International Journal of Obstetrics and Gynaecology Research (IJOGR)
Vol. 3 (2016) No.5, pp. 356-367
http://www.ijogr.com/

Comparison of the Efficacy of Progesterone and Nifedipine in Inhibiting Threatened Preterm Labor: A Randomized Study

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Abstract

The goal of this study is to compare the efficacy of natural vaginal progesterone with that of oral nifedipine in treatment of threatened preterm labor.150 women, with singleton pregnancy and threatened preterm labor between 28 to 36 weeks of gestation, were randomly grouped into two, 75 in each group. Group 1: pregnant females who used natural progesterone 200mg twice daily inserted vaginally as a tocolytic agent and group 2: pregnant females who used nifedipine 20mg orally every 30 minutes for 3 times then maintenance with nifedipine SR 20mg every 12hours. Natural progesterone and nifedipine were successful to inhibit contractions in threatened preterm labor in 82.6% (62/75 cases) and 78.6% (59/75 cases) respectively with no statistically significant difference between the two groups. Also, the mean gestational age at delivery and the Apgar scores of fetuses were similar with no significant difference between the two groups. There were more side-effects and complications in nifedipine group as compared to the progesterone group with highly significant difference between two groups.

Keywords

progesterone; nifedipine; threatened preterm labor.

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I. Introduction

Preterm birth is the leading cause of perinatal morbidity and mortality, and its prevention is an important healthcare priority [1]. In 2005, 12.9 million births worldwide were preterm [2]. Preterm labor is the onset of regular uterine contractions associated with progressive cervical change between viability and 37 completed weeks of gestation. The incidence is between 5% and 10% in most developed nations. In the US, the incidence has increased from 9% to 12% in the past two decades. Preterm delivery can be associated with immediate and long-term neonatal complications. Long-term morbidity includes cerebral palsy, neurodevelopmental delay and chronic lung disease. The lower the gestational age, the higher the risk of mortality and morbidity .The management of preterm labor involves identification of high-risk women, prevention and treatment [3].

The most important components of management are aimed at preventing neonatal complications through the use of corticosteroids and antibiotics to prevent group B streptococcal neonatal sepsis, and avoiding traumatic deliveries. Delivery in a medical center with an experienced resuscitation team and the availability of a newborn intensive care unit will ensure the best possible neonatal outcomes. Obstetric practices for which there is little evidence of effectiveness in preventing or treating preterm labor include the following: bed rest, hydration, sedation, and home uterine activity monitoring, oral terbutaline after successful intravenous tocolysis [4].

A lot of methods of intervention have been used to prevent preterm labor for a long time including good antenatal care, bed rest, intravenous hydration seemed to improve outcome but there was no strong evidence supporting those intervention in preterm labor prevention. Only fetal fibronectin in cervical mucus and cervical length are used with good evidence based to predict preterm birth [5].

Progesterone is useful in allowing pregnancy to reach its physiologic term because at sufficient levels in the myometrium, it blocks the oxytocin effect of prostaglandin F2α and α-adrenergic stimulation and therefore, increases the α-adrenergic tocolytic response [6]. Natural progesterone is free of any disturbing teratogenic, metabolic, or hemodynamic effects which is not true for certain artificial progestagens7. Progesterone has long been considered important agents in the maintenance of uterine quiescence and has been used extensively in primary and secondary prevention of preterm labor [8-9]. In a study published in 2007, vaginal progesterone treatment reduced the rate of preterm birth among women who were at high risk for preterm labor because of short cervix [10]. Progesterone has also been shown to delay parturition in animals [11].

Calcium-channel Blockers interfere with the calcium ions transfer through the myometrial cell membrane. They decrease intracellular free calcium concentration and induce myometrial relaxation [12]. Nifedipine was first reported in 1980 in an observational study to be an effective tocolytic agent with minimal side effects [13]. Nifedipine is an

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efficient tocolytic agent, with an easy oral route of administration, few side effects and a low neonatal complications rate. However, it should be used with caution in patients with compromised cardiovascular condition as they may be at risk of pulmonary edema and cardiac failure [14]. The efficacy of maintenance tocolytic therapy after successful arrest of preterm labor remains controversial. This question is not limited to the use of specific drug as the data are similar for terbutaline, magnesium sulfate, and calcium channel blockers [15]. The aim of the study is to compare the efficacy of progesterone with that of nifedipine in treatment of threatened preterm labor.

