

# Maternal and Fetal Doppler Blood Flow Velocimetry Changes in the Management of Asymptomatic Preterm Labor With Vaginal Progesterone Tablet

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**Abstract-** Doppler sonography has been used for evaluation of different fetal responses to various drugs on doppler blood flow patterns in fetal circulation that may indicate poor fetal prognosis. To assess the uterine and fetal doppler blood flow velocimetry changes in the management of asymptomatic preterm labor with vaginal progesterone tablet, it is found that using a vaginal tablet of progesterone affects uterine, umbilical and fetal middle cerebral arteries in the second and third trimesters of pregnancy. This prospective Case series (uncontrolled longitudinal study) was conducted in an outpatient clinic and emergency unit in Moheb Yas hospital during 2015-2016. For all subjects, 200 mg vaginal progesterone tablet (one tablet before bedtime) was administered. Additionally, transvaginal Doppler sonography was performed to measure uterus, umbilical, and middle cerebral arteries before the treatment with progesterone and 24 hours after the treatment with that, respectively. The mean gestational age of participants was  $28.8 \pm 2.9$  weeks, ranging from 23 to 32 weeks of gestation. There was no significant change in the fetal middle cerebral artery-peak systolic velocity (MCA-PSV), middle cerebral artery resistance index (MCA-RI), MCA-PI, Umbilical arterial Systolic-Diastolic (UA S/D), Right UtA-RI and Left UtA-RI before the beginning of progesterone treatment to 24 hours after. The current study indicated that the 200 mg vaginal tablet of progesterone for treatment of preterm labor leads to a reduction in the middle cerebral artery and the uterine artery PI and RI and an increase in umbilical artery S/D, respectively. Vaginal progesterone can improve fetoplacental perfusion in pregnancies complicated by preterm labor. This a preliminary result from a case series study and it has to be confirmed by a randomized clinical trial in future.

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**Keywords:** Doppler ultrasonography; Blood flow; Velocimetry; Asymptomatic preterm labor; Vaginal progesterone tablet

## Introduction

Preterm labor is defined as regular contractions of the uterus resulting in changes of the cervix length (the length between the internal cervical os (that opens to the vagina) and the external cervical os (that opens to the uterus) that starts before the 37th week of pregnancy (1).

The causes of preterm labor are classified as uterine bleeding, stretching of the uterus, bacteria or inflammation, physical or psychological stress that has been reviewed in the literature (1). The exact mechanisms of preterm labor are largely unknown, but in our knowledge, including decidual hemorrhage, cervical incompetence, uterine distortion, cervical inflammation

as a result of infection, maternal inflammation/fever, hormonal changes, and uteroplacental insufficiency (1). Preterm labor is the most important problem among women around the world that could be associated with perinatal and neonatal morbidity and mortality. The incidence of preterm labor is increasing in the world and is reported in 15% of pregnancies in developed countries (2-3). Preterm labor is strongly related to the impaired neurological development and neurological disability in life, lately (4-7). But preterm labor is an important issue with controversial issues among obstetricians and perinatologists. For management of preterm labor, scientific evidence supporting the use of some of these treatment modalities is not very effective, such as

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tocolytic drugs, corticosteroids, and antibiotics (8).

Progesterone has a well-established role in the maintenance of pregnancy early or late gestation in preterm birth (9-12). The stringent mechanism for the prevention of preterm birth has remained unknown, yet, but proposed theories are: progesterone can prevent development of the myometrial gap junction, its effect on the cervix directly and anti-inflammatory effects (13), it inhibits oxytocin and prostaglandin receptors (14) and dilates the vessels of fetus and uterus (15-17).

The sonography of short cervix is still a powerful predictor of preterm delivery (18), the implementation of the screening program for all pregnant women requires the availability of a clinical intervention, prevention of preterm delivery and improvement of neonatal outcome (19).

Doppler sonography has also been used for evaluation of different fetal responses to various drugs on Doppler blood waveforms. In 1979, Doppler sonography used for the study of cerebral blood flow velocity waveforms for the first time (19).

Fetal circulation has been evaluated by Doppler sonography, which can prepare useful information about neonatal prognosis and fetal well-being in at-risk pregnancies. While Doppler measurements was not routine in the management and treatment of the preterm labor, we aimed to assess uterine and fetal Doppler blood flow velocimetry changes in the management of asymptomatic preterm labor with vaginal progesterone tablet, and even the use of vaginal tablet of progesterone affects uterine, umbilical, and fetal middle cerebral arteries in the second and third trimesters of pregnancy who were compromised preterm labor.

