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Pregnancy Outcomes of Pre-viable Preterm Premature Rupture of Membranes: A Systematic Review

THESIS

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MASTER OF SCIENCE

in Biomedicine and Translational Science

by

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ABSTRACT OF THE THESIS

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Master of Science in Biomedical and Translational Science

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OBJECTIVE: The aim of my study was: to assess the maternal and neonatal outcomes of pre-viable PPROM pregnancies and to describe the predictors for better outcomes of these pregnancies.

METHODS: I performed a systematic review of the literature published on the pregnancy outcomes of pre-viable PPROM following expectant management. I collected 17 high quality studies through PubMed database search and reviewed them to obtain data on: neonatal survival; maternal and neonatal morbidity; predictors for better neonatal survival and proportion of women opting for termination of pregnancies.

RESULTS: The overall survival to hospital discharge was 41.1%. Of these, 49.2% neonates survived without a major morbidity. Respiratory morbidity was the most common morbidity among surviving neonates. 37% neonates suffered from respiratory distress syndrome, 28% from broncopulmonary dysplasia, and 9.8% from pulmonary hypoplasia. Sepsis occurred in 22.7% neonates. 49.3% pre-viable PPROM women developed chorioamnionitis. Other common maternal morbidities included cesarean delivery (33%)

and placental abruption (30%). The predictors of better neonatal survival to discharge included later gestational age at PPROM, absence of oligohydramnios, iatrogenic etiology of PPROM, and the C-reactive protein (CRP) level <1mg/dl on the first day of presentation. Later gestational age at birth was associated with less neonatal morbidity. Overall, 21.1% of pre-viable PPROM women opted for the termination of pregnancy instead of expectant management.

CONCLUSION: The survival rate of pre-viable PPROM is poor, but it is not zero. 4 of every 10 affected neonates do survive and half of them are without any major morbidity. Maternal morbidity is still high, but serious maternal morbidities are rare.

CHAPTER 1: INTRODUCTION

Preterm premature rupture of membranes (PPROM) is the rupture of fetal membranes prior to 37 weeks of gestation, before the onset of labor. It affects approximately 3% of the pregnancies and is responsible for one third of the preterm births worldwide (1). PPROM is associated with high maternal and neonatal morbidity and poor neonatal survival. When the fetal membranes rupture before 24 weeks gestation, the condition is known as 'pre-viable PPROM'. The incidence of PPROM at this early gestation is 4 per 1000 pregnancies (2).

The outcome of the pregnancies with PPROM is highly dependent on the gestational age at which the membranes rupture. When they rupture at an advanced gestation (between 32-36 weeks), the prognosis is generally good and the neonatal mortality and morbidity is almost absent. The risk of the neonatal mortality and morbidity is moderate when the membranes rupture at an earlier gestation (between 24-32 weeks). However, when PPROM occurs at a pre-viable gestation (before 24 weeks), the risk of the maternal and neonatal morbidity is very high and there is a sharp decline in the neonatal survival rate (3, 4).

There are two main reasons for the extremely poor perinatal outcomes associated with pre-viable PPROM. When there is an immediate delivery of the fetus following pre-viable PPROM, the neonate may die due to extreme prematurity, as the age of fetal viability is generally accepted to be 24 weeks or greater. On the other hand, when the delivery is delayed, there is a higher risk of maternal and neonatal infections and the complications related to prolonged rupture of fetal membranes with lack of fluid around the fetus (5, 6).

The prolonged stay of a fetus with minimal amount of fluid around it may lead to two types of complications: 1) restricted fetal abnormalities including limb defects and Potter syndrome like facial abnormalities (e.g. low-set ears and epicanthic folds); and 2) poor lung development that manifests as pulmonary hypoplasia and pulmonary hypertension. Pulmonary hypoplasia is the single most important cause of neonatal mortality in these pregnancies. This complication arises from the fluid leakage leading to oligohydramnios (amniotic fluid volume <2cm on an obstetrical ultrasound), as normal amniotic fluid volume is essential for the normal fetal lung development. Lethal pulmonary hypoplasia rarely develops subsequent to PPROM at >24 weeks. The possible explanation is that the alveolar growth adequate to support postnatal development has already occurred (7, 8). The overall perinatal outcome of the pregnancies suffering from pre-viable-PPROM remains disappointing.

The management of the pregnancies complicated by pre-viable PPROM is controversial. In the presence of infection i.e. chorioamnionitis, termination of pregnancy (TOP) is the only management option. However, when there are no signs of infection, decision between expectant management vs. TOP becomes challenging both at personal and ethical level. The decision is primarily based on patient's preference based on her personal and moral beliefs after a detailed discussion with her obstetrician regarding the benefits and risks of both management options.

