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Effect of Progesterone Replacement Therapy on Uteroplacental Circulation in Treatment of Threatened Abortion

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ABSTRACT

Background: Miscarriage is interruption or termination of pregnancy before 20 weeks based upon the day of the last normal menses or it is the expulsion of the product of conception before the age of medicolegal viability which is 26th weeks of gestation in Egypt or fetal weight < 500gm or fetal length ≤ 25 according to WHO definition.

Objective: This study was performed to compare the effect of vaginal micronized progesterone and oral dydrogesterone on utero-placental circulation in threatened miscarriage.

Patients and Methods: A prospective clinical study in Zagazig University Hospital during the period from December 2018 to August 2019. Included fifty pregnant cases complaint of first trimester vaginal bleeding and diagnosed as threatened miscarriage. They were classified into two groups on a randomized basis, the first group received micronized vaginal progesterone (400 microgram daily) while the second one received dydrogesterone orally (40 mg at once then 10 mg every 8 hours). Both groups were followed up every two weeks for three visits by serial transvaginal Doppler ultrasound measurement of pulsatility index, resistance index, and systolic/diastolic (S/D) ratio of the spiral arteries, uterine arteries & intrachorionic area.

Results: The study demonstrated that vaginal progesterone administration, contrary to oral dydrogesterone treatment, decreased spiral artery pulsatility and resistive indices. No major changes in the uterine artery blood flow impedance were observed, only S/D ratio significantly decreased in the dydrogesterone group.

Conclusion: It could be concluded that vaginally administrated progesterone was nearly as equally effective as oral dydrogesterone in prevention of miscarriage in pregnant women with threatened abortion with different effects on the uteroplacental circulation.

Keywords: Progesterone, Dydrogesterone, Threatened abortion, Utero-placental, Miscarriage.

INTRODUCTION

Threatened miscarriage, which occurs in 20% of all pregnancies, is diagnosed when vaginal bleeding with or without abdominal pain occurs during the first half of pregnancy. The required prerequisites for threatened miscarriage are a closed cervix and an intrauterine viable fetus. Unfortunately, nearly half of threatened miscarriage end in miscarriage [1]. A suitable level of progesterone is an important factor that determines uncomplicated embryo development. Thus, progesterone supplementation can decrease the miscarriage rate [2]. Progestagens enhance implantation, affect the cytokine balance, inhibit natural killer cell activity at the fetomaternal interface, inhibit the release of arachidonic acid, prevent myometrial contractility and prevent cervical dilatation [3].

Progesterone can be administered orally, intramuscularly, vaginally, and most recently subcutaneously, with each route having different bioavailability and tolerability profiles [4]. Oral administration is the easiest route of administration, and generally the most acceptable route for the patient. Vaginal administration results in higher uterine concentrations but is often uncomfortable in the presence of vaginal bleeding, or may be washed out if bleeding is severe [5]. In contrast, intramuscular progesterone is associated with injection-site pain and abscesses [6].

Oral micronized progesterone has low bioavailability and is associated with systemic adverse events such as drowsiness, dizziness and headaches [7]. Micronized vaginal progesterone (MVP) is now preferred over oral and intramuscular progesterone, but it is associated with its own administration related side effects such as vaginal irritation [8].

Dydrogesterone is a retroprogesterone that has been used since the 1960s for the treatment of conditions associated with progesterone deficiency [9]. Dydrogesterone has a good safety and tolerability profile. It is structurally and pharmacologically similar to natural progesterone has good oral bioavailability and few side effects. Dydrogesterone has no androgenic effects on the fetus, and does not inhibit the formation of progesterone in the placenta [10]. Importantly, oral administration of dydrogesterone circumvents the inconvenience and side effects related to intravaginal or intramuscular administration [6].

Adequate oxygen and nutrient supply are other important factors that determines proper embryo development. Efficient blood transport depends on an adaptive capacity of the uterine vascular system. Arterial blood is transported to the uterus by way of the uterine and ovarian arteries.

