# INTRODUCTION

Prelabour premature rupture of membranes (PPROM) can be defined as spontaneous rupture of the amnion and chorion membranes before the onset of labour or before 34 weeks gestation. The latency period is the time from PROM or PPROM to onset of labour ***(Mercer, 2003)***.

Preterm rupture of the fetal membranes (PROM) complicates 2-4% of pregnancies and is responsible for approximately 10-30% of preterm births and perinatal deaths. When PROM occurs very early in gestation, the result is often early preterm birth accompanied by substantial neonatal morbidity and/or death ***(Ananth et al., 2005)***.

To minimize these risks, a strategy of expectant management is often adopted, with a goal of prolonging the pregnancy until a more favourable gestational age is reached ***(ACOG, 2013)***. However, even with conservative treatment, 50-60% of women with PROM deliver within 1 week ***(Combs et al., 2004).***

Some adjunctive medications may improve the outcome of expectant management of PROM according to recent meta-analysis. Antenatal corticosteroids reduce the rates of several neonatal complications, which include respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and death. Antibiotics also reduce neonatal morbidity, in part by prolonging the latency period from PROM to delivery. Tocolytic agents may prolong the latency period slightly, but any benefit of this may be negated by an increased rate of chorioamnionitis. No other treatments have proved useful ***(Kenyon et al., 2013)***.

Progestogens might be especially beneficial after PPROM because their properties include suppression of myometrial activation, reduced expression of myometrial gap junctions and contraction-related proteins, reduced production of inflammatory cytokines, inhibition of cervical ripening, and reduced cell death in the chorion and decidua ***(Kenyon et al., 2013)***.

Vaginal progesterone and 17-hydroxyprogesterone (17OHP-C) reduce the rate of preterm birth in women with a short cervix or with a history of spontaneous preterm birth. These agents are recommended in these settings if the membranes are intact. However, a previous trial found no benefit of 17OHP-C for women with PROM, although the trial had limited statistical power because of small sample size ***(Meis et al., 2003)***.

Preterm delivery is defined as the delivery before the end of the 37$^{th}$ week of gestation and is possibly the single most important health related issue in pregnancy. One of the main etiologies for premature birth is Preterm premature rupture of membranes (PPROM) which occurs in 3% of all pregnancies. Preterm delivery is one of the most important risk factors for future morbidity and mortality among the neonates comprising up to 85% of prenatal morbidity and mortality ***(Blencowe et al., 2012).***

# AIM OF THE WORK

The present study aims to investigate the effect of 17-OH progesterone on primegravida and the possible change in the premature delivery rates and other pregnancy outcomes and complications regarding its use.

# Chapter (1):
# PREMATURE RUPTURE OF MEMBRANE

## Definition:

The definition of PROM is rupture of membranes before the onset of labor. Membrane rupture before labor and before 37 weeks of gestation is referred to as preterm PROM. Management is influenced by gestational age and the presence of complicating factors, such as clinical infection, abruption-placentae, labor, or non-reassuring fetal status ***(ACOG, 2016).***

## Incidence

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 weeks ***(Jantien et al., 2014).***

In a large randomized trial, one half of women with PROM who were managed expectantly gave birth within 5 hours and 95% gave birth within 28 hours of membrane rupture. The most significant maternal consequence of term PROM is intrauterine infection, the risk of which increases with the duration of membrane rupture ***(ACOG, 2016).***

## Pathogenesis

The pathogenesis of spontaneous membrane rupture is not completely understood. The strength and integrity of fetal membranes derive from extracellular membrane proteins, including collagens, fibronectin, and laminin. Matrix metalloproteases (MMPs) decrease membrane strength by increasing collagen degradation ***(Birkedal-Hansen, 1995).*** Tissue inhibitors of MMPs (TIMMPs) bind to MMPs and inhibit MMP-associated proteolysis, thereby helping to maintain membrane integrity ***(Kumar et al., 2016).***

A variety of pathologic events (eg, subclinical or overt infection, inflammation, mechanical stress, bleeding) can disrupt this and other homeostatic processes and initiate a cascade of biochemical changes that culminate in PROM. Although the pathway varies depending on the initiating event, it is likely that all pathways lead to a final common pathway ending in membrane rupture ***(Kumar et al., 2016).***

## Risk factors

A history of PPROM in a previous pregnancy, genital tract infection, ante-partum bleeding, and cigarette smoking have a particularly strong association with PPROM ***(Harger et al., 1990):***