II. Patients and Methods

This was a randomized study performed in Ain Shams Maternity University Hospital from March 2014 - October 2014 involving 150 women. Written consents were obtained.
Sample size justification: Sample size was calculated using Epicalc 2000 software with the following inputs: The minimal sample size was 150 according to data from Chawanpaiboon et al, 2011[5].

Inclusion criteria:

1. Singleton pregnancy in cephalic presentation with threatened preterm labor gestational age between 28-36 weeks.
2. Uterine contractions at least one contraction in 10 minutes. The examination was done over at least 30 minutes.
3. Intact membranes.
4. No cervical effacement.
5. No cervical dilatation.

Exclusion criteria:

1. Cardiovascular diseases.
2. Diabetes mellitus.
3. Bronchial asthma.
4. Pregnancy induced hypertension
5. Severe anemia
6. Multiple pregnancy and polyhydroamnios
7. Malpresentations

All patients were subjected to:

1. ***History taking:***

a) Personal history: name, age, date of marriage, education, occupation and special habits as smoking.
b) Menstrual history: the first day of last menstrual period (LMP) to calculate the gestational age (reliable date).
c) Obstetric history: the number of previous pregnancies and abortions.
d) Past history: medical conditions (e.g. hypertension, diabetes mellitus), surgical operations, blood transfusion, and drug allergies.

2. ***Physical examination:***

a. General examination: pulse, temperature, blood pressure, body weight and height, body mass index.
b. Abdominal examination: uterine contractions were assessed.
c. Pelvic examination (Vaginal examination): cervical dilatation was assessed.
d. Cusco speculum examination with complete aseptic technique.

3. ***Ultrasonography:*** to estimate gestational age, fetal growth, amniotic fluid index and to exclude any congenital malformation.

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4. ***All routine investigations:*** Complete blood picture blood grouping, blood sugar, kidney functions tests, liver enzymes.
5. Complete urine analysis and culture & sensitivity.
6. ***All pregnant women were distributed randomly into two groups:***

• Group 1: pregnant women who used natural Progesterone (Prontogest) 200 mg vaginal Progesterone suppository twice daily as a tocolytic agent.
• Group 2: pregnant women who used nifedipine (Epilat) 20mg orally every 30 minutes for 3 times then maintenance with nifedipine SR (Epilat Retard) 20mg every 12 hours.
• The treatment was continued until 36 weeks gestation

7. The primary outcome is the inhibition of threatened preterm contractions.
8. Randomization table was used.
9. The ethical committee of Ain Shams University Maternity Hospital approved the study.

Statistical methodology

• Analysis of data was done by IBM computer using SPSS (statistical program for social science version 12) as follows

- Description of quantitative variables as mean, SD and range
- Description of qualitative variables as number and percentage
- Chi-square test was used to compare qualitative variables between groups.
- Fisher exact test was used instead of chi-square when one expected cell or more less than or equal 5.
- Unpaired t-test was used to compare quantitative variables, in parametric data (SD<50% mean)'

• P value >0.05 insignificant
• P < 0.05 significant
• P < 0.01 highly significant [16].

III. Results

The current study was conducted at Ain Shams University Maternity Hospital during the period between March 2014 and October 2014. A total of 150 women, with singleton pregnancy and threatened preterm labor between 28 to 36 weeks of gestation, were randomly grouped into two, 75 in each group. Group 1: pregnant females who used natural progesterone 200mg twice daily inserted vaginally as a tocolytic agent and group 2: pregnant females who used nifedipine 20mg orally every 30 minutes for 3 times then maintenance with nifedipine SR 20mg every 12hours.

