The Effect of Vaginal Progesterone after Tocolytic Therapy on Latency Period in Threatened Preterm Labor

Thesis

Submitted for partial fulfillment of Master Degree in Obstetrics and Gynecology

Presented by

Salah Mohammad Alhady Ahmed

M.B.B.Ch –Mansoura University – 2003

Resident of Obst&Gyn., Talkha Central Hospital

Under Supervision of

Prof. Abdel-Megeed Ismail Abdel-Megeed

Professor of Obstetrics and Gynecology

Faculty of Medicine, Ain Shams University

Dr. Hayam Fathy Mohammad

Lecturer of Obstetrics and Gynecology

Faculty of Medicine, Ain Shams University-

Faculty of Medicine

Ain-Shams University

2014

Acknowledgement

First of all, I should express my deep thanks to **ALLAH.**

I would like to express my sincere appreciation and deepest gratitude to ***Prof. Dr. Abdel -Megeed Ismail*** *Professor of Obstetrics & Gynecology, Ain Shams University for his meticulous advice, continuous encouragement and valuable instructions all through this work, Its was a pleasure and privilege to work under his guidance and supervision .I learned a lot from his humanistic attitude, kind patience and thoughts.*

Many thanks should be expressed to ***Dr. Hayam Fathy Mohammad,*** *Lecturer of Obstetrics & Gynecology, Ain Shams University for his help, honest assistance, active guidance and the precious time he had given in this study.*

I would like to thanks My Patients for their cooperation and trust, and I wish for all of them the best of health. All my thanks and loves are offered to my family for their continuous encouragement and support. I really can't express my thanks and love to them.

Salah Mohammed Alhady

2014

List of Contents

Subject *Page No.*

List of Abbreviations

ACOG : American College of Obstetricians and Gynecologists

ACTH : Adrenocorticotropic hormone

AFP : Alpha fetoprotein

ANCS : Antenatal corticosteroids

AVF : Abnormal vaginal flora

CRH : Corticotrophin releasing hormone

DHEA-S : Dehydroepiandrosteron sulfate

ELISA : Enzyme linked immunosorbent assay

E2 : Estradiol

E3 : Esteriol

FDA : Food and drug administration

GA : Gestational age

GW : Gestational weeks

HPA : Hypothalamic pituitary adrenal axis

HUAM : Home uterine activity monitoring

IM : Intramuscular

IVF : In vitro fertilization

LLETZ : Large loop excision of transformation zone

NICE : National institute for health and care excellence

NICU : Neonatal intensive care unite

NO : Nitrous oxide

NOS : Nitric oxide oxidase

17OHPC : 17 hydroxy progesterone caproate

List of Abbreviations *(Cont...)*

PGE2 : Prostaglandin E2

PGF2 : Prostaglandin F2

PIGFBP-1 : Phosphorylated insulin like growth factor binding protein-1

PROM : Premature rupture of membranes

PR : Progesterone receptor

PTB : Preterm birth

PTL : Preterm labor

RDS : Respiratory distress syndrome

SD : Standard deviation

ZEB1 : Zinc finger E-box binding homeobox protein-1

List of Tables

List of Figures

Introduction

Preterm labor is defined as the presence of uterine contractions of sufficient frequency and intensity to effect progressive effacement and dilation of the cervix prior to term gestation (before completing 37 weeks of gestation) ***(ACOG Practice Bulletin, 2001).***

Preterm birth is the leading cause of neonatal mortality and the most common reason for antenatal hospitalization. In the United States, approximately 12% of all live births occur before term, and preterm labor preceded approximately 50% of these preterm births. Although the causes of preterm labor are not well understood, the burden of preterm births is clear. Preterm births account for approximately 70% of neonatal deaths and 36% of infant deaths as well as 25–50% of cases of long-term neurologic impairment in children ***(ACOG Practice Bulletin, 2012).***

Two thirds of preterm deliveries commence spontaneously, out of which one-third as a result of premature uterine contractions ***(Romero, 2007).***

Although secondary or tertiary interventions such as antenatal corticosteroids, postnatal surfactant, and improved neonatal care have led to reduced morbidity and mortality caused by preterm birth (PTB), effective primary preventive interventions have remained elusive ***(Tita and Rouse, 2009).***

The cornerstone in management of preterm birth is the successful inhibition of uterine contractions (via tocolytic agents) and the concomitant administration of corticosteroids to enhance lung maturity, in parallel ***(Lewis et al., 1997).*** A strong evidence from many trials and systematic reviews states that such an approach significantly prolongs gestation and significantly improves perinatal morbidity and need for neonatal ICU admissions ***(King et al., 2005).***

Currently tocolytics are used only to allow for the implementation of steroid therapy and in some cases to transfer pregnant women to tertiary medical centers ***(Roberts and Dalziel, 2006).***

The study on the use of progesterone in the prevention of preterm birth in patients at high-risk pregnancies showed that it not only significantly reduces the risk of preterm delivery but also improves the effectiveness of tocolytic therapy ***(Da Fonseca et al., 2003).***

Experimental studies have also shown that: Firstly progesterone increases the spasmolytic effect of beta-mimetics ***(Chanrachakul et al., 2005).*** Secondly progesterone receptor activity inhibits the production of proteins associated with uterine contractility oxytocin receptors, prostaglandin receptors and cohesin 45 responsible for the connection between muscle cells and synchronization of uterine contractions ***(Mesiano and Welsh, 2007).***

Vaginal progesterone has a potential beneficial effect in postponing of preterm labor by suppression of prostaglandins cascades. Although different studies evaluated the use of progesterone for preterm birth, the exact effect of which on prolongation of pregnancy remains unclear ***(Saleh Gargari et al., 2012)***.

