Journal of Medicine in Scientific Research

Volume 5 | Issue 3 Article 8

Subject Area:

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Recommended Citation

Badr, Ahmed A. and El-Maghraby, Ibrahim M. (2022) "Role of vaginal progesterone on uterine artery Doppler changes in pregnant women at risk of preterm labor," *Journal of Medicine in Scientific Research*: Vol. 5: Iss. 3, Article 8.
DOI: https://doi.org/10.4103/jmisr.jmisr_18_21

Original Article

Role of vaginal progesterone on uterine artery Doppler changes in pregnant women at risk of preterm labor

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Abstract

Background
Progesterone is increasingly being used in women at high risk for preterm labor and for maintenance tocolysis. Ultrasound evaluation of uterine in pregnant women in the second trimester of pregnancy can be a predictor of birth complications.

Objective
To study the effect of vaginal progesterone on uterine by doppler sonography among women in the second and third trimesters of pregnancy who are at risk of preterm labor.

Patients and methods
A prospective study was carried out on 60 patients attending Obstetrics and Gynecology Department, Menoufia Teaching Hospital, Menoufia, Egypt, during the period from March 2019 to March 2020. The patients were admitted to the hospital for preterm labor, which was arrested by acute tocolysis within 48 h. All participants were subjected to routine baseline investigations and Doppler flow assessment.

Results
There was a highly statistically significant difference ($P < 0.001$) in uterine artery pulsatility index (PI) before and after treatment ($P = 0.000$). Uterine artery PI decreased significantly after treatment (0.817 ± 0.16) than before treatment (0.969 ± 0.27). Uterine artery PI decreased significantly after treatment than before treatment in different periods of gestation (weeks). Moreover, there was no statistically significant difference ($P>0.05$) between the studied women as change in umbilical artery PI before and after treatment in different periods of gestation (weeks). Moreover, uterine artery PI was significantly correlated ($P < 0.05$) with period of gestation (week) before and after progesterone treatment.

Conclusion
Uterine artery pulsatility index (PI) decreased significantly after progesterone treatment than before treatment in different periods of gestation (weeks). Umbilical artery PI and middle cerebral artery Doppler PI were not significant different among the studied patients before and after progesterone treatment in different periods of gestation (weeks). Uterine artery PI and middle cerebral artery Doppler PI were negatively associated with period of gestation (week) before and after progesterone treatment.

Keywords: Doppler sonography, plasticity index, preterm labor, uterine artery, vaginal progesterone

Introduction

Preterm birth (before 37 completed weeks of gestation) is a 'major cause of [postnatal] death and a significant cause of long-term loss of human potential.' There is a substantial long-term health effect from preterm birth owing to increased risk of both death and developing a wide range of chronic physical and neurological disabilities compared with full-term births [1].

Approximately 70% of neonatal deaths, 36% of infant deaths, and 25–50% of cases of long-term neurologic impairment in children can be attributed to preterm birth [2]. The estimated cost of preterm births exceeds $26.2 billion annually with an

Access this article online

Quick Response Code:

Website: www.jmsr.eg.net

DOI: 10.4103/jmisr.jmisr_18_21

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Submitted: 18-Feb-2021 **Revised:** 13-Mar-2021 **Accepted:** 16-Jun-2021 **Published:** 23-Nov-2022

How to cite this article: El-Maghraby IM, Badr AA. Role of vaginal progesterone on uterine artery Doppler changes in pregnant women at risk of preterm labor. J Med Sci Res 2022;5:247-53.

average cost of care for a preterm birth 10 times greater than that of a full-term birth ($32 325 to $3325, respectively). In 2015, preterm birth occurred in 9.6% of approximately four million births in the USA and 11.7% of 59 632 births in the state of Alabama [3].

