

**Intramuscular 17Alpha-hydroxyprogesterone,
Progesterone suppositories and Dydrogesterone
tablets in preventing Preterm labor:
Randomized Control Trial**

Thesis

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بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

وَاتَّقُوا اللَّهَ وَيُعَلِّمُكُمُ اللَّهُ

وَاللَّهُ بِكُلِّ شَيْءٍ عَلِيمٌ

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List of Abbreviations

<i>Abbr.</i>	<i>Full-term</i>
ACOG	: American College of Obstetricians and Gynecologists
ACTH	: Adrenocorticotrophic hormone
AEDV	: Absence of end-diastolic flow velocity.
AF	: Amniotic fluid index.
AFP	: Alpha fetoprotein
AHRQ	: Agency for Healthcare Research and Quality
AIUM	: American institute of ultrasound medicine
ANCS	: Antenatal corticosteroids
ANOVA	: Analysis of variance
AUC	: Area under curve
AVF	: Abnormal vaginal flora
CAPs	: Contraction-associated proteins
CDC	: Center For Disease Control
Cmax	: Maximum plasma concentration
CRH	: Corticotrophin releasing hormone
DHEA-S	: Dehydroepiandrosteron sulfate
DHEA-S	: Dehydro-epiandrosterone sulfate
EDD	: Expected day of delivery.
ELBW	: Extremely low birth weight
FDA	: Food and drug administration
FMs	: Fetal movements.
GA	: Gestational age
GABA	: γ -aminobutyric acid
GIT	: Gastrointestinal tract
GW	: Gestational weeks
HCG	: human chorionic gonadotropin
HPA	: Hypothalamic pituitary adrenal axis
IL6	: Interleukin 6
IL8	: Interleukin 8
IM	: Intramuscular
IUGR	: Intra uterine growth restriction.

IVH	: Intra-ventricular hemorrhage
LBW	: Low birth weight
LMP	: Last menstrual period.
M.C.A.	: Middle cerebral artery.
MMP8	: Matrix metalloproteinase-8
NICE	: National institute for health and care excellence
NICU	: Neonatal intensive care unite
NIH	: National institutes of health
P.I.	: Pulsatility index.
PGE2	: Prostaglandin E2
PGs	: Prostaglandins
PMR	: Perinatal mortality rate.
PPROM	: Preterm Premature rapture of the membrane
PR	: Progesterone receptor
PTB	: Preterm birth
PTL	: Preterm labor
PW	: Pulse wave
R.I.	: Resistance index.
RDS	: Respiratory distress syndrome
REDV	: Reversal of end-diastolic flow velocity.
SD	: Standard deviation
SGA	: Small for gestational age.
Tmax	: Maximum time for absorbtion
U.A	: Umbilical artery.
VLBW	: very low birth weight
WHO	: World health organization
ZEB	: Zinc finger E-box binding homeobox protein
17OHPC	: 17 hydroxy progesterone caproate.

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Abstract

Background: Preterm birth is the major cause of neonatal mortality and morbidity. A history of a prior spontaneous PTB remains the greatest risk factor for spontaneous PTB, These high-risk women have been the focus of recent trials for the prevention of recurrent prematurity. **Aim of the Work:** This study aims to compare between the efficacy of intramuscular 17alpha-hydroxyprogesterone, progesterone vaginal suppositories and dydrogesterone oral tablets in prevention of preterm labor in high risk women. **Patients and Methods:** Study Setting: Ain Shams University Maternity Hospital. Study Duration: From January 2016 to August 2016. Number of patients: A total of 120 pregnant women at risk of preterm labor were recruited in the study. **Type of the study:** Randomized control trial. **Results:** The present study found that there was a statistically significant difference between the 3 groups regarding gestational age at delivery. It was significantly higher in vaginal &IM group when compared to oral group, However there was no statistical difference between the vaginal & IM groups in mean gestational age. **Conclusion:** In the current study we concluded that The only independent predictor of preterm labor was short cervical length p value (.01), neither the route of administration of any type of progesterone, nor the presence of history of preterm labor was independently related to occurrence of preterm labor (p values more than 0.05. **Recommendations:** The prevalence of preterm delivery is still high worldwide and more research with bigger sample size is required.