Compared with oral administration, vaginal progesterone bypasses hepatic first-pass effects and, therefore, has better bioavailability. Vaginal administration is virtually without side effects such as sleepiness, fatigue, and headache that can occur with oral use. Endometrial bioavailability after vaginal progesterone use is also reported to be higher than with the intramuscular (IM) route despite lower serum levels with the former. This is attributed to direct transport of progesterone from vagina to the uterus: the so-called uterine first pass effect ***(Tita and Rouse, 2009).***

Aim of the work

The aim of the study is to assess the efficacy of vaginal progesterone therapy after successful tocolysis on the latency period in pregnant women with threatened preterm labor.

Research Hypothesis

Research Question:

Does vaginal progesterone therapy after successful tocolysis superior to placebo in prolongation of latency period in women with threatened preterm birth?

Research Hypothesis:

Vaginal progesterone therapy after successful tocolysis is superior to placebo in prolongation of latency period among women with threatened preterm birth.

Objectives:

The aim of the study is to study the effect of administration of vaginal progesterone therapy after successful tocolysis on the latency period (time until delivery), gestational age at delivery and delivery rate before 37 weeks of gestation.

Outcome Measures:

- The primary outcome measures will be the occurrence of another attack of threatened preterm labor needing for another tocolysis, time elapsed from end of tocolysis till delivery (latency period), gestational age at delivery and delivery rate before 37 weeks of gestation.
- Secondary outcome measures will be the neonatal outcome as birth weight, admission to the neonatal intensive care unit (NICU)) and respiratory distress syndrome.

Chapter (1)
Preterm Birth

Preterm birth (PTB) refers to the birth of a baby that occurs before 37completed weeks of gestation. PTB can be further sub-categorized as late preterm delivery- 34 to 36 completed weeks gestation, moderately preterm- 32 to 34 completed weeks, very preterm- less than 32 weeks, and extremely preterm- less than 28 weeks gestation. Preterm birth can also be defined by birth weight: low birth weight- less than 2500g, very low birthweight- 1500g, and extremely low birth weight- less than 1000g ***(Lockwood et al., 2011).***

Significant progress has been made in the care of premature infants, but not in reducing the prevalence of preterm birth. In the United States, there has been a 21% rise in the rate of preterm births since 1990, which peaked in 2006 with 12.8% of all 4 million annual live births born at less than 37 weeks of gestation. The incidence in Europe and other developed countries lies between 5-9%.East Asian and Hispanic women typically have a low pre-term birth rate. However, the incidence of preterm birth continues to rise. Part of this escalation is due to the increased indicated preterm delivery of artificially conceived multiple pregnancies, which account for 15-20% of all pre-term births ***(Goldenberg et al., 2008).***

Preterm birth is the principal cause of infant mortality in developed countries. One in 8 births in the United States in 2005 were preterm, compared to 1 in 18 births in Ireland and Finland. The infant mortality rate in Ireland in 2010 was 3.89 per 1000 live births and in the United States 6.8 per 1000 live births. The main cause of the United States' high infant mortality rate when compared with Europe is the very high percentage of preterm births in the United States, the period when infant mortality is greatest ***(Mac Dorman & Mathews, 2010).***

Chapter (2)
Pathophysiology of preterm labor

The cervix during pregnancy

The collagen content of the cervix, both type I and type III, undergoes marked changes in pregnancy. The spaces between the collagen bundles become dilated as early as 8 to 14 weeks gestation. Although there is an increase in the total collagen content of the cervix at term, the collagen concentration is reduced by 30 to 50 percent compared with the non- pregnant cervix. This arises because other components of the cervix, the water, and non-collagen proteins are increasing in relatively greater amounts. In addition, the collagen fibrils are reduced in size ***(Granstrom et al., 1989)***.

During pregnancy, hyaluronic acid concentration in the cervix is very low, but increases rapidly at the onset of labor. Hyaluronic acid has a high affinity for water molecules and hence can maintain tissue hydration. Hyaluronic acid can stimulate collagenase production ***(El Maradny et al., 1997).***

Collagenase is a lytic enzyme, now called matrix metalloproteinase which is produced by fibroblasts and leukocyte is secreted in a latent form, procollagenase, which is activated by cleavage of the pro-enzyme by plasmin or stromelysin to the active form ***(Osmers et al., 1992).***

Ripening refers to the increased softening, dispensability, effacement, and early dilatation of the cervix that can be detected by pelvic examination ***(Calder et al., 1992).***

Cervical ripening is an active biochemical process, which occurs independent of uterine contractions, and is similar to an inflammatory reaction. During this process the inflammatory cascade is activated, including the release of proinflammatory cytokines,the infiltration of white blood cells, the release and activation of degradative enzymes (matrix metalloproteinases), a changing synthesis of extracellular matrix proteins and glycoproteins, an increase in collagen turnover, a disruption of tightly aligned collagen fibrils, changes in the decorin/collagen ratio, and increased extracellular fluid due to hyaluronic acid ***(Leppert,1992), (Rechberger et al., 1996).***

Various human agents are involved in cervical ripening, including progesterone, relaxin, prostaglandins, and local mediators such as proinflammatory cytokines and nitrous oxide (NO). However, the exact biochemical mechanisms responsible for the rearrangement of extracellular matrix during cervical ripening are still poorly understood. Nevertheless, the dissolution of collagen fibers via enzymatic degradation and/or 'dilution' by increasing proteoglycan concentrations is the pivotal event during cervical ripening, resulting in the subsequent decrease in cervical resistance ***(Garfield et al., 1998).***