The Effect of Oral Isosorbide Mononitrate Therapy on Umbilical Artery Doppler Resistance Index in Pregnancies with Intrauterine Growth Restriction: A Prospective Randomized Control Trial

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Abstract

Background: There is no clear evidence that any intervention improves the growth of growth limited fetuses in healthy pregnant women. In limited, randomized trials, a variety of therapies have been tested, including maternal nutritional supplementation, interventions to enhance blood flow to the placenta, such as low-dose aspirin, bed rest, and anticoagulation. The use of nitric oxide (NO) donors such isosorbid mononitrate appeared promising and was being researched.

Objective: Evaluation of the efficacy and tolerability of isosorbide mononitrate in reducing umbilical artery Doppler resistance index.

Methods: This randomized controlled trial included 46 pregnant women who had early onset fetal growth restriction. They were randomly assigned into two groups were group A received Isosorbide-5-mononitrate (Imdur®, 30 mg) and group B received Osteocare ®. Both were taken twice daily for 4 to 6 weeks them umbilical artery Doppler resistance index, fetal growth was compared before and after treatment.

Results: Mean umbilical artery Doppler resistance index was statistically significant improved in isosorbide mononitrate group 0.81 ± 0.02 versus 0.75 ± 0.05, before and after treatment respectively with a mean decrease of 0.06. In the isosorbide mononitrate group, the mean EFW is 1113.22 gm before treatment that is increased to 1419.78 gm after treatment, showing an increase in weight by 27.538 %. Also, the mean gestational age at delivery was statistically non-significant difference between the two groups where in group A it was 36.75 weeks ± 0.8 while in group B 36.25 weeks ± 0.95.

Conclusion: NO donor plays no role in the therapy of FGR with minor Doppler alterations and maternal side effects. It had a minor positive effect on the umbilical artery Doppler and placental circulation.

Keywords: Isosorbide Mononitrate; Umbilical Artery Doppler; Intrauterine Growth Restriction.

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Introduction

Intrauterine growth restriction (IUGR) occurs when a foetus is unable to grow to its genetically determined potential size. This definition excludes fetuses that are small for gestational age (SGA) but not pathologically tiny. Weight increase that is at or below the 10th percentile for all foetuses at that gestational age is defined as SGA. Not all SGA foetuses are pathologically stunted; in fact, some may be constitutionally small.[1]

Nearly 40% of all foetuses with growth at or below the 10th percentile face perinatal death, which may be preventable. Another 40% of these foetuses are of average size. Because this diagnosis can only be made with certainty in infants, many healthy foetuses with SGA will be subjected to high-risk operations, which may result in iatrogenic prematurity.[2]

The remaining 20% of SGA foetuses are essentially small due to genetic or environmental factors. Examples include fetuses with trisomy 18, CMV infection, or foetal alcohol syndrome. Prenatal intervention is less likely to benefit these foetuses, and their prognosis is most strongly linked to the underlying cause.[3]

FGR can be caused by intrauterine infections and chromosomal abnormalities (Trisomy 13, 18, and 21). (STORCH). As potential causal reasons, a foetal karyotype, maternal serology for infectious processes, and a history of environmental exposure can all be considered.[4]

However, the more common cause of FGR is extrinsic (utero-placental) insufficiency, in which the fetus' nutrition and gastric exchange are insufficient to support its growth in utero. This process can also be caused by a dysfunctional oxygen delivery system caused by maternal vascular disease (e.g., chronic or pregnancy-related hypertension, diabetes with vascular disease, autoimmune disease causing vasculopathy, thrombophilia, chronic placental abruption, cord & placental agenesis). Cyanococcal heart disease, hemoglobinopathies, smoking, substance addiction, and autoimmune disorders that produce vasculopathy are examples of these ailments.[5]

In growth-restricted foetuses with severe impairment of umbilical artery (UA) blood flow, adverse outcomes such as intrauterine foetal death and neonatal death, as well as increased neonatal morbidity such as hypoglycemia, hyperbilirubinemia, hypothermia, intraventricular hemorrhage, necrotizing enterocolitis, seizures, sepsis, and RDS, are more likely to occur.[6]