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The ascending branch of the uterine artery is an essential source of the blood supply to the embryo. The spiral arteries constitute the terminal portions of the uterine vasculature and penetrate the implantation and placental site. Suitable implantation depth and adequate amount of blood that bathes the trophoblast are important factors for the embryo development. Some data suggest that impaired uterine blood perfusion can be a cause of infertility. It can be assumed that undisturbed uteroplacental circulation supports uncomplicated embryo development. Thus, the drugs that are applied in the threatened miscarriage treatment should have favorable effects on uteroplacental blood flow [11].

The introduction of transvaginal ultrasonography has greatly improved the evaluation of early pregnancy in threatened miscarriage. The use of this technique allows the assessment of embryo vitality by visualizing cardiac activity in real-time, B-mode sonography, even in embryos with a crown–rump length of <5 mm. The introduction of transvaginal color Doppler sonography has allowed assessment of the uteroplacental circulation in early pregnancy**.**

The aim of this study was to compare the influence of vaginal micronized progesterone and oral dydrogesterone supplementation on uterine blood flow indices in early pregnancy that is complicated by threatened miscarriage.

PATIENTS & METHODS

This prospective clinical study included a total of 50 pregnant women complaining of mild vaginal bleeding with or without colic, between 6th and 12th weeks of gestation, and diagnosed as threatened miscarriage, referred from the Emergency Department or the Obstetrics & Gynecology outpatient clinic, Zagazig University Hospital. This study was conducted between December 2018 to August 2019.

Ethical approval:

Written informed consent was obtained from all participants and **the study was accepted by the Research Ethics Committee of the Faculty of Medicine, Zagazig University. Study has been carried out on experiments involving human subjects in compliance with the Code of Ethics of the World Medical Association (Declaration Helsinki).**

The included subjects were randomly divided into two equal groups of 25 cases each. **Group (1)**; Patients received micronized vaginal progesterone 400 microgram daily (Recommended dose for threatened miscarriage, FARCO company). **Group (2)**; Patients received dydrogesterone orally 40 mg at once (four tablets) then 10 mg (one tablet) every eight hours (Recommended dose for threatened miscarriage, Abbott company).

Inclusion criteria: Singleton pregnancy. Gestational age ranging from 6-12 weeks calculated from the first day of the last menstrual period. Mild vaginal bleeding with or without abdominal pain (uterine cramps). Visible intrauterine gestational sac with a living embryo visualized on real time ultrasound.

Exclusion criteria: Multiple pregnancies. Patients with missed abortion, blighted ovum and incomplete abortion. Allergy to any component of the drugs that would be administered in the study Ectopic or molar pregnancy.

The selected patients were subjected to careful history taking including age, gravidity, parity, date of onset and severity of vaginal bleeding, presence of abdominal pain, any maternal medical problem, date of the last menstrual period from which the gestational age was calculated.

All the patients in both groups were advised for bed rest and they were followed up every 2 weeks for two other visits from start of the treatment by transvaginal ultrasound examination supplemented (grey scale and color Doppler studies) with Doppler imaging of the uteroplacental circulation (Voluson 730 pro 50/ 60 HZ) using a transvaginal probe, then pregnancy outcome at the end of the third visit at 20 weeks of gestation was measured according to change of Doppler indices in the following visits, rate of patients who continue pregnancy, rate of miscarriage. Measured the fetal CRL from the top of the head to the bottom of the rump in millimeters (mm) Figure 1.

