Introduction

Preterm premature rupture of membranes (PPROM) occurs in women with membranes rupture before labor and before 37 weeks of gestation. PPROM is the primary etiology for 25% of preterm births which can result in major perinatal morbidity and mortality. PPROM occurs in 3 percent of pregnancies ;approximately 0.5 percent of pregnancies <27 weeks, 1 percent of pregnancies 27 to 34 weeks, and 1 percent of pregnancies 34 to 37 ***(Heyden,2014).***

In contemporary obstetric practice, antenatal corticosteroids have become integral to the clinical management of PPROM to reduce the risk of neonatal mortality and morbidity, after a systematic reviews of randomized trials that showed neonatal death, respiratory distress syndrome, intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and duration of neonatal respiratory support were significantly reduced by antenatal glucocorticoid treatment, without an increase in either maternal or neonatal infection. Mean risk reduction for these adverse events ranged from 30 to 60 percent. ***(Roberts D et al., 2017)***

The most common cause of deaths among preterm babies is respiratory distress syndrome (RDS), an acute lung disease related to immaturity of the lungs and, specifically, surfactant deficiency ***(Avery et al., 2007)***. The incidence and severity of RDS show an inverse relationship with gestational age ***(Whitsett et al., 2004).***

Antenatal steroid treatment for women who are at risk of preterm delivery has emerged as the most effective intervention for the prevention of RDS, reducing early neonatal mortality and morbidity ***(Roberts et al., 2008).*** Most glucocorticoid hormones, natural and artificial, are capable of crossing the placenta and trigger the maturational process that leads to the production and release of surfactant into the alveoli of the fetal lung ***(Rayburn et al., 2007).***

For women with PPROM, there is controversy about the use of a single course or a repeated single course of antenatal corticosteroids ***(Peltoniemi et al., 2007).*** For women with PPROM before 34 weeks' gestation, one course of antenatal corticosteroids has been recommended by the American College of Obstetricians and Gynecologists (ACOG) and a National Institute of Health consensus panel ***(Practice Bulletins, 2013)***.

However, surveys from Australia and Canada indicate that, for women at risk of preterm labor and birth, steroid prescribing patterns of obstetricians vary markedly ***(Hui et al., 2007).***

Although the opportunity to administer a second course of steroids is not an uncommon clinical scenario in the setting of PPROM, it remains uncertain whether rates of neonatal morbidity differ between those receiving a repeat course of antenatal corticosteroids versus a single corticosteroid course. Therefore, analyzing perinatal outcomes of women with PPROM exposed to a single or a repeat course of corticosteroids has potentially important clinical relevance. ***(Hui et al., 2007).***

Aim of the Work

This study aims to compare between effects of single course versus repeated single course of antenatal corticosteroids in PPROM on neonatal outcomes.

1. **Primary outcome:**

To compare the effect of single versus repeated single course of antenatal corticosteroid in PPROM on RDS.

2. **Secondary outcomes:**

To compare the effect of single versus repeated single course of antenatal corticosteroid in PPROM on;

- Chorioamnionitis (intra- amniotic infection).
- NEC(necrotizing enterocolitis),
- IVH (interventricular haemorrhage).
- culture-proven sepsis,
- NICU admission.

Research Question:

In women with PPROM does repeated single course of antenatal corticosteroid decrease the risk of neonatal RDS compared to single course?

Research Null Hypothesis:

In women with PPROM, repeated single course of antenatal corticosteroids may have similar effect on decreasing neonatal RDS as compared to single course.

Chapter (1)

Preterm Premature Rupture of the Membranes (PPROMs)

Definition:

Premature rupture of the fetal membranes (PROMS) is defined as the rupture of the amniotic membranes with release of the amniotic fluid more than 1 hour prior to the onset of labour. PROMS may be subdivided into term PROMS (TPROMS, i.e. PROMS after 37 weeks of gestation) and preterm PROMS (PPROMS, i.e. PROMS prior to 37 weeks of gestation). PPROMS occurs in approximately 3% of pregnancies and is responsible for a third of all preterm births ***(Mercer, 2003).***

Incidence:

PPROMS occurs in 3 percent of pregnancies ***(Mercer, 2008)*** approximately 0.5 percent of pregnancies <27 weeks, 1 percent of pregnancies 27 to 34 weeks, and 1 percent of pregnancies 34 to 37 weeks ***(Heyden, 2014).***

PROMS is linked to significant maternal and fetal morbidity and mortality. It has been shown to be the cause of 18%–20% and 21.4% of prenatal mortalities and morbidity respectively ***(Liu et al., 2010).***

The three causes of fetal death associated with PROMS are sepsis, asphyxia, and pulmonary hyperplasia. Women with intrauterine infection deliver earlier than non-infected women, and infants born with sepsis have a mortality rate four times higher than those without sepsis do ***(Velemínský and Sák, 2006).***

Etiology:

The etiology of preterm premature rupture of membranes (PPROMS) is multifactorial ***(Tutor and Villa, 2003).***

Three items are involved in its etiology:

- The special anatomy of the membranes.
- Risk factors for their rupture.
- Protecting factors against PPROMS.