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Table (1): clinic-demographic data of the population under study

Variables	Drugs		T	P
	Nifedipine	Progesterone		
Maternal age (years)	28.4±6	26.7±4.6	1.7	0.08
Gestational age (weeks)	32.2±1.8	31.9+2.1	1.1	0.23

This table shows no statistically significant difference between two groups with regard to different variables by using unpaired test.

Table (2) Comparison between two groups as regards the parity

Variables	Drugs				X^2	P
	Nifedipine		Progesterone			
PG	21	(28%)	19	(25.3%)	3.7	0.70
P1	17	(22.7%)	24	(32%)		
P2	21	(28%)	15	(20%)		
P3	11	(14.7%)	11	(14.7%)		
P4	4	(5.3%)	3	(4%)		
P5	1	(1.3%)	2	(2.7%)		
P6	0	(0.0%)	1	(1.3%)		
Mean±SD	2+1.1		2±1.4			

This table shows no statistically significant difference between two groups as regards the parity by using chi-square test.

Table (3) Comparison between two groups as regards the gestational age at delivery, fetal birth weight and Apgar score of infants

Variables	Drugs		t	P
	Nifedipine	Progesterone		
Gestational age at delivery	37.6±4	37.5±3	0.6	0.53
Fetal birth weight	2.547±253	2679±455	0.55	0.56 NS
Apgar score of infant	9±0.6	9±0.7	0.56	0.57 NS

This table shows no statistically significant difference between two groups as regards the gestational age at delivery, fetal birth weight and Apgar score of infants by using unpaired test.

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Table (4): Comparison between two groups with regards to mode of delivery and obstetric history

Variables	Drugs				P
	Nifedipine		Progesterone		
VD	53	(70.7%)	60	(80%)	0.13
CS	22	(29.3%)	15	(20%)	
Previous CS	20	(26.7%)	18	(24%)	0.67
Previous preterm	54	(72%)	50	(66.7%)	0.80

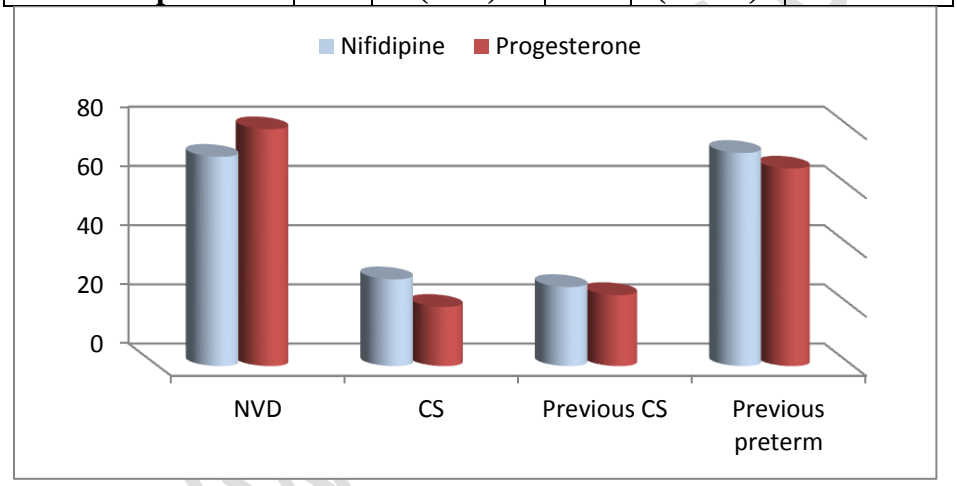

Fig. (1): Comparison between two groups as regard mode of delivery and obstetric history.

Table (4), Fig. (1): show no statistically significant difference between two groups as regards the mode of delivery and obstetric history.

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Table (5): Comparison between two groups in regard to the success rate of inhibition of threatened preterm labor and number of uterine contractions.