Typically, most women with pre-viable PPROM are presented the option of TOP given the poor neonatal survival and high rate of maternal and neonatal morbidity associated with this condition. In 1984, Taylor and Garite reported that with conservative management of PPROM at <25 weeks, the perinatal survival was only 22 percent and the

maternal morbidity was as high as 59 percent (9). Similarly in 1988, Moretti et al. demonstrated that the perinatal survival rate associated with conservative management was 13.3 percent when PPROM occurred at ≤ 23 weeks gestation and 32.2 percent when it occurred before 26 weeks (10).

Later publications have shown that the neonatal survival after conservative management has improved over the past two decades (11-15). The average survival rate with PPROM near the limit of fetal viability has been reported to be 44.4% for the studies published between 2000-2008 (2). This improved survival is attributable to the better obstetrical and neonatal care including the use of antibiotics, antenatal corticosteroids, surfactant therapy, and the modern ventilation strategies (16). These recent advances in the management of patients with pre-viable PPROM have shifted patients' counseling more towards the expectant management.

Current trend towards Evidence Based Medicine requires that all medical decisions should be based on evidence-based practice, which is defined as, "Integration of best research evidence with clinical expertise and patient values"(17). Therefore, the physicians follow clinical practical guidelines to make management decisions about individual patients. There is currently no consensus regarding the optimal management of the patients with pre-viable PPROM. All international and national guidelines provide clear guidance for the management of PPROM at >24 weeks gestation, but guidelines for the management of pre-viable PPROM are lacking.

The American College of Obstetricians and Gynecologists (ACOG) October 2016 guidelines on PPROM, recommend immediate delivery with Induction of labor (IOL) when PPROM occurs after 34 weeks and expectant management with 'watchful waiting' when it

occurs between 24-34 weeks. However, ACOG does not recommend either expectant management or immediate delivery when this event occurs before 24 weeks. According to these guidelines, pre-viable PPROM patients should be counseled regarding the benefits and the risks of expectant management versus immediate delivery. They should be provided with the most current data and then allowed to make the ultimate decision (18).

The purpose of my research is to outline the most up to date data on the perinatal outcomes of pregnancies with pre-viable PPROM. This document aims to serve as a guide for counseling of these patients suffering from this morbid condition and support them to make a decision regarding the choice of either expectant management or immediate delivery.

Research Questions:

This study was designed to answer the following questions,

1. What are the maternal and neonatal outcomes of the pregnancies with preterm premature rupture of membranes at <24 weeks (pre-viable PPROM) following expectant management?
2. What are the predictors of better maternal and neonatal outcomes of the pre-viable PPROM pregnancies following expectant management?
3. What is the proportion of pre-viable-PPROM women who opt for the termination of their pregnancies instead of expectant management?

Research Methodology Overview:

I performed a systematic review of the published literature by applying the standards recommended by the Institute Of Medicine (IOM) Committee On Standards For Systematic Reviews of Comparative Effectiveness Research (19). I searched PubMed

database to find the studies published during the past decade that evaluated the perinatal outcomes of PPROM prior to 24 weeks gestation following expectant management. After assessing the quality of these studies, I collected the data about the primary (neonatal survival) and the secondary outcomes (neonatal and maternal morbidity, proportion of pre-viable PPROM women opting for TOP) of my study to create the body of evidence. This was followed by the interpretation of the review findings.

CHAPTER 2: BACKGROUND

Fetal (amniochorionic) membranes are the structures that hold and protect the fetus during its development throughout the pregnancy. They consist of two membranes: The inner membrane called Amnion surrounds the amniotic sac, containing the fetus and the amniotic fluid. The outer membrane known as Chorion, contains the amnion and is the part of the placenta. The amniotic fluid surrounding a fetus has many important functions. It acts as a barrier to the infection; allows symmetrical outer growth of the developing fetus; permits free limb movement; is responsible for the normal lung development; maintains the fetal body temperature; and provides a cushion to protect the fetus against trauma. Therefore, its adequate volume is essential for the normal development of a growing fetus (20).