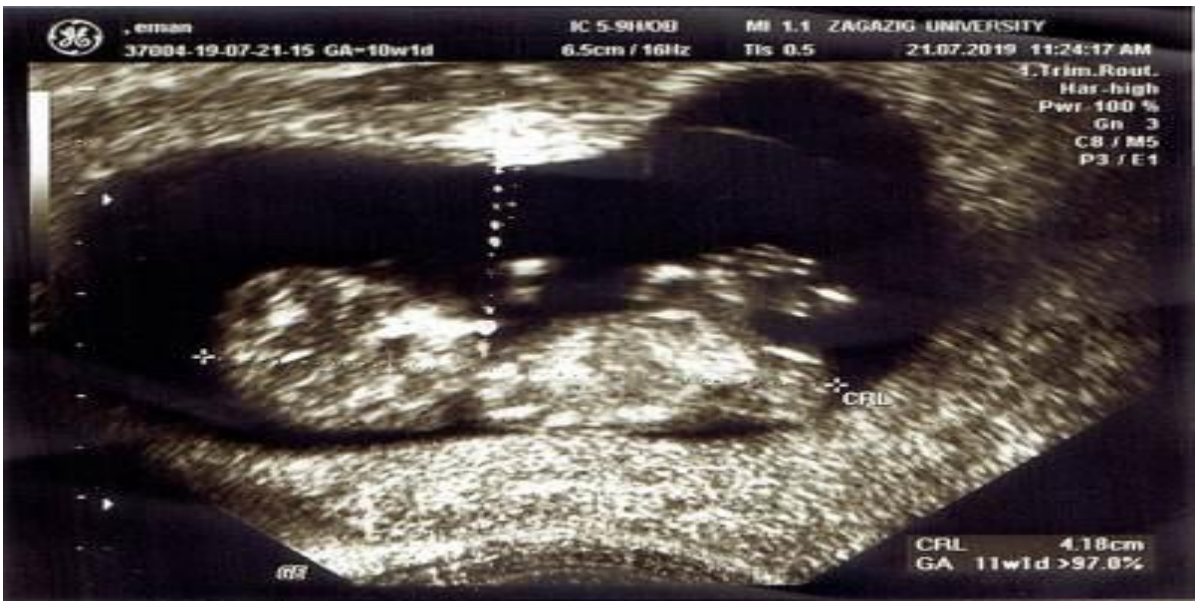

Figure (1): Measured the fetal CRL

Uterine arteries, spiral arteries, and small arteries in the intrachorionic area were examined in Doppler scans.

Uterine artery; were placed the transducer in the lower lateral quadrant of the uterus and angled it medially, an apparent cross- over of the external iliac artery and vein and the main uterine artery can be identified, and then we measured the RI, PI, (S/D) of the uterine artery for each ultrasound session.

Spiral arteries; the spiral artery was identified near the junction of decidua and myometrium, and then we measured the RI, PI, (S/D) of the spiral artery for each ultrasound session.

Intrachorionic area; the view usually assumed for Doppler study of the Intrachorionic area was a transverse or slightly oblique views as most of the vessels in an implanted ovum would lie in the posterior part of the decidua basalis. Several vessels were selected by the help of color Doppler and the arteries were identified then were measure the resistance index (RI), Pulsatility index (PI), and systolic/diastolic ratio (S/D) for each ultrasound session.

All the patients were screened for vaginal infections. Treatment was introduced immediately after the first visit. During the last visit, pregnancy outcome was evaluated.

Statistical analysis

Analysis of data was done using Statistical Program for Social Science version 20 (SPSS Inc., Chicago, IL, USA). Quantitative variables were described in the form of mean and standard deviation. Qualitative variables were described as number and percent. In order to compare parametric quantitative variables between two groups, Student t test was performed. Qualitative variables were compared using chi-square (X^2) test or Fisher's exact test when frequencies were below five. Pearson correlation coefficients were used to assess the association between two normally distributed variables. When a variable was not normally distributed, Man Whitney test for comparing two non-Parametric variables. Kruskal wallis test for comparing more than two non-Parametric variables. Spearman's correlation P value < 0.05 is considered significant coefficients were used to assess the association between two variables which are not normally distributed.

RESULTS

Table 1 showed that there was non-significant difference between the studied groups as regard demographic data.

Figure 2 showed that there was no significant difference between the studied groups as regard Clinical symptoms.

Figure 3 showed that the rate of miscarriage in group 1 was 16% and in group 2 is 12% with no significant difference between the two studied groups.

Table 2, showed that vaginal micronizd progesterone treatment group was associated with the decrease in the spiral artery PI . Similar changes were not observed in the dydrogesterone group. The RI of the spiral arteries decreased in the micronized progesterone group only when compared with dydrogesterone group. A significant decrease in the spiral artery S/D ratio was observed only in the vaginal progesterone group.

