Original Article

Rosuvastatin for Improving Fetal Growth Restriction in Pregnant Women: A Double-Blind Randomized Clinical Trial

Maryam Kasraeian[1], MD; Fatemeh Askari[1], MD; Homeira Vafaei[1], MD; Nasrin Asadi[1], MD; Azam Faraji[1], MD; Khadijeh Bazrafshan[2], MSc; Marjan Zare[2], PhD

[1]Maternal-fetal Medicine Research Center, Department of Obstetrics and Gynecology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran;
[2]Maternal-fetal Medicine Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

Correspondence:
Fatemeh Askari, MD;
Maternal-fetal Medicine Research Center, Shiraz University of Medical Sciences, Zand Blvd., Postal code: 71936-35899, Shiraz, Iran
Tel: +98 71 36281572
Email: hosseinmoradisarvestani0003@gmail.com
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Abstract

Background: Fetal growth restriction (FGR) results from uteroplacental insufficiency and currently lacks an absolute cure. Statins may offer therapeutic potential by addressing this insufficiency. This study aimed to investigate the effectiveness of rosuvastatin in improving the perinatal outcomes in FGR pregnancies.

Methods: A double-blind, randomized placebo-controlled clinical trial was conducted on 78 FGR pregnancies referred to tertiary centers affiliated with Shiraz University of Medical Sciences (Shiraz, Iran) from January 21, 2023, to March 21, 2023. The participants were randomly divided into two groups using the block randomization method to receive either 5 mg rosuvastatin or placebo daily from FGR diagnosis until delivery. Evaluated outcomes included birth weight, umbilical artery pulsatile index reduction, fetal weight gain, vaginal delivery rate, preterm birth (PTB) incidence, 5-min Apgar score <7, neonatal death, neonatal intensive care unit admission, intraventricular hemorrhage, respiratory distress syndrome, necrotizing enterocolitis, and preeclampsia. The data were analyzed using regression models, reporting mean difference (95% CI), frequency (relative frequency), and odds ratio with 95% confidence interval (OR [95% CI]). Statistical significance was set at $P<0.05$.

Results: The study included 34 subjects in the rosuvastatin group and 44 subjects in the placebo group, with no significant differences in baseline characteristics. However, the rosuvastatin group showed significantly better outcomes in birth weight (276.27 g, 95% CI=32.61-519.93, OR=1.002, 95% CI=1-1.003), umbilical artery pulsatililty index reduction (0.21 g, 95% CI=0.00-0.43, OR=6.600, 95% CI=1.680-25.930), fetal weight gain (312.51 g, 95% CI=90.50-534.52, OR=1.001, 95% CI=1-1.002), and vaginal delivery rate (6/34 [17.6%] vs. 1/44 [2.3%]; OR=9.210, 95% CI=1.050-80.680). Additionally, the rosuvastatin group had significantly lower PTB rates (15/34 [44.10%] vs. 30/44 [68.20%]; OR=0.370, 95% CI=0.150-0.930). Neonatal health status showed no significant differences between groups.

Conclusion: Rosuvastatin demonstrated improved perinatal outcomes in FGR pregnancies without adverse neonatal effects.

Trial registration number: IRCT20140317017035N8.

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Keywords ● Fetal growth restriction ● Rosuvastatin calcium ● Clinical trials, randomized

What's Known

- Fetal growth restriction (FGR), or the inability of a fetus to reach full growth potential, is caused by uteroplacental insufficiency. Statins have been shown to improve fetal blood supply by affecting the umbilical artery pulsatile index, thereby enhancing pregnancy outcomes. However, no absolute cure for FGR currently exists.

What's New

- Rosuvastatin demonstrated no adverse effects on neonates and significantly improved perinatal outcomes, including increased birth weight, reduced umbilical artery pulsatile index, enhanced fetal weight gain, higher rates of vaginal delivery, and decreased preterm birth. It also ameliorated uteroplacental insufficiency in fetal growth restriction (FGR) pregnancies.
- Rosuvastatin might serve as a potential treatment for FGR.

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Introduction

Fetal growth restriction (FGR), defined as failure to reach full growth potential, affects 7-10% of pregnancies and results from uteroplacental insufficiency.[1] FGR fetus faces 5-10 times higher risks of intrauterine death and perinatal morbidity,[2] with no absolute cure currently available.[3] Statins, known for inhibiting cholesterol biosynthesis, exert antioxidant effects through antithrombotic and vasorelaxant properties that reduce free radical production. The efficacy of low-dose statins in reducing low-density lipoprotein cholesterol (LDL-C) has been demonstrated in patients with atherosclerotic cardiovascular disease, with significant benefits compared to placebo.[4] Studies showed that statins therapy during pregnancy improved angiogenic profile without increasing the risk of congenital anomalies.[5, 6] Given the potential of statins to mitigate placental insufficiency, the U.S Food and Drug Administration (FDA) has recommended that statin therapy during pregnancy might be considered when the benefits outweigh the risks. Importantly, the current labeling restrictions were predominantly based on a lack of established indications rather than definitive safety concerns.[7] Previous studies investigated the effects of pravastatin and L-arginine on umbilical artery blood flow and demonstrated a reduction in the pulsatile index (UAPI). These agents promote vascular relaxation, prolong gestation, and improve pregnancy outcomes.[6, 8] Although these findings derive from *in vitro* studies, Brownfoot and others reported that rosuvastatin and simvastatin exhibited greater potency than pravastatin in reducing circulating soluble fms-like tyrosine kinase-1 (sFLT-1), which was secreted from human endothelial cells, trophoblasts, and placental explants.[9]