- **Previous PPROM**- Studies have reported that a history of PPROM is a strong risk factor for recurrence ***(Mercer et al., 2006).***
- **Genital tract infection**- Genital tract infection is the single most common identifiable risk factor for PPROM. Three lines

of epidemiologic evidence strongly support this association: (1) women with PPROM are significantly more likely than women with intact membranes to have pathogenic microorganisms in the amniotic fluid, (2) women with PPROM have a significantly higher rate of histologic chorioamnionitis than those who deliver preterm without PPROM, and (3) the frequency of PPROM is significantly higher in women with certain lower genital tract infections (particularly bacterial vaginosis) than in uninfected women ***(Mercer et al., 2006).***

The association between bacterial colonization of the lower genital tract and PPROM is not surprising. Many of the microorganisms that colonize the lower genital tract have the capacity to produce phospholipases, which can stimulate the production of prostaglandins and thereby lead to the onset of uterine contractions. In addition, the host's immune response to bacterial invasion of the endocervix and / or fetal membranes leads to the production of multiple inflammatory mediators that can cause localized weakening of the fetal membranes and result in PPROM Genetic regulation of the host's immune and inflammatory response appears to play a role in susceptibility and response to infections associated with PPROM ***(Mercer et al., 2006).***

- **Ante-partum bleeding**– Ante-partum bleeding in the first trimester is associated with a small but statistically significant increase in the risk of PPROM Ante-partum bleeding in more than one trimester increases the risk of PPROM three- to seven fold ***(Lykke et al., 2010)***.

- **Cigarette smoking**- The risk of PPROM among smokers is increased two- to four fold compared with nonsmokers. The risk persists even after adjustment for other known risk factors for PPROM, including infection ***(Lykke et al., 2010).***

In addition, polyhydramnios and acute trauma, as well as several genetic polymorphisms of genes related to infection, inflammation, and collagen degradation, have been identified as potential risk factors for PPROM ***(Tchirikov et al., 2018).***

## Diagnosis

The diagnosis of PPROM is clinical, and is generally based on visualization of amniotic fluid in the vagina of a woman who presents with a history of leaking fluid. Laboratory tests can be used to confirm the clinical diagnosis when it is uncertain ***(Alexander et al., 2000).***

## *Findings on physical examination:*

Direct observation of amniotic fluid coming out of the cervical canal or pooling in the vaginal fornix is pathognomonic of PPROM. If amniotic fluid is not immediately visible, the woman can be asked to push on her fundus, Valsalva, or cough to provoke leakage of amniotic fluid from the cervical os ***(Alexander et al., 2000).***

Sterile speculum examination: For patients who are not in active labor, examination of the cervix and vagina should be performed using a sterile speculum. Digital examination should be avoided because it may decrease the latency period (i.e., time from rupture of membranes to delivery) and increase the risk of intrauterine infection The cervix may appear dilated and/or effaced and, rarely, prolapse of a fetal part or the umbilical cord may be detected ***(Alexander et al., 2000).***

## *Laboratory confirmation of clinically suspected PPROM*

**Nitrazine**— if PPROM is not obvious after visual inspection, the diagnosis can be confirmed by testing the pH of the vaginal fluid, which is easily accomplished with Nitrazine paper ***(Seeds et al., 1968).*** **Fern tests: a second** confirmatory test is the presence of arborization (ferning). Fluid from the posterior vaginal fornix is swabbed onto a glass slide and allowed to dry for at least 10 minutes ***(Abe, 1940, Davidson, 1991).*****AmnioSense**: In the United Kingdom, an absorbent pad (AmnioSense) that changes color at pH >5.2 is used as a panty liner and marketed to pregnant women. In a study of 157 pregnant women, the sensitivity and specificity of this device for diagnosis of membrane rupture were 98 and 65 percent, respectively ***(Mulhair et al., 2009).*** **Commercial tests** — several tests for diagnosis of rupture of membranes are now commercially available such as: Insulin-like growth factor binding protein 1 (IGFBP-1 [Actim PROM]). Placental alpha microglobulin-1 protein assay (PAMG-