## Materials and Methods

After approval by the Ethical Board Committee of Tehran University of Medical Sciences, ethical number 130-898, this Case series study (uncontrolled longitudinal study) was conducted in the clinical outpatient and emergency unit of Moheb Yas hospital during 2015-2016. Thirty women participated in this research project with their own consent. Inclusion criteria were: the singleton pregnancy at 16-32 weeks, indication of transvaginal sonography, cervical length 10-20 mm, asymptomatic cervical length  $\leq$  25 mm and therapeutic indications of progesterone. Women receiving progesterone with steroids or tocolytic drugs, indicated cerclage, acute cervical dilatation, progesterone allergies, during the last 4 weeks of treatment with progesterone, chronic underlying disease that is affecting treatment and

evaluation, major fetal anomalies, the chromosomal abnormality is known and anatomical malformations of the uterus, known as vaginal bleeding or suspected clinical chorioamnionitis, and delivery history of multiple pregnancies were excluded.

For all subjects, 200 mg vaginal progesterone tablets (one tablet before bedtime) were administered. For all patients, transvaginal sonography was performed to measure uterus, umbilical and middle cerebral arteries doppler before the treatment and 24 hours after the treatment with progesterone, respectively.

If the symptoms of preterm labor progressed, according to the standard protocol including hospital admission, bed rest, given intravenous fluids, treatment tocolysis, and steroid therapy was prescribed. Our protocol treatment continued to the base of the protocol in the absence of premature rupture of membranes (PROM) until delivery. Transvaginal Doppler ultrasound 3.5 MHz (Mediso, Japan) before and 24 hours after receiving the first dose of progesterone was performed. Uterine arteries were assessed after observation of lateral ascending branch to the corpus uterus and the umbilical artery on the edge of the placenta. After evaluation of fetal middle cerebral arterial (MCA) with color flow, imaging may be seen as a main lateral branch of the circle of Willis, running anterolateral at the border among the anterior and the middle cerebral fossa. Evaluation of umbilical artery (UA) was done in the free-floating loop of the cord. Assessment of the uterine artery (UtA) was performed after the embodiment of the ascending branch of the UtA lateral to the corpus, mensuration of both the right and left UtA indices were done, and the mean was thought-out. Measurements of Doppler were taken across five to six cardiac cycles and peak systolic-to-lowest diastolic velocity (SD) in the umbilical artery, the minus lowest diastolic velocity/mean maximal velocity (PI), the peak systolic velocity (PSV) in the MCA, the resistance index (RI), the PSV minus lowest diastolic velocity/PSV in the uterine arteries and the MCA, PSV (cm/s) in the MCA measured by the insonation angle close to zero as possible.

In this study, episode of preterm labor was defined as regular uterine contractions with changes of dynamic of cervix, changes in effacement and dilation of the cervix examination, changes of cervical length, less than or equal to 25 mm in ultrasound, asymptomatic patients with cervical length less than or equal to 25 mm in the second trimester in the ultrasound with or without experience of delivery before 34 weeks of pregnancy. All women were followed up in the prenatal care clinic in every two weeks until delivery. At each visit, adverse events, concomitant

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drugs, and the problems caused by the use of progesterone were asked. The treatment with progesterone was continued to 34 weeks of gestation.

### Statistical analysis

Our statistical power calculation showed that 30 patients were needed in the study for 90% power, with an MCA-RI value ( $0.85\pm 0.06$ ) and an alpha of 95%. Data were analyzed by the SPSS 19.0 software (Chicago, IL, USA) for Windows. The distribution of data was normal, which was assessed with Kolmogorov-Smirnov test. Mean ( $\pm$ SD) of quantitative variables were calculated. Doppler blood flow velocimetry index values before and after administration of progesterone were evaluated by

the paired t-test. The value of  $P < 0.05$  was considered as statistically significant.

### Results

The mean gestational age of the study population was  $28.8\pm 2.9$  weeks, ranging from 23 to 32 weeks gestation. Mean change of MCA-PI was 1.99 in patients with preterm labor after 24 h of treatment (Figure 1,  $P=0.372$ ), Mean change of MCA-PSV (cm/s) was 43.53 in patients with preterm labor after 24 h of treatment (Figure 2,  $P=0.568$ ).

