The Effect of Prophylactic Vaginal Progesterone after The Arrest of Preterm Birth: A randomized, Controlled Trial

Thesis

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List of Contents

Title	Page No.
List of Abbreviations	i
List of Tables	ii
List of Figures	iii
Introduction	1
Aim of the Work	8
Review of Literature	
⮚ Preterm Birth	9
⮚ Tocolysis	48
⮚ Progesterone	66
⮚ Progesterone and Preterm Birth	76
Patients and Methods	79
Results	86
Discussion	95
Summary and Conclusion	103
Recommendations	106
References	107
Arabic Summary	

List of Abbreviations

Abb.	Full term
ART	*Assisted Reproductive Technology*
CI	*Confidence Interval*
CRH	*Corticotropin-Releasing Hormone*
CYP17A1	*17α-Hydroxylase*
CYP21A2	*21-Hydroxylase*
DHEAs	*Dehydroepiandrosterone Sulfates*
E1	*Estrone*
E2	*Estradiol*
E3	*Estriol*
ELBW	*Extremely Low Birth Weight*
ER-alpha	*Estrogen Receptor-alpha*
hCG	*Human Chorionic Gonadotropin*
HPA	*Hypothalamic-Pituitary-Adrenal*
IQR	*Inter-Quartile Range*
IPD	*Individual Patient Data*
IVF	*In Vitro Fertilization*
IVH	*Intraventricular Hemorrhage*
LBW	*Low Birth Weight*
MMPs	*Matrix Metalloproteinases*
NEC	*Necrotizing Enterocolitis*
NICU	*Neonatal Intensive Care Unit*
OMP	*Oral Micronized Progesterone*
PAR	*Protease-Activated Receptors*
PR	*Progesterone Receptor*
PTB	*Preterm Birth*
RDS	*Respiratory Distress Syndrome*
VLBW	*Very Low Birth Weight*
WHO	*World Health Organization*

List of Tables

Table No.	Title	Page No.
Table (1):	Neonatal Morbidity and Mortality by Gestational Age	44
Table (2):	Mechanisms of intracellular calcium control	48
Table (3):	Effect of tocolytics compared to a placebo or no tocolytic drug on prolongation of pregnancy and neonatal outcome	54
Table (4):	Available forms of progesterone	75
Table (5):	Computer-Generated Random Number List	82
Table (6):	Demographic data of study group	87
Table (7):	Primary tocolytic agent received	87
Table (8):	Cervical changes at enrollment	88
Table (9):	Cervical length at follow up	89
Table (10):	Pregnancy prolongation (days) among the study group	90
Table (11):	Gestational age at delivery (weeks) among the study group	92
Table (12):	Neonatal outcomes among the study group	93
Table (13):	Correlation between pregnancy prolongation and basal cervical length among the study group	94
Table (14):	Side effects of progesterone among the study group	94

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Percentage of newborns with birthweight 501– 750 g with IVH grades I– IV and with periventricular leucomalacia (PVL) reported in the 2000 Vermont-Oxford Neonatal Network Database	30
Figure (2):	Percentage of newborns with birthweight 501–750 g with NEC and with intestinal perforation reported in the 2000 Vermont-Oxford Neonatal Network Database	34
Figure (3):	Percentage of newborns with birthweight 501– 50 g RDS, pneumothorax and requirement for oxygen at the time of discharge or the diagnosis of BPD reported in the 2000 Vermont-Oxford Neonatal Network Database	38
Figure (4):	Control of myometrial cell contractility and sites of tocolytic drug activity.	49
Figure (5):	Infant survival rates from 23 to 26 weeks gestation	51
Figure (6):	Progesterone levels across the menstrual cycle in normally cycling and ovulatory women	70
Figure (7):	The Marker semisynthesis of progesterone from diosgenin	72
Figure (8):	Stigmasterol to progesterone synthesis	72
Figure (9):	The Johnson total synthesis of progesterone	73

List of Figures

Fig. No.	Title	Page No.
Figure (10):	Progesterone and uterine contractility: mechanisms of action	77
Figure (11):	Progesterone levels and uterine contractility in pregnancy	78
Figure (12):	Hormonal regulation of smooth muscle cell function	78
Figure (13):	Flow chart of the studied cases.	86
Figure (14):	Pregnancy prolongation among the study group.	90
Figure (15):	Kaplan meier curve for delivery after treatment among the study group.	91
Figure (16):	Gestational age at delivery among the study group.	92
Figure (17):	Neonatal outcome among the study group.	93

ABSTRACT

Background: Preterm birth is known to be the birth before 37 weeks of gestation. The incidence of preterm birth is in increase over the recent years. It is affecting about 12 % of births in the United States and also responsible for 2/3 of neonatal mortality. Although there is improvement in the neonatal care, the preterm birth is considered the main cause of long term disabilities in children born without congenital anomalies. Thus the prevention of preterm birth is the target of obstetric care.

