Effect of Oral Dygesterone on Latency Period and Prenatal Outcomes in Pregnant Females with Preterm Prelabour Rupture of Membrane Between 30-33 Weeks of Pregnancy (A Randomized Controlled Trial)

Thesis

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List of Abbreviations

Abb.	Full term
17ohp	*17 hydroxy progesterone*
ACOG	*American committee of obstetric and gynecology*
AFI	*Amniotic fluid index*
APGAR	*Appearance, pulse, grimace, activity and respiration*
CDC	*Centers for Disease Control and Prevention*
CI	*Confidence interval*
GBS	*Group B streptococcus*
MMPs	*Matrix metalloproteinases*
MPV	*Mean platelet volume*
NHLBI	*National Heart, Lung, and Blood Institute*
NICHD-MFMU	*National Institute of Child Health and Human Development - Maternal Fetal Medicine Units*
PPROM	*Preterm premature rupture of membranes*
PROM	*Premature rupture of membranes*
RCT	*Randomized controlled trial*
RDS	*Respiratory distress syndrome*
RDS	*Respiratory distress syndrome*
ROM	*Rupture of membranes*
RR	*Relative risk*
SPROM	*Spontaneous preterm rupture of the membranes*
TIMPs	*Tissue inhibitors of matrix metalloproteinases*

INTRODUCTION

Preterm rupture of the fetal membranes (PROM) complicates 2%-4% of pregnancies and is responsible for about 10-30% of preterm births and perinatal, the result is often early preterm birth accompanied by substantial neonatal morbidity and/or death ***(Combs et al., 2015).***

To minimize these risks, a strategy of expectant management is often adopted, with a goal of prolonging the pregnancy until a more favorable gestational age is reached ***(ACOG, 2013).*** But even with conservative management, 50-60% of women with PROM deliver within 1 week. Because of the high risks of preterm delivery as infection, placental abruption, and cord accidents, any of which can occur with little or no warning, patients with PROM are generally hospitalized until delivery ***(Caughey et al., 2008).***

During expectant management, gestational age increases, and the balance naturally shifts toward favoring delivery. Once the gestational age reaches 36 weeks, the risk of lethal or permanent squeal of prematurity is minimal, so most clinicians agree that delivery is warranted ***(Caughey et al., 2008).***

Some adjunctive medications may improve the outcome of expectant management of PROM according to recent metaanalyse. Antenatal corticosteroids reduce the rates of several neonatal complications. Antibiotics also reduce

neonatal morbidity, in part by prolonging the latency period from PROM to delivery ***(Mackeen et al., 2014)***. Tocolytic agents appear to be largely ineffective at either prolonging pregnancy or reducing neonatal morbidity after PROM, yet some clinicians use them for 48 hours to prolong for two days for corticosteroids administrations. No other treatments have proven useful ***(Combs et al., 2004).***

Progestogens have properties that might be especially beneficial in women with PROM, infection stimulates the production of pro-inflammatory cytokines that are commonly associated with preterm birth and PROM. In vivo studies have suggested that progesterone can modulate infection-related cytokine production. In high-risk patients with a prior spontaneous preterm birth or short cervix, progesterone works at the cellular level to prolong pregnancy and prevent coordinated contractions ***(Peltier et al., 2008).*** Progesterone appear to reduce the rate of preterm birth and they are recommended in these settings ***(Combs, 2013).***

So progesterone is included in suppression of myometrial activation, reduced expression of myometrial gap junctions; contraction- related proteins, reduced production of inflammatory cytokines, station of cervical ripening, and reduced cell death in the chorion and deciduas ***(Roberts and Dalziel, 2006).*** No studies have yet been conducted to prove or disprove the effect of progesterone on latency period (defined as the period from the onset of PPROM until of labor).

Progesterone is rapidly absorbed following administration by any route, its half-life in the plasma is approximately 5 minutes, and small amount are stored temporarily in body fat. It is almost completely metabolized in one passage through the liver, in the liver, progesterone is metabolized to pregnanediol and conjugated with glucuronic acid. It is excreted into the urine as preganediol glucuronide. An oral progesterone formulation was used because its ability to increase both plasma and myometria concentration of progesterone in pregnant women had been previously demonstrated ***(Khudur et al., 2012)***.

