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Original Article

Effectiveness of pentoxifylline in severe early-onset fetal growth restriction: A randomized double-blinded clinical trial

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ABSTRACT

Objective: Management of pregnancy complicated by severe early-onset fetal growth restriction (FGR) is one of the most challenging obstetrical issues. So far, there has not been a proven option for the treatment or improvement of this condition. Improper immune response during placentation leads to inadequate trophoblast invasion and impaired utero-placental perfusion. Pentoxifylline improves the endothelial function and induces vasodilation by reducing the inflammatory-mediated cytokines. We have evaluated the effect of Pentoxifylline on fetal-placental perfusion, neonatal outcome, and the level of oxidative stress markers before and after the intervention in the setting of severe early-onset FGR.

Materials and methods: This study is a pilot randomized clinical trial on 40 pregnant women who had developed early-onset growth restricted fetus. Pentoxifylline and placebo were given with a dose of 400 mg per os two times daily until delivery. Serial ultrasound examination regarding fetal weight, amniotic fluid and also utero-placenta-fetal Doppler's were done. For the assessment of serum Antioxidant level, blood sampling was done once at the beginning of the study and again, at least, three weeks after the investigation. After delivery, umbilical-cord blood gas analysis, APGAR score at 1 and 5 min, NICU admission, and neonatal death were recorded and compared between the two groups.

Results: Utero-placenta-fetal Doppler's in the Pentoxifylline group did not significantly change compared to the control group. Fetal weight gain was significantly higher in the Pentoxifylline group before (996.33 ± 317.41) and after (1616.89 ± 527.90) treatment ($P = 0.002$). Total serum antioxidant capacity significantly increased in the Pentoxifylline group ($p < 0.036$). Average 5 min Apgar score was significantly higher ($P < 0.036$) and the percentage of babies admitted to NICU was significantly lower ($P < 0.030$) in the treated group.

Conclusion: Using Pentoxifylline in pregnancy affected by FGR might show promising effects. In this study, Pentoxifylline improved the neonatal outcome, increased fetal weight gain, and reduced neonatal mortality by decreasing the level of oxidative stress markers and cutting down the inflammatory cascade.

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Introduction

Fetal growth restriction (FGR) is a condition in which the fetus cannot reach its genetic growth potential [1]. By definition, early-onset FGR is defined as a clinical manifestation of growth restriction presented at or below 32 weeks of gestation [2]. FGR-related risk assessment of all mothers is very important at the beginning of pregnancy [3] since it is associated with higher mortality and morbidity [4,5] despite the fact that it is an uncommon pregnancy complication. Several factors play a role in the pathology of early-onset FGR. Some of them are placenta-mediated risk factors, and the rest are not mediated by the placenta [6]. It seems that improper immune response during placentation leads to inadequate trophoblast invasion and impaired utero-placental perfusion in severe early-onset FGR [7].

Poor placentation may also create a vicious cycle by an imbalance between reactive oxygen species (ROS), reactive nitrogen species (RNS), lipid peroxidation (LPO), and super-oxidative ions production, which leads to endothelial dysfunction and vasoconstriction in the cycle [8–12]. Hydrogen peroxide can also induce cell death and apoptosis and have destructive effects on the tissues [13]. Impaired detoxification of ROS in the human placenta may play a role in developing adverse pregnancy outcomes such as abortion, pre-eclampsia, and preterm rupture of the membranes [14]. Hypoxias and ROS activation could also affect the syncytial knots in the placenta of pregnancy affected by FGR or pre-eclampsia [15].

Lack of uterine arteries transformation to low-resistance vessels due to impaired trophoblastic invasion and maladaptive spiral arteries leads to the high uterine artery (UtA) mean pulsatility index (PI), decreased placental mass, and increased fetal afterload reflected by increased umbilical artery (UA) PI, absent or reverse end-diastolic flow (EDF) in the UA on the fetal side. Fetal hemodynamic response to hypoxia is redistribution of the blood to the brain and other vital organs, which is represented by fetal middle cerebral artery (MCA) vasodilatation and reduced MCA-PI [1,16].

So far, there has not been a proven option for the treatment or improvement of the condition of the pregnancy affected by FGR; currently, its management is based on the close fetal and maternal monitoring and timely delivery to ensure the balance between intrauterine hypoxia, preterm delivery, and consequences of prematurity [1,17]. Several clinical trials were designed for induction of vasodilation or reduction of oxidative factors in severe early-onset FGR to improve prenatal outcome; however, none of them had been conclusive [17–20].

