# Evaluating the Effect of Utrogestan on Idiopathic Intrauterine Growth Retardation

**Abstract**

**Background:** Intrauterine growth factor (IUGR) is one of the most important causes of neonatal mortality. The aim of this study was to evaluate the therapeutic effect of utrogestan on the treatment of IUGR and its complications. **Materials and Methods:** In this clinical trial, 66 pregnant women with idiopathic IUGR embryos were enrolled. Patients in the intervention group, in addition to receiving routine treatment of control group (high-protein diet, resting), took utrogestan capsules (100 mg) twice daily. The primary and secondary outcomes of the disease were recorded in a checklist. Data were analyzed using SPSS 18 using an independent $t$-test, Chi-square test, and Fisher's exact test. **Results:** In the intervention group, mean neonatal weight ($P = 0.003$), mean neonatal Apgar score ($P = 0.001$), and mean gestational age at birth ($P = 0.001$) were significantly higher than those in the control group. There was no neonatal death in the intervention group, whereas in the control group, four cases of neonatal death were observed ($P = 0.03$). In the majority of subjects in the intervention group, resistance index, and pulsatility index of the umbilical artery decreased ($P = 0.002$). The difference in abdominal circumference and gestational age in the intervention group decreased ($P = 0.01$). In the intervention group, the diastolic flow of the umbilical artery increased ($P = 0.002$). **Conclusion:** Utrogestan was effective as an inexpensive and effective way to treat IUGR and improve pregnancy outcomes.

**Keywords:** *Fetal growth retardation, placenta, utrogestan*

**Belgheis Mohammadi, Marzieh Matinfar[1], Fatemeh Drees[2], Sheida Shabanian**

*Departments of Gynecology and Obstetrics and [2]Epidemiology and Biostatistic, Shahrekord University of Medical Sciences, [1]Departments of Gynecology and Obstetrics, Student of Research Committee, Shahrekord University of Medical Sciences, Shahrekord, Iran*

## Introduction

Intrauterine growth restriction (IUGR) is a serious complication of pregnancy, which, in addition to being one of the main causes of neonatal mortality,[1] also increases mortality in adulthood.[2] Risk factors for IUGR are infection,[3] maternal age, history of IUGR, maternal medical underlying problems, inadequate weight gain, substance abuse, certain medications, abnormal placenta, genetic factors, and impairment in the supply of food for the fetus (problems related to the placenta and maternal nutrition).[4] Placental insufficiency is one of the most important causes of IUGR.[5] Therefore, treatments and preventive measures should focus on the most important risk factors. Progesterone supplementation in patients with IUGR may lead to an increase in the blood flow of the uterus and the placenta. Progesterone acts on the myometrium and results in the inhibition of estrogen activity by inhibiting the replacement of estrogen

receptors.[6] However, some studies have shown that progesterone has no effect on placental blood circulation.[7] The effect of utrogestan on the pregnancy outcome or its effect on maternal factors has not yet been studied simultaneously. In addition, more suitable treatments for women with IUGR fetuses can reduce associated side effects and risks in mothers and infants.[8] This study was conducted to compare the effects of utrogestan (one of the progesterone imitators) and conventional methods on idiopathic IUGR.

## Materials and Methods

The present study was a single-blind randomized clinical trial that was conducted on women with idiopathic IUGR pregnancy referred to the Gynecology and Obstetrics Clinic of Shahrekord, southwest Iran. The women were matched by age, body mass index (BMI), and gestational age. After the procedure of the study was explained to the women and they completed the informed consent form to participate in the study,

*Address for correspondence:*
*Dr. Marzieh Matinfar,*
*Student of Research Committee, Shahrekord University of Medical Sciences, Shahrekord, Iran.*
*E-mail: dr.matinfar56@gmail.com*

66 pregnant women with idiopathic IUGR were selected according to a sample size calculation formula used in a similar study,[9] and were included in the study.