Despite some severe low-income and middle-income countries having halved their preterm deaths within a decade, many countries have made minimal progress, reflecting a wide survival gap for preterm babies in different countries, with more neonatal deaths in African babies [4]. The percentage of under-five deaths from preterm birth complications is still high in Egypt, and our country is ranked as 144 worst on the list of 162 countries with prematurity-related deaths, comprising ~28.5% of all under-five deaths in Egypt [5].

Maintenance tocolysis is continued tocolysis after arrested preterm labor to prevent the recurrence of preterm labor pains. The oral route of administration has low cost and a possible efficacy in reducing neonatal morbidity, favoring the use of calcium channel blockers. Nifedipine is found to be a safe and effective drug for acute tocolysis, with minimal adverse effects. However, its use for maintenance tocolysis has yielded conflicting results [6].

Progesterone is an important agent for maintaining uterine quiescence. It is increasingly used in women at high risk for preterm labor and for maintenance tocolysis [7]. Administration of progesterone, including vaginal administration of progesterone gel or progesterone tablets and intramuscular injection of 17 alpha-hydroxyprogesterone caproate for preventing preterm birth has been investigated in various studies [8]. In addition, several attempts have indicated that ultrasound evaluation of uterine and fetal arteries in pregnant women in the second trimester of pregnancy can be predictors of birth complications. However, far too few studies have focused on the possible effects of progesterone on maternal or fetal circulation in late pregnancy, especially in high-risk women [8]. Barda *et al.* [9] suggested a statistically significant decrease in the fetal middle cerebral artery (MCA) pulsatility index (PI) with no effects on other fetal and uterine vessel flow following progesterone treatment. Borna [10] concluded that administration of vaginal progesterone suppository leads to a reduction in fetal MCA-PI and umbilical artery PI. The aim of this study was to study the effect of vaginal progesterone on uterine by Doppler sonography among women in the second and third trimesters of pregnancy who are at risk of preterm labor.

Patients and methods

A prospective study was carried out on 60 patients attending Obstetrics and Gynecology Department, Menoufia Teaching Hospital, Menoufia, Egypt, during the period from March 2019 to March 2020. Patients included in the study were admitted to the hospital with preterm labor, which was arrested by acute tocolysis within 48 h. They received 400-mg vaginal tablets (Cyclogest; Actavis UK, Devon, UK) by an independent gynecologist after a while from the first Doppler flow assessment.

Ethical consideration: all of the patients signed a written informed consent after explaining to them the aim of the study before the study initiation. Approval was obtained from ethical committee in Menoufia Teaching Hospital.

Inclusion criteria were patients with preterm labor or threatened preterm labor (preterm labor was defined as the occurrence of regular uterine contractions ≥4 in 20 min and cervical changes, effacement ≥80%, and cervical dilatation ≥1 cm, whereas threatened preterm labor was defined as above but without any appreciable cervical changes) [2]; singleton pregnancy, and a living fetus with gestational age (GA) 18–34 weeks (calculated according to date of last menstrual period confirmed with earlier ultrasound examination).

Exclusion criteria were medical or obstetric conditions requiring termination of pregnancy, contraindication to progesterone administration or its use earlier in this pregnancy, congenital fetal anomalies, and cervical cerclage.

Women who had received other tocolytic drugs, such as $MgSO_4$, NSAIDs, and calcium channel blockers accompanying with progesterone were also excluded.

All participants were subjected to complete history taking, thorough clinical examination, and laboratory investigations included routine baseline investigations (complete blood picture, RH, fasting blood sugar, 2 h postprandial blood sugar, liver functions, kidney functions, urine analysis, as well as Doppler assessment: a complete Doppler flow assessment of the maternal and fetal circulation equipped with a 2–5 MHz convex abdominal transducer with color imaging capabilities was used). The patients were treated with 400-mg vaginal tablets (Cyclogest; Actavis UK) by an independent gynecologist after a while from the first Doppler flow assessment. The Doppler flow assessment was repeated 72 h after the first assessment. Doppler signals were obtained from a free loop of umbilical cord, and the number of waveforms was obtained at least three to five cycles. For all the patients, Doppler sonography and PI measurement of the umbilical artery blood flow, MCA, and mean of uterine arteries, were done.