Furthermore, epidemiological studies have shown that FGR foetuses are predisposed to the development of metabolic syndrome in adults as well as cognitive impairment in children (e.g., obesity, diabetes, coronary artery disease, and stroke).[7]

The trophoblast produces nitric oxide (NO), a potent venous and arterial vasodilator that also inhibits platelet aggregation, during a healthy pregnancy. In FGR-complicated pregnancies, placental hypoxia and endothelial dysfunction are associated to decreased NO release and increased phosphodiesterase type 5 (PDE-5) activity. As a result, the NO donor isosorbide mononitrate and the PDE-5 inhibitor sildenafil citrate can prevent and treat FGR.[8]

L-arginine is a substrate for the nitric oxide synthases (NOS) that produce nitric oxide (NO). It is produced by vascular endothelial cells and diffuses into neighboring vascular smooth muscle cells to increase the concentration of the second messenger cyclic guanosine monophosphate (cGMP), causing the smooth muscle to relax.[9]

The study's idea was that oral isosorbide mononitrate might offer advantage in reducing umbilical artery Doppler indices in pregnancies with intrauterine growth restriction.

METHODS

This randomized controlled trial was registered on clinicaltrial.gov with the following ID: NCT05800938. Before the study began, the Faculty of Medicine Ain Shams University Research Ethics Committee (FMASU REC) granted ethical permission with the following number MS 382/ 2022 and all subjects provided verbal agreement.

It was conducted in Obstetrics and Gynecology Department at Ain Shams University Maternity Hospital from February 2022 till February 2023. This study included 46 pregnant women attended outpatient clinic with FGR for routine antenatal care.

Inclusion criteria

Pregnant women aged 18-35 years old had BMI ranged between 18-30 kg/m2, with singleton pregnancy, gestational age between 28-30 weeks, reactive nonstress test (NST) and all criteria of FGR were enrolled.

Exclusion criteria

Women with multifetal pregnancy, known or suspected chromosomal or structural anomalies or had a condition required urgent delivery as preeclampsia, persistent reversed a-wave of the ductus venosus with gestational age ≥ 30 weeks or fetal surveillance tests indicated fetal compromise (eg, nonreactive NST, poor fetal heart rate baseline variability, persistent late decelerations, oligohydraminos, or BBP score < 4) were excluded.

Randomization

Women who met the inclusion criteria and gave their agreement were randomly allocated to one of two groups. Forty sex opaque envelopes were serially numbered, and the appropriate letter, which designated the assigned group, was placed in each envelope according to a randomization table. The envelopes were then sealed and placed in a single box. MedCalc version 13 was used to build a computer generated randomization sheet.

Allocation and concealment

A computer-generated randomization sheet using MedCalc version 13 was used to assign women to the research. A total of 46 envelopes were serially numbered, and the appropriate letter denoting the assigned group was placed in each envelope according to the randomization table. The envelopes were then sealed and placed in a single box. When the first patient arrived, who opened the first envelope, and the patient was assigned based on the letter inside, and so on.

Blinding

The study was double-blinded, where neither the researcher, nor the participants knew what type of medication each participant received, as a nurse gave each patient a closed envelope containing 21 tablets of one of the two medications in a randomized fashion.

Ethical considerations

Before the beginning of the study, ethical approval from faculty of Medicine Ain Shams University Research Ethics Committee (FMASU REC) was obtained with the following number MS 382/ 2022 and consents from all the participants were obtained.

Before being enrolled into the study, the patient consented to participate after explanation of study interventions to her. Only the patient initials were recorded in the case report form. Protocol approval was obtained from ethical committee of OB/GYN department.

Study procedures

Patients were randomized into one of the following two groups; group A received (IMDUR®, 30 mg, tablet, AstraZeneca, Egypt) (Isosorbide-5-mononitrate Biphasic) twice daily for 4-6 weeks and group B (n=23) received (Osteocare®, tab, VITABIOTICS, Egypt) twice daily for 4-6 weeks.