Pentoxifylline, also known as trental, is a xanthine derivative known for vasodilatation effect in the treatment of peripheral arterial disease [21,22]. Pentoxifylline improves the endothelial function and induces vasodilation by reduction of inflammatory-mediated cytokines which play a role in the pathology of pre-eclampsia and early-onset FGR [23–25]. It can also improve fetal placental perfusion by inhibition of platelet aggregation, increased erythrocyte flexibility, and hence, reduction of blood viscosity [21,23].

Pentoxifylline has FDA approval in the treatment of intermittent claudication syndrome [26]. Although its clinical efficiency in many diseases is rather doubtful, it was shown to have a beneficial effect on testicular perfusion [27], placental circulation in preterm labor [28], zygote intra fallopian transfer outcome [29], endometrial response to hormone therapy in premature ovarian failure [30], and multi-infarction dementia [31].

In this study, we evaluated the effect of Pentoxifylline on fetal-placental perfusion and neonatal outcome in the setting of severe early-onset FGR; we also demonstrate the level of oxidative stress markers before and after the intervention to predict Pentoxifylline anti-inflammatory effect.

Method and material

This study is a pilot randomized, clinical trial on 40 pregnant women aged 18–45 years old with the diagnosis of severe early-onset FGR from November 2019 to August 2020, who were referred to Hafez Clinic, Shiraz University of Medical Sciences. The sample size for this pilot study was calculated by assuming the variation of the mean UA-PI indices between the two groups would be 20% in the effect of Pentoxifylline on fetal Doppler [28]. At least 20 patients were required, considering the dropout rate, in each group for a power of 80% and a significance level of 5% (list of blocks was extracted from www.sealedenvelope.com).

Ethical considerations

Our study received the ethics committee approval according to the ethical standards of Shiraz Medical University (NO: IR.SUMS.-REC.1398.559) with the Iranian Clinical Trials Registry (IRCT20140317017034N9, 09/11/2019); all participants were enrolled after filling out the informed consent and they were allowed to withdraw from the study without any descriptions at any time during the study.

Exclusion and inclusion criteria

Inclusion criteria were: Early-onset FGR according to Delphi consensus diagnosis at gestational age (GA) < 32 weeks defined with [2]Abdominal Circumference (AC)/Estimated Fetal Weight (EFW) below 3rd centile or AC/EFW <10th centile combined with UtA-PI >95th centile and/or UA-PI >95th centile, accurate gestational age determined based on the last regular menstrual date compatible with the GA of fetal crown–rump length (CRL) at 8–14 weeks or the date of conception in the setting of assisted reproductive technology [32], fetal viability described as the GA of 24 weeks or greater and estimated fetal weight reached to 500 gr or more [33], Stage I FGR defined as a EFW <3rd centile, MCA pulsatility index <5th centile or mean UtA-PI >95th centile (persisting in two examinations at least 12 h apart) [34], Stage II FGR defined as (AEDV) in UA-PI Doppler or reverse flow in fetal Aortic Isthmic (AOI) (persisting in two examinations at least 12 h apart) [34] Exclusion criteria included multi-fetal pregnancy, rupture of amniotic membrane, maternal medical disease such as coronary artery disease, overt diabetes mellitus, renal failure and rheumatoid disorders, Preterm labor pain, Stage 3 or 4 FGR defined with reversed EDF in UA-PI Doppler or abnormal Doppler in fetal ductus venous [34], Morbid placenta adherent spectrum, any conditions that may lead to vaginal bleeding during pregnancy such as placenta Previa, vasa Previa, Placental abruption, carrying a fetus with congenital anomaly, known aneuploidy or congenital infections, polyhydramnios, maternal infectious disease, immunosuppressive drug consumption, pentoxifylline contraindication, especially Methylxanthines and caffeine hypersensitivity.

Pentoxifylline administration

Pentoxifylline and placebo tablets in the same shape and color were provided by Shiraz School of Pharmacy and prepared in similar bottles. After coding, drugs were given to us in a way that the person administering the drug, patient and sonographer were unaware of the content of the bottles. The nurse delivered the bottles to the participants according to the randomized block table. At the end of the study, the formulations were decoded and the patients assigned to each group were identified. We prescribed Pentoxifylline 400 mg per oz. two times daily until delivery [25].

