Efficacy of Prophylactic Progesterone in Prevention of Preterm Delivery in Women with Major Placenta Previa

A Randomized Controlled Trial

Thesis

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List of Abbreviations

Abb.	Full term
ACOG	*American College of Obstetricians and Gynecologists*
APH	*Ante partum hemorrhage*
BhCG	*Plasma human chorionic gonadotropin*
CH	*Cesarean hysterectomy*
CS	*Cesarean section*
EMG	*Electromyographic*
FDA	*Food and Drug Administration*
GA	*Gestational age*
ICU	*Intensive care unit*
IM	*Intramuscular*
IQR	*Interquartile range*
IVH	*Intraventricular hemorrhage*
LBW	*Low birthweight*
LIF	*Light-induced fluorescence*
MAP	*Morbidly adherent placenta*
MD	*Mean difference*
MPA	*Medroxyprogesterone acetate*
MRI	*Magnetic resonance imaging*
mRNA	*Messenger RiboNucleic Acid*
NE	*Not estimable*
NEC	*Necrotizing enterocolitis*
NICU	*Neonatal intensive care unit*
NNT	*Number needed to treat*
NS	*Non-significant*
PPH	*Postpartum hemorrhage*
PPROM	*Preterm prelabor rupture of the membranes*
PTB	*Preterm birth*
PTL	*Preterm labor*

List of Abbreviations (Cont...)

Abb.	Full term
RDS	*Respiratory distress syndrome*
RR	*Risk ratio*
S	*Significant*
S.C.	*Subcutaneous*
SD	*standard deviation*
SOGC	*Society of Obstetricians and Gynecologists of Canada*

ABSTRACT

Placenta previa is associated with life-threatening hemorrhages that can occur antepartum, intrapartum and postpartum. Cesarean section, administration of uterotonic agents, surgical hemostatic sutures and blood transfusions are classically performed to manage this situation. Despite this, some cases cannot be controlled properly and emergent peripartum hysterectomy remains a valuable and lifesaving option. Not surprisingly, the need for hysterectomy is significantly enhanced in women with placenta previa with a relative risk of 30–40 . It is, however, a demanding surgical procedure that is associated to a high rate of complications and to the risk of maternal death. There is thus the need to clearly identify the risk factors for this condition, so that women at high risk may be referred and counseled properly.

Symptomatic placenta previa are being treated with tocolytic agents. The progesterone is necessary for the preservation of pregnancy and aids in the extension of pregnancy. The progesterone is also a key metabolic intermediate in the making of other endogenous steroids such as the sex hormones and the corticosteroids. They show a vital part in brain function as a neurosteroid. Reduction of the rate of long-term morbidity requires delayed delivery which facilitates the maturity of vital organs. Though the thorough mechanism of action is not known but proposed mechanisms were: It acts principally through creating uterine inertness and upholds cervical length. It has immunosuppressive activity and stops consequence of oxytocin on myometrium. It is a powerful inhibitor of gap junctions between myometrial cells.

Keywords: Preterm prelabor rupture of the membranes - Postpartum hemorrhage - Necrotizing enterocolitis

INTRODUCTION

Placenta previa is defined when the placenta is inserted wholly or in part into the lower segment of the uterus. It is further classified into major placenta previa, when the placenta lies over the internal os; and minor (or partial), when the placenta lies in the lower uterine segment, but not covering the internal os ***(RCOG, 2011).***

The overall incidence of placenta previa is 2.8/1000 in singleton pregnancy and 3.9/1000 in twin pregnancy ***(Oppenheimer et al., 2001).***

The pathogenesis of placenta previa is unknown. One hypothesis is that the presence of areas of suboptimal endometrium in the upper uterine cavity due to previous surgery or pregnancies promotes implantation of trophoblast toward the lower uterine cavity ***(Faiz and Ananth, 2003).*** Another hypothesis is that a particularly large placental surface area, as in multiple pregnancy or in response to reduced uteroplacental perfusion, increases the likelihood that the placenta will cover or encroach upon the cervical os ***(Lockwood et al., 2015).***

Maternal and perinatal morbidity and even mortality from placenta previa are considerable ***(Ananth et al., 2003; Salihu et al., 2003).*** Most of the relevant morbidity and mortality associated with placenta previa is related to

antepartum bleeding and the subsequent risk of prematurity ***(Lockwood et al., 2015).***