Aim of the Work: to evaluate the effect of prophylactic vaginal progesterone on reducing the incidence of preterm birth and neonatal morbidity or mortality.

Patients and Methods: This is a prospective double blind, randomized, placebo-controlled trial. This research included women who had an arrested preterm birth episode using tocolysis and we will give them vaginal progesterone 200 µg as a prophylactic treatment to preterm birth and to evaluate its efficacy on prolonging pregnancy.

Results: This study shows a positive correlation between using of vaginal progesterone suppositories (200mg) and decreasing the risk of preterm birth after the arrest of episode of preterm birth using tocolysis.

Conclusion: Pregnant women should be encouraged to use vaginal progesterone as a prophylactic treatment after the arrest of preterm birth.

Keywords: *Prophylactic Vaginal Progesterone - Preterm Birth*

INTRODUCTION

Preterm birth is known to be the birth before 37 weeks of gestation. The incidence of preterm birth is in increase over the recent years. It is affecting about 12 % of births in the United States and also responsible for 2/3 of neonatal mortality. Although there is improvement in the neonatal care, the preterm birth is considered the main cause of long term disabilities in children born without congenital anomalies**.** Thus the prevention of preterm birth is the target of obstetric care ***(Hamilton et al., 2010)***.

Preterm birth was the main cause of both neonatal mortality (35% of 2.8 million deaths) and the childhood mortality (17% of 6.3 million deaths) worldwide ***(UNICEF, 2014).*** Neonates born preterm have an increased risk of both short-term complications, due to immaturity or multiple organ systems failure ***(Saigal et al., 2008),*** and long-term adverse health outcomes, like neurodevelopmental disabilities ***(Romero et al., 2012),*** behavioral problems, childhood asthma ***(Been et al., 2014),*** cardiovascular disease ***(Parkinson et al., 2013),*** Diabetes ***(Li et al., 2014),*** and depression ***(Loret et al., 2014),*** in adult life. It is also associated with adverse psychological and emotional effects on families ***(Saigal et al., 2008).***

The baseline risk of preterm birth is about 10%. Four groups of women have an increased risk of about 30% for preterm delivery; women who had preterm delivery previously

(Iams et al., 2010); women with a short cervical length at midgestation ***(Romero et al., 2007);*** women with a twin pregnancy ***(Chauhan et al., 2010);*** and women who used tocolysis for an episode of preterm birth ***(Norman et al., 2005).***

Complications of preterm birth in known to be a main cause of neonatal deaths worldwide, with surviving infant at risk of series neonatal complication and long term disability ***(Blemcomwe et al., 2013)***.

The economic cost of preterm birth was estimated 2.9 billion Euros for a single year in the UK ***(Mangham et al., 2009*)*,*** with the psychological, social and financial costs to families ***(Carson et al., 2015)***. Preterm birth is also identified to be a priority setting exercise as a "top ten" research priority to 2025. Discovery research preventing preterm birth is a global strategy to reduce newborn deaths. It's also a goal set from United Nations, sustainable (development to 2030) ***(Lawn et al., 2016)***.

Management and prevention of preterm birth (PTB) in pregnant women is a great issue of debate between researchers regarding the clinical care, a short and long term intervention, must be set facing preterm birth regarding women's histories. This clinical setting also has a major role for cost effectiveness on the individual, social and economic structure, thus making the main shape of women antenatal care, knowing the difficulties it is agreed that health of pregnant women and their babies using evidence based guideline ***(Abales et al., 2016).***

Aim of the Work

The aim of this study was to evaluate the effect of prophylactic vaginal progesterone on reducing the incidence of preterm birth and neonatal morbidity or mortality.