All women who met the inclusion criteria were completely assessed. This assessment included full history taking with special

emphasis on factors for FGR as maternal age, previous stillbirth, previous SGA fetuses, cocaine intake, cigarette smoking, and maternal diseases as preeclampsia.

Complete clinical examination was done with special emphasis on local abdominal examination; symphysio-fundal height (measured from fundus {variable point} to symphysis pubis {fixed point} with centimeters values).

Investigations included blood pressure measurement, urine dipstick, CBC, KFTs, LFTs and coagulation profile.

Ultrasound was performed for basic fetal biometry as estimated fetal weight (EFW) using Hadlock's formula, liquor and placental assessment.

The same operator performed umbilical artery Doppler using a Samsung HS 60 ultrasound scanner with a 3.5-MHz convex probe. It was done with the patients in semi-Fowler position, during a period of absent fetal movement and breathing. A minimum of three uniform Doppler waveforms were measured.

Fetal wellbeing was done including a biophysical profile (BPP) that is a test that combines a nonstress test with ultrasound to check the health of the fetus.

A course of antenatal corticosteroids was given to pregnancies in the week before preterm delivery is anticipated (<34 weeks).

When fetal surveillance tests indicated, fetal compromise delivery was considered and taken by expert supervisors. Patients were assessed for properly taking their medication in the right dose or development of any maternal side effects.

Study outcomes

Primary outcome was reduction in umbilical artery Doppler resistance index. Secondary outcomes were enhancement of fetal growth as measured by the increase in estimated fetal weight (EFW) and abdominal circumference (AC), in percentiles, development of fetal complications as IUFD, fetal distress and deterioration of Doppler indices requiring delivery, interval to delivery and maternal side effects caused by the medication such as headache, palpitations and postural hypotension.

STATISTICAL ANALYSIS

The statistical software for social sciences, version 23.0 (SPSS Inc., Chicago, Illinois, USA), was used to analyze the collected data. The quantitative data was presented in the form of mean, standard deviation, and ranges. Qualitative variables were also given numerically and as percentages. The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to examine the data for normality.

RESULTS

Table 1: Comparison between Group A and Group B according to baseline characteristics.

Baseline characteristics	Group A (n=23)	Group B (n=23)	t-test	p-value
Age (years) Mean±SD Range	28.83±4.66 22-35	27.00±5.33 18-36	1.237	0.223
BMI (kg/m^2) Mean±SD Range	28.26±5.03 20-38	26.04±4.54 19-37	1.570	0.124
Gestational age (wks) Mean±SD Range	30.00±0.67 29-31	30.13±0.97 28-33	0.530	0.599

Table 2: Comparison before treatment and after treatment according to umbilical artery Doppler resistance index, estimated fetal weight and abdominal circumference in group A

Variable	Group A (n=23)		Paired Sample t-test		
	Before treatment	After treatment	MD±SE	t-test	p-value
Umbilical artery Doppler resistance Index					
Mean±SD	0.81±0.02	0.75±0.05	0.06±0.01	6.005	<0.001**
Range	0.75-0.85	0.68-0.85			
Estimated fetal weight					
Mean±SD	1113.22±176.42	1419.78±209.30	306.6±40.20	7.626	<0.001**
Range	950-1590	1030-1760			
Abdominal circumference					
Mean±SD	212.48±11.06	248.43±17.03	36.0±3.74	9.617	<0.001**
Range	190-240	210-280			

Table 3: Comparison before treatment and after treatment according to umbilical artery Doppler resistance index, estimated fetal weight and abdominal circumference in group B

Variable	Group A (n=23)		Paired Sample t-test		
	Before treatment	After treatment	MD±SE	t-test	p-value
Umbilical artery Doppler resistance Index					
Mean±SD	0.79±0.03	0.77±0.04	0.02±0.01	2.025	0.055
Range	0.75-0.85	0.71-0.85			
Estimated fetal weight					
Mean±SD	1163.48±176.82	1339.78±248.46	176.3±46.03	3.830	<0.001**
Range	966-1490	980-1760			
Abdominal circumference					
Mean±SD	216.78±7.54	237.22±17.35	20.4±3.00	6.806	<0.001**
Range	200-237	210-275			