1 [AmniSure]) for diagnosis of rupture of membranes concluded PAMG-1 (AmniSure) was more accurate than IGFBP-1 (Actim PROM) for diagnosis of rupture of membranes in all patient populations (eg, known rupture status, uncertain rupture status) ***(Ramsauer et al., 2013).*** These tests are not widely used because of their cost and the complexities of credentialing providers and maintaining quality control. Doctors consider using one of the commercial tests only in cases where the diagnosis of PPROM is problematic, such as when the patient's history is somewhat suggestive, but no pooling is evident and ultrasound shows low-normal amniotic fluid volume ***(Liang et al., 2014).***

## *Findings on ultrasonography:*

Fifty to seventy percent of women with PPROM have low amniotic fluid volume on initial sonography Oligohydramnios can be defined as the absence of a single pocket of amniotic fluid that is < 2 cm in depth or an amniotic fluid index < 5 cm. If the patient has a normal amniotic fluid volume, it is very unlikely that she has experienced rupture of membranes, even with a seemingly convincing history ***(Mercer et al., 2006).***

## **Differential diagnosis**

Other causes of vaginal/perineal wetness are urinary incontinence, vaginal discharge (normal or related to infection) Perspiration. While other causes of a mild reduction of amniotic fluid volume on ultrasound are anhydramnios, severe oligohydramnios, renal agenesis, obstructive uropathy and severe utero-placental insufficiency ***(Mercer et al., 2006).***

## Complications of PROM:

- ***Fetal-neonatal complications:***
  - **Fetal-neonatal infection:**

The risk of fetal/ neonatal infection following PROM is greater with increasing prematurity, with the presence of chorio-amnionitis and with an increasing interval from the first vaginal examination and delivery. Genital tract colonization with pathogenic organisms at time of rupture increases the likelihood of fetal/ neonatal infection. The most important organism contributing to neonatal sepsis is the group β – hemolytic streptococci ***(Bevilacqua et al., 2005).***

  - **Intra-ventricularhge & Cerebral palsy:**

There is increasing evidence demonstrating a relationship between intrauterine infection and the development of intra-ventricular hemorrhage and peri-ventricular leukomalacia with subsequent occurrence of cerebral palsy, which is thought to be mediated through the generation of pro-inflammatory cytokines by the fetus ***(Svigos, 2001).***

  - **Broncho-pulmonary dysplasia and chronic lung disease:**

There is evidence that chorioamnionitis leads to lung injury and subsequently broncho-pulmonary dysplasia. Microorganisms, pro-inflammatory cytokines can be aspirated during fetal breathing and lead to in-utero pneumonitis, making the lung more susceptible to damage by barotraumas and oxygen toxicity and increase the risk of broncho-pulmonary dysplasia ***(Yoon et al., 1997).***

- **Perinatal asphyxia and fetal distress:**

PROM can predispose to fetal asphyxiation through several mechanisms. These include cord compression or prolapse, malpresentation and fetal compromise secondary to maternal fever and chorioamnionitis. Clinical markers of asphyxia include low Apgar score, meconium staining, abnormal fetal heart rate patterns and low biophysical profile score ***(Blackmon et al., 1996)***

- ***Prematurity:***

The fetus and neonate are at greater risk of PPROM related morbidity and mortality than the mother. Prematurity related morbidity varies with gestational age and is higher in the setting of chorioamnionitis ***(Soraisham et al., 2013).***

- **Fetal malpresentation is common:** Due to the preterm gestational age and the frequent occurrence of reduced amniotic fluid volume. The risk of cord prolapse is especially high (11 percent in one study in the setting of both non vertex fetal presentation and PPROM. Non-cephalic presentation may also increase the risk of abruption, infection, and fetal death in utero ***(Lewis et al., 2007).***

- **Facial with deformation, and orthopedic abnormalities:** Early, severe, prolonged oligohydramnios can be associated. Such complications are most likely when membrane rupture occurs at less than 23 weeks of gestation ***(Goodman et al., 2013).***

- ***Maternal complications:***
  - *Maternal infection:*
    - ***Intrauterine infection:***

***Tiufekchieva in (2006)*** concluded that there is a relationship between the incidence of the infectious complications and the duration of the latent period after the PROM. The risk of intrauterine infection rises sharply between the $24^{th}$ and the $72^{nd}$ hour after the PROM.