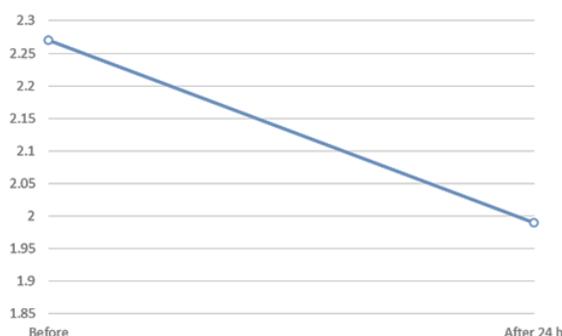


Figure 1. The mean of the pulsatility index in the fetal middle cerebral artery before and after 24 hours of receiving progesterone

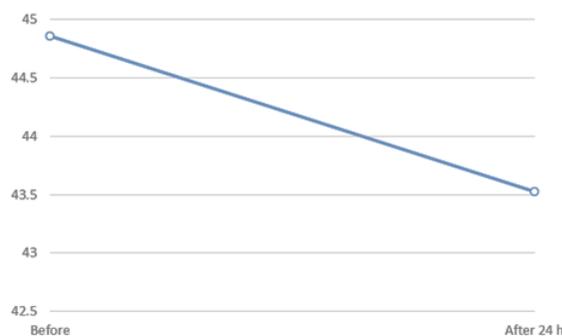


Figure 2. The mean of MCA-PSV (cm/s) in the fetal middle cerebral artery before and after 24 hours of receiving progesterone

The fetal MCA-peak systolic velocity (PSV) was decreased after progesterone administration but didn't show any significant difference between before and after progesterone administration ( $44.86\pm 11.04$  (cm/s) vs.  $43.53\pm 8.63$  (cm/s),  $P=0.568$ ). MCA-RI decreased after progesterone administration, but did not show any significant difference between different times of the study ( $0.84\pm 0.06$  vs.  $0.82\pm 0.06$ ,  $P=0.202$ ), MCA-PI decreased after progesterone administration, but didn't show any significant difference between different times of the study

( $2.27\pm 1.28$  vs.  $1.99\pm 0.51$ ,  $P=0.372$ ), UA S/D increased after progesterone administration, but didn't show any significant difference between before and after progesterone administration ( $2.71\pm 0.53$  vs.  $2.87\pm 0.51$ ,  $P=0.299$ ), respectively. Right UtA-RI ( $0.45\pm 0.09$  vs.  $0.49\pm 0.09$ ,  $P=0.736$ ) and Left UtA-RI ( $0.50\pm 0.07$  vs.  $0.49\pm 0.09$ ,  $P=0.820$ ) decreased after progesterone administration, but didn't show any significant difference between before and after progesterone administration (Table 1).

**Table 1. Doppler flow parameters of maternal and fetal circulation before and after progesterone administration in the women (n=30)**

Parameter	Before	After	P
MCA-PSV (cm/s)	44.86±11.04	43.53±8.63	0.568
MCA-RI	0.84±0.06	0.82±0.06	0.202
MCA-PI	2.27±1.28	1.99±0.51	0.372
UA S/D	2.71±0.53	2.87±0.51	0.299
Right UtA-RI	0.45±0.09	0.45±0.08	0.736
Left UtA-RI	0.50±0.07	0.49±0.09	0.820

## Discussion

Progesterone is a steroid hormone produced by the adrenal gland, gonads, nervous system, and the placenta. Vaginal progesterone can direct effect on the uterus (19-20). In some previous investigations, different routes and dosage of progesterone are evaluated for prevention of preterm birth (21-24). The effective role of vaginal progesterone in the at-risk women for preterm labor was demonstrated (25). Farine *et al.*, in a meta-analysis of RCT demonstrated vaginal progesterone with the dose of 200 mg daily in women with the length of cervix<15 confirmed by TVS scanning in the treatment of preterm labor (22-26 weeks gestation) is recommended by scientific evidence (26).

Romero *et al.*, in a systematic review and meta-analysis, found that receiving vaginal route of progesterone in the women without symptoms, according to sonographic findings, that have a short length of the cervix, decreased the incidence of neonatal morbidity and mortality in preterm birth (27). Also, the results of a multi-centered, randomized, double-blind, placebo-controlled trial, showed that there is no evidence for the effect of vaginal progesterone 200 mg daily in the reduction of preterm birth (24-33 weeks gestation) or improving neonatal outcome in women with preterm labor (28).