Table 3 showed that the PI of the uterine arteries was the lowest at third visit, regardless of treatment regimen. The gradual, but statistically insignificant, decrease in this index during successive ultrasound examinations was observed only in the dydrogesterone group. This group was also characterized by

statistically significant drop in S/D ratio between particular visits. The decrease in the uterine artery RI was not significant in both groups

Table 4, showed that the Doppler waveform analysis of the intrachorionic area showed no statistically significant changes in PI, RI, and S/D indices, in both the micronized vaginal progesterone and the dydrogesterone groups.

Table (1): Demographic data in between the studied groups:

Variable	Group 1 (n=25)	Group 2 (n=25)	t-test	P value
Age: (Years):				
Mean ± SD	32.5±4.5	31.4±5.2	1.13	0.26 (NS)
Gravidity				
Median range	3 (1-7)	4 (1-8)	MW 102	0.234 (NS)
Parity				
Median range	1 (0-4)	2 (0-4)	MW 79	0.055 (NS)
Previous abortion:				
Median range	2 1-3	2 1-3	MW 121	0.891 (NS)

MW =Mann whitney test P value is significant if <0.05

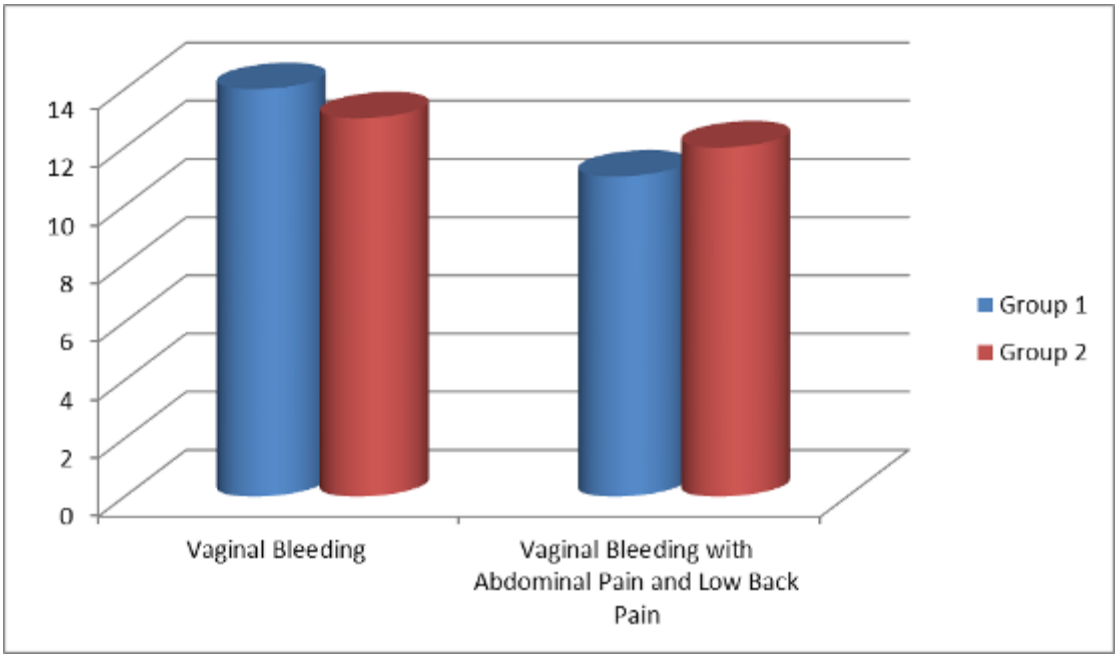

Fig. (2): Clinical symptoms of the studied groups.