- ***Postpartum endometritis****:* Similar to chorioamnionitis, endometritis is usually polymicrobial in nature. Established risk factors include prolonged ruptured fetal membranes, prolonged labor and operative delivery**.** Endometritis is more common after cesarean than vaginal delivery. The incidence of infection is higher at earlier gestational ages ***(Casey and Cox, 1997).***

A prolonged interval from prelabor rupture of the membranes to delivery for $\geq$ 24 hours is associated with an increased incidence of maternal postpartum endometritis, clinical chorioamnionitis and postpartum fever ***(Casey and Cox, 1997).***

- ***<u>Abruptio placentae and prolapse of the umbilical cord</u>***:

PPROM is also associated with increased risks of abruptio placentae and prolapse of the umbilical cord. Placental abruption occurs in 2 to 5 percent of pregnancies complicated by PPROM. Placental abruption may be the precipitating event for, or a consequence of, PPROM. The risk is increased seven- to nine fold in PPROM pregnancies in which intrauterine infection or oligohydramnios is present ***(Ananth et al., 2005***).

## Management:

PPROM can be separated into three general groups to guide evaluation and treatment**:** ***Early Term and Term (37 0/7 weeks of gestation or more)***: Proceed to delivery and GBS prophylaxis as indicated. ***Late Preterm (34 0/7–36 6/7 weeks of gestation):*** Same as for early term and term Preterm. ***Preterm (24 0/7–33 6/7 weeks of gestation:*** Expectant management, antibiotics recommended to prolong latency if there are no contraindications, single-course corticosteroids and GBS prophylaxis as indicated. ***Less than 24 weeks of gestation:*** Patient counseling, expectant management or induction of labor, antibiotics may be considered as early as 20 0/7 weeks of gestation, GBS prophylaxis is not recommended before viability. Corticosteroids are not recommended before viability, tocolysis is not recommended before viability and Magnesium sulfate for neuroprotection is not recommended before viability ***(ACOG, 2017).***

## *Components of expectant management*

**1-** **A course of corticosteroids** should be administered to pregnancies that present with PPROM between 23 and 34 weeks of gestation. A course of antenatal corticosteroids consist of four does of 6mg dexamethasone intramuscularly 12 hours apart or betamethasone suspension 12mg intramuscular every 24 hours for two doses ***(ACOG, 2017).***

Mechanism of action: antenatal administration of corticosteroids accelerate development of type1and type 2 pneumocytes, leading to structural and biochemical changes that improve lung volume ,compliance and gas exchange ***(Bonanno et al., 2009).***

Induction of type 2 pneumocytes increases surfactant production and induction of pulmonary beta-receptors, which play a role in surfactant release and absorption of alveolar fluid when stimulated and induction of fetal lung antioxidant enzymes ***(ACOG, 2016).*** For these change to occur, the lung need to have reached a stage of development that is biologically responsive to corticosteroids, gestational age at administration 22weeks to 33+6 weeks who are at increased risk of preterm delivery within the next one to seven days since only a few primitive alveoli are present below this gestational age ***(Roberts et al., 2017).*** A single rescue course of dexamethasone has been administered to pregnancies up to 34 weeks in this setting: clinically estimated to be at high risk of delivery within the next one to seven days, prior exposure to antenatal corticosteroids at least 14 days earlier and initial course of antenatal corticosteroids administered at less than 28weeks of gestation ***(ACOG, 2016).*** Use of a single repeat course of antenatal corticosteroids has been termed salvage, rescue, or booster therapy, this appears to be effective and may minimize neonatal complications ***(ACOG, 2016).*** Maternal side effects such as: 1) transient hyperglycemia occur in many woman, the steroid effect start 12 hours after the first dose and may last for five days.in women with diabetes, hyperglycemia can be severe if not closely monitored and treated. 2) the total leukocyte count increases by approximately 30% within 24 hours and return to baseline within 3 days this may complicate the diagnosis of infection ***(Hagberg et al., 2002).***

2- **Magnesium sulfate for neuroprotection**— Magnesium sulfate is administered prior to delivery according to standard clinical protocols for fetal neuroprotection e.g., pregnancies at least 24 but < 32 weeks of gestation at risk of imminent delivery ***(Lorthe et al., 2017)***.

**The mechanism for the neuroprotective effects** of magnesium sulfate in preterm infants is not well understood. The following mechanisms have been proposed: stabilization of cerebral circulation by stabilizing blood pressure and normalizing cerebral blood flow, prevention of excitatory injury by stabilization of neuronal membranes and blockade of excitatory neurotransmitters, such as glutamate, protection against oxidative