Statistical analysis

Analysis of data was done by DELL computer using Statistical Package for the Social Sciences (SPSS), version 22 (SPSS Inc., Chicago, Illinois, USA) as follows: description of quantitative variables as mean, SD or median and range as appropriate, and description of qualitative variables as number or frequency and percentage. Student *t* test was used to collectively indicate the presence of any significant difference between two groups for a normally distributed quantitative variable. Paired *t* test was used to compare the same groups regarding quantitative variables (mean ± SD). Pearson's correlation analysis was used to show strength and direction of association between two quantitative variables. *P* value less than 0.05 was considered a

significant difference, *P* value more than 0.05 was considered a nonsignificant difference, and *P* value less than 0.001 was considered highly significant.

Results

The age of the studied patients ranged from 20 to 36 years, with a mean of 28.62 ± 4.13 years, whereas GA of them ranged from 18 to 34 weeks, with a mean of 27.60 ± 3.73 weeks. Regarding cervical length (mm), it ranged from 15 to 33 mm, with mean of 22.50 ± 4.63 mm. However, the number of children among the pregnant women ranged from 1 to 6, with a mean 2.65 ± 1.25, as shown in Table 1.

The current study showed that most of the studied women had normal vaginal delivery (65%), and 31.7% had cesarean section, whereas 3.3% had normal vaginal delivery and cesarean section. Most of the studied women (48.3%) had closed cervical dilatation. On the contrary, 26.7, 15, and 10% of the studied women had opened cervical dilatation by 1, 2, and 3 cm, respectively. Most of the studied patients (46.7%) had GA between 24 and 29 week, followed by those between 30 and 35 weeks, which represented by 38.3% of patients, whereas 15% of the studied patients had GA between 18 and 23 week, as shown in Table 2.

Moreover, the present study shows that there was statistically highly significant difference ($P < 0.001$) in uterine artery PI before and after treatment ($P = 0.000$). Uterine artery PI decreased significantly after treatment (0.817 ± 0.16) than before treatment (0.969 ± 0.27). On the contrary, there was no statistically significant difference ($P>0.05$) between the studied women regarding umbilical artery PI and MCA Doppler PI before and after treatment, as shown in Table 3.

The current study revealed that there was a statistically significant difference ($P \leq 0.05$) between the studied women with respect to change in uterine artery PI before and after treatment regarding different periods of gestation. Uterine artery PI decreased significantly after treatment than before treatment in different periods of gestation (weeks), as shown in Table 4.

Moreover, there was no statistically significant difference ($P>0.05$) between the studied women with respect to change in umbilical artery PI before and after treatment in different periods of gestation (weeks), as shown in Table 5.

In addition, there was no statistically significant differences ($P>0.05$) between the studied women with respect to change in MCA Doppler PI before and after treatment in different periods of gestation (weeks), as shown in Table 6.

Moreover, there was no relation between umbilical and MCA Doppler PI with period of gestation ($P>0.05$), whereas uterine artery PI was significantly correlated ($P < 0.05$) with period of gestation (week) before and after progesterone treatment, as shown in Table 7 and Figs. 1-4.

Table 1: Distribution of the studied patients regarding their sociodemographic characteristics

Sociodemographic characteristics	Number of cases ($n=60$)
Age (year)	
Range (year)	20-36
Mean±SD	28.62±4.13
Gestational age	
Range	18-34
Mean±SD	27.60±3.73
Cervical length (mm)	
Range	15-33
Mean±SD	22.50±4.63
Number of children	
Range	1-6
Mean±SD	2.65±1.25

Table 2: Distribution of the studied patients regarding history mode of delivery, cervical dilatation, and gestational age

Items	Number of cases ($n=60$) [*n* (%)]
History mode of delivery	
NVD	38 (65.0)
CS	19 (31.70)
NVD and CS	2 (3.30)
Cervical dilatation	
Closed (0)	29 (48.3)
1 cm	16 (26.7)
2 cm	9 (15.0)
3 cm	6 (10.0)
Gestational age (weeks)	
18-23	9 (15.0)
24-29	28 (46.7)
30-35	23 (38.3)

CS, cesarean section; NVD, normal vaginal delivery.