Variables	Drugs				Chi-square test	
	Nifedipine		Progesterone			
	No.	%	No.	%	x2	p-value
Full term	59	78.7	62	82.7	0.171	0.679
Pre term	16	21.3	13	17.3		
Total	75	100.0	75	100.0		
Number of uterine contractions						
1 uterine conration /30min	40	(53.3%)	42	(56%)	0.39	0.83 NS
2 uterine conrations /30min	33	(44%)	30	(40%)		
3 uterine contractions /30min	2	(2.7%)	3	(4%)		

x^2 - Chi-square test; p-value >0.05 NS

Table (5): showed that there was no statistically significant difference between two groups as regards the success rate of inhibition of threatened preterm labor and the number of uterine contractions.

Table (6) Comparison between two groups with regard to the side-effects.

Variables	Drugs				X^2	P
	Nifedipine		Progesterone			
No Complication	42	(56%)	75	(100%)	**42**	**0.000 HS**
Palpitation	15	(20%)	0	(0.0%)		
Hypotension	10	(13.3%)	0	(0.0%)		
Dizziness	8	(10.7%)	0	(0.0%)		
Unsatisfied	32	(42.7%)	30	(40%)	1.06	0.56 NS
Satisfied	43	(57.3%)	45	(60%)		

Table (6) showed that the nifedipine group had more complications and side-effects than the progesterone group with highly significant difference between the two groups.

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IV. Discussion

Many interventions have been used to prevent preterm labor including good antenatal care, bed rest and intravenous hydration. They seemed to improve outcome but there was no strong evidence supporting those interventions in preterm labor prevention [17].

Of all treatments evaluated for the prevention of spontaneous preterm birth, progestational agents have demonstrated the greatest promise. The exact mechanism of progesterone in the prevention of preterm birth is not known, although progesterone has been shown to prevent the formation of gap junctions, to have an inhibitory effect on myometrial contractions, and to prevent spontaneous abortion in women in early pregnancy after excision of the corpus luteum. Progesterone has also been shown to delay parturition in animal [18].

Progestational agents initiated in the second trimester of pregnancy, may reduce the risk of delivery less than 37 weeks gestation, among women at increased risk of spontaneous preterm birth, but the effect on neonatal outcome is uncertain [18].

The administration of vaginal progesterone gel to women with a sonographic short cervix in the mid-trimester is associated with a 45% reduction in the rate of preterm birth before 33 weeks of gestation and with improved neonatal outcome [19].

A recommendation has been made by the Royal College of Obstetricians and Gynecologists to use nifedipine (or atosiban) as the first line treatment in preference to beta-mimetics [20]. Nifedipine was studied and was strongly recommended for administration to inhibit contraction. The side effects and complications of nifedipine to mother and fetus are fewer than for beta-agonist and magnesium sulfate [5].

Chawanpaiboon et al, 2011 conducted a study from May 2007 to December 2008[5]. One hundred and fifty (150) pregnant women with a diagnosis of threatened preterm labor were admitted to the labor room in Siriraj Hospital. Each group consisted of 50 pregnant women and then contractions were inhibited with nifedipine, proluton depot and bed rest, respectively. There was no statistically significance in maternal age, mean gestational age of admission, mean gravidity, parity, abortion and cervical length among the patients in the three groups. Nifedipine, proluton depot and bed rest were used to inhibit contractions with a success rate of 80%, 66% and 64%, respectively without statistical significance. The mode of delivery, gestational age, the mean neonatal body weight and the mean Apgar score between these groups were statistically insignificant. Gestational age was calculated on the basis of the last normal menstrual period, and ultrasonographic examination. Medication started after observation of one uterine contraction in 10 minutes after examination taken at least 30 minutes and administration of antenatal corticosteroids. The pregnant ladies were

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showed how to use the medication and schedule of follow up[5].