We also monitored the patient about common Pentoxifylline adverse effect such as belching, stomach upset, nausea, vomiting, flushing, dizziness and hypersensitivity. Except for Pentoxifylline therapy, all pregnancy managements were similar in the two groups and the decision for termination was based on the standard clinical guidelines and clinical assessment [1,17].

Doppler assessment

Ultrasound examination was done by two expert perinatologists, using Voluson E6 machine regarding to EFW, AC, amniotic fluid index and also Doppler assessment of mean UtA PI, UA PI, MCA PI. All Doppler and biometric parameters were measured by the standard methods mentioned in ISOUG guidelines for at least three times and the average was recorded in each examination [32,35]. Fetal surveillance was done and recorded at least once a week and fetal biometry every two weeks till pregnancy termination.

Serum antioxidant measurement

All participants underwent blood sampling once at the beginning of the study and again at least three weeks after the study. After the serum preparation, all samples were stored at minus 70 °C until the end of the study.

Serum reactive oxygen species

For assessing ROS formation in serum samples, 100 μL of the serum was mixed with 1 mL of Tris–HCl buffer (40 mM, pH = 7.4) and 2′, 7′-dichlorofluorescein diacetates (10 μL; final concentration 10 μM). The mixture was incubated in the dark (15 min, 37 °C). Finally, the fluorescence intensity of the samples was assessed (FLUOstar Omega®, Germany) with multifunctional microplate reader (λ of excitation = 485 nm and λ of emission = 525 nm) [36].

Total antioxidant capacity of the serum

The total antioxidant capacity of the serum samples was determined by FRAP assay. First, the FRAP reagent was freshly prepared by mixing 10 volumes of the acetate buffer (300 mmol/L, pH = 3.6), with one volume of $FeCl_3$ (20 mmol/L in water), and one volume of TPTZ (10 mmol/L in 40 mmol/L HCl). Then, 100 μL of the serum samples was added to 900 μL of the FRAP reagent. The mixture was incubated for 5 min in the dark (37 °C). Finally, the samples were centrifuged (17,000 g, 2 min, 4 °C), and the absorbance was assessed (λ = 595 nm, EPOCH® plate reader, USA) [36,37].

Serum lipid peroxidation

The thiobarbituric acid reactive substances (TBARS) were used to measure the serum lipid peroxidation [1,38]. Briefly, 100 μL of serum samples was added to 1 mL of a reaction mixture which contained thiobarbituric acid (0.375% w:v in double-distilled water), trichloroacetic acid (15% w: v), and 1 mL of 100 μL of hydrochloric acid (12 N). Samples were vortexed (5 min) and heated in a water bath (100 °C, 15 min) [1,38]. Finally, they were centrifuged (10,000 g, 10 min) and the absorbance was measured at λ = 532 nm (EPOCH® plate reader, USA) [36,39].

Antenatal assessment

We observed the possible side effect of Pentoxifylline in all mothers. We also recorded weekly random spot urine protein to creatinine, level of maternal blood pressure, and any sign or symptom of pre-eclampsia during the study to compare the effects of Pentoxifylline on developing the pre-eclampsia during the study.

Post-natal assessment

After delivery, umbilical cord blood gas analysis, APGAR score at 1 and 5 min, NICU admission, and neonatal death were recorded and compared between the two groups at the end of the study.

Data analysis

In this study, normal and non-normal continuous variables were reported as mean with standard deviation (sd) and median with interquartile range, respectively. The differences between groups were analyzed by independent sample t-test or Mann–Whitney U test. Continuous variables before and after treatment were compared using pair t-test or Wilcoxon signed-rank test. Categorical variables were presented as number and percentage and Chi-square and Fisher exact test were used to estimate the significant values. The data were analyzed using the statistical package for social sciences (SPSS Inc., Chicago, version 23), and p-value < 0.05 was considered statistically significant.

Result

Eighty-eight pregnant women were diagnosed as early-onset FGR and consulted for participation. However, 22 women refused to use the medications. Fourteen patients were excluded due to comorbid maternal medical disease or complicated with high blood pressure, preeclampsia and vaginal bleeding during study. Six participants with fetal anomalies and placenta abnormalities were kept out; Finally after exclusion of six pregnancies affected by FGR stage 3 or 4 or pregnancy termination due to emergency obstetric conditions, Finally, 20 participants in each group (placebo group and Pentoxifylline group) completed study: (Fig. 1).

