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Evaluation of different routes of prophylactic progesterone for preterm birth prevention. A randomized controlled trial

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Abstract: The intent of this study was to speculate the prophylactic role of progesterone administration in reducing the incidence of preterm birth among women susceptible for spontaneous preterm birth and to compare the efficacy of vaginal suppositories versus intramuscular injection of progesterone in decreasing risk of preterm delivery. The selected women were randomized into three groups, 22 women for each. Group A: 22 pregnant were instructed to self-administration of 200 mg natural progesterone as (Prontogest) vaginal suppositories, group B: 22 pregnant who received 100 mg intramuscular natural progesterone (Prontogest) injection every third day until 37gestational weeks or delivery and group C: (control group) 22 pregnant who have the lowest risk to PTB and are the least susceptible to preterm birth followed till time of delivery without progesterone administration until required. There was no significant difference among groups regard age, basic demographic, past history distribution and present history items. There was a decrease in the incidence of preterm birth among the control group and the other two groups with no statistically significant difference among the two groups. No statistically significant difference between the two groups (I.M, Vaginal) concerning number of NICU admission and neonatal morbidity, but lower percentage among vaginal progesterone group. Birth weight was higher among vaginal group. NICU stay was higher among intramuscular group. Preterm birth was significantly associated with threatened abortion (p= 0.001), UTI (p= 0.001) and Preterm contraction (p= 0.00). It could be concluded that regular administration of progesterone for women susceptible for PTB is associated with lower rates of PTB when compared with intramuscular progesterone, vaginal progesterone is associated with lower percentage of preterm birth, less recurrent SPTB, less adverse maternal side effects, fewer NICU admissions, better compliance.

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1. Introduction:

Preterm births are responsible for 75% of neonatal mortality and 50% of long-term neurological *deterioration* in children. Moreover, survival infants also may suffer from other serious short and long term morbidity such as respiratory distress syndrome, broncho-pulmonary dysplasia, intra-ventricular hemorrhage, retro-lental fibroplasias and developmental problems (**Meintire and Leveno; 2008)**.

American college of Obstetricians and Gynecologists (ACOG) defined preterm birth as existence of regular uterine contractions of sufficient frequency and intensity to affect progressive effacement and dilatation of the cervix before full term gestation (before 37 weeks) (**Sayres; 2010**). Approximately 50% of preterm births are idiopathic (spontaneous). It is responsible for about 50% of all preterm deliveries rising up to 70% in population without any risk factor (**Goldenberg et. al., 2008**)., 25% are related to preterm premature rupture of membrane (pPROM) Preterm PPROM complicates approximately 3% of pregnancies and accounts for about 25% of all preterm births. Although sometimes PROM is preceded by spontaneous preterm labour pain; the main cause of PROM is regarded as infection (**Ehrenberg et al., 2003**) and another 25% are attributed to medically indicated or elective preterm deliveries. (**Ananth and Vintzileos 2006** and **RCOG 2009**). Preeclampsia, placental abruption, expected fetal compromise and fetal growth restriction are the most common sign for iatrogenic preterm delivery (**Ananth Vintzileos 2006)**. Risk factors are similar for both PROM and spontaneous preterm birth and include maternal demographic characteristics (**Ehrenberg et al., 2003**), past obstetric history (**Goldenberg et al., 2008),** pregnancy characteristics **(Sayres; 2010).**

Several techniques have been proposed to withdraw functional progesterone including confinement of free active progesterone, intracrine inactivation of local progesterone bioactivity, expulsion of a natural progesterone antagonist, modification of progesterone receptor (PR) coactivator and corepressor levels, and changes in progesterone receptor (PR) subtype levels (**Al-Asmakh 2007**). In high risk groups for PTL, P4 is commonly utilized to inhibit premature starting of spontaneous labor and may significantly reduce an individual's risk of idiopathic preterm delivery, but the inclusive impact on absolute numbers of preterm births is small (0.01%); thus P4 does not greatly impact on perinatal mortality, low birth weight, or neonatal death.