Our Doppler velocimetry evaluation showed the reduction of the fetal MCA-PSV and MCA-RI, MCA-PI, 24 hours after progesterone administration. The decrease in the mean of RI in the MCA mainly reflected the accepted regimen for maintenance of the drug for the inhibition of premature labor. Thus, the reduced resistance of the MCA may be related to the decrease in its PSV, which is a component of the numerator in the RI formula that including the evaluation of PSV that contributed by improving our understanding of the mechanisms that involved in changing the RI. The reduction in RI may also be explained by the pharmacodynamics and kinetics of progesterone itself. The drug's ability to cross the placental barrier is well

known (29).

In addition, the medication acts by inhibiting calcium entry into the myocytes by blocking the membrane channels, leading to decrease the tonus of vascular smooth muscle that it could reduce the resistance of the MCA (30).

The changes of the MCA could indicate the local effect of progesterone, by the blocking action in the calcium channels of the vascular tunica media leading to the reduction of RI.

The vasodilatory effect of progesterone reduces the vessel resistance. The decrease in fetal MCA-PI is probably due to the higher sensitivity of the fetal middle cerebral artery to progesterone during the growth period. The vasodilatory effect of progesterone was shown in previous studies (31-32). Omar *et al.*, investigated the effect of progesterone on vascular placental tone and confirmed the effect of increasing dosage of progesterone on arteriovenous vasodilation (33).

Hermenegildo *et al.*, demonstrated that progesterone and medroxyprogesterone acetate induced prostacyclin synthesis dependent on the dose of that drug and receptor-related pathways in endothelial cells of the human umbilical vein. Progesterone increased endothelial prostacyclin by enhancing expression and activity of cyclooxygenase-1 and 2 (32).

Although Right UtA-RI and Left UtA-RI decreased 24 hours after progesterone administration, UA S/D increased 24 hours after progesterone administration. It didn't show any significant differences in the change of the variables. In DeFranco E.A *et al.*, investigation, showed that vaginal progesterone in women with a short cervix is associated with vascular relaxation and increased uterine blood flow in 18-24 weeks in compared to women that receiving no treatment (34).

The positive vasodilatory effect of progesterone on the umbilical artery and the middle cerebral artery of the fetus seems to be a promising finding for enhancing the blood supply to the fetus. Therefore, it is evident that any successful prenatal therapies have the potential to improve mortality and reduce short and long-term

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complications of prematurity. Therefore, prenatal therapies with progesterone may reverse abnormal fetal Doppler velocimetry and delay preterm labor (35).

There was no significant changes in the fetal MCA-PSV, PI, RI or the S/D ratio of the umbilical artery, or RI of the uterine arteries before and after 24 h receiving 200 mg vaginal progesterone tablet.

Progesterone with effects of vasodilatory on the vessels of the uterus and the fetus could be useful in the treatment of preterm labor. Previous studies investigated about progesterone and found its vasodilatory effect in pregnant women in the first trimester and also women without pregnancy.

The vasodilatory effect of progesterone has been demonstrated previously in non-pregnant women as well as in the first trimester of pregnancy (15-17).

The mechanism of the effect of vasodilatory vaginal progesterone in prevention of preterm labor is still unknown. The possible mechanisms are in the non-genomic effect (13), and regulation of vascular tone with rapid inhibition of platelet aggregation (36).

Nevertheless, Czajkowski *et al.*, (16) found that type of vaginal progesterone with various effects from oral dydrogesterone, that due to a slow reduction in spiral artery PI without a risk of pregnancy, which was imputable to increase progesterone level (37).

Barda *et al.*, in their study identified that a statistically significant reduction in fetal MCA-PI 24 hours after progesterone treatment (mean reduction of 18.2%, mean PI change of 0.44,  $P < 0.001$ ). They still have not found any significant changes in fetal MCA-PSV and the PI of the uterine arteries and umbilical artery (9).

Another study by Borna, *et al.*, demonstrated that the use of vaginal progesterone suppository led to a decrease in the MCA PI after 24 hours and a decrease in the PI of the umbilical artery after two weeks of treatment (38).