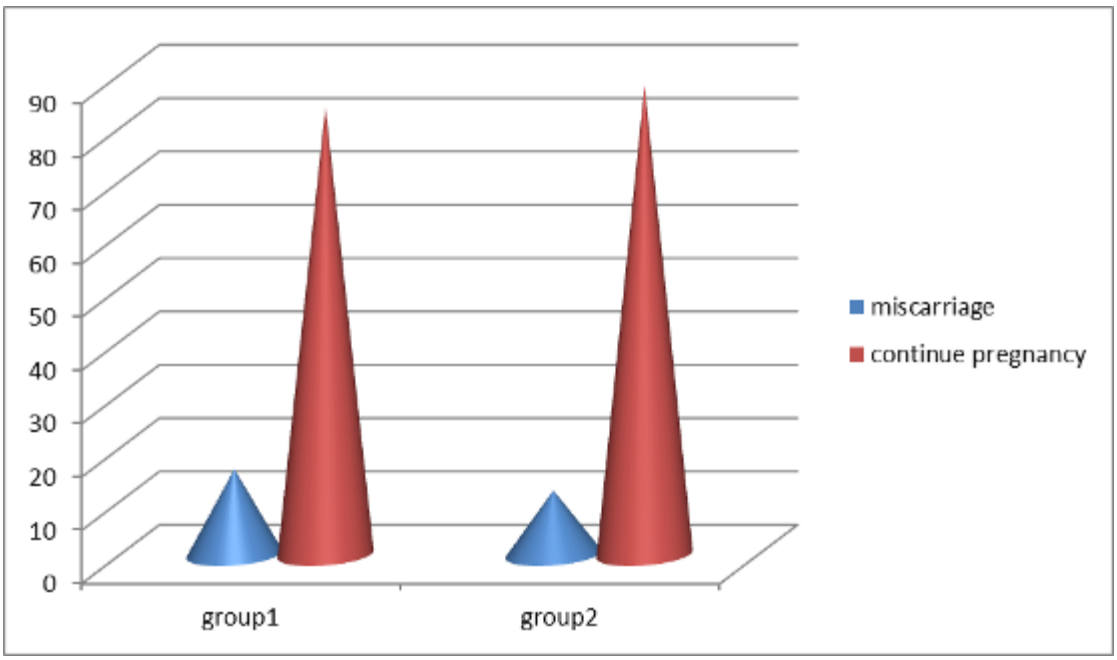

Fig. (3): Rate of miscarriage in the studied groups

Table (2): Comparison between the studied groups as regard spiral artery indices

Micronized Progesterone group	**first visit (n=25)**	**second visit (n=25)**	**Third visit (n=25)**	**F**	**P value**
RI:					
Mean ± SD	0.86 ± 0.12	0.78 ± 0.15	0.72 ± 0.17	5.62	**0.005 (S)**
PI					
Mean ± SD	2.21 ±0.71	1.73 ± 0.44	1.44 ± 0.47	12.34	**<0.001 (HS)**
S/D					
Mean ± SD median	7.61 ±7.1 5.67	4.9 ± 2.9 3.4	3.02 ±2.5 2.7	32.5*	**<0.001 (HS)**
Dydrogesterone group	**First visit (n=25)**	**Second visit (n=25)**	**Third visit (n=25)**	**F**	**P value**
RI:					
Mean ± SD	0.74 ± 0.12	0.82 ± 0.19	0.77 ±0.15	1.67	0.193 (NS)
PI					
Mean ± SD	2.1 ±0.55	2.47 ± 0.8	1.65 ± 0.34	11.95	**<0.001 (HS)**
S/D					
Mean ± SD median	5.55 ±6.49 3.47	5.31 ± 2.6 4.1	4.05 ± 1.58 3.2	30.5	**<0.001 (HS)**

F is for repeated measure ANOVA

Table (3): Comparison between the studied groups as regard uterine artery indices

Micronized Progesterone group	First visit (n=25)	Second visit (n=25)	Third visit (n=25)	F	P value
RI:					
Mean ± SD	0.98 ±0.41	0.92 ± 0.24	0.83 ± 0.13	1.76	0.178
PI					
Mean ± SD	2.9 ±0.4	3.2 ± 0.6	2.4 ± 0.9	9.21	**<0.001 (HS)**
S/D					
Mean ± SD	7.27 ± 1.4	5.59 ±1.6	7.15 ± 2.4	6.40	**0.002 (S)**
Dydrogesterone group	**first visit (n=25)**	**second visit (n=25)**	**Third visit (n=25)**	**F**	**P value**
RI:					
Mean ± SD	0.9 ±0.11	0.92 ± 0.21	0.86 ± 0.16	0.855	0.429
PI					
Mean ± SD	3.04 ± 0.98	2.88 ± 0.25	2.28± 0.58	8.85	**<0.001 (HS)**
S/D					
Mean ± SD	7.72 ± 1.83	5.67 ± 1.27	5.29 ± 1.49	17.8	**<0.001 (HS)**