Physiology:

The amnion is clearly more than a simple avascular membrane that contains amniotic fluid. The amnion is a metabolically active membrane that is involved in solute and water maintaining amniotic fluid homeostasis. The amniotic membrane secretes nutrients and suppresses the semi-

allogenic immune response against the fetus ***(Calvin and Oyen, 2007).***

The amnion is responsive both acutely and chronically to mechanical stretch, which alters amniotic gene expression ***(Nemeth et al ., 2000).***

The chorion is the specialized outer fetal envelope which is adjacent to the outer aspect of the amnion. The chorion leave is generally more nearly translucent than the amnion and rarely exceeds 1 mm thickness ***(Cunningham et al., 2005).***

Risk factors:

The membranes may resist to a pressure higher than the intrauterine one. They rupture if damaged by any risk factor, as those listed below ***(Tutor and Villa, 2003):***

- Infection (cervico-vaginitis).
- Cervical incompetence.
- Invasive procedures in the cervix.
- Low placental insertion; and placental abruption.
- Ehler Danlos syndrome.
- Smoking.
- Lower socioeconomic status.

- Previous preterm delivery.
- Vaginal bleeding.
- Coitus.
- Uterine distension (e.g., polyhydraminos, multiple pregnancy).
- Race.

It is likely that multiple factors predispose certain patients to preterm PROMS ***(Tutor and Villa, 2003).***

(1) Collagen degradation:

Mechanical strength is provided to fetal membranes by an extracellular collagen matrix (ECM). Types I, II and IV are the main collagen types in these membranes ***(Tejero et al., 2002).***

A collagen rich ECM region connects amnion and chorion cells and provides the functional integrity of the membranes throughout pregnancy ***(Menon et al., 2008).***

Damage to type I collagen, the primary supporting element in the chorioamnion, is believed to represent the final step in the sequence leading to membrane rupture. **(*Mingione et al., 2007*).**

Collagen, the main strength-bearing component of extracellular matrix in the Fetal membrane (FM). The regulation of MMP (matrix metallo proteinase) activity is complex and involves proenzyme activation and suppression by specific tissue inhibitors of metalloproteinases (TIMPs). A dynamic balance between MMPs and TIMPs is thought to facilitate tissue remodeling of the FM to accommodate fetal growth ***(Kumar et al., 2006).***

(2) Chorio Decidual Infection:

Local infection in the fetal membranes underlying the cervix is believed to be an important mechanism of membrane rupture. In some cases, primary infection causes membrane weakening and local prostaglandin release**.** The initiating event is likely a change in the normal vaginal flora or introduction of pathogens from an exogenous source into the cervix leading to an inflamed vaginal milieu ***(Mingione et al., 2007).***

The pathogens ascent into the deciduas and enter the fetal membrane where they generate a cascade of maternal and fetal inflammatory events that culminate in membrane weakening and rupture ***(Mingione et al., 2007).***

Although preterm premature rupture of the membranes (PPROMS) is associated with intra-amniotic infections, there is now strong evidence linking PPROMS with placental abruption (i.e. decidual hemorrhage) ***(Lockwood et al., 2005).***

In infection-derived PPROMS, proinflammatory cytokines enhance protease expression and neutrophil infiltration ***(Romero et al., 2002).***

By contrast, mechanisms underlying abruption-associated PPROMS are primarily unknown **.** Decidual cells are a rich source of tissue factor the primary initiator of hemostasis ***(Lockwood et al., 2005).***

After abruption-related hemorrhage, decidual cell (DC) tissue factor is thought to bind to plasma-derived factor VIIa to activate factor X. Factor Xa then complexes with its co-factor, factor Va, to convert prothrombin to thrombin ***(Lockwood et al., 2001*)**.