The inclusion criteria were idiopathic IUGR based on weight <10 percentiles without any specific maternal, fetal, and placental causes, 18–35 years of age, singleton pregnancy, BMI of 19–25, and the gestational age of 28–34 weeks. Congenital or chromosomal anomalies in the mother and fetal infections, high blood pressure, diabetes, kidney disease, cardiovascular disease, connective tissue disease, and digestive disease, hematological disease, and uterine anomalies, fetal infections, cigarette smoking, alcohol use, antiepileptic drugs and neoplasm, abnormal placenta in ultrasonography such as accreta, hematoma, abruption, and the positive first or second 3-month screening test were considered exclusion criteria. Diagnosis of IUGR was made based on ultrasonography and weighing <10 percentile or abdominal circumference (AC) reduction for 2 weeks compared to gestational age and decreased diastolic flow of the umbilical artery.[10] This study was done based on asymmetrical and idiopathic IUGR, whose causes are absolutely unknown.

All pregnant women with the gestational age of 28–34 weeks and idiopathic IUGR embryo were randomly assigned to the intervention and control groups. The eligible women were selected by convenience sampling, and Randomized Allocation Software was used to randomly assign them to the groups. The two groups were matched by mother's age, maternal weight at the beginning of pregnancy, maternal BMI at the beginning of pregnancy, maternal systolic blood pressure, maternal diastolic blood pressure, and gestational age based on last menstrual period (LMP). In the intervention group (33 patients), two utrogestan capsules (100 mg) were daily administered along with routine therapy (high-protein diet and rest) and in the control group (33 patients), the patients underwent routine treatment alone. Patients were examined and underwent sonography for fetal monitoring once a week until delivery and after starting the treatment [Figure 1].

Fetal monitoring was performed using clinical examinations and sonography. Clinical examinations, including general examinations, focused on hypertension, edema, and weight loss and gain; abdominal examinations were also conducted. The primary outcomes under study, including birth weight, birth Apgar, and perinatal mortality, were recorded in a checklist. The secondary outcomes under study were Doppler index, pulsatility index (PI), resistive index (RI), umbilical artery, the $\frac{PI\,MCA}{PI\,umbelical\,arteries}$ ratio, the gestational age at delivery and the need for cesarean section for birth and embryo weight.[11] The calculation of fetal weight was performed using the Hadlock formula,
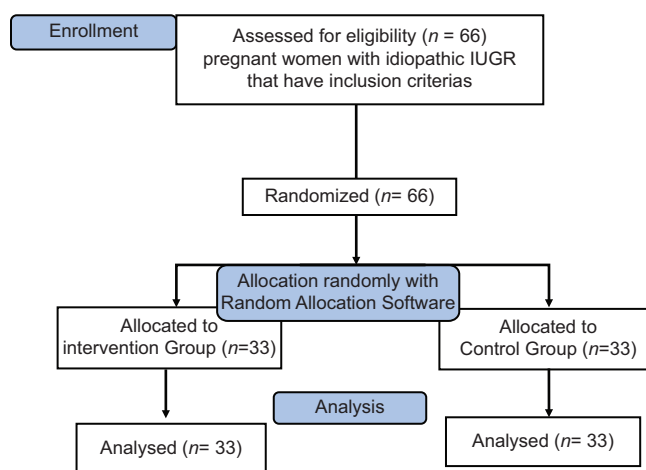


Figure 1: Consort 2010 flow diagram for this study

Doppler velocimetry, and systolic diastolic (S/D) ratio in the umbilical artery.[12]

Declaration of Helsinki ethical standards was observed in conducting the study and the protocol of the study was registered as IRCT2017081510222N11 in the Iranian Registry of Clinical Trials.

Data were collected by the SPSS version 18 using descriptive statistics frequency, percentage, and mean (± standard deviation [SD]) and analytical statistics (including independent *t*-test, Chi-square test, Fisher's exact test, and analysis of variance). $P < 0.05$ was considered significance level.