Other studies have investigated the potential benefits of statins in placental insufficiency. However, their findings were limited by small sample sizes and non-randomized designs.[5, 8, 10] Although studies evaluated the use of statins on preeclampsia (PEC) and antiphospholipid syndrome,[11-13] no studies have focused on FGR. This randomized placebo-controlled clinical trial aimed to investigate the efficacy of rosuvastatin in FGR pregnancies, hypothesizing that rosuvastatin-treated pregnancies would have better prenatal outcomes than untreated controls.

Patients and Methods

Study Design and Subjects

This double-blind, randomized placebo-controlled clinical trial (RCT) was conducted on 78 pregnant women aged 18-50 years with FGR from three tertiary perinatal centers, including Nemazi Hospital, Mottahari Clinic, and Zeynabieh Hospital, affiliated with Shiraz University of Medical Sciences (Shiraz, Iran), from January 21, 2023 to March 21, 2023. The study was conducted in accordance with the Helsinki Declaration (1964) and approved by the institutional ethics committee (code: IR.SUMS.REC.1401.526), with registration in the Iranian Registry of Clinical Trials (code: IRCT20140317017035N8). All participants received standard prenatal care and provided written informed consent after receiving detailed information about potential statin-related adverse effects through an educational brochure.[14] They were informed that they could withdraw from the study at any time. The safety of rosuvastatin during pregnancy was confirmed, and newborn health status data were obtained from the neonatal ward.

Data/Safety Monitoring Plan

Pharmacokinetic evaluation of pravastatin during pregnancy was conducted through drug/metabolite concentration monitoring in physiological fluids.[15] Participants underwent comprehensive monitoring by nurses, midwives, and physicians during scheduled and unscheduled visits until delivery. All patients were instructed to immediately report any health or pregnancy-related concerns. Demographic data and maternal/and fetal vital signs were recorded, and clinical obstetric examinations were performed. The patient's medical records were used to document any health problem concerns affecting both mother and fetus. Medical staff recorded all adverse effects and complications during the study period. Exclusion criteria incorporated factors affecting statin risk to ensure optimal data safety . Genetic counseling was recommended for patients diagnosed with FGR<32 weeks of gestational age (GA), or FGR in combination with polyhydramnios or fetal malformation.[16] Besides, aneuploidy screening/testing was performed before enrollment.

Inclusion and Exclusion Criteria

The inclusion criteria were maternal age of 18-50 years with a singleton pregnancy at 28-34 weeks gestational age (GA) confirmed by ultrasound, along with either estimated fetal weight (EFW) <3rd percentile, abdominal circumference (AC) <3rd percentile, or EFW <10th percentile accompanied by abnormal Doppler findings,[17, 18] plus the provision of written informed consent.

The exclusion criteria were concurrent PEC at the time of diagnosis, chromosomal or fetal anomalies, statin intolerance or allergy, fetal demise, acute pulmonary edema, hepatic/ renal disorders, uncontrolled hypertension, hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome, severe neurological symptoms, any contradictions to statin therapy, human immunodeficiency virus (HIV) infection, active malignancy, and uterine malformation. Patients with PEC and HELLP syndrome were specifically excluded , since these conditions often require early delivery independent of FGR status, which would confound the evaluation of rosuvastatin's effects in pure FGR pregnancies.

Intervention/Placebo Groups

Intervention Group: The intervention group received 5 mg of rosuvastatin (Poursina Pharmaceutical Co., Iran) administrated once daily from diagnosis until delivery.

Control Group: The control group received an identical-appearing placebo tablet (5 mg, produced by the School of Pharmacy, Shiraz University of Medical Sciences, Iran) on the same schedule. As this study was the first trial investigating rosuvastatin for FGR in high-risk pregnancies, we selected the lowest moderate-intensity dose (5 mg) to minimize potential adverse effects.[4, 19] The placebo matched the active drug in appearance, shape, and color, differing only in the active formulation. Participants experiencing any rosuvastatin-related adverse events were immediately withdrawn from the study, with the continuation of the trial among the remaining subjects.

