THE EFFECT OF RECTAL PROGESTERONE ON DOPPLER PARAMETERS OF THE UTERINE ARTERIES FOR THE PREVENTION OF PRETERM DELIVERY IN IRAQI POPULATION

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ABSTRACT

Objective: The effectiveness of progesterone in the prevention of threatened preterm labor has been established for many years, but the preferable route, dose, and duration of treatment are until now under the evaluation of researches. The aim of this study was to determine the effect of rectal progesterone on Doppler indices of the uterine arteries in pregnant women with threatened preterm delivery.

Methods: A prospective case–control study was conducted at the obstetric ward and the Outpatients Department of Al-Yarmouk Teaching Hospital in Baghdad for the period of 1 year from April 1, 2017, to April 1, 2018. 100 women were enrolled in the study, 50 of them were pregnant women with a diagnosis of preterm labor assigned as a study group and the other 50 were apparently healthy pregnant women of the same gestational age assigned as a control group. Doppler study of uterine arteries was done to all participants, and the results were compared for both groups. The patients with preterm labor received nifedipine tocolysis initially until contractions subsided and Doppler study had been repeated for those women after 1 week of rectal progesterone therapy.

Results: The study group had a significantly higher resistance index (RI) than the control group (0.58 vs. 0.52) as $p<0.05$, in spite of the pulsatility index (PI) being higher for the study group compared to the control group (0.78 vs. 0.77) but this difference was not statistically significant. The RI before the therapy (0.58) was significantly higher than the index after therapy (0.52), and the PI was again significantly higher before therapy (0.78) than after therapy (0.71) as $p<0.05$. During the follow-up period, 3 (6.5%), 4 (8.7), and 39 (84.8%) patients delivered within 1 week, after 1 week, and at term, respectively.

Conclusion: Rectal progesterone can arrest threatened preterm labor, and this effect is possible in part explained by its action on uterine arteries.

Keywords: Preterm labor, Progesterone, Doppler study.

INTRODUCTION

Delivery of a baby before 37 completed weeks of pregnancy is a common health issue with a worldwide incidence of around 10%, and more than 1 million preterm babies die while long life handicap affects many of the survivors, this health issue is far more common in low-income countries with a worse prognosis where a reasonable survival not reached until 34 weeks gestation [1]. With the improvement of fertility treatment regimens, more cases with threatened preterm labor are seen due to the higher incidence of multiple gestations which constitutes a major cause for uterine overdistension [2]. It has been criticized as the single most important factor in adverse infant outcome as the infant mortality rate in 2011 was more than 25\1000 live deliveries compared to 1.5\1000 for those delivered at term [3]. The gestational age was significantly associated with various morbidities as developmental, behavioral, educational, and various influences on later health [4]. As the neonatal management has a little impact on these morbidities, all efforts should be directed toward the prevention of early birth and prolongation of pregnancy to achieve good survival and better outcome. Among these interventions are the progesterone supplementation which was chosen in this clinical trial to delineate its effect on those admitted with threatened preterm deliveries by means of clinical evaluation as well as ultrasonic evaluation including Doppler study of uterine arteries resistance which has been found as a useful modality for the prediction of preterm birth [5]. Various doses and routes of administration had been studied, but the use of rectal progesterone is more rationale as it is more convenient for the patients who are afraid from preterm delivery and does not need medical supervision. At present, the American College of Obstetricians and Gynecologists recommends progesterone therapy for a singleton fetus at risk of preterm birth based on the history of prior birth before 37 weeks [6]. While the Royal College for Obstetricians and Gynecologists recommends its use to be restricted to therapeutic trials, until its fetal effects both on short and long term become evident [7]. The novelty of the study comes from the priority of using rectal progesterone in the prevention of threatened preterm labor in our population and the evaluation of its effects on Doppler indices of the uterine arteries.