## Results

Mother's age, maternal weight at the beginning of pregnancy, maternal BMI at the beginning of pregnancy, maternal systolic blood pressure, maternal diastolic blood pressure, gestational age based on LMP did not differ significantly between control and treatment groups, but the maternal weight at the end of pregnancy and maternal BMI at the end of pregnancy were significantly higher in the treatment group than in control group ($P < 0.05$) [Table 1].

The mean ± SD age of the women was 28.30 ± 5.92 years in the control group and 27.70 ± 3.25 years in the intervention group, with no statistically significant difference ($P > 0.05$). The mean ± SD of maternal weight at the beginning of pregnancy was 57.67 ± 8.57 kg in the control group and 61.65 ± 9.47 kg in the intervention group, without any significant difference ($P > 0.05$), and the mean ± SD maternal weight at the end of pregnancy was 67.60 ± 9.15 kg in the control group and 74.24 ± 10.07 kg in the intervention group; the maternal weight at the end of pregnancy was significantly higher in the intervention group than in the control group ($P < 0.05$).

There was no significant difference in BMI between the two groups at the beginning of pregnancy ($P > 0.05$). However, at the end of pregnancy, the maternal BMI

| Variables | Mean±SD | | P |
|---|---|---|---|
| | Control group | Intervention group | |
| Mother's age (years) | 28.30±5.92 | 27.70±3.25 | 0.609 |
| Maternal weight at the beginning of pregnancy (kg) | 57.67±8.57 | 61.65±9.74 | 0.078 |
| Maternal weight at pregnancy (kg) | 67.60±9.15 | 74.24±10.07 | 0.007** |
| Maternal BMI at the beginning of pregnancy | 22.12±3.44 | 23.38±3.48 | 0.137 |
| Maternal BMI at the end of pregnancy | 25.94±3.71 | 28.07±3.86 | 0.025* |
| Mother's systolic blood pressure | 105.45±11.34 | 102.73±8.76 | 0.278 |
| Maternal diastolic blood pressure | 68.48±8.15 | 65.76±7.51 | 0.162 |
| Gestational age based on LMP (day) | 231.58±15.20 | 228.21±8.90 | 0.278 |

Table 1: Comparison of demographic and clinical characteristics of mothers between two groups

*$P<0.05$, **$P<0.01$. SD: Standard deviation, BMI: Body mass index, LMP: Last menstrual period

was significantly higher in the intervention group than in the control group ($P > 0.05$). The systolic and diastolic blood pressure of the two groups was not significantly different ($P > 0.05$). In addition, gestational age based on LMP in the two groups was similar ($P < 0.05$) [Table 1].

The mean weight of infants ($P = 0.003$), Apgar score ($P = 0.001$), and gestational age ($P = 0.001$) at birth was significantly higher in treatment group than in control group ($P < 0.01$) [Table 2].

There was no neonatal death in the intervention group, whereas in the control group, four cases of neonatal death (12.1%) were observed. Termination of pregnancy in the intervention group was normal vaginal delivery in the majority of subjects (54.5%) and cesarean section in the majority of the subjects in the control group (60.6%). In the majority of subjects in the intervention group (54.5%), PI and RI of the umbilical artery decreased ($P = 0.002$). However, in PI, majority cases in treatment group, 18 (54.5%) was reduced and in the control group 27 (81.8%) was increased, a significant relation was observed between two groups ($P = 0.002$).

In the majority of the subjects in the intervention group (63.6%), a decrease in the difference between AC and gestational age was observed ($P = 0.015$), and in the majority of the subjects in the control group (60.6%), an increase in the significant difference between AC and gestational age was observed [$P = 0.015$, Table 3].

In addition, none of the patients showed side effects after taking utrogestan tablets.