Study Variables and Definition

The following parameters were collected: maternal age (years), body mass index (BMI, Kg/m^2), UAPI at the time of FGR diagnosis,[1]

$$(UAPI = \frac{(maximum\ systoloc\ velocity - minimum\ diastoloc\ velocity)}{mean\ velocity})$$

(measured in the umbilical artery at the time of FGR diagnosis), GA at the time of FGR diagnosis (days since the last menstrual period [LMP]), first aspartate aminotransferase (AST, before and 3 days after taking rosuvastatin [U/L], first alanine transaminase (ALT, before and 3 days after taking rosuvastatin [U/L], first ALT and second ALT difference (first ALT minus second ALT [U/L]). Fetal parameters included EFW at the time of FGR diagnosis (sonographic estimation of fetal weight calculated with Hadlock formula)[20] (g), *in vitro* fertilization (IVF, a sequence of procedures that involve extracorporeal fertilization of gametes)[21] (yes/no), history of small gestational age (SGA, birth weight <10th percentile for GA)[22] (yes/no), preterm birth (PTB) history (delivery less than 259 days)[23] (yes/no). Additional maternal factors comprised the history of stillbirth (birth at ≥20 weeks of gestation with no sign of life, and death before or during delivery)[24] (yes/no), history of chronic hypertension (HTN, present pre-conception or before 20 weeks of gestation)[25] (yes/no), history of diabetes mellitus (DM) (yes/no), history of low dose aspirin use <16-week use (yes/no), low molecular weight heparin use (yes/no), steroid administration for fetal lung maturation (yes/no), use of magnesium sulfate for fetal neuro-protection (yes/no). FGR staging (normal/ stages 1-4), GA at first Doppler impairment (GA at first Doppler impairment diagnosis, [days]), pregnancy duration (days), birth weight (g), UAPI reduction (UAPI at time of FGR diagnosis minus minimum UAPI after rosuvastatin), weight gain (birth weight minus EFW at time FGR diagnosis [g]) were recorded. Neonatal outcomes included delivery mode (vaginal/elective/emergency C/S), 5- minute Apgar score <7 (yes/no), neonatal death (newborn death before 28 days of age)[26] (yes/no), NICU admission (yes/no), intraventricular hemorrhage (yes/no), vaginal delivery (yes/no), duration of NICU admission (day), respiratory distress syndrome (RSD) (yes/no), necrotizing enter colitis (yes/no), PTB (yes/no), cause of PTB (fetal distress, oligohydramnios, and labor pain+previous C/S), cause of C/S (failed induction, fetal distress, IVF, patient desire, and previous C/S), PEC (yes/no), early-onset PEC (PEC before 34 weeks of gestational age)[27] (yes/no), and PECsf (PEC with severe features is a term used to distinguish multiorgan involvement and has therapeutic implications).

Severe preeclampsia was defined by any of the following: blood pressure (BP)≥160/110 mmHg, HELLP syndrome, acute kidney injury, pulmonary edema, or neurologic manifestations (including cerebral edema consistent with posterior reversible encephalopathy syndrome) (yes/no).[28] GA was recorded in days (rather than weeks) due to the critical importance of even single-day increments for fetal development in FGR pregnancies. Given the increased risk of oocyte-related complications in patients aged >45 years, these individuals received specific monitoring for oocyte status.

The variables were compared between the rosuvastatin and placebo groups to comprehensively evaluate pregnancy outcomes in FGR cases. The primary outcome was pregnancy duration (days). Secondary outcomes included fetal weight gain, history of PTB, birth

weight, UAPI reduction, 5-minute Apgar score, vaginal delivery, NICU admission, duration of NICU admission, emergency cesarean rates, elective cesarean rates, PEC, early-onset PEC, PECsf, stillbirth, neonatal death, intraventricular hemorrhage, respiratory distress syndrome (RDS), and necrotizing enterocolitis.

Early- and late-onset FGR definitions (excluding congenital anomalies) followed the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines based on Delphi consensus, as detailed in table 1.[17]

The FGR pregnancies were categorized into four groups to show the severity of FGR as follows: (increase in level)

Normal: No fetal Doppler abnormalities and / or uterine artery pulsatile index (PI)>95th centile

Stage 1: UAPI >95th percentile and/or cerebroplacental ratio<5th percentile

Stage 2: Umbilical artery absence of end-diastolic flow

Stage 3: Umbilical artery reversed end-diastolic flow and/or ductus venosus PI>95th percentile or absent ductus venosus a-wave

Stage 4: reverse ductus venosus a-wave

Elective delivery timing was stratified by FGR severity: ≥37 weeks in cases with normal or stage 1 Doppler abnormalities, ≥34 weeks for stage 2, ≥32 weeks for stage 3, and ≥26 weeks for stage 4. Cardiotocography indications for elective delivery were fetal heart rate sinusoidal training, absence of fetal heart rate variability accompanied by recurrent late decelerations, recurrent variable decelerations, or bradycardia.[25] Neonatal evaluations included: vital signs (heart /respiration rate, normal/abnormal), skeletal disorders caused during the delivery process (hip dislocation, skull fracture, cranial hemorrhage/malformation- yes/no, cleft palate (yes/no), hearing screening test (abnormal/normal), sight screening test (abnormal/normal), jaundice (yes/no), hypothyroidism (yes/no), phenylketonuria (yes/no), and genital screening (abnormal/normal).

Sampling Considerations

The sample size was calculated based on the sFLT-1/placenta growth factor (PLGF) ratio data from a previous study,[5] where "the sFLT-1/PLGF was measured in maternal serum at two different times: before pravastatin was started (ratio M0) and during pravastatin treatment (ratio M1)";

Pravastatin group (n=40): Median (IQR) M0-M1 ratio change=-10.1 (-53.1 to -0.07)

Control group (n=174): Median (IQR) M0-M1 ratio change 67 (-34.8 to 197.3)

Using G*Power 3.1.9.2 with the following parameters: the difference between two independent means, tail=two, Type I error=0.05, Power=0.80, Allocation ratio=1, Effect size (the mean difference)=77, the minimum required sample size was estimated at 88 subjects (44 per group).