Progestogen pretreatment is leading to block TNF- and thrombin induced fetal membrane weakening by preventing both the production and action of GM-CSF. These results are in accordance with the administration of progestogens in the prevention of preterm premature rupture of the membranes (**Deepak et al., 2015).**

The vaginal route of administration furnishes many features such as lack of local pain, preventing the first-pass hepatic metabolism and rapid absorption (**Alexander et al., 2004**). After the vaginal administration of progesterone, levels of plasma progesterone reach maximal concentrations through 3h-8hrelying on the formulation used. This way of administration leads to localize the availability of the active component at endometrial level causing high concentrations of the hormone at the uterine level (1st uterine passage). Vaginally administrated progesterone disappears more quick from the circulation than the intramuscular route. The vaginal route of progesterone has been associated with some side effects as discharge, irritation or local warmth (**Miles et al., 1994**).

Concerning the pharmacokinetics of IM progesterone, it has been noticed that gluteal progesterone injection lead to longer half-life more than that administration of hormone in arm. Which may be explained by the variable adipose cells concentrations of between the arm and gluteus. In fact, progesterone shows a high affinity for adipose cells. After IM injection, intermittent emission of hormone only with decreased serum level. this fact permit single dose administration of the hormone even though progesterone's half-life in the blood is very short (5-20min.). The intramuscular injection of progesterone is painful, bruising and even sterile abscess. Moreover, IM administration is the only method that ensures adequate serum level. Rising plasma progesterone levels are reached through 2hrs and peak concentrations are reached through 8hrs (**Miles et al., 1994**).

The aim of present study is to evaluate the prophylactic role of progesterone administration in reducing the incidence of preterm birth among women susceptible for spontaneous preterm birth and to compare the efficacy of vaginal suppositories versus intramuscular injection of progesterone in decreasing risk of preterm delivery.

2. Patients and Methods:

Patients:

The study was carried out on pregnant women seen for routine prenatal care in the outpatient clinic of Obstetrics department of zagazig University Hospital all of them accepted the work and procedures with the following criteria:

Inclusion criteria included women with age between 18-34 years, gestational age between (20-24) weeks accurately dated from the first day of the last menstrual period and confirmed by Transabdominal ultrasonography, history of previous preterm birth, positive family history of previous PTB or if women was born preterm, history of threatened abortion in the first trimester, interpregnancy interval of less than 6 months, and ervical length of > 15mm measured by transvaginal ultrasonography at (20 -24) weeks.

Exclusion criteria included fetal abnormalities diagnosed by ultrasound, sonographic evidence of fetal growth restriction, preterm premature rupture of membranes, clinical evidence of chorioamnionitis, history of adverse reaction to progesterone or progesterone treatment within 4 weeks before enrollment, history of acute or chronic congestive heart failure, renal failure, uncontrolled diabetes mellitus, chronic hypertension, systemic lupus, an active liver disorder and history of breast or genital tract malignancy, history of thromboembolic disease, uterine malformation diagnosed by ultrasonography, cervical cerculage placement during the current pregnancy and inability to continue with the study procedures. Sample size was 66pregnant women randomized into 3groups each include 22 women.

Ethical Considerations:

The study was presented for approval from the ethical committee of the department of Obstetrics and Gynecology, faculty of medicine, Zagazig University. Informed consent after explaining the study purpose and methods to the subjects. Data presentation was not by the patient name but by diagnosis.

Study procedures:

The selected women were randomized into three groups, 22 women for each. Group A: 22 pregnant were instructed to self-administration of 200 mg natural progesterone as (Prontogest) vaginal suppositories at approximately the same time every

night until 37 gestational weeks or delivery, group B: 22 pregnant who received 100 mg intramuscular natural progesterone (Prontogest) injection every third day until 37gestational weeks or delivery and group C: (control group) 22 pregnant who have the lowest risk to PTB and are the least susceptible to preterm birth followed till time of delivery without progesterone administration until required.

A written informed consent was taken from all the participants. Each participant was given a code number to facilitate registration and to keep privacy of all women; a file having the same number was made to collect all data about the participant and results of investigations done throughout the period of research.

All participants will undergo the following; history taking, general clinical examination, obstetric examination, conventional laboratory investigations for pregnant women and trans-abdominal ultrasonographic examination to estimate gestational age, assess fetal growth, fetal well-being and to exclude fetal malformations and pelvic lesions. All the participants will have thorough examination of how to use the drug, importance of compliance to the prescribed regimen, about the safety precautions for intramuscular injection to be given under complete aseptic technique and the importance of attending the scheduled visits for regular follow up. During the visits; the women will be asked about the severity of frequency of symptoms related to progesterone administration. Ultrasound assessment of fetal growth and fetal well-being will be done every 4weeks until 36w+6d gestational age. The participants will be followed till delivery regarding gestational age at and mode of delivery and baby well-being and the need for incubation after delivery or not.