Discussion

The current study showed that age of the studied patients ranged from 20 to 36 years, with mean of 28.62 ± 4.13 years, whereas GA ranged from 18 to 34 weeks, with mean of 27.60 ± 3.73 weeks. Regarding cervical length (mm), it ranged from 15 to 33 mm, with a mean of 22.50 ± 4.63 mm. The same finding was supported by Argollo *et al.* [11], who reported that maternal age (years) of the studied patients was 28.14 ± 7.11 years, which ranged from 15 to 41 years, with a median of 28.50 years. However, the mean GA of the patients was 30.29 ± 3.15 weeks, with a median (range) of 31 (25–36) weeks. In addition, Yalti *et al.* [12] found that maternal age (year) of the patients was 29.1 ± 7.5 years, and GA at recruitment (week) was 37.3 ± 1.6 weeks. In other study, it was observed that women with cervical length more than 25 mm in second and early third trimesters were associated with more prolonged duration of pregnancy and decreased incidence of preterm labour.

The current study showed that most of the studied women had normal vaginal delivery (65%), and 31.7% had cesarean

Table 3: Comparative study between the studied women with respect to change in uterine, umbilical, and middle cerebral artery Doppler pulsatility index before and after treatment

Artery Doppler PI	Progesterone treatment		Paired *t* test	
Uterine artery PI	**Before**	**After**	***t***	***P***
Number of case	60	60		
Range	0.66-2.22	0.47-1.46	5.506	0.001**
Mean±SD	0.969±0.27	0.817±0.16		
Umbilical artery PI				
Number of case	60	60		
Range	0.60-1.39	0.60-1.39	0.730	0.581NS
Mean±SD	0.870±0.18	0.863±0.18		
Middle cerebral artery Doppler PI				
Number of case	60	60		
Range	0.99-2.30	0.99-2.33	0.818	0.670NS
Mean±SD	1.882±0.286	1.880±0.286		

NS, nonsignificant; PI, pulsatility index; *t*, paired *t* test. **High significant differences.

Table 4: Comparative study between the studied women with respect to change in uterine artery pulsatility index before and after treatment regarding period of gestation

Gestation period (weeks)	Uterine artery PI			
	Progesterone treatment			
	Before	After	Paired *t* test	
	Mean±SD	Mean±SD	*t*	*P*
18-23	0.914±0.14	0.782±0.16	6.72	0.001**
24-29	0.962±0.18	0.824±0.17	3.16	0.027*
30-35	0.968±0.14	0.816±0.12	3.85	0.014*

PI, pulsatility index; *t*, paired *t* test. *Significant differences. **Highly significant differences.

Table 5: Comparative study between the studied women with respect to change in umbilical artery pulsatility index before and after treatment regarding period of gestation

Gestation period (weeks)	Umbilical artery PI			
	Progesterone treatment			
	Before	After	Paired *t* test	
	Mean±SD	Mean±SD	*t*	*P*
18-23	0.881±0.19	0.853±0.16	1.26	0.473NS
24-29	0.864±0.18	0.852±0.20	0.87	0.621NS
30-35	0.870±0.16	0.863±0.16	0.63	0.890 NS

NS, nonsignificant differences; PI, pulsatility index; *t*, paired *t* test.

section, whereas 3.3% had normal vaginal delivery and cesarean section. This result comes in agreement with Yalti *et al.* [12], who found that 22 (64.7) of the studied patients had vaginal delivery, whereas 12 (35.3) had cesarean section. Moreover, Shen *et al.* [13] found that 36% (n = 356/988) of the studied patients had cesarean section. Besides, Hussein *et al.* [14] studied the effect of vaginal versus intramuscular progesterone on the uterine and fetal blood flow in patients with history of recurrent preterm labor. They found that

