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The effect of prenatally administered vaginal progesterone on uterine artery Doppler in asymptomatic twin pregnancies

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ABSTRACT

Objectives: This study investigated the influence of vaginal progesterone on uterine circulation in asymptomatic twin gestations.
Study design: This study was a secondary analysis of a randomized, double-blind, placebo-controlled trial of twin pregnancies exposed to vaginal progesterone or placebo. We included all trial participants who had undergone uterine artery pulsatility index evaluation at the time of randomization. During each ultrasound examination, the uterine artery pulsatility index was evaluated transabdominally. The mean uterine artery pulsatility index between the progesterone and placebo groups were compared for each gestational age, starting between 18 to 34 weeks and 6 days and were analyzed at three (Time 1), six (Time 2) and nine (Time 3) weeks after randomization.
Results: The final analysis included 128 women in the progesterone group and 122 women in the placebo group. The baseline characteristics were similar in both groups. No difference in the mean uterine artery pulsatility index was observed between the progesterone and placebo groups at each week of gestation or throughout gestation.
Conclusions: In twin pregnancies, the use of vaginal progesterone in the second half of pregnancy does not influence uterine circulation.

Introduction

Progesterone is an essential hormone for pregnancy. It is produced by the corpus luteum and the placenta and is indispensable in creating a suitable endometrial environment for implantation and maintenance of pregnancy [1]. In obstetrics, progesterone is most frequently used to prevent recurrent miscarriage and support the luteal phase in assisted reproduction and threatened preterm labor [2].

Several mechanisms have been attributed to the effects of progesterone, such as its anti-inflammatory effect, inhibition of gap-junction formation in myometrium and a direct effect on the uterine cervix, which are probably regulated by genomic and non-genomic pathways [3]. It is also important for suppressing the maternal immunologic response to fetal antigens, thereby preventing maternal rejection of the trophoblast [4]. In addition, progesterone has a vasodilatory effect in non-pregnant women [5,6]. Administration of this hormone in the mid-luteal phase decreases impedance to uterine artery blood flow in the presence of normal/high estrogen [5,6].

Only two studies have investigated the effect of progesterone on uterine arteries in singleton pregnancies during the gestational period. In a study involving early pregnancies complicated with threatened miscarriage, Czajkowski et al. demonstrated that vaginal progesterone had a vasodilatory effect on uterine circulation with a reduction of the pulsatility index (PI), resistance index and systolic/diastolic ratio in the uterine arteries [7]. In contrast, treatment with vaginal progesterone in the second or third trimester did not affect the Doppler flow parameters of uterine arteries in women at high risk for preterm birth [8].

There is minimal information about the effect of progesterone on uterine circulation in twin pregnancies. Serra et al. analyzed the use of vaginal progesterone to prevent preterm birth in unselected twin gestations and found that treatment with this hormone did not have any effect on uterine artery PI at 24 and 28 weeks of gestation [9].

It has been established that an increased uterine artery mean PI during the second trimester can indicate a proportion of twin pregnancies destined to develop adverse outcomes related to

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uteroplacental insufficiency [10]. Because the vasodilatory property of progesterone in the uterine circulation during the first trimester is well recognized [7] and considering the lack of detailed results and specific analyzes regarding the effect of vaginal progesterone in the uterine artery Doppler in twin pregnancies, we sought to address these questions by performing a secondary analysis of a randomized, placebo-controlled trial studying the effectiveness of vaginal progesterone for the prevention of preterm birth in twin pregnancies [11].

Materials and methods

This study is a secondary analysis of data from a single-centre, double-blind, placebo-controlled, randomized trial comparing the effect of progesterone compared to placebo in twin pregnancies, and it was conducted in the Multiple Pregnancy Unit of Department of Obstetrics and Gynaecology of São Paulo University Medical School [11]. In the previous study, consenting women with naturally conceived twin pregnancies were randomized for the daily use of either 200 mg of natural micronized progesterone ovules (Utrogestan – Besins Healthcare, Brussels, Belgium) or placebo ovules. Treatment was initiated between 18 weeks and 21 weeks and 6 days and was continued until 34 weeks and 6 days or delivery, whichever occurred first. Subsequent randomization, clinical and ultrasound examinations were scheduled every three weeks at our Multiple Pregnancy Unit. The care providers, the investigators, and the patients were all blinded to the trial allocation (progesterone or placebo).