Key words: preterm birth, recurrent prematurity, dydrogesterone

Introduction

Preterm birth is a common problem in obstetric care, with estimates ranging from 5% in several European countries to 18% in some African countries (*Blencowe et al., 2012*). Preterm labor defined as delivery before 37 completed weeks is the leading cause of perinatal and neonatal morbidity and mortality and strongly related to the developmental and neurological disabilities later in life (*Blencowe et al., 2013*).

Mortality and morbidity are inversely related to gestational age at delivery, and the most severe consequences occur when delivery occurs, before 34 weeks of gestation (*Klein et al., 2011*). Preterm birth prevention is considered a major challenge for obstetricians. Progesterone is an important hormone for the maintenance of pregnancy early as well as later in gestation.

In singleton pregnancies, prophylactic progesterone treatment during the second and third trimesters has been shown to reduce the rate of preterm delivery in those with a history of previous spontaneous preterm delivery (*Rode et al., 2009*), specially in those with short cervix diagnosed during mid trimesteric transvaginal ultrasound scanning (*Da Fonseca et al., 2007*) but in some other risk factors such as multiple gestations it was found to have no impact on either PTL or perinatal morbidity (*Rouse et al., 2007*).

Progesterone is essential for the initiation and maintenance of pregnancy. After the discovery of the progesterone receptor (PR) in 1970, it was realized that a progesterone receptor antagonist (PA) would have a major impact on female reproductive health (*Chwalisz et al., 2002*).

Progesterone (abbreviated as P4), also known as pregn-4-ene-3, 20-dione (*Norman Adleret al., 2015*), is an endogenous steroid and progestogen sex hormone involved in the menstrual cycle, pregnancy, and embryogenesis of humans and other species. It belongs to a group of steroid hormones called the progestogens (*Tekoa et al., 2010*) and is the major progestogen in the body.

Progesterone is sometimes called the "hormone of pregnancy" (*Bowen, 2008*) and it has many roles relating to the development of the fetus:

Progesterone converts the endometrium to its secretory stage to prepare the uterus for implantation. At the same time progesterone affects the vaginal epithelium and cervical mucus, making it thick and impenetrable to sperm. Progesterone is anti-mitogenic in endometrial epithelial cells, and as such, mitigates the tropic effects of estrogen (*Patel et al., 2014*).

- During implantation and gestation, progesterone appears to decrease the maternal immune response to allow for the acceptance of the pregnancy.

- Progesterone decreases contractility of the uterine smooth muscle (*Bowen, 2008*).
- A drop in progesterone levels is possibly one step that facilitates the onset of labor.
- There is still considerable uncertainty regarding the optimal progesterone type, route of administration, dosage and timing of start of therapy to prevent PTL in risky women (*Tita Rouse, 2009*).

The vasodilator effect of progesterone on uterine circulation in the non pregnant female (*Deichert et al., 1996*) and during the first trimester of pregnancy is well known (*Czajkowski et al., 2007*). But little information is available on its effect on uterine and fetal circulation later in gestation.

In one study performed by Barda et al., it showed that vaginal micronized progesterone used for the prevention of PTL was associated with a significant reduction in the fetal middle cerebral artery (MCA) pulsatility index (PI) but with no effect on uterine circulation (*Brada et al., 2010*).

Study Hypothesis

In pregnant women at risk for preterm labor, intramuscular 17 alpha hydroxyprogesterone, progesterone vaginal suppositories and oral dydrogesterone; may prevent preterm labor with an equal efficacy.

Question

In women at risk for preterm labor, Do intramuscular 17 alpha-hydroxyprogesterone, progesterone vaginal suppositories and oral dydrogesterone; prevent preterm labor with an equal efficacy?

Aim of the Study

This study aims to compare between the efficacy of intramuscular 17alpha-hydroxyprogesterone, progesterone vaginal suppositories and dydrogesterone oral tablets in prevention of preterm labor in high risk women.