## Discussion

This study was conducted to compare the effect of utrogestan and conventional methods for the treatment of IUGR in pregnant women. Utrogestan is a progesterone imitator drug that is classified as a female hormone. In the present study, maternal weight at the end of pregnancy was higher in subjects treated with utrogestan tablets than in the control group. In this regard, Kalem *et al.* reported a significant difference between the two

groups in terms of maternal weight, which was higher in the progesterone group than in the control group.[13] In addition, at the end of pregnancy, the maternal BMI, mean weight, mean Apgar score, and mean gestational age at birth were higher in subjects treated with utrogestan tablets than those in the control group. Wadhwa *et al.* conducted a study to comparatively investigate the effects of dydrogesterone (oral progesterone analog) and the routine treatment (resting and high-protein diet) in pregnant women in 28–34 weeks of pregnancy with a fetus with IUGR. Based on the results, the mean birth weight was higher in the group treated with dydrogesterone or oral progesterone analog than in the control group. In addition, the need for hospital services, the low Apgar score at birth, and the mortality rate were also higher in the intervention group than in the control group.[9]

In this study, there was no fetal death in the intervention group, while in the control group, four cases of fetal death were observed. In this regard, a study showed that in the first trimester, utrogestan in women at risk of abortion can be effectively administered to women with the proper indications.[14] A study reported that suppository progesterone could reduce the rate of abortion in women at risk of abortion and 20 weeks of their pregnancy.[15] Diemert *et al.* reported that progesterone by 1 ng/ml in the second trimester was associated with an augmentation in birth weight.[16]

Termination of pregnancy in the intervention group in the majority of subjects (54.5%) was normal vaginal delivery, and in the control group (60.6%) was cesarean section. In the majority of subjects in the intervention group, PI and RI of the umbilical artery decreased. In the majority of the intervention group (54.5%), umbilical arterial end-diastolic flow increased. Along with these results, in a study conducted by Vafaei *et al.*, significant reduction in the PI of the uterine artery was seen after progesterone administration.[17] A study has also shown that in IUGR pregnancies, RI, PI and S/D ratio of the umbilical artery were higher than the normal group.[7]

Besides that, the results of another study showed that decreased progesterone during the last weeks of pregnancy

**Table 2: Comparison of Apgar score, neonatal weight, and gestational age at birth between two groups**

| Variables | Mean±SD | | *P* |
|---|---|---|---|
| | Control group | Intervention group | |
| Apgar score | 8.30±1.26 | 9.00±0.000 | 0.001** |
| Neonatal weight (g) | 2027.27±474.25 | 2757.27±356.12 | 0.003** |
| Gestational age at birth (day) | 250.52±14.68 | 264.45±5.48 | 0.001** |

**P<0.01. SD: Standard deviation

**Table 3: Comparison of the frequency of the variables studied in studied groups**

| Variables | Control group | Intervention group | *P* |
|---|---|---|---|
| Neonatal death | | | |
| Yes | 4 (12.1) | 0 (0) | 0.039* |
| No | 29 (87.9) | 33 (100) | |
| Type of delivery | | | |
| Vaginal delivery | 13 (39.4) | 18 (54.5) | 0.218 |
| Cesarean section | 20 (60.6) | 15 (45.5) | |
| PI Doppler index umbilical artery | | | |
| Unchanged | 0 (0) | 0 (0) | 0.002** |
| Increase | 27 (81.8) | 15 (45.5) | |
| Decrease | 6 (18.2) | 18 (54.5) | |
| RI Doppler index | | | |
| Unchanged | 0 (0) | 0 (0) | 0.002** |
| Increase | 27 (81.8) | 15 (45.5) | |
| Decrease | 6 (18.2) | 18 (54.5) | |
| AC difference trend and gestational age | | | |
| Unchanged | 1 (3) | 3 (9.1) | 0.015[a],** |
| Increase | 20 (60.6) | 9 (27.3) | |
| Decrease | 12 (36.4) | 21 (63.6) | |
| Umbilical arterial end-diastolic flow | | | |
| Unchanged | 0 (0) | 0 (0) | 0.002** |
| Increase | 6 (18.2) | 18 (54.5) | |
| Decrease | 27 (81.8) | 15 (45.5) | |