Both groups were homogenous in age (year), BMI (kg/m^2), gestational age (weeks), FGR stages (n), gravid, number of previous abortions, Random protein/creatinine (mg/mmol), systolic blood pressure (mmHg), EFW (gram), and utero-placental-fetal Doppler without significant differences (Table 1).

Table 2 shows the main outcomes of delivery and the neonatal condition in both groups. Both groups were similar in the percentage of progression of pre-eclampsia during the follow up, caesarean section delivery, gender of neonates, and neonatal death. However, the groups were not similar in the statistically significant percentage of babies admitted to NICU (P = 0.030).

The mean of delivery time (weeks of gestation), Birth height (cm), Head circumference (cm), Apgar min 1, PH, PCO_2, HCO_3 and median of PO_2, Random protein/creatinine (mg/mmol), and Systolic blood pressure (mmHg) were similar in both groups after treatment. Mean of Apgar min 5 had a significant difference between the groups (P = 0.036).

Laboratory data as LDH (U/L), creatinine (mg/dl), platelet, uric acid (mg/dl), SGOT (U/L), SGPT (U/L), ALK (U/L), BUN (mg/dl)0 and random protein/creatinine are displayed in Table 3. There was no significant difference in laboratory data before and after the treatment in both groups.

Utero placental fetal Doppler blood flow results including umbilical artery PI, MCA-PI and mean of uterine blood flow before delivery time are shown in Table 4. The results of utero-placenta fetal Doppler PI in the treatment group was not significantly lower than the control group. Also, the fetal weight gain was significantly increased in the treatment group before (996.33 ± 317.41) and after (1616.89 ± 527.90) the treatment (P = 0.002) in comparison with the control group before (1138.87 ± 359.16) and after (1549 ± 663.04) administering the placebo. The weight difference before and after treatment in Pentoxifylline group (552.78 ± 351.43) was higher than control group