PRETERM BIRTH

Preterm birth refers to a delivery that occurs before 37 weeks of gestation. Although term pregnancy has been defined as 370/7ths to 416/7ths weeks of gestation, the period 370/7ths to 386/7ths weeks is considered "early term" because neonates born in this gestational age range have higher neonatal morbidity and mortality than infants born at "full term" from 390/7ths to 406/7ths week ***(Spong, 2013).***

Classification:

Preterm births are described by gestational age, birth weight, and initiating factor.

Gestational age criteria:

- World Health Organization ***(WHO, 2015):***
  - Moderate to late preterm: 32 to <37 weeks.
  - Very preterm: 28 to <32 weeks
  - Extremely preterm: <28 weeks
- Centers for Disease Control and Prevention ***(CDC, 2015):***
  - Late preterm: 34 to 36 weeks
  - Early preterm: <34 weeks

- Birth weight criteria ***(WHO, 2011):***
  - Low birth weight (LBW): <2500 grams
  - Very low birth weight (VLBW): <1500 grams
  - Extremely low birth weight (ELBW): <1000 grams
  - Initiating factor: spontaneous or iatrogenic (ie, indicated, providerinitiated).
  - Spontaneous (majority): due to preterm birth or preterm premature rupture of membranes.
  - Provider-initiated: due maternal or fetal issues (eg, preeclampsia, placenta previa, abruptio placenta, fetal growth restriction, multiple gestation). Complications of pregnancy can lead to both spontaneous and providerinitiated preterm births.

Incidence:

In Europe and many developed countries the preterm birth rate is generally 5.9%, and in the USA it has even risen to 12-13% in the last decades ***(ACOG Committee Opinion, 2013).***

The obstetric events that precede Preterm birth are:

- Spontaneous Preterm birth constitutes 40-45% of all Preterm births.
- 25-30% of Preterm births occur after premature rupture of membranes.

- The remainder 30-35% of Preterm births are induced for obstetrical reasons; obstetricians may have to deliver the baby preterm because of a deteriorating intrauterine environment (i.e. infection, intrauterine growth retardation) or significant endangerment of the maternal health (i.e. preeclampsia, cancer) ***(Goldenberg et al., 2000).***

Risk factors:

Preterm birth likely results from local changes that prematurely stimulate the cascade of events resulting in spontaneous labor or prematurely withdraw suppressive factors that maintain uterine quiescence and thus inhibit this cascade ***(Snegovskikh et al., 2015).***

A) Reproductive factors:

1. **History of preterm birth:** Some risk factors for preterm birth likely persist from pregnancy to pregnancy. Prior preterm birth is the strongest risk factor for future preterm birth, and recurrences often occur at the same gestational age ***(Bejar et al., 2010).***

The risk of preterm birth is highest when:

- The previous preterm birth was in the pregnancy prior to the current pregnancy (ie, no intervening term pregnancies).
- There is a history of multiple preterm births.

2. **Twins after prior preterm singleton birth:** The overall risk of spontaneous preterm birth in twin pregnancy is significantly higher in multiparous women whose previous singleton delivery occurred preterm ***(Bejar et al., 2010).***
3. **History of abortion:** Spontaneous abortion, especially if recurrent has been associated with an increased risk of preterm birth ***(Donders et al., 2009).***
4. **Multifetal gestation:** Multiple gestation accounts for only 2 to 3 percent of all births, but 17 percent of births under 37 weeks of gestation and 23 percent of births under 32 weeks. The wide spread availability of assisted reproduction has resulted in a large increase in the incidence of multiple gestation and this increase, in turn, has led to an increase in the preterm birth (PTB) rate ***(ACOG Committee Opinion, 2013).***
5. **Vaginal bleeding:** Decidual hemorrhage manifested as vaginal bleeding in the first and/or second trimester is associated with an increased risk of preterm birth and preterm premature rupture of membranes ***(Gibbs et al., 1992).***

B) Infection:

1. **Genital infections:** Intrauterine infection is a major cause of preterm birth with and without intact membranes.
2. **Exragenital infections:** Urinary tract infection includes asymptomatic bacteriuria and acute pyelonephritis are associated with increased risk of preterm birth. Approximately 80% of cases are caused by Escherichia coli.

(Matuszkiewicz-Rowińska et al., 2015)