The studied cases were interviewed during the antenatal period every two weeks. During the follow up visits, the participants of groups were asked about any adverse events and occurrence of symptoms related to progesterone administration (vaginal or intramuscular) these symptoms were reported as side effects of progesterone administration. Transabdominal and transvaginal ultrasound assessment of fetal growth and cervical length were done at enrollment every4weeks till 37weeks.

Confirmation of safety of progesterone treatment, symptoms of preterm birth the and possible maternal side effects from progesterone therapy that may include headache, breast tenderness, nausea, cough, and local irritation if given IM.

Study Interventions:

Participants assigned to the intramuscular progesterone group received every third day intramuscular injections of 100 mg natural progesterone whereas those in vaginal group received 200 mg vaginal progesterone suppositories that participants used daily at home. Treatment was continued until completed 37 weeks or the date of preterm birth. If a patient developed PTB during the study period, she treated and remained in the study until delivery, provided that rapture of membranes didn't occur. The treatment protocol for PTB included hospitalization, hydration, bed rest, short-term tocolysis and steroids. At delivery, all data regarding the timing of labor onset, along with maternal and neonatal complications, was documented.

Outcome Measures:

The primary outcome measures are time until delivery, preterm birth before 34 and 37 weeks, length of admission at the neonatal intensive care unit. Secondary outcome measure is composite neonatal morbidity. This composite morbidity rate contains Neonatal ICU admission.

Statistical Analysis

Data collected throughout history, basic clinical examination, laboratory investigations and outcome measures coded, entered and analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) (Statistical Package for the Social Sciences) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD, the following tests were used to test differences for significance. Difference and association of qualitative variable by Chi square test (X2). Differences between quantitative independent groups by t test or Mann Whitney multiple by ANOVA or Kruskal Wallis, correlation by Pearson's correlation or Spearman's. P value was set at <0.05 for significant results & <0.001 for high significant result, data were collected and submitted to statistical analysis.

3. Results:

Present study is a prospective randomized controlled one that was conducted at Zagazig University Maternity Hospital. This study aimed to evaluate the prophylactic role of progesterone administration in reducing the incidence of PTB among women susceptible for PTB and to compare the efficacy of vaginal suppository versus intramuscular injection of progesterone in decreasing the risk of PTB among women susceptible for PTB. In this study, 66 women were eligible for the study and divided into three groups with 22 women in each. They were randomized to the mode of administration of progesterone. The first group (control) consists of 22 pregnant women, concerning the demographic data of

the first group. Table (1) showed that there was no significant difference among groups regard age (p=0.57), Table (2) also showed that There was no significant difference among groups regarding basic demographic and past history distribution studied items.

Table (1): Age distribution among studied groups.

		N	Mean ±SD	F	P
Age	Control	22	25.0909 ±2.11365	**0.55**	**0.57**
	IM	22	24.5455 ±1.99350		
	Vaginal	22	25.0455 ±1.55769		

Table (2): Basic demographic and past history distribution

	Group			Total	X2	P
	Control	IM	Vaginal			
Occupation	**13.6%**	**22.7%**	**22.7%**	**19.7%**	**0.76**	**0.68**
Smoking husband	**40.9%**	**36.4%**	**27.3%**	**34.8%**	**0.93**	**0.62**
Co morbidity	**22.7%**	**18.2%**	**13.6%**	**13.6%**	**0.85**	**0.52**
Operation	**27.3%**	**36.4%**	**31.8%**	**31.8%**	**0.41**	**0.81**
Threatened abortion	**45.5%**	**45.5%**	**45.5%**	**45.5%**	**0.0**	**1.0**
Threatened PTL	**27.3%**	**27.3%**	**31.8%**	**28.8%**	**0.15**	**0.92**
Abortion	**36.4%**	**27.3%**	**36.4%**	**36.4%**	**0.0**	**1.0**
Preterm	**13.6%**	**9.1%**	**4.5%**	**9.1%**	**1.1**	**0.57**
Family History	**31.8%**	**31.8%**	**27.3%**	**30.3%**	**0.14**	**0.93**
Total	**100.0%**	**100.0%**	**100.0%**	**100.0%**		

In Table (3) it is clear that no significant difference was recorded among groups regarding evaluated present history items. Concerning the date of delivery, there were (10) preterm deliveries (before completing 37 weeks of gestations). The incidence of preterm delivery in the control group was 5(22.7%) (3 preterm and 2 late preterm), while in vaginal progesterone group were 2(9.09%) (late preterm) and in the intramuscular group it was 3 (13.6%) (1 preterm and 2 late preterm) and the difference was statistically insignificant with lower percentage of preterm deliveries among the vaginal progesterone group (Table 4).