A census-based sampling method was employed for case selection. Given that FGR is a rare condition, all eligible patients presenting to the participating centers during the study period were consecutively enrolled until the predetermined minimum sample size of 88 cases was obtained.

Random Allocation and Blinding

To ensure double-blinding in the study, identical tablets were prepared (44 containing rosuvastatin and 44 containing placebo). An independent pharmacist manufactured the tablets, which were then coded, packaged in identical envelopes by the investigator, and subsequently administered by the treating physician. Both the patients and the physicians remained blinded to the treatment allocation throughout the study. Randomization was performed using Random Allocation Software (version 1.0.0, available at: https://mahmoodsghaei.tripod.com/Softwares/randalloc.html). To ensure balanced allocation between groups, subjects were randomly assigned to either the treatment or placebo arm using block randomization with a block size of 4 and a 1:1 allocation ratio. The randomization process was designed for two groups with a total sample size of 88, using numeric codes for identification. The randomness of the allocation sequence was verified through a run test,

Table 1: Definitions for early- and late-onset FGR

Early FGR:	Late FGR:
GA<32 weeks, in the absence of congenital anomalies	GA≥ 32 weeks, in the absence of congenital anomalies
AC/EFW <3rd percentile or UA-AEDF	AC/EFW <3rd percentile
Or	Or at least two out of three of the following
AC/EFW <10th percentile combined with	1- AC/EFW < 10th percentile
UtA-PI >95th percentile and/or	2-AC/EFW crossing percentiles >2 quartiles on growth percentiles*
3-UAPI>95th percentile	3-CPR <5th percentile or UAPI >95th percentile

*Growth percentiles are non-customized centiles. AC: Fetal abnormal circumference; AEDF: Absent end-diastolic flow; CPR: Cerebroplacental ratio; EFW: Estimated fetal weight; GA: Gestational age; PI: Pulsatility index; UA: Umbilical artery; UtA: uterine artery; UAPI: Umbilical artery pulsatile index

which examined whether the pattern of assignments deviated from random distribution. The test showed P=0.238 for the null hypothesis of non-random sequence distribution, that the sequence was non-random, suggesting that the allocation sequence did not significantly deviate from randomness.

Blocks were generated, and a randomized sequence of interventions was specified. Accordingly, either treatment or a placebo was administered to the subjects. The interventions (placebo and rosuvastatin) were packaged in identical envelopes, and the allocation codes were written on them. Upon clinical diagnosis of FGR, the envelopes were immediately dispensed to the patients. Standardized care was maintained for all participants throughout the study period. During the analysis phase, the allocation codes were revealed by the investigator, and the results were documented.

Statistical Analysis

Quantitative variables were expressed as mean±SD or/ mean difference with a 95% confidence interval (OR [95% CI]), while qualitative variables were reported as frequency (relative frequency). We assessed data normality using the Kolmogorov-Smirnov test. Statistical analyses included the Chi square test, Fisher's exact test (for small sample sizes), Mann-Whitney U test, and univariate linear/binary regression models using the "enter method selection variable". Results were reported as odds ratios with 95% confidence intervals (OR [95% CI]). All analyses were performed using Random Allocation Software 1.0.0 (Isfahan University of Medical Sciences, Iran), G*Power 3.1.9.2 (Universitat Kiel, Germany), and SPSS software (version: 22, IBM Corp., Armonk, NY, USA).

An interim analysis of the primary endpoint was conducted when 50% of the participants were randomized and completed follow-up.[29] The significance threshold was set at P<0.05 for all tests.

Results

The trial enrolled 78 participants, 34 receiving rosuvastatin and 44 receiving placebo (figure 1).

Rosuvastatin demonstrated an excellent safety profile, with no serious adverse events (0/34) and only minor side effects (myalgia and headache) occurring in 2/34 (5.8%) of cases.