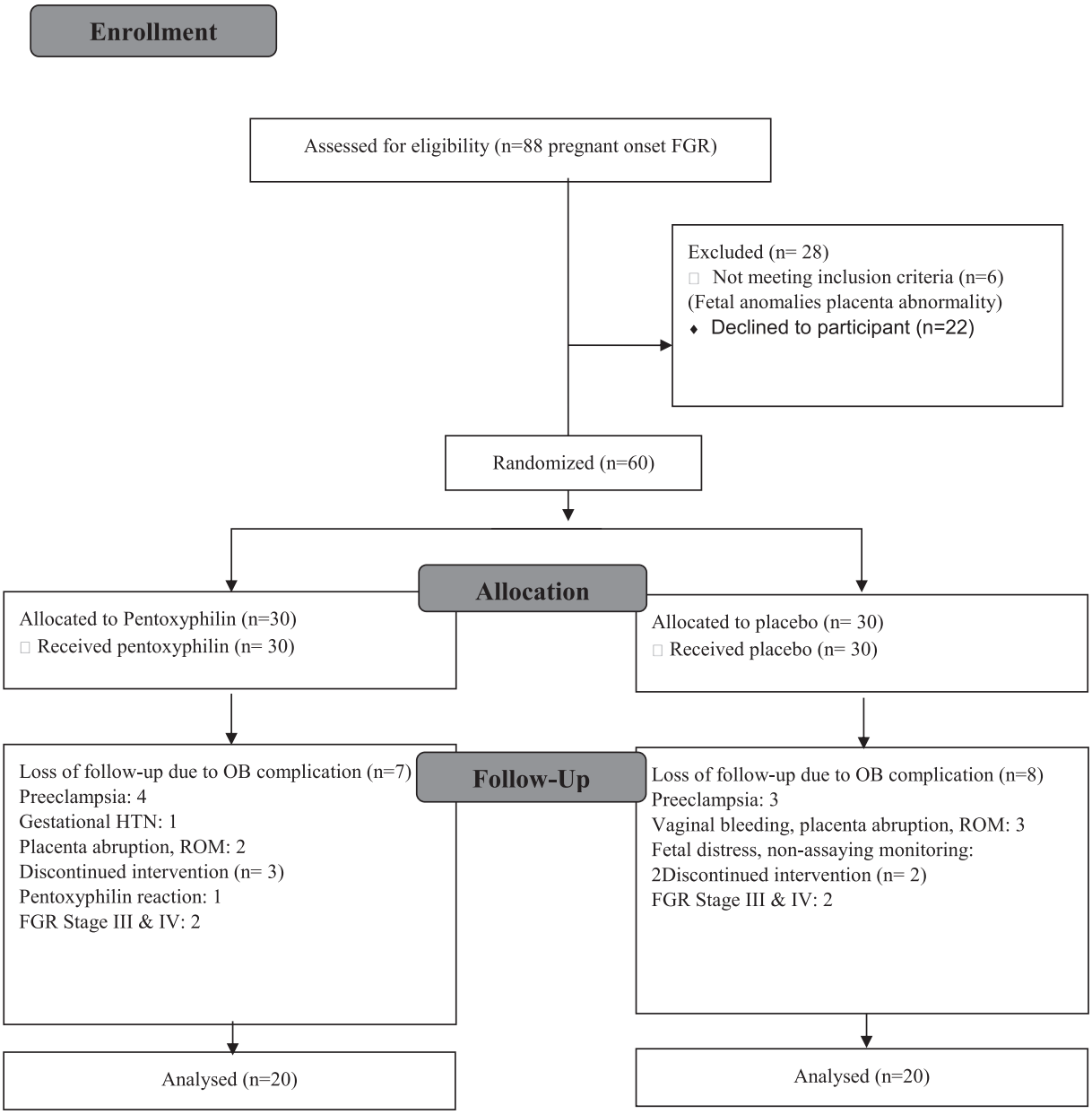

Fig. 1. CONSORT flow diagram for this randomized, single-blinded, placebo controlled clinical trial of the use of pentoxifylline in pregnant women with early onset FGR.

(342.33 ± 338.09) however, this is not statistically significant based on change score analysis (Fig. 2).

Total serum antioxidant capacity (% control), significantly increased in the Pentoxifylline group after the treatment ($p < 0.036$). Measuring the level of Serum Reactive Oxygen Species (ROS) (DCF Fluorescence Intensity), and the serum lipid peroxidation (nmol of TBARS/mg protein) as the ROS mediated indicator did not show a significant difference between the two groups before and after the study (Table 5, Fig. 3).

The most common side effect of Pentoxifylline in this study was nausea without vomiting which is presented in almost all cases. Hypersensitivity reaction to Pentoxifylline occurred just in one case.

Discussion

Management of a pregnancy complicated by severe early-onset FGR is a challenging obstetrical issue. Currently, there is no proven and safe option for the treatment or improvement of the condition. Low-dose aspirin for prevention of FGR is not universally accepted, and the use of heparin in this issue is more controversial [40,41]. The result of maternal sildenafil consumption on growth-restricted fetus is debated and not promising [42,43].

Production of superoxide anions in parallel with anti-angiogenic factors by malperfused placenta in FGR fetus makes a vicious cycle [9,10,23]. The effect of Pentoxifylline in down-regulation of the inflammatory factors and inactivation of superoxide anions has been shown previously in different studies [44–47]. In the study by Zhang and his colleagues, Pentoxifylline could prevent the embryo damage by dose–dependent effect on reducing the hydrogen peroxide production [48]. In the present study, after Pentoxifylline consumption, the serum level of total anti-oxidant capacity significantly increased, which led to a slight decrease in the serum level of ROS and Lipid peroxidation (LPO). However, the decrease in the level of ROS and LPO was not statistically significant. It might

Table 1
Baseline characteristics of the participants.

Variables		Pentoxifylline (N = 20)	placebo (N = 20)	p-value
Age, year		30.66 ± 5.67	30.94 ± 6.06	0.894
Gestational age Weeks		29.13 ± 2.29	30.44 ± 2.30	0.113
BMI (kg/m2)		32.07 ± 5.29	29.98 ± 5.40	0.272
FGR	stage I	8 (40)	12 (60)	0.127
	stage II	12 (60)	8 (40)	
Gravid, Null		9 (45)	11 (55)	0.611
Number of previous abortions		2 (1–3)	1 (1–2)	0.425
Random protein/creatinine (mg/mmol),		0.09 (0.06–0.19)	0.12 (0.05–0.33)	0.782
Systolic blood presser (mm hg)		120 (120–130)	120 (110–130)	0.404
Umbilical artery PI		1.87 ± 0.58	1.56 ± 0.39	0.055
Middle cerebral artery PI		1.81 ± 0.52	1.77 ± 0.56	0.856
Estimated fetal weight (gr)		996.33 ± 317.41	1138.87 ± 359.16	0.340
Amniotic fluid index (cm)		11.03 ± 2.22	12.20 ± 2.95	0.293
Mean Uterine artery PI		1.38 ± 0.81	1.21 ± 0.53	0.511

Variables were described using mean ± SD (continuous normally distributed variables), median and interquartile range(Q1-Q3) (continuous nonnormally distributed variables), or number and percent (categorical variables).

