement of umbilical artery resistive index and umbilical artery PI **(Table 3).**

**Table 3: Changes in the Doppler indices are observed in the examined groups**

| Parameter | Changes | LMWH | Sildenafil | p-value |
|---|---|---|---|---|
| **Middle cerebral artery pulsatility index (PI)** | Improvement | 0 (0%) | 0 (0%) | - |
| | Deterioration | 0 (0%) | 0 (0%) | - |
| | No changes | 25 (100%) | 25 (100%) | - |
| **Umbilical artery PI** | Improvement | 12 (48%) | 5 (20%) | 0.03# |
| | Deterioration | 1 (4%) | 2 (8%) | 0.55# |
| | No changes | 12 (48%) | 18 (72%) | 0.08# |
| **Umbilical artery resistive index (RI)** | Improvement | 11 (44%) | 4 (16%) | 0.03# |
| | Deterioration | 0 (0%) | 1 (4%) | 0.31# |
| | No changes | 14 (56%) | 20 (80%) | 0.06# |
| **Absent/reversed end-diastolic blood flow in the umbilical artery** | Improvement | 2 (8%) | 1 (4%) | 0.55# |
| | Deterioration | 1 (4%) | 2 (8%) | 0.55# |
| | No changes | 22 (88%) | 22 (88%) | 1# |
| **Ductus venosus Doppler** | Improvement | 0 (0%) | 0 (0%) | - |
| | Deterioration | 1 (4%) | 2 (8%) | 0.55# |
| | No changes | 24 (96%) | 23 (92%) | 0.55# |
| **Cerebroplacental ratio** | Improvement | 2 (8%) | 1 (4%) | 0.55# |
| | Deterioration | 0 (0.0%) | 0 (0%) | - |
| | No changes | 23 (92%) | 24 (96%) | 0.55# |

**#: Chi-square test**

There has been a statistically significant *difference* between the examined groups regarding APGAR 1, APGAR 5, birth weight, prematurity, intraventricular hemorrhage, NICU admission, maternal headache, and maternal flushing **(Table 4).**

**Table 4: Maternal complications and Neonatal outcome between the examined groups**

| Variables | | LMWH (N = 25) | Sildenafil (N = 25) | P- value |
|---|---|---|---|---|
| **APGAR 1** | IQR | 5.2–7.2 | 3.5–5 | <0.001## |
| | Median | 6.1 | 4.1 | |
| **APGAR 5** | IQR | 5.6–7.5 | 2.5–4.2 | <0.001## |
| | Median | 6.1 | 3.1 | |
| **Birth weight (mean ± SD)** | | 1708± 360 | 1501 ± 220 | <0.001* |
| **Prematurity (n, %)** | | 19 (76.0%) | 24 (96.0%) | 0.04# |
| **Respiratory distress syndrome (n, %)** | | 2 (8.0%) | 5 (20.0%) | 0.138# |
| **Intraventricular hemorrhage (n, %)** | | 1 (4.0%) | 6 (24.0%) | 0.04# |
| **Necrotizing enterocolitis (n, %)** | | 2 (8.0%) | 3 (12.0%) | 0.63# |
| **Anemia (n, %)** | | 1 (4.0%) | 3 (12.0%) | 0.29# |
| **Blood transfusion (n, %)** | | 1 (4.0%) | 2 (8.0%) | 0.55# |
| **NICU admission (n, %)** | | 11 (44.0%) | 22 (88.0%) | <0.001# |
| **Hypoxic ischemic encephalopathy** | | 1 (4.0%) | 2 (8.0%) | 0.55# |
| **Persistent pulmonary hypertension** | | 2 (8.0%) | 3 (12.0%) | 0.63# |
| **Neonatal deaths** | | 1 (4.0%) | 2 (8.0%) | 0.55# |
| **Maternal headache** | | 1 (4.0%) | 7 (28.0%) | 0.02# |
| **Maternal flushing** | | 1 (4.0%) | 8 (32.0%) | 0.009# |
| **Maternal nasal congestion** | | 0 (0.0%) | 2 (8.0%) | 0.14# |
| **Maternal skin reactions and bruising** | | 2 (8.0%) | 0 (0.0%) | 0.14# |
| **Severe preeclampsia** | | 1 (4.0%) | 2 (8.0%) | 0.55# |

**##: Mann–Whitney U**
**#: Chi-square test**
*: **Independent samples t-test**

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## DISCUSSION

Regarding general and basic clinical characteristics between the examined groups, our outcomes showed that there has been a statistically insignificant difference between the examined groups regarding age, weight, BMI, parity, inter-pregnancy interval (months), previous placental-mediated diseases, pregnancy by in vitro fertilization, regular antenatal care, caffeine intake >200 mg/day, and smoking with a p value <0.05.

In accordance with our outcomes, **Mousa *et al.*** [12] who aimed to establish the impact of SC on the umbilical artery Doppler and the uterine artery Doppler for the purpose of enhancing the neonatal result in high-risk pregnant cases, the investigation was performed on ninety cases, which have been categorized into two groups: group A (Sildenafil group) and group B (Heparin group). and they presented that there has been a statistically insignificant difference between the examined groups regarding maternal age, parity, and previous placental-mediated diseases, with a p value > 0.05.

Concerning the basic ultrasound changes between the studied groups, our findings demonstrated that there has been a statistically insignificant variance within the examined groups at the time of diagnosis with regard to estimated fetal weight, gestational age, abdominal circumference, and amniotic fluid index, while a highly statistically significant variance was observed within the examined groups at delivery time with regard to estimated fetal weight, gestational age, and abdominal circumference.