Table (4): Comparison between the studied groups as regard Intrachorionic area indices

Micronized Progesterone group	First visit (n=25)	Second visit (n=25)	Third visit (n=25)	F	P value
RI:					
Mean ± SD	0.7 ±0.34	0.66 ±0.13	0.57 ± 0.2	1.78	0.074
PI					
Mean ± SD	1.39 ±0.4	1.14 ±0.3	0.95 ± 0.46	1.23	0.081
S/D					
Mean ± SD	2.77 ± 0.9	2.74 ±0.8	2.71 ± 2.08	1.1	0.231
Dydrogesterone group	**first visit (n=25)**	**second visit (n=25)**	**Third visit (n=25)**	**F**	**P value**
RI:					
Mean ± SD	0.71 ± 0.35	0.59 ±0.19	0.55 ± 0.17	1.74	0.091
PI					
Mean ± SD	2.54 ± 0.5	1.04 ±0.31	0.93 ± 0.49	1.67	0.082
S/D					
Mean ± SD	2.54 ± 0.74	2.77 ± 0.75	3.11 ± 2.97	1.21	0.421

DISCUSSION

The present study assessed the demographic characteristics of the participants and revealed that there is non-significant difference between the studied groups as regard demographic data. **Omar *et al.*** [12] designed a study conducted on 140 cases randomly selected and divided into two groups, the first received oral dydrogesterone 10 mg three times daily and the other group received placebo, data obtained showed that progestogens administered to women with threatened miscarriage in the first trimester is beneficial in maintenance of pregnancy beyond 20 week gestation. The pregnancy success rate, in terms of viable pregnancies was 95.9% in the women who were treated with dydrogesterone and 86.3% in women who was treated conservatively; this difference was statistically significant (P= 0.037).

El-Zibdeh [13] conducted study in 2005 on 146 pregnant women complaining of threatened miscarriage. They received either dydrogesterone (10 mg orally twice daily, n=86), or no treatment at all (n=60). Abortion occurred in 17.4% of treated patients and 25% of untreated patients which was statistically significant (P < 0.05).

The present study revealed that the rate of miscarriage in Vaginal Micronized Progesterone group

was 16% and in oral dydrogesterone was 12% with no significant difference between the two studied groups.

This was in agreement the study of **Czajkowski *et al.*** [11] who conducted a randomized, parallel group double-blind, controlled study on patients with threatened miscarriage, the subjects were assigned randomly to a progesterone or dydrogesterone group. The patients received either 300 mg of micronized vaginal progesterone daily plus oral placebo or 30 mg of oral dydrogesterone daily plus vaginal placebo, six of 53 patients (11.3%) spontaneously aborted during the study. there was no statistical significance between the two groups regarding the success of pregnancy.

In our study, the miscarriage rate was 14% and was higher than that of **Weiss *et al.*** [14] where the miscarriage rate was 11 % among the participants. They also found that less favorable outcomes have been associated with earlier age at the time of vaginal bleeding. reported a spontaneous abortion rate of 13.7% after bleeding before 8 weeks of gestation, compared with 5.7% when the bleeding occurred after 8 weeks of gestation.

Before the eighth week of pregnancy, the maternal arterial connections with the intervillous space are restricted to a tortuous network of intercellular spaces. Then, a network of direct channels is formed. Until 11 or 12 weeks, the capillaries become fully matured, sizable, and clearly delineated [15] .

Therefore, the vascular changes that take place during the first trimester are crucial for further fetus development and the occurrence of numerous complications of pregnancy. This trial concerned uteroplacental circulation in very early pregnancy. To our knowledge, very few previous studies addressed this issue.

Spiral arteries are responsible directly for adequate blood supply to the embryo. Impaired function of those vessels can result in further pregnancy complications (i.e., intrauterine growth restriction or pregnancy-induced hypertension). Serial measurements conducted by **Mäkikallio *et al.*** [16] demonstrated a gradual decrease in the spiral artery PI at 5–10 weeks of uncomplicated pregnancy (from 0.93± 0.3 to 0.67± 0.3).