*P<0.05, **P<0.01, Values in cells are frequency (%). [a]Test for this variable is Fisher's exact test and for other variables, Chi-square test was done. PI: Pulsatility index, RI: Resistive index, AC:Abdominal Circumference

in mice reduced the growth of the fetus and the placenta, and progesterone was considered a trophic stimulus for the placenta. The effect of progesterone reuptake in the last months of pregnancy was more pronounced in the placental basal zone, which was due to the high expression of mRNAs that encoded PR-A and PR-B isoforms.[18] Another study showed that vaginal progesterone may produce vasodilatory effects on the umbilical cord [17] due to decreased PI in the uterine arteries in the second and third trimesters of pregnancy. Nama *et al*. observed that

dydrogesterone significantly increased the birth weight of neonates with IUGR.[19] In some other studies, it has also been shown that progesterone and estrogen increase blood supply to the uterus and ultimately increase endometrial thickness.[20-22] Female sex hormones such as estrogen and progesterone trigger the regulation of trophoblastic invasion and restoration of the uterine arteries by modulating the synthesis and release of angiogenic factors by placenta cells, and thus play a leading role in developing IUGR.[22-24] However, in a study on the effect of maternal progesterone level on IUGR and its relationship with Doppler ultrasonography, progesterone caused no effect on the rate of placental blood flow.[7]

Progesterone vaginal suppository can reduce PI and RI middle cerebral artery and umbilical artery in Doppler ultrasound and can improve fetal-placental perfusion in pregnancies with preterm delivery IUGR.[7] The progesterone compounds do not affect the blood flow and thickness of the uterus.[25] It is likely that the main reason for the inconsistency in the results of studies is the multifactorial nature of IUGR and the difference in the methodology and type of progesterone used in various studies.[26]

In the present study, taking utrogestan tablets did not show any side effects in patients. In a study, utrogestan was prescribed for patients at risk of miscarriage in the first 3 months. During the study, patients did not experience any particular side effects; only a few patients reported morning headache, and at the completion of the study, 61 out of 68 patients were discharged with complete health and no complications.[13] Taken together, utrogestan does not cause any maternal and fetal side effects and is a safe drug during pregnancy.[26]

## Conclusion

It seems that utrogestan, a progesterone imitator, is effective in reducing IUGR and ultimately improving pregnancy outcomes. More clinical trials are required to determine the role of utrogestan in treating IUGR.

### Acknowledgments

### Financial support and sponsorship

### Conflicts of Interest

There are no conflicts of interest.

### References

1. Sharma D, Shastri S, Farahbakhsh N, Sharma P. Intrauterine

growth restriction – Part 1. J Matern Fetal Neonatal Med 2016; 29(24):3977-87.

2. Said, Joanne M. The role of proteoglycans in contributing to placental thrombosis and fetal growth restriction. J Pregnancy 2011;2011:1-5.

3. Pereira L, Petitt M, Fong A, Tsuge M, Tabata T, Fang-Hoover J, *et al*. Intrauterine growth restriction caused by underlying congenital cytomegalovirus infection. J Infect Dis 2014;209 (10):1573-84.

4. Gaudineau A.[Prevalence, risk factors, maternal and fetal morbidity and mortality of intrauterine growth restriction and small-for-gestational age]. J Gynecol Obst Bio R 2013; 42 (8):895-910.

5. Sharma D, Shastri S, Sharma P. Intrauterine Growth Restriction: Antenatal and Postnatal Aspects. Clin Med Insights Pediatr 2016; 10:CMPed-S40070.

6. Bazer FW, editor. Endocrinology of pregnancy. Springer Science & Business Media; 2012 Dec 6. [Last accessed on 2015 Dec 07]

7. Borna S, Bandarian M, Abdollahi A, Bandarian F, Malek M. Maternal progesterone level in fetal growth restriction and its relationship with Doppler velocimetry indices. Iran J Radiol 2011;8(1):33-7.

8. Alberry M, Soothill P. Management of fetal growth restriction. Arch Dis Child Fetal Neonatal Ed 2007; 92(1):F62-7.

9. Wadhwa L, Batra S, Tempe A. Role of dydrogesterone in the treatment of idiopathic IUGR. Int J Reprod Contracept 2016;2:157-60.