Table (3): Present history distribution among groups.

		Group			Total	X2	P
		Control	IM	Vaginal			
PROM		4.5%	9.1%	4.5%	6.1%	0.53	0.76
Threatened abortion		18.2%	22.7%	13.6%	18.2%	0.61	0.73
UTI		31.8%	31.8%	22.7%	28.8%	0.59	0.74
Preterm contraction		27.3%	13.6%	9.1%	16.7%	2.83	0.24
Gravidity	**G1**	4.5%	9.1%	4.5%	6.1%	1.33	0.85
	G2	40.9%	27.3%	31.8%	33.3%		
	G3	54.5%	63.6%	63.6%	60.6%		
Mode	**C**	13.6%	18.2%	27.3%	19.7%	1.34	0.51
	V	86.4%	81.8%	72.7%	80.3%		
NICU		40.9%	31.8%	13.6%	28.8%	4.13	0.12
Total		100.0%	100.0%	100.0%	100.0%		

Table (4): Gestational age at birth among groups

	Control	I.M	Vaginal
Full term>37week	17 (77.3%)	19 (86.4%)	20 (90.9%)
Late preterm34-36w+6d	2 (9.1%)	2 (9.1%)	2 (9.1%)
Preterm <34week	3 (13.6%)	1 (4.5%)	0 (0%)

As shown in Table (5) The current study showed that there is decrease in the incidence of preterm birth between the control group and the other two groups with no statistically significant difference between the two groups (I.M, Vaginal) regarding number of NICU admission and neonatal morbidity but lower percentage among vaginal progesterone group. Birth weight was higher among vaginal group. NICU stay was higher among intramuscular group.

On the other hand Preterm birth was significantly associated with threatened abortion (p= 0.001), UTI (p= 0.001) and Preterm contraction (p= 0.00) as illustrated in Table (6).

Table (5): Neonatal outcome distribution among groups.

	Group			Total	X2	P
	Control	IM	Vaginal			
Preterm	**22.7%**	**13.37%**	**9.1%**	**21.2%**	**3.44**	**0.19**
Low birth weight	**31.8%**	**22.7%**	**13.6%**	**25.7%**	**4.43**	**0.1**
NICU	**31.8%**	**22.7%**	**13.6%**	**28.8%**	**4.13**	**0.12**
Mortality	**4.5%**	**4.5%**	**0.0%**	**3.1%**	**0.12**	**0.93**

Table (6): Comparison between preterm and full term.

	Term		Total	X2	P
	Full-term	Preterm			
Threatened abortion	5 (9.6%)	7 50.0%	12 (18.2%)	12.09	0.001**
UTI	10 (19.2%)	9 (64.3%)	19 (28.8%)	10.92	0.001**
Preterm contraction	3 (5.8%)	8 (57.1%)	11 (16.7%)	20.9	0.00**

** High significant

4. Dissuasion:

In this study, 66 women were qualified for the study and divided into three groups with 22 women in each. They were randomly selected to the mode of administration of progesterone. Our results are in consistent with (**Maher et al., 2013**) who studied primary outcome (deliveries before 34 weeks of pregnancy) were compared among the studied groups; vaginal route leads to less incidence of preterm deliveries than the IM injection (p 0.02). Also, deliveries between 28 and 32 weeks of gestation are reduced significantly (P= 0.04). No significant differences between groups regarding deliveries at other weeks of pregnancy. This decrease in PTB was associated with less neonatal intensive care unit admissions (15.4% vs. 25.7%) in the vaginal vsintramuscular groups: p=0.006).

Our results are also in consistent with **(Saccone et al., 2017)** in which vaginal progesterone led to decreased level of spontaneous preterm birth<34 weeks significantly (17.5% vs. 25.0%; RR 0.71) and <32 weeks, (8.9% vs. 14.5%; RR 0.62), in comparison with patients receive 17-hydroxyprogesterone.