Table 2
Delivery and neonatal outcomes in both groups after treatment.

Variables	Pentoxifylline (N = 20)	placebo (N = 20)	p-value
Preeclampsia	4 (20)	3 (15)	>0.999
cesarean section delivery	18 (90)	20 (100)	0.455
Delivery Time	32.80 ± 3.07	32.77 ± 2.57	0.982
Sex, male	15 (75)	11 (55)	0.290
Birth height (cm)	40.20 ± 5.89	40.66 ± 4.40	0.797
Babies admitted to NICU	12 (60)	19 (95)	0.030
neonatal death	1 (5)	4 (20)	0.346
Head circumference (cm)	28.90 ± 2.93	29.83 ± 3.67	0.433
Apgar min 1	7.20 ± 1.61	6.50 ± 1.58	0.219
Apgar min 5	8.86 ± 0.99	7.94 ± 1.34	0.036
PH	7.32 ± 0.06	7.31 ± 0.07	0.642
PCO2	41.66 ± 13.28	47.68 ± 7.58	0.116
PO2	23 (18–47)	19 (18–25)	0.466
HCO3	23.87 ± 5.92	24.31 ± 3.32	0.791
Random protein/creatinine (mg/mmol)	0.17 (0.09–0.38)	0.24 (0.11–0.57)	0.168
Systolic blood pressure (MM Hg)	129 (120–142)	129 (117–136)	0.772

Variables were described using mean ± SD (continuous normally distributed variables), median and interquartile range(Q1-Q3) (continuous nonnormally distributed variables), or number and percent (categorical variables).

Table 3
Laboratory variables before and after treatment in both groups.

	Pentoxifylline (N = 20)		P-value	placebo (N = 20)		P-value
	Before	After		Before	After	
LDH (U/L)	508.93 ± 131.85	565.06 ± 173.41	0.284	469.93 ± 130.57	490.37 ± 290.02	0.740
Creatinine (mg/dl)	0.68 ± 0.12	0.66 ± 0.08	0.546	0.68 ± 0.13	0.68 ± 0.11	0.868
Platelet	194.00 ± 39.59	187.73 ± 37.24	0.297	217.82 ± 59.40	209.00 ± 51.64	0.212
Uric Acid (mg/dl)	4.02 ± 0.90	4.44 ± 1.07	0.086	4.27 ± 1.38	4.57 ± 1.77	0.412
SGOT (U/L)	29 (25–32)	29 (23–30)	0.754	31 (23–35)	35 (26–41)	0.103
SGPT (U/L)	20 (14–30)	19 (18–27)	0.460	26 (20–30)	29 (20–36)	0.266
ALK(U/L)	211 (151–262)	201 (133–378)	0.116	209 (147–298)	225 (191–327)	0.182
BUN(mg/dl)	9 (8–10)	9 (8–12)	>0.999	10.5 (7.5–12.25)	11 (9.5–13.5)	0.159

Variables were described using mean ± SD (continuous normally distributed variables), or median and interquartile range(Q1-Q3) (continuous nonnormally distributed variables).

Table 4
Utero-Placenta-Fetal Doppler's and Amniotic fluid index results after investigation in both groups.

	Pentoxifylline (N = 20)	Placebo (N = 20)	P-value
Umbilical artery PI	1.70 ± 0.41	1.76 ± 0.73	0.796
Middle cerebral artery PI	1.60 ± 0.45	1.46 ± 0.53	0.467
Amniotic fluid index	9.95 ± 3.56	9.54 ± 2.63	0.789
Mean Uterine artery PI	1.36 ± 0.73	1.13 ± 0.50	0.333

Variables were described using mean ± SD (continuous normally distributed variables).

have shown better results if the sample size was larger. McKinney et al. in their study mentioned the positive effect of Pentoxifylline on inhibition of ROS activation and also reduction of LPO in human spermatozoa [49].