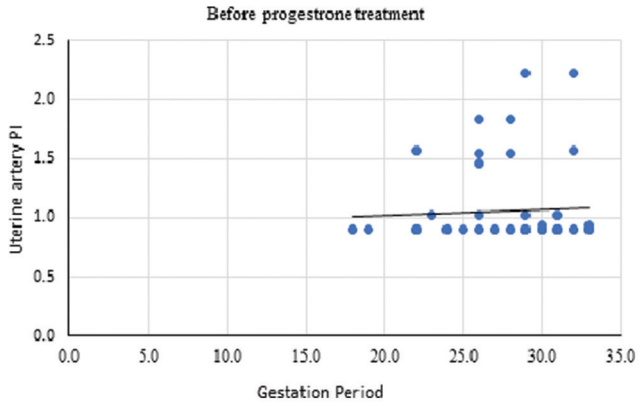

Figure 1: Correlation of uterine artery PI with period of gestation (POG) before progesterone treatment. PI, pulsatility index.

12 (34.3%) of the studied patients had cesarean section and 23 (65.7%) had vaginal delivery. Another study conducted by Houlihan *et al.* [15] concluded that six (15%) of the studied patients had vaginal delivery, two (5%) had vaginal/cesarean section, whereas 32 (80%) had cesarean section. Moreover, Malik *et al.* [16] found that of 100 patients in the high-risk group, abnormal C/U ratio was seen in 62 (62%) cases, of which 27 cases were delivered by cesarean section, and the incidence of operative delivery was 43.5%.

The current study showed that most of the studied women (48.3%) had closed cervical dilatation. However, 26.7, 15, and 10% of the studied women had opened cervical dilatation by 1, 2, and 3 cm, respectively. The same results were supported by the study of Borna [10], which performed ultrasound examination at admission, where 35 women were found to have a short cervix; the cervical length being less than 15 mm in 13 (37.1%) women and 16–25 mm in 22 (62.9%) women. Moreover, Vafaei *et al.* [17] showed that a statistically significant association was observed between short cervix complication in the current pregnancy and medical history of preterm labor pain in the previous pregnancy.

Table 6: Comparative study between the studied women with respect to change in middle cerebral artery Doppler pulsatility index before and after treatment regarding period of gestation

Gestation period (weeks)	Middle cerebral artery Doppler PI			
	Progesterone treatment			
	Before	After	Paired *t* test	
	Mean±SD	Mean±SD	*t*	*P*
18-23	1.771±0.33	1.766±0.32	0.11	0.473^{NS}
24-29	1.905±0.07	1.903±0.07	0.02	0.973^{NS}
30-35	1.880±0.06	1.878±0.07	0.03	0.641^{NS}

NS, nonsignificant differences; PI, pulsatility index; *t*, paired *t* test.

Table 7: Correlation of uterine, umbilical, and middle cerebral artery Doppler pulsatility index with period of gestation

Items	Period of gestation			
	Before treatment		After treatment	
	r	*P*	*r*	*P*
Uterine artery PI	0.537	−0.044*	0.634	−0.011*
Umbilical artery PI	0.123	0.349	0.174	0.185
Middle cerebral artery Doppler PI	0.733	−0.028*	0.847	−0.026*

r: correlation coefficients.

The current study indicated that most of the studied patients (46.7%) had GA between 24 and 29 weeks, followed by 30–35 weeks, which represented by 38.3% of patients. However, 15%, of the studied patients had GA between 18 and 23 weeks. These findings agree with Martinez de *et al.* [18], who found that 17 (38.6%) women gave birth before 37 weeks, including nine (20.4%) before 34 weeks. Preterm delivery was documented in seven of the 15 (46.6%) patients with a previous history of preterm delivery and 11 (31.4%) of the 28 patients with an incidental finding of short cervix. However, Goldenberg *et al.* [19] concluded that by GA, 5% of preterm labors occur at less than 28 weeks (extreme prematurity), 15% at 28–31 weeks (severe prematurity), 20% at 32–33 weeks (moderate prematurity), and 60–70% at 34–36 weeks (near term).