Natural progesterone is identical to the Progesterone produced by the placenta and corpus luteum and so is readily metabolized and associated with minimal side effects. The current study is a randomized; clinical trial, the objective of this study was to compare the effect of administration of progesterone and nifedipine therapy on threatened preterm labor. The current study included one hundred and fifty (150) pregnant women selected on basis of being singleton pregnancy, gestational age between 28 and before 37 weeks of gestation, intact membranes, no progressive effacement or dilatation. The pregnant women were randomly assigned in two groups (progesterone and nifedipine group), seventy five (75) women in each group. Gestational age was calculated on the basis of the last normal menstrual period, and ultrasonographic examination. Medication started after observation of one uterine contraction in 10 minutes after examination taken at least over 30 minutes and administration of antenatal corticosteroids. The pregnant ladies were showed how to use the medication and schedule for follow up.

In the current study, distribution of the studied group as regards the general data was as follows; average age was 27.5yrs, (±6.1) SD, (age range:18-41yrs); average gestational age was 32wk, SD (±1.9) , (range:28-36wk); and average parity was 2, SD (±1.3), (range:0-6). The studied cases were distributed randomly into two groups: group 1 (75 cases) received nifedipine and group 2 (75 cases) received progesterone. There was no statistically significant difference between the two groups as regards the age, parity and gestational age. This agrees with the study of Chawanpaiboon et al. (2011)[5].

There was no statistically significant difference between two groups as regards the gestational age at the time of delivery. The mean gestational age at delivery of nifedipine group was 36.9wk, SD (±1.7) and progesterone group was 36.3wk, SD (±2.1). This also agreed with the study of Chawanpaiboon et al. (2011) [5].

The percentage of full term in nifedipine group and progesterone group was 78.7% and 82.7% respectively. The percentage of preterm in nifedipine group and progesterone group was 21.3% and 17.3% respectively. The P value (0.679) shows no statistically significant difference between two groups. This agreed with the results of Chawanpaiboon et al. (2011), the success rate of inhibition of contraction was 66% (33/50) with progesterone and 80% (40/50) with nifedipine. There was no statistically significant difference between two groups [5].

The nifedipine group had higher frequency of side effects than in the progesterone group. The P value was (0.000) with highly statistically significant difference between two groups. There was no statistically significant difference between two groups as regards the fetal birth weight. Mean fetal birth weight in the nifedipine group was 2.547kg, SD (±253), (range:2.130-3.180kg), and in the progesterone group it was 2.679kg, SD (±455), (range:2.350-3.000kg). The P

value was 0.798. These findings are agreed with the results of Chawanpaiboon et al. (2011) [5]. The mean fetal birth weight in nifedipine group was 2.856kg, SD (±351), and whereas in the progesterone group it was 2.685kg, SD (±456).P value >0.05, the difference was not statistically significant.

The difference in fetal birth weight between the current study and the others may be attributed to use of progesterone in threatened phase of preterm while in others after tocolysis in established preterm labor and number of the patients of each study. There was no statistically significant difference between two groups in regard to Apgar score. These results also agreed with results of Chawanpaiboon et al. study 2011[5].

Progesterone and nifedipine can be similarly used to inhibit contraction in threatened preterm labor. Progesterone 400 mg can be used vaginally per day while nifedipine 20 mg was given orally every 30 minutes for 3 times then maintenance with nifedipine SR 20 mg every 12hours.

Another study showed that progesterone was associated with a reduction in the risk of preterm birth and infant birth weight of less than 2500 grams in the patients who had previous history of the preterm birth [21]. Nifedipine was studied and was strongly recommended to inhibit contractions [22]. The side effect and complication of nifedipine to mother and fetus are fewer than beta-agonist and magnesium sulfate [23]. Therefore, natural progesterone and nifedipine were still the promising medication to use with minimal side effects.

In conclusion, progesterone has an efficacy as that of nifedipine in treatment of threatened preterm labor with relatively fewer side-effects and complications. So, the current study recommends using progesterone in the treatment of threatened preterm labor.

V. Conclusion

This study recommends the use of natural vaginal progesterone in the treatment of threatened preterm labor as progesterone has similar efficacy to oral nifedipine in treatment of threatened preterm labor with comparatively fewer complications and side-effects.

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