Table 4: Comparing the outcomes between the two groups after treatment

Umbilical artery Doppler	Group A (n=23)	Group B (n=23)	T-test	p-value
Mean+SD Range	0.75±0.05 0.88-0.85	0.77±0.04 0.71-0.85	1.359	0.181
Estimated Fetal weight				
Mean+SD Range	1419.78±209.30 1030-1760	1339.78±248.46 980-1760	1.181	0.244
Abdominal circumference				
Mean+SD Range	248.43±17.03 210-280	248.43±17.03 210-280	2.213	0.032

Table 5: Comparison between Group A and Group B according to incidence of IUFD, fetal distress and deterioration of Doppler indices requiring delivery

	Group A (n=23)	Group B (n=23)	x^2	p-value
IUFD	0 (0%)	0 (0%)	--	--
Fetal distress	0 (0%)	0 (0%)	--	--
Deterioration of Doppler indices requiring delivery	0 (0%)	3 (13.0%)	3.209	0.073

Table 6: Comparison between Group A and Group B according to side effects

Side effects	Group A (n=23)	Group B (n=23)	x^2	p-value
Headache	7 (30.4%)	0 (0.0%)	8.066	0.005*
Palpitation	2 (8.7%)	0 (0.0%)	2.047	0.153
Postural hypotension	2 (8.7%)	0 (0.0%)	2.047	0.153
Overall all side effects	11 (47.8%)	0 (0.0%)	14.133	<0.001**

Table 7: Comparison between Group A and Group B according to interval to deliver

Interval to delivery	Group A (n=23)	Group B (n=23)	T-test	p-value
Mean+SD Range	36.75 ± 0.8 36.2 - 37	36.25 ± 0.95 35 - 36.5	-1.931	0.060

Discussion

The same findings were reported in a randomized controlled trial comparing isosorbide mononitrate to sildenafil citrate in pregnancies complicated by FGR by Abd El Fatah et al. The results showed that isosorbide mononitrate 30 mg twice daily is as effective as sildenafil citrate 50 mg twice daily in lowering the umbilical artery Doppler resistance index (RI), thereby improving fetal growth in FGR pregnancies and lowering overall perinatal morbidity and mortality caused by iatrogenic prematurity or FGR itself.[10]

Similar findings were observed in NO donor (L-Arginine) trials, emphasizing the relevance of NO in pregnancy and fetal growth, and how its deficit contributes to the development of asymmetrical FGR; hence, supplementing improves fetal growth. According to Singh et al, Xiao et al, and Sieroszewski et al, maternal L-Arginine supplementation raises NO levels, which results in a moderate reduction in systolic/end-diastolic velocity ratio (S/D ratio) on doppler blood flow research, and hastened fetal growth.[11-13]

Furthermore, Chen et colleagues found that NO donor (L-Arginine) enhanced birth weight and delayed gestational age at labor in IUGR fetuses.[14]

The current study, on the other hand, compares the intervention group to a placebo (using calcium supplementation) and finds that the improvement in umbilical artery Doppler resistance index was statistically non-significant (P= 0.181). The same was true for EFW enhancement, where the increase was suboptimal when compared to the growth curve at this gestational age and did not achieve a significant value (P= 0.244). In contrast to the statistically significant (P= 0.032) improvement in AC measurement. Furthermore, the mean gestational age at delivery was statistically non-significantly different between the two groups, with group A having 36.75 weeks 0.8 and group B having 36.25 weeks 0.95 (P= 0.060).