In the two recent studies, fetal MCA-PI was decreased 24 hours after administration of progesterone. The study by Borna *et al.*, showed no significant decrease in PI, systolic/diastolic ratio, and resistance index (RI) of the umbilical artery after 24 hours treatment with progesterone, while the decrease in PI was significant after two weeks of treatment. One possible explanation for these differences may be the length of treatment. In the present study, the findings are similar to other studies (9-38).

The main limitation of the study is the widening of the gestational age range (16-32 weeks) that may have introduced potential confounders, such as different causes of preterm labor, different development stages of fetal brain and possibly, the different response of the various

blood vessels.

Our study demonstrates that the use of 200 mg vaginal progesterone tablet for the treatment of preterm labor led to reduction in the PI and RI of the middle cerebral artery and the uterine artery, and an increase in S/D of the umbilical artery. Vaginal progesterone can improve fetoplacental perfusion during the complicated pregnancies by preterm labor. This a preliminary result from a case series study and it has to be confirmed by a randomized clinical trial in future.

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## References

1. Edmund F Funai. Patient education: Preterm labor (Beyond the Basics). (Accessed May 2017, 14, at <https://www.uptodate.com/contents/preterm-labor-beyond-the-basics/abstract/1-5>).
2. Hamilton BE, Minino AM, Martin JA, Kochanek KD, Strobino DM, Guyer B. Annual summary of vital statistics: 2005. *Pediatrics* 2007;119:345-60.
3. Steer P. The epidemiology of preterm labor. *BJOG* 2005;112:1-3.
4. National Center for Health Statics (NVSR). Deaths and percentage of total deaths for the 10 leading causes of neonatal and postnatal deaths: United States, 2001.
5. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. *Lancet* 2008;371:75-84.
6. Moster D, Lie RT, Markestad T. Long-term medical and social consequences of preterm birth. *N Engl J Med* 2008;359:262-73.
7. O'Brien JM, Adair CD, Lewis DF, Hall DR, Defranco EA, Fusey S, et al. Progesterone vaginal gel for the reduction of recurrent preterm birth: primary results from a randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol* 2007;30:687-96.
8. Chandraharan E, Arulkumaran S. Recent advances in management of preterm labor *J Obstet Gynecol India* 2005;55:118-24.
9. Barda G, Ben-Haroush A, Barkat J, Malinger G, Luria O, Golan A, et al. Effect of vaginal progesterone, administered to prevent preterm birth, on impedance to blood flow in fetal and uterine circulation. *Ultrasound Obstet Gynecol* 2010;36:743-8.
10. Dodd J, Jones L, Flenady V, Cincotta R, Crowther C.