In this study, the comparison of the fetal weight gain in both groups showed a significant difference in the treatment with Pentoxifylline. We assume that the preventive effect of Pentoxifylline on ROS activation and oxidative anion production may decrease the cell death and damage which leads to increased fetal

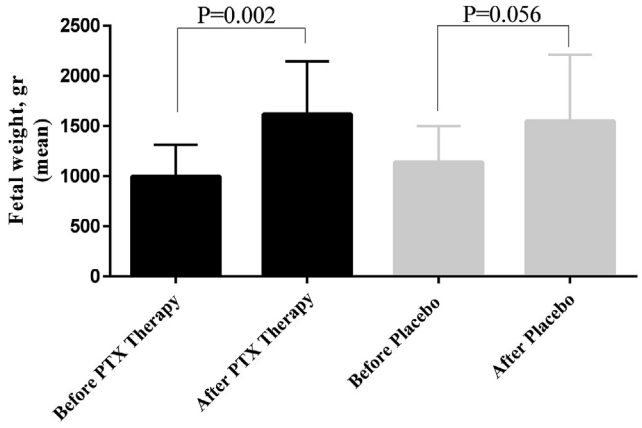

Fig. 2. Fetal weight between two groups before and after treatment (P = 0.340, P = 0.829) and fetal weight gains within two groups before and after treatment (P = 0.002, P = 0.056) (PTX; Pentoxifylline).

weight. Destruction of Cellular DNA and proteins by significant deficiencies in cellular antioxidant activities and ROS mediated activation were shown in growth-restricted neonates in different studies [50–52]. Kim et al. determined that there was a significant and reverse correlation between low birth weight and maternal urine oxidative stress agent in full-term babies [53].

We also hypothesized the positive effect of Pentoxifylline on utero-placenta-fetal vessel Doppler velocity by improvement in the endothelia function and flexibility of red blood cells [21,23]. Previously, Lauterbach et al. confirmed a significant decrease in UA-PI and an increase in MCA-PI after three weeks of administrating Pentoxifylline for prevention of preterm birth [28]. In our work, there were not any significant differences in utero-placenta-fetal Doppler's variables including UA-PI, mean Ut-A PI and MCA-PI between the two groups before and after the study. Our data supported the result of a study conducted by Baileya et al. to evaluate the effect of Pentoxifylline on uterine artery blood flow in pregnant mares [54]. In another study, Klycheva et al. demonstrated the partial beneficial effect of Pentoxifylline on utero-placental blood flow in pregnancies was complicated by FGR [55].

We did not observe a significant difference between the two groups before and after the study in terms of proteinuria and pre-eclampsia progression [2,47]. However, the amount of proteinuria was one percent higher in the control group than the Pentoxifylline group. Based on the hypothesis of preventive effects of Pentoxifylline on pre-eclampsia and proteinuria by down-regulation of oxidative stress agents and improvement of the endothelial function [23,56], it is concluded that the amount of proteinuria was decreased by Pentoxifylline usage.

After birth, 5-min APGAR in the babies who were born from the mothers undertaking Pentoxifylline was significantly higher, and NICU admissions were significantly lower in this group in comparison with the placebo group. In terms of neonatal death, although there was not a significant difference between the two groups, 80 percent (4 out of 5) of them occurred in the placebo group. The lower number of NICU admissions and neonatal death in Pentoxifylline group could be due to promising anti-inflammatory and antioxidant effect of Pentoxifylline which may ultimately

Table 5
Serum Reactive Oxygen Species (ROS), Lipid peroxidation and Total antioxidant capacity before and after treatment in the Pentoxifylline and control groups.

	Pentoxifylline (N = 20)		P-value	Control (N = 20)		P-value
	Before	After		Before	After	
ROS, (DCF Fluorescence Intensity)	125,474 (101,312–142,918)	105,678 (99,070–118,954)	0.156	99,901 (93,362–114,974)	104,107 (97,149–115,171)	0.267
Lipid peroxidation, (nmol of TBARS/mg protein)	0.5 (0.38–0.70)	0.43 (0.32–0.73)	0.105	0.61 (0.54–0.71)	0.62 (0.51–0.75)	0.500
Antioxidant capacity, (% control)	0.21 (0.17–0.24)	0.25 (0.21–0.31)	0.036	0.25 (0.20–0.33)	0.25 (0.22–0.28)	0.679

Variables were described using median and interquartile range(Q1-Q3) (continuous nonnormally distributed variables).