10. Gunningham FG, Gant NF, Leveno KJ, Gilstrap LC, Hauth JC, Wenstrom KD. Williams Obestetrics. 22th ed. Philadelphia: McGrow-Hill; 2005. p. 1049.

11. Khong SL, Kane SC, Brennecke SP, da Silva Costa F. First-trimester uterine artery Doppler analysis in the prediction of later pregnancy complications. Dis Markers 2015;2015:1-10.

12. Njoku C, Emechebe C, Odusolu P, Abeshi S, Chukwu C, Ekabua J. Determination of accuracy of fetal weight using ultrasound and clinical fetal weight estimations in calabar South, South Nigeria. Int Sch Res Notices 2014;2014:1-6.

13. Kalem MN, Kalem Z, Bakırarar B, Ergün A, Gürgan T . The effect of progesterone use in the first trimester on fetal nuchal translucency. J Turk Ger Gynecol Assoc 2018;19:29-33.

14. Marinov B, Petkova S, Dukovski A, Georgiev G, Garnizov T, Manchev V, *et al*. Utrogestan and high risk pregnancy. Akush Ginekol (Sofiia) 2004;43(5):22-4.

15. Yassaee F, Shekarriz-Foumani R, Afsari S, Fallahian M. The effect of progesterone suppositories on threatened abortion: A randomized clinical trial. J Reprod Infertil 2014;15(5):147-51.

16. Diemert A, Goletzke J, Barkmann C, Jung R, Hecher K, Arck P. Maternal progesterone levels are modulated by maternal BMI and predict birth weight sex-specifically in human pregnancies. J Reprod Immunol 2017;121:49-55.

17. Vafaei H, Zamanpour T, Raeisi Shahraki H. Preterm birth prevention: Effects of vaginal progesterone administration on blood flow impedance in uterine-fetal circulation by Doppler sonography. Glob J Health Sci 2015;8:172-8.

18. Mark PJ, Smith JT, Waddell BJ. Placental and fetal growth retardation following partial progesterone withdrawal in rat pregnancy. Placenta 2006;27:208-14.

19. Nama N, Ehsan N. Synopsis effect of oral dydrogesterone on mean neonatal birth weight in the treatment of idiopathic intra uterine growth restriction-A synopsis. J Pioneer Med Sci 2016;6(2):23.

20. Farahbod F, Soureshjani SH. A systematic review of medicinal plants and plant derivatives affecting increase in endometrial thickness. Int J Pharm Sci Rev Res (IJPSR). 2018;9(1):53-7.

21. Noé G, Sitruk-Ware R, Zegers-Hochschild F, Variano B, Montero JC, Arriagada P, *et al*. Endometrial effect of progesterone delivered by vaginal rings in estrogen-treated postmenopausal women. Climacteric 2010;13:433-41.

22. Maliqueo M, Echiburú B, Crisosto N. Sex steroids modulate uterine-placental vasculature: Implications for obstetrics and neonatal outcomes. Front Physiol 2016;7:152.

23. Flood PF, Tyler NJ, Read EK, Rodway MJ, Chedrese PJ. Ovarian and placental production of progesterone and oestradiol during pregnancy in reindeer. Anim Reprod Sci 2005;85:147-62.

24. Omar HA, Ramirez R, Gibson M. Properties of a progesterone-induced relaxation in human placental arteries and veins. J Clin Endocrinol Metab 1995;80:370-3.

25. Yavangi M, Rabiee S, Nazari S, Farimani-Sanoee M, Amiri I, Bahmanzadeh M, *et al*. Comparison of the effect of oestrogen plus *Foeniculum vulgare* seed and oestrogen alone on increase in endometrial thickness in infertile women. J Clin Diagn Res 2018;12 (1):QC1-QC4.

26. Zhu X, Zhang X, Fu Y. Utrogestan as an effective oral alternative for preventing premature luteinizing hormone surges in women undergoing controlled ovarian hyperstimulation for *in vitro* fertilization. Medicine (Baltimore) 2015;94:e909.