Patients and method

This interventional prospective case–control study was conducted at Al-Yarmouk Teaching Hospital which is a tertiary referral hospital receives more than 3500 pregnant women per year in Baghdad, for a period of 1 year from April 1, 2017, to April 1, 2018. The protocol of the study was approved by the Ethical Committee of Scientific Researches of Obstetrics and Gynecology at Al-Yarmouk Teaching Hospital. The study involved 100 pregnant women who attained the Outpatients Department and those admitted to the Obstetric ward of AL-Yarmouk Hospital. 50 of them were assigned as the control group who were apparently healthy pregnant women. The other 50 women were those with a diagnosis of threatened preterm labor in the current pregnancy who were assigned as a study group. Verbal informed consent was taken from all participants included in the study.

Inclusion criteria
The following criteria were included in the study:
1. Singleton pregnancy.
2. 28–37 weeks gestation.
3. Diagnosis of threatened preterm labor.

Exclusion criteria

The following criteria were excluded from the study:

1. Multiple pregnancy
2. Polyhydramnios or oligohydramnios
3. Diabetic or hypertensive patients
4. Over or underweight women
5. Ruptured membrane
6. Smoking.

The two groups were matched for the age, gravidity, parity, weeks of gestation, and body mass index (BMI) which was calculated according to the following equation (BMI = weight in kg\height in square meter). Detailed history was taken from all participants, full physical examination including general and abdominal examination to assess the intensity and the frequency of uterine contractions was done to all pregnant women involved in the study. Pelvic examination including sterile speculum examination was performed only for those with signs and symptoms of threatened preterm labor looking for cervical dilatation and effacement. Patients with threatened preterm delivery were those with at least 3 contractions per 10 min associated with cervical changes. Blood sample (5 cc) was taken from all participants for; complete blood count looking for white blood cells, and C reactive protein to exclude infection, and midstream urine sample to exclude urinary tract infection.

Examination was done by B-mode ultrasonography with the patient on left lateral position without uterine contractions. Color and spectral Doppler studies were done using transabdominal sonography (2.5 Mhz). All cases were evaluated by the same radiologist 2D. Ultrasound and Doppler evaluation were done using GE Voluson E6 Machine that was equipped with a transabdominal volumetric probe. The patients with preterm labor received nifedipine tocolysis initially until contractions subsided and 400 mg rectal progesterone in the form of cyclogest suppository every day for 1 week and another Doppler ultrasound was done to those who completed the study after this period to evaluate the change in the Doppler blood flow indices of uterine arteries. The patients in the study group were followed until the time of delivery.

Statistical analysis

The data were analyzed using Statistical Package for the Social Sciences version 24. The data were presented as mean with standard deviation/standard error mean and median with range. Student's *t*-test (two-tailed) was used to compare the demographic data between the study and control groups. Mann–Whitney U nonparametric test was used to compare the Doppler parameter values between the two groups. p value level of <0.05 was considered as statistically significant.

RESULTS

The demographic data for the participants in this study is shown in Table 1 which clarifies that there are no significant differences between the study and control groups regarding age, weeks of gestation, BMI, gravidity, and parity as p>0.05.

Doppler examination results for both those with preterm labor and apparently healthy pregnant women were analyzed, and the comparison results are demonstrated in Table 2.

In Table 2, the study group has a significantly higher resistance index (RI) than the control group (0.58 vs. 0.52) as p<0.05; however, the pulsatility index (PI) is higher in the study group compared to the control group (0.78 vs. 0.77) but this difference is not significant statistically as p>0.05.

The Doppler examination results after progesterone treatment for those with threatened preterm labor who completed the study and not delivered or lost in the follow-up (43 patients) were analyzed, and the results of comparison are shown in Table 3.