In accordance with our results, **Mousa *et al.*** [12] revealed that there has been a statistically insignificant variance among the examined groups with regard to gestational age, with a p value equal to 0.12, whereas there has been a greatly statistically significant variance within the examined groups regarding estimated fetal weight at delivery, with a p value =0.001 and there has been a statistically insignificant variance within the

examined groups at the time of diagnosis with regard to EFW.

Also, according to **Von Dadelszen *et al.*** [13] the main indicator used to evaluate the efficacy of sildenafil on fetal growth measurements was fetal weight (EFW). The distinction between the 2 groups was a greatly statistically significant difference with regard to EFW.

As well, we agreed with **Rasheedy *et al.*** [9] who found that there had been a statistically insignificant variance within the examined groups at the time of diagnosis with regard to EFW, AFI, gestational age, and abdominal circumference, while there had been a greatly statistically significant variance within the examined groups at delivery time regarding estimated fetal weight, gestational age, and abdominal circumference.

Regarding to Doppler indices changes between the examined groups, our outcomes found that there has been statistical significant difference between examined groups in several cases indicating an enhancement in other Doppler indices as regard umbilical artery PI, umbilical artery resistive index (RI) while there has been statistical significant variance within the examined groups in the number of cases reporting a deterioration and no changes in other Doppler indices as regard umbilical artery PI, umbilical artery resistive index (RI) and there has been statistically insignificant difference between examined groups according to absent/reversed end-diastolic blood flow in the umbilical artery, cerebroplacental ratio and ductus venosus Doppler.

Also, agreed with **Miller *et al.*** [14] who illustrated that sildenafil decreased uterine blood flow, which correlated with a significant deterioration in fetal health.

Similarly, in accordance with **Rasheedy *et al.*** [9] found a statistically significant variance within the examined groups in several patients reporting an enhancement in other Doppler indices as regard umbilical artery PI, umbilical artery resistive index (RI), while there has been statistical significant difference between examined groups in the number of patients reporting a deterioration and no changes in other Doppler indices according to umbilical artery PI and umbilical artery resistive index (RI), and a statistically insignificant difference was observed within the examined groups regarding absent or reversed end-diastolic blood flow in the umbilical artery, cerebroplacental ratio, and ductus venosus Doppler.

Concerning maternal complications and neonatal outcomes between the examined groups, our outcomes showed that LMWH group achieved significantly better results, including higher APGAR scores at one and five minutes, increased birth weight, and fewer NICU admissions. Importantly, NICU admission rates were 88% in the sildenafil group versus 44% in the LMWH group, a striking difference that highlights the clinical relevance of LMWH in improving neonatal prognosis. Rates of prematurity and intraventricular hemorrhage were also significantly lower in the LMWH group ($p = 0.04$ for each). Although maternal bruising and skin reactions occurred slightly more frequently in the LMWH group (8%), sildenafil was associated with significantly higher rates of maternal headache ($p = 0.02$) and flushing ($p = 0.009$). No significant variances have been observed regarding respiratory distress syndrome, neonatal deaths, hypoxic ischemic encephalopathy, necrotizing enterocolitis, anemia, persistent pulmonary hypertension, severe preeclampsia, or blood transfusion requirements.

Similarly, agreed with **Rasheedy *et al.*** [9] found that LMWH group achieved significantly better results, including higher APGAR 1, APGAR 5, increased birth weight, and fewer NICU admissions, although a statistically significant variance was observed within the studied groups as regard prematurity, intraventricular hemorrhage, maternal headache, and maternal flushing. There have been statistically insignificant differences between the examined groups regarding respiratory distress syndrome, anemia, necrotizing enterocolitis, hypoxic ischemic encephalopathy, persistent pulmonary hypertension, blood transfusion, neonatal deaths, maternal skin reactions, bruising, maternal nasal congestion, and severe preeclampsia.

Moreover, these results consistent with STRIDER UK and NZAus trials that didn't illustrate proof of harm to the neonate; as well as there was no correlation of sildenafil with PPH of the newborn or neonatal death **Sharp *et al.*** [15], **Groom *et al.*** [16]. In the contrary the Dutch STRIDER trial was suspended after increased incidence of PPH of the newborn and elevated neonatal deaths with treatment **Groom *et al.*** [16]. These findings raise significant safety concerns, suggesting that while sildenafil may improve uteroplacental perfusion theoretically, its potential to cross the placenta and affect neonatal circulation warrants caution, reinforcing LMWH as the safer alternative.

LMWH has a documented safety profile in pregnancy and acts in the maternal compartment of the placenta, not crossing it. **Many *et al.*** [17] whereas Sildenafil citrate crosses the placenta **Dastjerdi *et al.*** [18] with the concern that it may be correlated with raised neonatal mortality. **Groom *et al.*** [16] making low-molecular-weight heparin a safer therapeutic option.

This study has several limitations. First, the relatively small sample size of only 50 participants may limit the generalizability of the findings. Second, it was conducted at a single center, which reduces external validity and applicability to other populations. Third, follow-up was limited to the delivery and immediate neonatal period, without assessment of long-term maternal or neonatal outcomes. Finally, safety

monitoring, particularly for long-term effects of sildenafil exposure, was not addressed beyond the perinatal period.

## CONCLUSION

In comparison to Sildenafil citrate use, the usage of low molecular weight heparine in pregnancies with fetal growth restriction showed a significant elevation in pregnancy time from randomization to delivery and increases neonatal body weight, an enhancement in fetoplacental blood flow, as well as fewer maternal and neonatal complications.

## DECLARATIONS

**Consent for publication:** I certify that each author has granted permission for the work to be submitted.
**Funding:** No fund
**Availability of data and material:** Available
**Conflicts of interest:** None
**Competing interests:** None

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