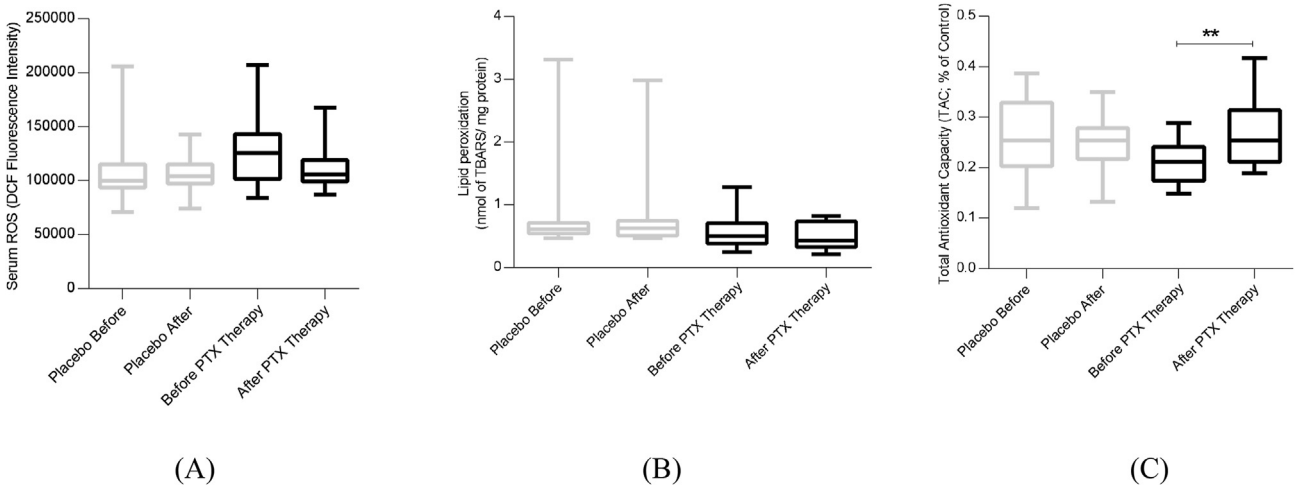

Fig. 3. A: Serum Reactive Oxygen Species (ROS), B: Lipid peroxidation and C: Total antioxidant capacity before and after treatment in Pentoxifylline (PTX) and control groups. **; show significant difference before and after treatment.

improve the neonatal condition. Neonatal sepsis is one of the main causes of death among the very low birth weight newborns [57].

The beneficial effect of Pentoxifylline therapy in neonatal sepsis was observed in several studies [28,58–61]. In Cochrane review, which was done in 2015, Pentoxifylline in combination with antimicrobial treatment could decrease all neonatal mortalities and hospital stays in neonatal sepsis [62]. In the study done by Hamilçıkan and colleagues, Pentoxifylline therapy significantly decreased the level of CRP as an acute phase reactant agent and improved blood gas parameters in the septic neonates with very low birth weight [58].

The most common side effect of Pentoxifylline in this study was nausea without vomiting which is presented in almost all cases. Fortunately, it improved after several days without any medication. Hypersensitivity reaction occurred just in one case which is presented by urticaria and nose bleeding about 3 h after the first dose administration, leading to the discontinuation of the medication.

One of the main limitations of this study was the small sample size. A large number of mothers did not accept the drug usage, whereas they were not sure about its benefits over the risks. Prescription of many conventional drugs during pregnancy due to unknown side effects on mothers and their fetuses and unproven benefits is one of the biggest problems and challenging issues regarding the ethical aspects in all clinical trials. Another problem we were faced with during the study was the loss of cases due to an emergency leading to pregnancy termination, which resulted in missing the data and the small sample size.

Conclusion

We concluded that using Pentoxifylline in a pregnancy affected by FGR could have promising effects. In this study, Pentoxifylline improved the neonatal outcome, increased the fetal weight gain, and reduced neonatal mortality by decreasing the level of oxidative stress anions and cutting down the inflammatory cascade. It is recommended that more randomized clinical studies with larger sample size should be conducted to confirm and support our hypothesis.

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Declaration of competing interest

There is no conflict of interest to be declared regarding the manuscript.

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