AIM OF THE WORK

The aim of the present study is to assess efficacy of oral dydrogesterone on latency period and prenatal outcome on patients with preterm prelabour rupture of membranes between 30 to 33 week of gestation.

Research question:

In women with preterm prelabour rupture of membranes dydrogesterone therapy prolong latency period and decrease neonatal morbidiy?

Research hypothesis:

Administration of dydrogesterone therapy in women with preterm prelabour rupture of membranes prolong latency period and decrease neonatal morbidity.

Chapter One

Premature Rupture of Membranes (PROM)

Premature rupture of membranes (PROM), or pre-labor rupture of membranes, is a condition that can occur in pregnancy. It is defined as rupture of membranes (breakage of the amniotic sac), commonly called breaking of the mother's water(s) ***(Mercer et al., 2005)***, more than 1 hour before the onset of labor ***(Practice Bulletin No. 160, 2016)***. The sac (consisting of 2 membranes, the chorion and amnion) contains amniotic fluid, which surrounds and protects the fetus in the uterus (womb). After rupture, the amniotic fluid leaks out of the uterus through the vagina.

Premature rupture of membranes (PROM) refers to a patient who is beyond 37 weeks' gestation and has presented with rupture of membranes (ROM) prior to the onset of labor. Preterm premature rupture of membranes (PPROM) is ROM prior to 37 weeks' gestation. Spontaneous preterm rupture of the membranes (SPROM) is ROM after or with the onset of labor occurring prior to 37 weeks. Prolonged ROM is any ROM that persists for more than 24 hours and prior to the onset of labor.

At term, programmed cell death and activation of catabolic enzymes, such as collagenase and mechanical forces, result in ruptured membranes. Preterm PROM occurs probably

due to the same mechanisms and premature activation of these pathways. However, early PROM also appears to be linked to underlying pathologic processes, most likely due to inflammation and/or infection of the membranes. Clinical factors associated with preterm PROM include low socioeconomic status, low body mass index, tobacco use, preterm labor history, urinary tract infection, vaginal bleeding at any time in pregnancy, cerculage, and amniocentesis ***(Mercer et al., 2005)***.

Eighty-five percent of neonatal morbidity and mortality is a result of prematurity. PPROM is associated with 30-40% of preterm deliveries and is the leading identifiable cause of preterm delivery. PPROM complicates 3% of all pregnancies and occurs in approximately 150,000 pregnancies yearly in the United States ***(Practice Bulletin No. 160, 2016)***. When PPROM occurs remote from term, significant risks of morbidity and mortality are present for both the fetus and the mother. Thus, the physician caring for the pregnant woman whose pregnancy has been complicated with PPROM plays an important role in management and needs to be familiar with potential complications and possible interventions to minimize risks and maximize the probability of the desired outcome ***(Mercer et al., 2005; Mercer, 2004; Aagaard-Tillery et al., 2005)***.

Women with PROM usually experience a painless gush of fluid leaking out from the vagina, but sometimes a slow steady leakage occurs instead.

When premature rupture of membranes occurs at or after 38 weeks completed gestational age (at term), there is minimal risk to the fetus and labor typically starts soon after.

If rupture occurs before 37 weeks, called preterm premature rupture of membranes (PPROM), the fetus and mother are at greater risk for complications. PPROM causes one-third of all preterm births, and babies born preterm (before 37 weeks) can suffer from the complications of prematurity, including death. Open membranes provide a path for bacteria to enter the womb and puts both the mother and fetus at risk for life-threatening infection. Low levels of fluid around the fetus also increase the risk of the umbilical cord compression and can interfere with lung and body formation in early pregnancy ***(Mercer, 2004)***.

Women who experience premature rupture of membranes should be evaluated promptly in the hospital to determine if a rupture of membranes has indeed occurred, and to be treated appropriately to avoid infection and other complications.

Classification

- Premature rupture of membranes (PROM): when the fetal membranes rupture early, at least one hour before labor has started ***(Aagaard-Tillery et al., 2005)***.
- Prolonged PROM: a case of premature rupture of membranes in which more than 24 hours has passed