CONSORT Flow Diagram

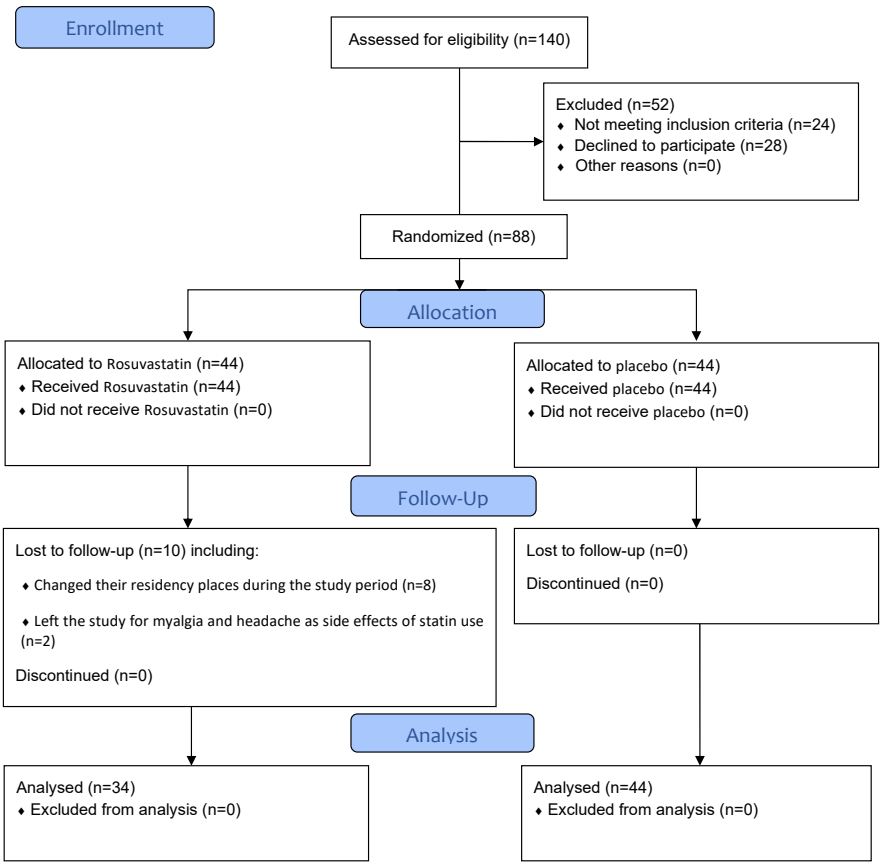

Figure 1: This figure represents the CONSORT flow diagram of the study.

The baseline characteristics of all 78 subjects were comparable between groups, as detailed in table 2.

The rosuvastatin and placebo groups showed no significant differences in maternal demographics and clinical characteristics, including maternal age (P=0.85), BMI (P=0.36), UAPI at FGR diagnosis (P=0.08), gestational age at diagnosis (P=0.23), AST changes (P=0.90), ALT changes (P=0.70), EFW at diagnosis (P=0.59), IVF status (P=0.15), history of SGA (P=0.51), PTB history (P=0.96), stillbirth history (P=0.58), chronic hypertension (P=0.70), diabetes mellitus (P=0.17), early aspirin use <16 weeks (P=0.86), heparin use (P=0.59), steroid administration for lung maturation (P=0.42), or magnesium sulfate use for neuroprotection (P=0.85).

Among the 78 subjects, FGR staging distribution was: normal (n=43), stage 1 (n=23), and stage 2 (n=12). The rosuvastatin and placebo groups showed comparable distributions of stage 1 (P=0.07) and stage 2 (P=0.11) FGR relative to normal cases. Similarly, gestational age at first Doppler impairment did not differ between treatment groups for stages 2-3 (P=0.76). At delivery, 33 patients (42.3%) reached ≥37 weeks gestation, while 45 (57.7%) delivered at <37 weeks. Comparative perinatal outcomes between treatment groups are presented in table 3.

The rosuvastatin group demonstrated significantly better outcomes than controls, including increased birth weight (P=0.02; OR=1.002), greater UAPI reduction (P=0.01;

Table 2: Comparison of background features between the rosuvastatin and placebo groups

Variable		Total, n=78	Rosuvastatin, n=34	Placebo, n=44	P value
Maternal age (year, mean±SD)		31.87±6.30	32.03±6.68	31.75±6.07	0.85*
BMI (Kg/m^2, mean±SD)		24.99±5.07	24.39±5.57	24.45±4.66	0.36*
UAPI at time of FGR diagnosis (mean±SD)		1.37±0.57	1.51±0.66	1.27±0.48	0.08*
GA at time of FGR diagnosis (day, mean±SD)		214.92±12.62	213.15±13.32	216.29±12.03	0.23*
First AST and second AST difference (U/L, mean±SD)		-0.06±4.74	-0.29±4.72	0.11±4.08	0.90*
First ALT and second ALT difference (U/L, mean±SD)		-0.23±5.23	-0.59±4.99	0.04±0.44	0.70*
EFW at time of FGR diagnosis (g, mean±SD)		1268.59±292.89	1248.15±308.11	1284.38±283.15	0.59*
IVF, n (%)	Yes	17 (21.80%)	10 (29.40%)	7 (15.90%)	0.15†
	No	61 (78.20%)	24 (70.60%)	37 (84.10%)	
History of SGA, n (%)	Yes	9 (11.50%)	3 (8.80%)	6 (13.60%)	0.51†
	No	69 (88.50%)	31 (91.20%)	38 (86.40%)	
History of PTB delivery, n (%)	Yes	9 (11.50%)	4 (11.80%)	5 (11.40%)	0.96†
	No	69 (88.50%)	30 (88.20%)	39 (88.60%)	
History of stillbirth, n (%)	Yes	3 (3.80%)	2 (5.90%)	1 (2.30%)	0.58§
	No	75 (96.20%)	32 (94.10%)	43 (97.70%)	
History of chronic HTN, n (%)	Yes	8 (10.30%)	4 (11.80%)	4 (9.10%)	0.70†
	No	70 (89.70%)	30 (88.20%)	40 (90.90%)	
History of DM, n (%)	Yes	9 (11.50%)	2 (5.90%)	7 (15.90%)	0.17†
	No	69 (88.50%)	32 (94.10%)	37 (84.10%)	
History of low dose aspirin<16-week use, n (%)	Yes	29 (37.20%)	13 (38.20%)	16 (36.40%)	0.86†
	No	49 (62.80%)	21 (61.80%)	28 (63.30%)	
Low molecular weight heparin use, n (%)	Yes	14 (17.90%)	7 (20.60%)	7 (15.90%)	0.59†
	No	64 (82.10%)	27 (79.40%)	37 (84.10%)	
Taken steroid for fetal lung tissue maturation, n (%)	Yes	43 (55.10%)	17 (50%)	26 (59.10%)	0.42†
	No	35 (44.90%)	17 (50%)	18 (40.90%)	
Taken magnesium sulfate for fetal neuroprotection, n (%)	Yes	14 (17.90%)	9 (26.50%)	25 (73.50%)	0.85†
	No	64 (82.10%)	5 (11.40%)	39 (88.60%)	
FGR stage, n (%)	Normal(ref category)	43 (55.10%)	14 (41.20%)	29 (65.90%)	>0.99†
	Stage 1	23 (29.50%)	13 (38.20%)	10 (22.70%)	0.07†
	Stage 2	12 (15.40%)	7 (20.60%)	5 (11.40%)	0.11†
Variable		**Total, n=35**	**Rosuvastatin, n=20**	**Control, n=15**	**P value**
GA at first Doppler impairment≈ (day, mean±SD)		211.06±11.38	211.55±11.37	210.40±11.75	0.76*