The current study showed that there was a highly significant difference in uterine artery PI before and after progesterone treatment. Uterine artery PI decreased significantly after treatment (0.817 ± 0.16) than before treatment (0.969 ± 0.27). In contrast, there was no statistically significant difference (P>0.05) between the studied women regarding umbilical artery PI and MCA Doppler PI before and after progesterone treatment. These results were confirmed by Vafaei *et al.* [17], who showed a significant reduction in the PI of the uterine artery following progesterone administration. Nevertheless, no significant changes were observed in the PI of other vessels. No significant difference was found in Doppler flow parameters in any of the examined vessels before

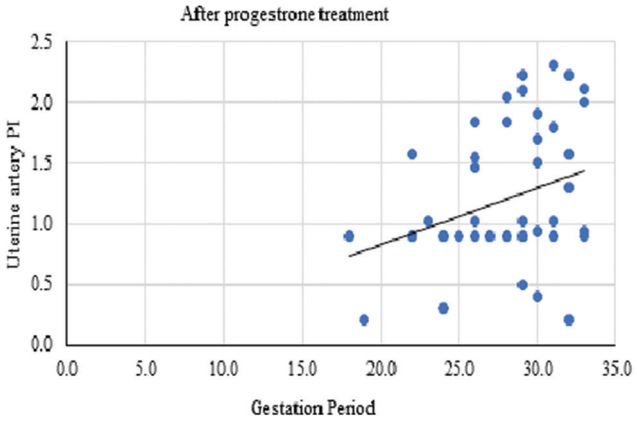

Figure 2: Correlation of uterine artery PI with period of gestation (POG) after progesterone treatment. PI, pulsatility index.

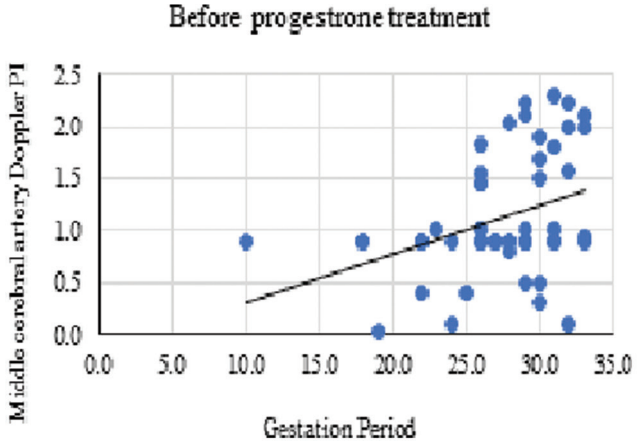

Figure 3: Correlation of middle cerebral artery Doppler PI with period of gestation (POG) before progesterone treatment. PI, pulsatility index.

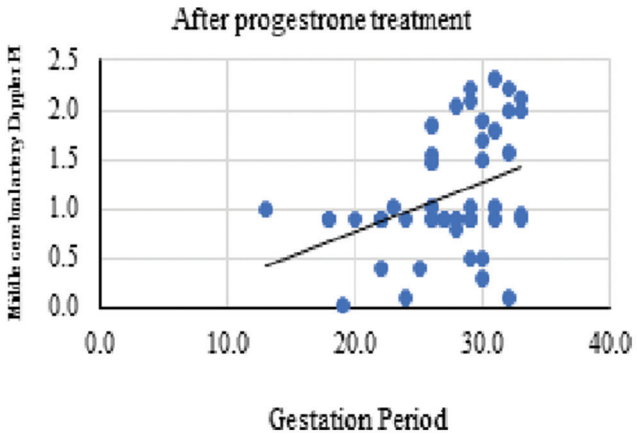

Figure 4: Correlation of middle cerebral artery Doppler PI with period of gestation (POG) after progesterone treatment. PI, pulsatility index.