No significant differences was obtained in the rate of SPTB<37 weeks, SPTB<28 weeks and SPTB<24 weeks.

Concerning neonatal parameters, vaginal progesterone led to a lower rate of NICU admission in contrast to injectable progesterone by about 30% (18.7% vs. 23.5%; RR 0.63). This agreed with another published systematic review with meta-analysis (**Oler et al., 2017**)

Another study **(Conde-Agudelo A, et al 2018) conducted** metaanealysis and systematic review of information from RCT (including OPPTIMUM) showed that vaginal progesterone supplementation is effective regarding decreasing of the risk of preterm birth and neonatal complications in particular patients with short cervical length ≤25 mm at mid trimester. For example, compared with placebo, vaginal progesterone:

- Decrease of idiopathic PTB<34 weeks of pregnancy (RR 0.72) as well as spontaneous PTB before 28, 30, 32, 35, and 36 weeks.
-Decrease of respiratory distress syndrome (RR 0.47)
- Decrease of composite neonatal morbidity and mortality (RR 0.59)
-Decrease of birth weight <1.5 kg (RR 0.62, 95% CI 0.44-0.86)
-Decrease of admission to the NICU (RR 0.68)

Most of them reported comparable efficacy of vaginal versus intramuscular preparations

(progesterone tablet or pessary) and (progesterone or 17 OHPC) to decrease PTB risk in risky women (**Abd El Hameed 2012 and Bafghi et al. 2015).** Also**,** comparable efficacy in decreasing PTBs in women with previous history of preterm birth was noticed with both preparations (16.6% versus14.3%), on the other hand, the two placebo controlled trials did not find vaginal progesterone useful **(Abd El Hameed 2012)**.

O'Brien et al. (2007) did not notice a decrease in frequent PTB 32 weeks with the dose of 8% progesterone vaginal gel. These results was explained according to the fact that women with a prior PTB are of heterogeneous nature of which only a group may respond favorably, and the responders to vaginal route of administration are more probable to be those with a short cervical length.

Norman et al. (2016) examined more than 1200 women at high risk for PTB were randomly assigned to receive either daily vaginal progesterone 200 mg or matched placebo, from 22 to 24 weeks of gestation to 34 weeks, they found that they found that Vaginal progesterone supplementation could not significantly reduce any of initial obstetric outcome i.e., fetal death or birth before 34 weeks, initial neonatal outcome i.e., death, brain injury, or bronchopulmonary dysplasia and primary childhood outcome "standardized cognitive score at two years of age" Even so, primary obstetric and neonatal composite outcomes were not improved, vaginal progesterone supplementation resulted in less neonatal mortality and decrease in neurological injury on neonatal U/S. In summary vaginal progesterone administration did not significantly reduce the:

-Primary obstetric outcome "fetal death or birth before 34 weeks" (adjusted (OR) 0.86).

-Primary neonatal outcome "death, brain injury, or bronchopulmonary dysplasia" (adjusted OR 0.62).

-Primary childhood outcome "standardized cognitive score at two years of age" (difference in means -0.48. Despite lack of significant improvement in the former studied outcomes, vaginal progesterone supplementation resulted in reduced neonatal mortality (1/600 versus 6/537; unadjusted OR 0.17 and a decrease in neurological injury on neonatal U/S (3 versus 6 percent; unadjusted OR 0.50.

Limitations of our study include that in contrast with previous trials which included three variable doses of daily vaginal progesterone were used (90mg gel, and 100 and 200mg suppository), this study included only one dose but variation of doses making it difficult to judge which dose and/or preparation of vaginal progesterone is the best. Also, lack of sufficient power of studied outcomes, including neonatal outcomes.

Conclusion

-Regular administration of progesterone for women susceptible for PTB is associated with lower rates of PTB.

-Compared with intramuscular progesterone, vaginal progesterone is associated with lower percentage of preterm birth, less recurrent SPTB, less adverse maternal side effects, fewer NICU admissions, better compliance.

Recommendations

Daily vaginal progesterone started at about 16w among women susceptible for PTB is associated with reduced rates of SPTB, and relatively decreased neonatal morbidity and mortality compared to intramuscular progesterone. This study need to be carried out on large number of women.

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