The pathophysiology behind unprovoked bleeding is thought to be related to gradual changes in the cervix and lower uterine segment, which apply shearing forces to the inelastic placental attachment site, resulting in partial detachment ***(Lockwood et al., 2015).***

One of the highly proposed precipitating factors for unprovoked antepartum bleeding in women with placenta previa is premature uterine contractions. It has been shown that contractions and cervical effacement and dilation that occur in the third trimester cause separation of the placenta, which leads to small amounts of bleeding. This bleeding may stimulate further uterine contractions, which, in turn, stimulates further placental separation and bleeding ***(Oyelese and Smulian, 2006).***

It is, therefore, assumed that prevention of such premature uterine contractions would prevent or reduce the risk of preterm antepartum bleeding, with subsequent reduction in the rates of preterm Cesarean sections for antepartum bleeding from placenta previa.

Many studies have examined the use of progesterone for prevention of preterm labor. Three meta-analyses were published regarding this issue. Mackenzie et al. found only

three trials that were appropriate for inclusion in their meta-analysis on therapy in the second trimester, which showed that the use of progestins in women at risk for preterm labor reduced its occurrence by 43% (RR 0.57 [0.36–0.90]) ***(Mackenzie et al., 2006). Dodd et al. (2006)*** concluded that women who received progesterone were statistically significantly less likely to give birth before 37 weeks (RR 0.58; 95% CI 0.48–0.70)***. Sanchez-Ramos and colleagues*** selected 10 papers for analysis, and their results were similar to those of the two other meta-analyses ***(Sanchez-Ramos et al., 2005).***

Natural progesterone is typically administered vaginally. The advantage of vaginal progesterone is its high uterine bioavailability since uterine exposure occurs before the first pass through the liver. It also has few systemic side effects. Doses of 90 to 400 mg have been effective, beginning as early as 18 weeks of gestation ***(Norwitz et al., 2015).***

Aim of the Work

The aim of the current study is to evaluate the efficacy of prophylactic progesterone suppositories administration in reduction of the episodes of ante partum hemorrhage and subsequent prevention of preterm delivery in women with placenta previa.

Chapter 1
EFFECT OF PROGESTERONE ON PREVENTION OF PRETERM LABOR

Preterm labor is defined as regular contractions of the *uterus* resulting in changes in the *cervix* that start before 37 weeks of pregnancy. Changes in the cervix include effacement (the cervix thins out) and dilation (the cervix opens so that the *fetus* can enter the birth canal) ***(ACOG, 2016).***

When birth occurs between 20 weeks of pregnancy and 37 weeks of pregnancy, it is called preterm birth ***(ACOG, 2016).***

Preterm birth is a concern because babies who are born too early may not be fully developed. They may be born with serious health problems. Some health problems, like *cerebral palsy*, can last a lifetime. Other problems, such as learning disabilities, may appear later in childhood or even in adulthood.

The risk of health problems is greatest for babies born before 34 weeks of pregnancy. But babies born between 34 weeks of pregnancy and 37 weeks of pregnancy also are at risk ***(Goldenberg-Robert et al., 2002).***

Factors that increase the risk of preterm birth include the following:

- Having a previous preterm birth.
- Having a short cervix.
- Short interval between pregnancies.

- History of certain types of surgery on the uterus or cervix
- Certain pregnancy complications, such as multiple pregnancy and vaginal bleeding.
- Lifestyle factors such as low pregnancy weight, smoking during pregnancy, and substance abuse during pregnancy.

(ACOG, 2016)

If you have had a prior preterm birth and you are planning another pregnancy, a preconception care checkup can help you get in the best possible health before you become pregnant. When you become pregnant, be sure to start *prenatal care* early. You may be referred to a health care professional who has expertise in managing high-risk pregnancies. In addition, you may be given certain medications or other treatment to help prevent preterm birth if you have risk factors. Treatment is given based on your individual situation and your risk factors for preterm birth ***(Queenan et al., 2002).***

Preterm birth before 37 weeks' gestation is a common problem in obstetric care, with estimates ranging from 5% in several European countries to 18% in some African countries ***(Blencowe, 2012)***.

In Australia, approximately 8% of all infants were born preterm in 2000, with 2.7% of these births occurring prior to 34 weeks' gestation ***(AIHW, 2003)***.