There is a significant decrease of spiral artery resistance index after the 5th week of pregnancy which may reflect vascular remodeling in the maternal-fetal interface. This is because vascular remodeling by trophoblast invasion occurs at placentation, causing a reduction in local arterial resistance [17].

The present study revealed that vaginal progesterone treatment was associated with the decrease in the spiral artery PI. Both 1st - and 2nd visit treatments resulted in significant PI changes in this group. Similar changes were not observed in the dydrogesterone group. The RI of the spiral arteries decreased in the progesterone group only when compared with dydrogesterone group. A significant decrease in the spiral artery S/D ratio was observed only in the vaginal progesterone group.

This was in agreement the study of **Czajkowski *et al.*** [11], who stated that PI and RI of the spiral artery decreased significantly in the micronized progesterone group. The corresponding changes were not observed in the dydrogesterone group.

This analysis of the spiral artery impedance indices suggests that vaginal progesterone supplementation partly normalizes increased vascular resistance in these vessels that may result potentially in improved oxygen and nutrient supply to the embryo. Nevertheless, it is not clear whether the kind of drug or the route of administration produces this effect.

Although several studies have been reported regarding the change in uterine artery (UA) blood flow to assess utero-placental circulation during early pregnancy, the findings given so far still seem to be controversial [18].

However, the change in uterine artery and spiral artery blood flow during early pregnancy is also controversial. According to the literature that retrochorionic blood flow, which reflects spiral artery blood flow, increased progressively between the 4th and 12th week of pregnancy, the pulsatility index of the uterine artery decreased between the 5th and 10th week of pregnancy **Erkinaro *et al.*** [19], On the other hand, **Bernstein *et al.*** [20] reported that uterine blood flow did not significantly change between the 4th and 12th week of pregnancy. Uterine vascular relaxation and the increase in uterine blood flow in early pregnancy appear to be important determinants of pregnancy outcome.

Sieroszewski *et al.* [21] who evaluated the Doppler indices of the flow velocity waveforms in uterine arteries (S/D and RI) in pregnant women in the first trimester of pregnancy. They concluded that there was statistically significant differences for RI in the uterine arteries in threatened miscarriage compared with normal early pregnancies ($p<0.05$).

Giacobbe *et al.* [22] reported that the RI in the uterine arteries were significantly higher in threatened miscarriage than in normal pregnancy. The RI of the uterine arteries decreased with the advance of gestational age in both groups.

The present study revealed that the PI of the uterine arteries was the lowest at third visit , regardless of treatment regimen. The gradual, but statistically insignificant, decrease in this index during successive ultrasound examinations was observed only in the dydrogesterone group. This group was also characterized by statistically significant drop in S/D ratio between particular visits. The decrease in the uterine artery RI was not significant in both groups.

Mäkikallio *et al.* [16] investigated uterine artery blood flow in singleton uncomplicated pregnancy between gestational weeks 5 and 10. Serial measurements revealed no changes in PI between

gestational weeks 5 and 8 and a marked decrease thereafter.

Simultaneously, a comparison of our results and those results that have been presented in the literature suggests that pregnancy that is complicated by threatened miscarriage is not associated with marked uterine artery PI changes, compared with normal pregnancy.

The present study revealed that Doppler waveform analysis of the intrachorionic area showed no statistically significant changes in PI, RI, and S/D indices, in both the progesterone and the dydrogesterone groups.

Similar to our study the study of **Czajkowski *et al.*** [11] that show no significant differences of blood flow indices of intrachorionic area between the vaginal progesterone and the dydrogesterone groups.

Limitation: Large-scale, multicenter, randomized, and controlled studies are needed to better evaluate the efficacy of progesterone therapy in pregnant women with threatened miscarriage.

CONCLUSIONS

In conclusion, vaginally administrated progesterone was nearly as equally effective as oral dydrogesterone in prevention of miscarriage in pregnant women with threatened abortion with different effects on the uteroplacental circulation.

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