- Prenatal administration of progesterone for preventing preterm birth in women considered to be at risk of preterm birth. *Cochrane Database Syst Rev* 2012;7:CD004947.
11. Di Renzo GC, Giardina I, Clerici G, Mattei A, Alajmi AH, Gerli S. The role of progesterone in maternal and fetal medicine. *Gynecol Endocrinol* 2012;28:925-32.
  12. Stites DP, Siiteri PK. Steroids as immunosuppressants in pregnancy. *Immunol Rev* 1983;75:117-38.
  13. Romero R. Prevention of spontaneous preterm birth: the role of sonographic cervical length in identifying patients who may benefit from progesterone treatment. *Ultrasound Obstet Gynecol* 2007;30:675-86.
  14. Challis JRG, Lye SJ. The physiology of reproduction. In: Knobil E, Neill JD, editors. *Parturition*. New York: Raven Press, 1994:985-1031.
  15. Deichert U, Albrand-Thielmann C, van de Sandt M. Doppler sonographic pelvic blood flow measurements and their prognostic value in terms of luteal phase and implantation. *Hum Reprod* 1996;11:1591-3.
  16. Czajkowski K, Sienko J, Mogilinski M, Bros M, Szczecina R, Czajkowska A. Uteroplacental circulation in early pregnancy complicated by threatened abortion supplemented with vaginal micronized progesterone or oral dydrogesterone. *Fertil Steril* 2007;87:613-8.
  17. Habara T, Nakatsuka M, Konishi H, et al. Elevated blood flow resistance in uterine arteries of women with unexplained recurrent pregnancy loss. *Hum Reprod* 2002;17:190-4.
  18. Hassan SS, Romero R, Vidyadhari D, Fusey S, Baxter JK, Khandelwal M, et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter, randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol* 2011;38:18-31.
  19. Cicinelli E, de Ziegler D, Bulletti C, Matteo MG, Schonauer LM, Galantino P, et al. Direct transport of progesterone from the vagina to uterus. *Obstet Gynecol* 2000;95:403-6.
  20. Fanchin R, de Ziegler D, Bergeron C, Righini C, Torrisi C, Frydman R. Transvaginal administration of progesterone. *Obstet Gynecol* 1997;90:396-401.
  21. Meis JM, Klebanoff M, Thorn E, Cleary-Goldman J, Rhea DJ, Stanziano GJ, et al. Prevention of recurrent preterm delivery by 17 alpha-hydroxyprogesterone caproate. *N Engl J Med* 2003;348:2379-85.
  22. Da Fonseca EB, Bittar RE, Carvalho MHB, Zugaib M. Prophylactic administration of progesterone by vaginal suppository to reduce the incidence of spontaneous preterm birth in women at increased risk: A randomized placebo-controlled double-blind study. *Am J Obstet Gynecol* 2003;188:419-24.
  23. Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH. Progesterone and risk of preterm birth among women with a short cervix. *N Engl J Med* 2007;357:462-9.
  24. DeFranco EA, O'Brien JM, Adair CD, Lewis DF, Hall DR, Fusey S, et al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a randomized, double-blind, placebo-controlled trial. *Ultrasound Obstet Gynecol* 2007;30:697-705.
  25. Khandelwal, M. Vaginal progesterone in risk reduction of preterm birth in women with a short cervix in the mid-trimester of pregnancy. *Int J Womens Health* 2012;4:481-90.
  26. Farine D, Mundle WR, Dodd J. The use of progesterone for prevention of preterm birth. *J Obstet Gynaecol Can* 2008;30:67-71.
  27. Romero R, Conde-Agudelo A, El-Refaie W, Rode L, Brizot ML, Cetingoz E, Serra V, et al. Vaginal progesterone in women with an asymptomatic sonographic short cervix in the mid-trimester decreases preterm delivery and neonatal morbidity: a systematic review and meta-analysis of individual patient data. *Am J Obstet Gynecol* 2017;49:303-14.
  28. Martinez R, Figueras F. The role of Doppler and placental screening. *Best Pract Res Clin Obstet Gynaecol* 2009;23:845-55.
  29. Garcia-Velasco JA, Gonzalez A. A prospective, randomized trial of nifedipine vs. ritodrine in threatened preterm labor. *Int J Gynecol Obstet* 1998;61:239-44.
  30. Economy KE, Abuhamad AZ. Calcium channel blockers as tocolytics. *Semin Perinatol* 2001;25:264-71.
  31. Li HF, Zheng TZ, Li W, Qu SY, Zhang CL. Effect of progesterone on the contractile response of isolated pulmonary artery in rabbits. *Can J Physiol Pharmacol* 2001;79:545-50.
  32. Hermenegildo C, Oviedo PJ, Garcia-Martinez MC, Garcia-Pérez MA, Tarín JJ, Cano A. Progestogens stimulate prostacyclin production by human endothelial cells. *Hum Reprod* 2005;20:1554-61.
  33. 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.
  34. DeFranco EA, DeArmond CH, Van Hook J. Progesterone administration for the prevention of preterm birth: effect on uterine blood flow dynamics. *Am J Obstet Gynecol* 2016;214:S293-4.
  35. Borna S, Borna H, Gotbizadeh F, Jahani M. Evaluation of Progesterone Effects on Fetal Doppler Velocimetry. *Obstet*

## Maternal and fetal doppler blood flow velocimetry changes

Gynecol Cancer Res 2016;1:e9399.

36. Bar J, Lahav J, Hod M, Ben-Rafael Z, Weinberger I, Brosens J. Regulation of platelet aggregation and adenosine triphosphate release in vitro by 17beta-estradiol and medroxyprogesterone acetate in postmenopausal women. *Thromb Hemost* 2000;84:695-700.
37. Mäkikallio K, Tekay A, Jouppila P. Uteroplacental hemodynamics during early human pregnancy: a longitudinal study. *Gynecol Obstet Invest* 2004;58:49-54.
38. Borna S. Progesterone effect on fetal Doppler velocimetry in pregnant women with IUGR and preterm labor. *Ultrasound Obstet Gynecol* 2014;44:265-6.