GA: Gestational age; FGR: Fetal growth restriction; AST: Aspartate aminotransferase; ALT: Alanine transaminase; First AST: AST before taking rosuvastatin; Second AST: AST three days after taking rosuvastatin; First AST and second AST difference: First AST minus second AST; First ALT: ALT before taking rosuvastatin; Second ALT: ALT three days after taking rosuvastatin; first ALT and second ALT difference: First ALT minus second ALT; EFW: Estimated fetal weight; HTN: Hypertension; DM: Diabetes mellitus; BMI: Body mass index; SGA: Small for gestational age; IVF: In Vitro Fertilization; UAPI: Umbilical artery pulsatile index; ≈The comparison was made in FGR stage 1 and FGR stage 2 patients, *Mann-Whitney U test; § Fisher's exact test; †Chi Square test; P<0.05 was considered statistically significant.

Table 3: Perinatal outcomes comparison between the Rosuvastatin and the control groups

Outcome		Univariate analysis			
		Rosuvastatin, n=34	Placebo, n=44	P value	OR (95% CI)
Pregnancy period (day, mean difference [95% CI])		5.17 (-1-11.34)		0.09	1.007* (0.990-1.010)
PEC, n (%)		1 (3%)	3 (7%)	0.45	0.414§ (0.041-4.169)
Early-onset PEC, n (%)		0 (0%)	1 (3%)	0.59	0.42§ (0.016-10.642)
PECsf, n (%)		0 (0%)	0 (0%)	0.89	1.289§ (0.025-66.664)
Birth weight (g, mean difference [95% CI])		276.27 (32.61-519.93)		0.02	1.002* (1-1.003)
UAPI decrement, (mean difference [95% CI])		0.21 (0.00-0.43)		0.01	6.600* (1.680-25.930)
Weight gain (g, mean difference [95% CI])		312.51 (90.50-534.52)		0.01	1.001* (1-1.002)
Vaginal delivery, n (%)	Yes	6 (17.60%)	1 (2.30%)	0.03	9.210§ (1.050-80.680)
	No	28 (82.40%)	43 (97.70%)		
C/S, n (%)	Yes	2 (5.90%)	2 (4.50%)	0.79	1.310§ (0.170-9.830)
	No	32 (94.10%)	42 (95.50%)		
Emergency C/S, n (%)	Yes	21 (61.80%)	33 (75%)	0.21	0.540§ (0.200-1.420)
	No	13 (38.20%)	11 (25%)		
Elective C/S, n (%)	Yes	7 (20.60%)	9 (20.50%)	0.98	1.008§ (0.330-3.050)
	No	27 (79.40%)	35 (79.50%)		
PTB, n (%)	Yes	15 (44.10%)	30 (68.20%)	0.03	0.370§ (0.150-0.930)
	No	19 (55.90%)	14 (31.80%)		
Stillbirth, n (%)	Yes	0 (0%)	0 (0%)	0.89	1.280§ (0.020-66.660)
	No	34 (100%)	44 (100%)		
5-minute Apgar score <7, n (%)	Yes	0 (0%)	1 (2.30%)	0.60	0.420§ (0.020-10.640)
	No	34 (100%)	43 (97.70%)		
Neonatal death, n (%)	Yes	0 (0%)	1 (2.30%)	0.60	0.420§ (0.020-10.640)
	No	34 (100%)	43 (97.70%)		
NICU admission, n (%)	Yes	14 (41.20%)	23 (52.30%)	0.33	0.640§ (0.260-1.580)
	No	20 (58.80%)	21 (47.70%)		
Duration of NICU admission (day, mean difference [95% CI])		-3.07 (-9.51-3.37)		0.35	0.980* (0.950-1.020)
Intraventricular hemorrhage, n (%)	Yes	0 (0%)	1 (2.30%)	0.60	0.420§ (0.020-10.640)
	No	34 (100%)	43 (97.70%)		
RDS, n (%)	Yes	14 (41.20%)	22 (50%)	0.44	0.700§ (0.280-1.720)
	No	20 (58.80%)	22 (50%)		
Necrotizing enterocolitis, n (%)	Yes	0 (0%)	0 (0%)	0.89	1.280§ (0.020-66.660)
	No	34 (100%)	44 (100)		
Cause of PTB, n (%)	Fetal distress	13 (86.70%)	22 (78.60%)	0.73	1.800§ (0.070-47.410)
	Oligohydramnios	2 (13.30%)	5 (17.90%)	0.86	1.360§ (0.040-46.650)
	Labor pain+previous C/S (reference category)	0 (0%)	1 (3.60%)	>0.99	1 (.-.)
Cause of C/S, n (%)	Failed induction	2 (7.10%)	7 (16.30%)	0.21	0.320§ (0.050-1.940)
	Fetal distress	15 (53.60%)	25 (58.10%)	0.47	0.670§ (0.220-2.010)
	IVF	2(7.10%)	0 (0%)	0.29	5.530§ (0.230-130.350)
	Patient desire	0 (0%)	1 (2.30%)	0.55	0.370§ (0.010-10.180)
	Previous C/S (reference category)	9 (32.10%)	10 (23.30%)	>0.99	1 (.-.)