This secondary analysis of the trial was planned after the primary study had already started. Therefore, only cases who had undergone uterine artery Doppler assessment at the time of randomization were included in the present analysis. During each ultrasound examination, uterine artery Doppler was evaluated transabdominally following standard techniques. The uterine arteries were assessed after visualization of the ascending branch lateral to the corpus of the uterus. The PI, which represents resistance to blood flow, of the uterine artery was measured by color-image pulsed Doppler ultrasonography, and the average PI of the bilateral uterine arteries was calculated [12]. A Voluson 730 Expert, a Voluson E8 (General Electric Healthcare, Vienna, Austria) and an Envisor (Phillips, Andover, MA, USA) ultrasound machine, equipped with a 3.5–5.0 MHz curvilinear abdominal transducer were used in all cases. The uterine artery Doppler measurements were described in the patient report, and all data were transferred to a Microsoft Excel spreadsheet.

The mean uterine artery PIs between the progesterone and placebo groups were compared for each gestational age, from 18 to 34 weeks and 6 days. To evaluate whether the length of progesterone use could influence the uterine artery PI, we also compared this Doppler parameter between the groups throughout gestation at three weeks (Time 1), six weeks (Time 2) and nine weeks (Time 3) after randomization. These intervals were chosen because patients were evaluated every three weeks.

Only one study of twin pregnancy has assessed the use of vaginal progesterone and the mean uterine artery PI; therefore, our sample size estimation was based on this analysis [9]. Assuming that we would observe the same difference between the progesterone and placebo groups observed by Serra et al. (average uterine artery PI values of 1.18 ± 0.40 for the placebo group and 1.31 ± 0.31 for the progesterone group), the sample size needed to demonstrate a significant difference (significance level, 5%; power, 80%) was 218 patients, with 109 patients in each group.

Numerical data are expressed as the mean and standard deviation, and categorical data are expressed as frequencies. The baseline characteristics between treatment groups were compared using the chi-squared test or Fisher's exact test for categorical variables, and Student's *t*-test was employed for continuous variables. The Mann–Whitney test was applied to compare the mean uterine artery PIs between the progesterone and placebo groups at each gestational age.

A p value < 0.05 was considered significant. The data were analyzed using the Statistical Package for the Social Sciences (IBM-SPSS Statistics – version 20).

Results

A total of 390 women participated in the original trial. However, 130 women (61 in the progesterone group and 69 in the placebo group) were not included in this secondary analysis because they did not have Doppler velocimetry data of the uterine arteries prior to randomization. Ten cases did not return for further follow up after randomization and were excluded from the analysis (four in the placebo group and six in the progesterone group). Therefore, the final data analysis was based on 250 twin pregnancies: 128 in the progesterone group and 122 in the placebo group.

Table 1
Baseline characteristics of the study population at randomization.

	Progesterone ($n = 134$)	Placebo ($n = 126$)	p
Maternal characteristics			
Age, years, mean ± SD[a]	27.90 ± 5.83	27.89 ± 6.58	0.99
Body mass index (kg/m^2), mean ± SD[a]	24.96 ± 4.66	25.11 ± 5.32	0.81
White color, *n* (%)[b]	73 (54.5%)	65 (52.0%)	0.56
Educational level, years, mean ± SD[a]	10.45 ± 2.56	10.43 ± 2.20	0.94
Parity, mean ± SD[a]	0.99 ± 1.05	1.02 ± 1.13	0.77
Smoking during pregnancy, *n* (%)[b]	10 (7.5%)	14 (11.1%)	0.39
Alcohol abuse during pregnancy, *n* (%)[c]	1 (0.7%)	2 (1.6%)	0.61
Illicit substance use during pregnancy, *n* (%)[c]	1 (0.7%)	1 (0.8%)	0.99
Medical disorders prior to pregnancy, *n* (%)[b]	36 (26.9%)	29 (23.0%)	0.56
Hypertension, *n*/*N* (%)[b]	16/134 (11.9%)	8/126 (6.3%)	0.13
Pregnancy characteristics			
Monochorionic, *n* (%)[b]	27 (20.5%)	20 (16.5%)	0.51
Cervical length, mm, mean ± SD[a]	37.59 ± 9.05	37.73 ± 7.93	0.89
Cervical length ≤ 25 mm, *n* (%)[b]	10 (7.7%)	4 (3.2%)	0.16
Average uterine artery PI, mean ± SD[a]	0.80 ± 0.25	0.80 ± 0.25	0.96

SD, standard deviation.
[a] Student's *t*-test.
[b] Chi-squared test.
[c] Fisher's exact test.