Table 1: Comparison of demographic parameters between the study groups

Parameters	Study group n=50	Control group n=50	p value
Age (years)			
Mean±SD/SEM	25.18±5.06/0.5	26.34±5.02/0.62	0.25
Median (range)	24 (20–30.2)	25 (21–31)	
Gestational age (weeks)			
Mean±SD/SEM	31.82±2.27/0.24	31.36±2.55/0.44	0.34
Median (range)	31.7 (28–34.3)	30.5 (27.5–34)	
BMI (Kg/m²)			
Mean±SD/SEM	21.84±1.65/0.15	20.96±1.42/0.23	0.24
Median (range)	20.02 (19.6–23)	19.6 (19–22.3)	
Gravidity			
Mean±SD/SEM	3.4±2.02/0.21	3.5±3.2/0.3	0.43
Median (range)	3 (1.5–5.5)	4.2 (2–6.7)	
Parity			
Mean±SD/SEM	1.26±0.9/0.12	2.3±1.9/0.26	0.22
Median (range)	1 (0.6–2.1)	3 (1.6–4.2)	

Sample size: Study group 50, control group 50. SD: Standard deviation. SEM: Standard error mean

Table 2: Comparison of Doppler study results between the two groups

Doppler parameter	Study group n=50	Control group n=50	p value
RI			
Mean±SD/SEM	0.58±0.06/0.01	0.52±0.04/0.02	<0.001*
Median (range)	0.61 (0.52–0.64)	0.49 (0.48–0.56)	
PI			
Mean±SD/SEM	0.78±0.19/0.21	0.77±0.25/0.25	0.24
Median (range)	0.6 (0.59–0.98)	0.61 (0.55–1.2)	

Sample size: Study group 50, control group 50. SD: Standard deviation, SEM: Standard error mean, *significant at 0.05 level. RI: Resistance index, PI: Pulsatility index

Table 3: Comparison of Doppler study results before and after treatment for the study group

Doppler parameter	Before therapy n=43	After therapy n=43	p value
RI			
Mean±SD/SEM	0.58±0.06/0.01	0.52±0.02/0.003	<0.001*
Median (range)	0.61 (0.52–0.64)	0.49 (0.48–0.56)	
PI			
Mean±SD/SEM	0.78±0.19/0.02	0.71±0.25/0.04	0.003*
Median (range)	0.6 (0.59–0.98)	0.51 (0.44–0.96)	

RI: Resistance index, PI: Pulsatility index. Sample size: Before therapy 43, after therapy 43. SD: Standard deviation, SEM: Standard error mean, *significant at 0.05 level

From Table 3, it is clear that the RI before therapy (0.58) is significantly higher than the index after therapy (0.52) as p<0.05.

With regard to the PI, it is significantly higher before therapy (0.78) than after therapy (0.71) as p<0.05.

The outcome of the patients whom recruited initially in the study and completed the study (46 patients as 3 patients lost in the follow-up and 1 patient stopped the therapy because of side effects) is demonstrated in Table 4.

From Table 4, we observed that 3 patients delivered within 1 week despite the therapy while 4 patients delivered after 1 week and 39 patients (84.8%) achieved a term delivery which could be

Table 4: The outcome of study group

Outcome	n (%)
Delivered within 1 week	3 (6.5)
Delivered after 1 week	4 (8.7)
Delivered at term	39 (84.8)
Total	46 (100)

Sample size: 46 patients

attributed to the beneficial effect of progesterone in inhibiting preterm birth.

DISCUSSION

All over the world, threatened preterm delivery constitutes the leading cause for hospitalization during pregnancy [5]. In spite of all the available measures to prevent its occurrence about 13 million preterm babies are born per year [8]. Early prediction of preterm delivery is vital because immediate medical interventions, such as steroid and maternal transfer to tertiary center are the cornerstone that can reduce neonatal mortality and morbidity. Unfortunately, there are no approved clinical screening or diagnostic tools for preterm delivery and the accuracy of most of these tools is limited [5,9]. Different biochemical markers are now available for research purposes not for routine clinical practice [10]. There are lots of controversies regarding the role of local progesterone in the arrest of threatened preterm delivery [11]. Some studies proved its anti-inflammatory and local cervical effects while others discussed its vasodilatory effects on fetomaternal circulations [9].