Moreover, elevated circulating thrombin-antithrombin complex levels predict the subsequent occurrence of preterm delivery due to preterm labor and/or PPROMs with a high sensitivity and specificity**.** Thus, marked decidua thrombin

production underlies abruption-associated prematurity and PPROMs ***(Lockwood et al., 2001).***

In addition to its haemostatic properties, thrombin induces an array of biological effects via cell surface protease-activated receptors. Thrombin also augments expression of interleukin-8 (IL-8), a potent neutrophil chemoattractant and activator, in cycling endometrium prompted speculation that abruption-associated PPROMS would lead to thrombin-induced IL-8 expression in term DCs and result in neutrophil infiltration because neutrophils are a rich source of extracellular matrix-degrading proteases ***(Lockwood et al., 2005).***

(3) Apoptosis (programmed cell death):

Apoptosis is a distinct mode of programmed cell death that is responsible for deletion of cells in normal and neoplastic tissue ***(Sagol et al., 2002).***

Recently reported that during PROMS, MMPs expression increases and was associated with an increase in the expression of apoptosis (programmed cell death) inducing factors like P53. P53 can transactivate MMPs gene expression through the AP-2 site in its Promoter region ***(Menon et al., 2008).***

The apoptotic process, thus, potentially weaken fetal membranes by eliminating fibroblastic cells which lay down new collagen, and simultaneously activates enzyme systems which break down existing collagen ***(Moore et al., 2009).***

(4) Stretch and Fetal Membranes Rupture:

Stretching of the fetal membranes in vitro upregulates several cytokines and enzymes that can drive collagen degradation, leading to membrane rupture. The sensitivity of this response appears to be specific for different cell types and is likely to result from differential activation of some key transcription factors and cofactors. Few cytokines in the fetal membranes respond to stretch: the most robust of these is pre-B-cell colony enhancing factor (PBEF). Therefore, it is proposed here that PBEF functions in normal pregnancy to protect the amnion cells as they become increasingly stretched, but if stimulated, it can initiate key events leading to parturition ***(Kendal-Wright, 2007).***

(5) Nutritional Factors:

The inadequate availability of some nutrients during gestation, such as β-carotenes, vitamin E, and vitamin C, has been identified as risk factors for PROMS ***(Tejero et al., 2002).***

Vitamin C is essential for the formation of collagen and vitamin C deficiency has been associated with PPROMS ***(Siega-Riz et al., 2003).***

(6) Cigarette smoking:

Cigarette smoking has been identified as a clinical risk factor for PPROMS in numerous studies ***(McParland and Bell, 2004).***

(7) Cervical incompetence:

The cervix provides mechanical strength and prevents ascending infection from penetrating the intra-uterine space ***(Manju et al., 2006).***

Incompetent cervix is characterized by painless dilatation of the cervix in the second trimester or perhaps early in the third trimester, with prolapse and ballooning of membranes into the vagina, followed by spontaneous rupture of membranes and expulsion of an immature fetus without the usual discomforts of labor ***(Lee and Silver, 2001)***.

(8) Uterine over-distention:

Multiple pregnancies and polyhydramnios increase the risk of PROMS ***(Lee and Silver, 2001).***

(9) Amniocentesis:

In studies involving women who had second-trimester amniocentesis for prenatal diagnosis of genetic disorders, the risk of PROMS was 1–1.2%, and the attributable risk of pregnancy loss was 0.06%. In most patients, the membranes reseal with restoration of normal amniotic fluid volume ***(Eddleman et al., 2006).***

(10) History of PROMS in prior pregnancy:

A pregnancy complicated by PPROMS is 6.3 times more likely to have been preceded by a pregnancy involving preterm than term delivery. This risk is greatest for women who had PPROMS in their previous pregnancy, who have a 21-32% recurrence risk in subsequent pregnancies ***(McParland and Bell, 2004).***

(11) Other risk factors:

Maternal age, parity and increase in maternal weight do not seem to cause PPROMS ***(Modena et al., 2004).***

The presence of uterine fibroids that distort the uterine cavity are also associated with PPROMS ***(Ouyang et al., 2006).***

Diagnosis of premature rupture of the fetal membranes

1- Careful history taking.

2- Sterile speculum examination.

3- Study of changes of (PH) by:

a. Nitrazine test.

b. King's test (bromo-thymol blue).

4-Biochemical tests:

a- Crystalization test.

b- Vaginal fluid markers.

5-Intra-amniotic injection of dyes:

6- Ultrasound examination

(ACOG Practice Bulletin, 2016)

1- History:

Patients often report sudden gush of fluid with continued leakage. Physicians should ask about uterine contractions, vaginal bleeding, fever and recent intercourse ***(Medina et al., 2006).***

2-Physical examination:

Evidence of fluid pooling in the vagina, or leaking from the cervical os when the patient coughs or when fundal