Unlike Dastjerdi et al, who wanted to know if isosorbide mononitrate and sildenafil

citrate affected uteroplacental perfusion. Forty-one pregnant women with proven intrauterine growth retardation at 24-37 weeks of gestation were investigated in a randomized double-blind, placebo-controlled experiment. They discovered that patients with FGR-complicated pregnancies who got a single dose of sildenafil citrate (50 mg) plus isosorbide improved significantly in umbilical artery Doppler indices 2 hours after receiving the medication.[15]

Lampariello et al conducted a study on the basis of the dual activity of NO, vasodilation, and GH-RH induction, 43 pregnant women were treated from the 30th week of gestation with L-arginine (Bioarginina, 6 g per os/day), diagnosed by ultrasonic examination and evaluation of Doppler velocimetry values. They reported that 32 individuals improved their clinical course of pregnancy: 19 recovered the entire retardation; 9 recovered in one week; and 4 had premature birth after 36 weeks with fetal weight matching gestational age.[16]

Schleussner et al investigated the efficacy of the NO-donor PETN for secondary prevention of IUGR, PE, and preterm birth in high-risk pregnancies. A prospective, randomized, placebo-controlled, double-blind trial of 111 women with impaired placental perfusion at 19-24 weeks of gestation (w.o.g.) was conducted. They disagreed with us, reporting that pentaerithrityl-tetranitrate greatly reduced the chance of IUGR and/or perinatal death, as well as IUGR. Preterm birth before 32 weeks of gestation was lowered, but not the risk of PE. There were no placental abruptions in the PETN group, but five in the placebo group. These findings suggested that secondary prevention of unfavorable pregnancy outcomes by PETN would be feasible in pregnancies with aberrant placentation.[17]

Thaler et al. reported contradictory evidence on isosorbide mononitrate. In 23 women with pregnancy-induced hypertension (PIH), they studied the effect of isosorbide dinitrate (ISDN) on maternal and fetal circulation. A randomized double-blind design was used. Each lady was given either an ISDN (5 mg) sublingual tablet or a placebo. For a total of 20 minutes, maternal blood pressure (BP) and heart rate (HR) were recorded before and every 2 minutes following the treatment or placebo. Using pulsed Doppler ultrasonography, flow velocity waveforms in the uterine and umbilical arteries were obtained at the same time intervals. In those arteries, the peak systolic to end-diastolic flow velocity ratio (S/D) was measured. After ISDN, mean maternal blood pressure dropped from 103 6 1.8 mm Hg to 90.5 6 2.9 mm Hg at 14 minutes (P.0001), but mean maternal heart rate increased from 97.3 6 3.8 beats/min to 115.7 6 3.5 beats/min at 12 minutes (P.0001). At 8 minutes, the mean S/D in the umbilical artery decreased from 3.07 6 0.33 to 2.58 6 0.23 (P.0007). At 10 minutes, the mean S/D in the uterine artery decreased from 3.27 6 0.6 to 2.38 6 0.28 (P.0001). Seven of the twelve women who had an early diastolic notch in their uterine artery flow velocity waveform saw the notch reduce or disappear within the first six minutes after taking the medicine. The placebo group showed no significant change in any of the evaluated measures. Their discovery that ISDN affected maternal and fetal hemodynamics in PIH lends credence to additional research into nitric oxide donors in the treatment and prevention of pregnancy-induced hypertension.[18]

The overall side effects of Isosorbide Mononitrate (Group A) were recorded in 11/23 (47.8%). Headache was the most prevalent side effect (7/23 (30.4%), followed by postural hypotension 2/23 (8.7%) and palpitation 2/23 (8.7%). These adverse effects were minor and did not necessitate a treatment interruption.

There were also no statistically significant differences between study groups in terms of IUFD, fetal distress, deterioration of Doppler indices necessitating delivery, and interval

to delivery, with p= 0.130, 0.32, 0.073, and 0.060, respectively.

In contrast to Chen et al., who reported higher incidences of delayed delivery. Chen et al. confirmed our findings in instances of IUFD.[14]

CONCLUSION

NO donor has no role in management of FGR with mild Doppler changes and associated with maternal side effects. It had mild improving effect on umbilical artery Doppler and placental circulation.

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