The current study clarified the effect of rectal progesterone on the uterine arteries resistance. The study groups were matched for age, weeks of gestation, parity, and BMI to avoid the effects of these parameters on the results of the study. The present study showed a statistical significance difference between the study groups regarding RI of the uterine arteries as $p<0.05$; however, the PI was higher in the study group compared to the control group, but this difference was statistically not significant as $p>0.05$, this might be due to the presence of uterine contractions that reduced the end-diastolic flow component of the PI and RI of the uterine arteries [5,12].

After 1 week of treatment with 400 mg rectal progesterone for the women with threatened preterm labor, there were significant differences in all Doppler indices of the uterine arteries. In 2016, Homeira *et al.* concluded that there was a great reduction in the PI of the uterine arteries after treatment with vaginal progesterone due to the vascular relaxation of the uterine arteries [9] which matches the results of this study but here the route of progesterone supplementation was rectal one. In 2015, Fadwah *et al.* studied the effects of rectal progesterone on the latency period of patients with pre-labor rupture of membrane, and they concluded that there was a significant increase in the latency period after treatment with progesterone. However, they did not include the changes in Doppler indices of fetomaternal circulations which support the beneficial effects of progesterone in threatened preterm labor [13].

In 2014, Barda *et al.* found that there was a significant reduction in the PI of the fetal middle cerebral and umbilical arteries after treatment with vaginal progesterone. Still, there were no effects on the uterine arteries indices [9] which disagreed with the finding of the current study and this might be due to the different route of progesterone therapy. In 2016, DeFranco *et al.* studied the effects of vaginal and systemic progesterone on the fetomaternal circulation and they concluded that vaginal treatment was associated with a significant difference in the uterine PI while the systemic one in the form of intramuscular injection of 17 hydroxyprogesterone caproate was not [14-16] this supports the idea of our results regarding the beneficial effect of local progesterone in the management of threatened preterm labor in comparison to systemic one. In the current study, a rectal route was used because many patients with threatened preterm labor were reluctant to take vaginal medication either because of fear of labor or excessive vaginal discharge. In addition that injectable progesterone was painful and not self-administrable.

In the current study and during the follow-up period of the patients; about 3 (6.5%), 4 (8.7%), and 39 (8.48%) delivered within 1 week, after 1 week, and at term, respectively, and it was so clear that progesterone had a significant effect on the latency period between the start of signs and symptoms of threatened preterm labor and the actual time of delivery. In 2016, Olgan and Celiloglu studied the relationship between uterine arteries PI and the time of delivery and they concluded that patients with high PI delivered within 1 week while those with lower PI delivered at a time exceeding 1 week. Still, they did not study the effect of progesterone on the prolongation of the duration of the pregnancy [5].

In spite of all these controversies, most of the studies showed the same results regarding the usefulness of progesterone treatment in the prevention of threatened preterm labor. However, the exact mechanism, dose, preferable gestational age, and route of administration are still not completely proven which require further researches to reach the ideal results. This work may help the obstetricians to understand the role of progesterone in suppressing preterm labor which represents a big dilemma in their work due to its major adverse effect on the baby's life and future physical health and mentality, in addition, to other medical care parameters such as health workers skills, antenatal care, and nutritional support which have a major role in preventing preterm birth in addition to other common medical problems [17-20].

CONCLUSION

Rectal progesterone has a vasodilatory effect on uterine arteries and this might be one of the mechanisms by which progesterone acts to arrest threatened preterm labor.

RECOMMENDATION

We recommend further studies with a larger population sample especially in our community to support our results, including the use of different routes and compare the results of these studies in a suitable meta-analysis to reach ideal and effective treatment protocols.

AUTHORS' CONTRIBUTIONS

1. In our study, we used the rectal route rather than vaginal and injectable routes as this was more convenient for our patients.
2. The duration of treatment in this study was 1 week to minimize the cost on the patient rather than few days.
3. The sample size was limited by the compliance of the patients for follow-up.

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