or after progesterone treatment in women with preterm labor pain. Besides, Dodd *et al.* [20] concluded that administration of vaginal progesterone suppository led to a reduction in fetal MCA-PI and umbilical artery PI. These results may be

owing to progesterone role importance, which is essential in the establishment and maintenance of pregnancy because of its roles in the transformation of the endometrium from a proliferative to a secretory state, relaxation of the uterus, and prevention of cervical dilatation [21]. Conversely, these results are in contradiction to those reported by several studies. Barda *et al.* [9] demonstrated a statistically significant decrease in fetal MCA-PI 24 h after progesterone administration. However, they detected no significant changes in fetal MCA-PSV and the PI of the uterine arteries and umbilical artery.

The current study showed that there were statistically significant differences between the studied patients with respect to change in uterine artery PI before and after treatment regarding period of gestation. Uterine artery PI decreased significantly after treatment than before treatment in different periods of gestation (weeks). However, there was no statistically significant difference between the studied women with respect to change in umbilical artery and MCA Doppler PI before and after treatment in different periods of gestation (weeks). These results matched with a study of Hussein *et al.* [14], who reported that Doppler ultrasound can be used to identify the uterine arteries, and several studies have documented that increased PI at 20–24 weeks of gestation can identify, at a false-positive rate of 5%, about 75% of women who subsequently develop pre-eclampsia of sufficient severity to require delivery before 33 weeks. Moreover, De Heus *et al.* [22] found that mean UtA-PI at 18–24 weeks of vaginal progesteron group was significantly lower compared with no progesterone. However, there was no significant UtA-PI difference for 17-OHPC, compared with the referent at 18–24 weeks. There were no differences observed in UtA-PI between P4 and 17-OHPC compared with the referent at 28–32 weeks, although sample size at visit 2 was below our calculated threshold. Moreover, Saccone *et al.* [23] showed that high UtA-PI at 30–34 weeks predicts about 50% of cases that subsequently deliver with preterm-preclamssia (PE) and 33% that deliver preterm Small for gestational age (SGA) in the absence of PE; the Detection rate (DR) for term PE and term SGA in the absence of PE was 13 and 9%, respectively.

In the current study, there was a negative correlation between uterine artery PI and MCA Doppler PI with respect to the period of gestation (weeks). However, there was no relation between umbilical artery PI and GA (P>0.05) before and after progesterone treatment. These results come in agreement with the study done by Poon *et al*. [24], who found that UtA-PI was inversely associated with GA at birth The UtA-PI was more than 90th percentile in 81% of stillbirths owing to impaired placentation less than 32 weeks, in 42% at 33–36 weeks, and in 34% more than or equal to 37 weeks; the respective percentages for stillbirths without impaired placentation were 16, 25, and 12%. Moreover, Konje *et al*. [25] from a prospective longitudinal study of 70 women found results similar to other studies [26]. Besides, Abramowicz *et al*. [27] in a longitudinal study found similar results. In their study, the Doppler indices decreased continuously with advancing GA. Moreover, all the Doppler indices of MCA showed significant reduction with increasing period of gestation. Resistance index showed a significant negative correlation with period of gestation, which was confirmed in other studies [28]. In contrast to our study, Costa *et al*. [28] found that uterine artery PI decreased from 0.69 to 0.56 between the 22nd and 38th weeks of gestation and was positively correlated with GA.

Conclusion

Uterine artery PI decreased significantly after progesterone treatment than before treatment in different periods of gestation (weeks). Umbilical artery PI and MCA Doppler PI were not significant different among the studied patients before and after progesterone treatment in different periods of gestation (weeks). Uterine artery PI and MCA Doppler PI were negatively associated with period of gestation (week) before and after progesterone treatment.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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