GA: Gestational age; FGR: Fetal growth restriction; EFW: Estimated fetal weight; C/S: Cesarean section; PTB: Preterm birth; RDS: Respiratory distress syndrome; NICU: Neonatal intensive care unit; UAPI: Umbilical artery pulsatile index; PEC: Preeclampsia; Early-onset PEC: PEC <34 weeks of gestational week; PECsf: PEC with severe features; *Linear regression; § Binary regression; P<0.05 was considered statistically significant.

OR=6.600), higher weight gain (P=0.01; OR=1.001), and more frequent vaginal delivery (P=0.03; OR=9.210). PTB rates were significantly lower with rosuvastatin (P=0.03; OR=0.370). No significant differences were observed between the groups in the following outcomes: pregnancy duration, PEC (P=0.45), early-onset PEC (P=0.59), PECsf (P=0.89), C/S (P=0.79), elective C/S (P=0.98), emergency C/S (P=0.21), stillbirth (P=0.89), 5-minute Apgar score <7 (P=0.60), neonatal death (P=0.60), NICU admission (P=0.33), duration of NICU stay (P=0.35), intraventricular hemorrhage (P=0.60), RDS (P=0.44), and necrotizing enterocolitis (P=0.89). In addition, rates of fetal distress (P=0.73) and oligohydramnios (P=0.86) did not differ between

Table 4: Comparison of the health status of 78 neonates between the rosuvastatin and placebo groups

Variable			Rosuvastatin, n=34	Placebo, n=44	P value
Vital sign	Heart rate, n (%)	Abnormal	0 (0%)	1 (2.27%)	>0.99*
	Respiration rate, n (%)	Abnormal	14 (41.20%)	22 (50%)	0.29†
Skeletal disorder	Hip dislocation, n (%)	Yes	0 (0%)	1 (2.27%)	>0.99*
	Skull fracture, n (%)	Yes	0 (0%)	0 (0%)	0.89*
	Cranial subcutaneous hemorrhage, n (%)	Yes	0 (0%)	0 (0%)	0.89*
	Cranial malformation, n (%)	Yes	0 (0%)	0 (0%)	0.89*
Cleft palate, n (%)		Yes	0 (0%)	0 (0%)	0.89*
Hearing screening test, n (%)		Abnormal	0 (0%)	0 (0%)	0.89*
Vision screening test, n (%)		Abnormal	0 (0%)	0 (0%)	0.89*
Jaundice, n (%)		Yes	5 (14.70%)	8 (18.18%)	0.68†
Hypothyroidism, n (%)		Yes	0 (0%)	0 (0%)	0.89*
Phenylketonuria, n (%)		Yes	0 (0%)	0 (0%)	0.89*
Genital screening, n (%)		Abnormal	0 (0%)	0 (0%)	0.89*

*Fisher's exact test; †Chi-square test; P<0.05 was considered statistically significant.

the groups when compared to those with labor pain or prior C/S. Similarly, no significant differences were found in failed induction (P=0.21), fetal distress (P=0.47), IVF (P=0.29), and patient preference for C/S (P=0.55) when compared to previous C/S cases. Among the 78 deliveries, one neonatal death occurred due to sepsis 4 weeks after birth. A comprehensive comparison of health status indicators for all 78 neonates is presented in table 4.

Comparative analysis revealed no significant differences between groups across all measured parameters: heart rate (P>0.99), respiration rate (P=0.29), hip dislocation (P>0.99), skull fracture (P=0.89), cranial subcutaneous hemorrhage (P=0.89), cranial malformations (P=0.89), cleft palate (P=0.89), hearing screening abnormalities (P=0.89), visual screening abnormalities (P=0.89), jaundice (P=0.68), hypothyroidism (P=0.89), phenylketonuria (P=0.89), and genital abnormalities (P=0.89).

Discussion

In the present RCT, birth weight, UAPI decrement, weight gain, vaginal delivery, and PTB in FGR pregnancies were improved in the rosuvastatin group compared with the placebo group. Clinically, the pregnancy period was longer in the rosuvastatin group than in the placebo group with a narrow confidence interval, which would be promising for further investigations. Given that the pathophysiology and risk factors for cardiovascular diseases and uteroplacental insufficiency are similar, the underlying mechanism of both diseases involves endothelial dysfunction with endothelial inflammation. The primary etiology of placental insufficiency (e.g., FGR) was reported to be placental underperfusion, and the upregulation of sFlt-1 (antiangiogenic factor) was enhanced by the oxidative stress, which created an antiangiogenic environment by blocking the activity of PLGF (proangiogenic factor) and downregulating its level.[30] The antioxidant activity of statins is mediated through multiple mechanisms, including vascular relaxation, antithrombotic effects, and suppression of free radical formation. Regarding their anti-inflammatory effects, statins modulate immune responses by increasing the circulating levels of inflammatory mediators and markers.[6] In a study, the levels of angiogenic factors (sFLT-1/PLGF) were significantly lower in women treated with statins than in the control group.[5] In the present study, the rosuvastatin group showed a significantly greater UAPI decrement, indicating a significant decrease in placental vascular resistance and improved fetoplacental circulation. However, further research is required before these findings can be confidently applied in clinical practice. Prior studies demonstrated that statins enhanced placental-fetal blood supply.[6, 21, 22] Based on this pathophysiology, statins seem to improve the endothelial dysfunction and angiogenic imbalance in the placenta, suggesting their potential for treating and preventing uteroplacental dysfunction. However, Mandy and others showed that pravastatin did not significantly improve Doppler parameters compared to the controls. This lack of significance might be attributable to the small sample size.[23]

In the present study, birth weight increased significantly in the rosuvastatin-treated group.

While Mendoza and colleagues observed a non-significant increase in birth weight following pravastatin treatment,[5] and this lack of significance might be due to their small sample size. Other studies demonstrated that statin use in pregnancies with uteroplacental insufficiency was associated with a significant increase in fetal weight.[18, 21] Although not statistically significant, the rosuvastatin group in our study showed fewer NICU admissions and shorter NICU stays than the controls. Given the potentially beneficial mechanisms observed in this study, these results warrant further investigation through larger-scale clinical trials to establish statistical power and generalizability. It was consistent with Hirsch and colleagues' study which found that pravastatin treatment significantly decreased NICU admission risk compared to the untreated women in the control group.[31] The findings of the present study demonstrated that statin use was associated with improved fetal blood supply, enhanced weight gain, and reduced incidence of PTB. These findings were consistent with a study conducted by Wackernagel and others, who similarly reported a reduction in PTB with statin treatment.[22]

A key strength of this study was its randomized, double-blind, placebo-controlled trial (RCT) design, which enabled causal inference through precise intervention allocation and administration while minimizing selection bias. Furthermore, rigorous control of potential confounding variables at baseline enhanced the internal validity of the findings. The other strengths of this study included the precise definition of variables, rigorous eligibility criteria, and a well-defined study population. Furthermore, a comprehensive data and safety monitoring plan was implemented throughout the study period to systematically document any potential adverse/side effects of rosuvastatin, as well as other maternal and fetal health concerns. Neonatal health status was rigorously assessed using standardized neonatal ward records. However, one limitation was the higher attrition rate observed in the statin group, primarily attributed to participants relocating to southern Iran during the study period. Additionally, rigorous safety monitoring and financial constraints precluded serial monitoring of lipid levels and angiogenic factors (sFLT-1&PLGF) throughout the study, which could have provided further mechanistic insights.

Conclusion

The present study demonstrated that rosuvastatin might safely improve perinatal outcomes in FGR pregnancies, with no observed adverse neonatal effects. As this adequately powered trial showed statistically significant differences, these findings supported rosuvastatin's potential therapeutic role in FGR management. However, several important research directions should be pursued to further validate and extend these results. Larger randomized clinical trials are required to confirm efficacy and safety across diverse populations. Future studies should specifically investigate rosuvastatin on FGR twin pregnancies, employ standardized diagnostic criteria (FGR defined as below the 10th percentile), and evaluate potential dose-response relationships through higher dosing regimens. Incorporating longitudinal monitoring of angiogenic factors (sFLT-1 and PLGF) would provide valuable mechanistic insights, while extended follow-up assessing neurodevelopmental and anthropometric outcomes would clarify the long-term effects on FGR-exposed infants. These comprehensive investigations would strengthen the evidence base for clinical applications of rosuvastatin in FGR management.

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Authors' Contribution

H.V, N.A, Kh.B and A.F: Contributed to the study design, drafting, and revising of the manuscript; M.K and F.A: Contributed to the study design, concept, data gathering, and interpretation of the results, drafting and revising the manuscript; M. Z: Involved in the study design, concept, data analysis, and interpretation of the results, drafting and revising the manuscript. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of Interest: None declared.

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