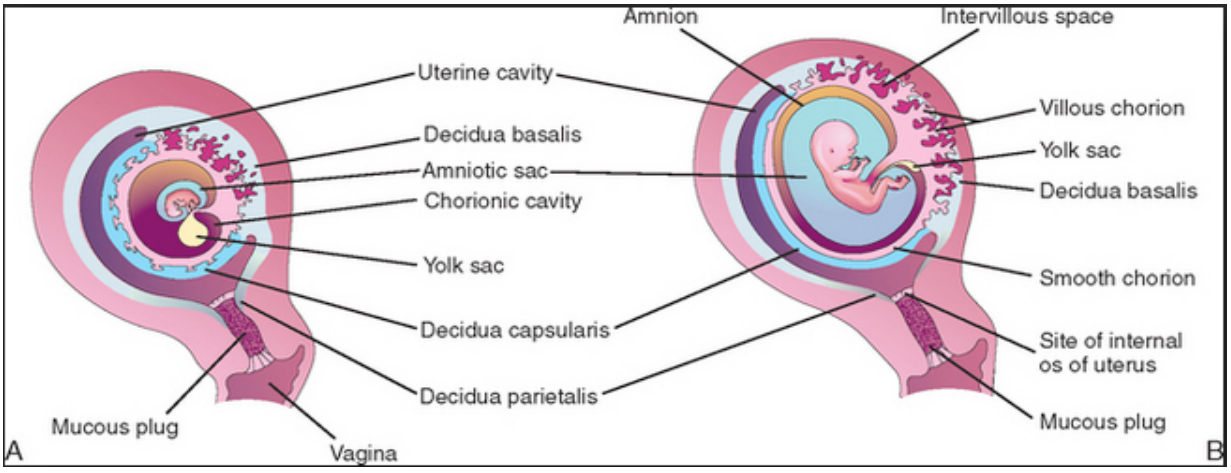

Figure 2.1: Anatomy of fetal membranes

The rupture of fetal membranes is an integral part of the normal labor and is necessary for the delivery of a baby. Normally, the labor starts with the uterine contractions leading to dilatation of the cervix. This is followed by the rupture of fetal membranes, which augments the labor. The amniotic fluid contains a large amount of prostaglandin hormone and the bathing of the cervix with this fluid increases the frequency

and the intensity of the uterine contractions. But in 10 percent of the pregnancies these membranes pathologically rupture more than 1 hour before the onset of the labor, known as premature rupture of membranes (PROM)(21).

The breech in the integrity of the fetal membranes allows the bacteria (which are the normal part of the vaginal flora) to ascend into the uterus leading to an increased risk of maternal and neonatal infections. It also decreases the amount of the amniotic fluid around the fetus, increasing the risk of: cord compression; abnormal lung development; and skeletal deformities. Frequently PROM occurs at term i.e. ≥37weeks gestation and there is a minimal risk of maternal and neonatal complications as the labor usually starts soon after this event. However, in 3 percent of the cases when it occurs before term, commonly known as preterm premature rupture of membranes (PPROM), the risk of maternal and the neonatal complications increases (22).

On the basis of etiology, the preterm premature rupture of membranes (PPROM) can be classified into two types: 'iatrogenic' PPROM (iPPROM) and 'spontaneous' PPROM (sPPROM). Iatrogenic PPROM (iPPROM) is caused by the invasive diagnostic and therapeutic procedures performed during the antenatal period. The surgical defect in the membranes remains patent after the removal of the needle or trocar used during the procedure, leading to amniotic fluid leakage. Usually the leakage is subclinical and the defect heals soon after the procedure, but sometimes the defect persists and the leakage becomes clinically significant, known as iPPROM. It usually occurs in the second trimester, as most of the invasive procedures are performed during this period (23, 24).

Genetic amniocentesis, which is commonly performed for prenatal diagnosis of the fetal chromosomal abnormalities is associated with 1-2 percent risk of iPPROM (25). The

risk is reported to be approximately 4 percent when amniocentesis is performed for a therapeutic purpose e.g. to reduce the maternal discomfort associated with the polyhydramnios (26). iPPROM complicates 9.8 percent of the laser coagulation procedures, performed for management of twin to twin transfusion syndrome (TTTS)(27). The incidence of iPPROM is higher for the more complex fetoscopic procedures, as it has been demonstrated to be 40 percent and 50 percent in cases of tracheal occlusion and umbilical cord ligation procedures, respectively (28, 29).

The exact cause of spontaneous PPROM (sPPROM) is not clearly understood. However, in the medical literature some risk factors have been identified for sPPROM. These include infections including urinary tract infections (UTI), sexually transmitted diseases (STDs), infections of lower genital tract (e.g. bacterial vaginosis); behavioral factors including cigarette smoking, substance abuse, and nutritional deficits; history of preterm birth or PPROM in previous pregnancy; previous history of cervical surgical procedures; incompetent cervix; history of vaginal bleeding in current pregnancy; uterine distension either due to polyhydramnios or multiple gestation; and low socioeconomic status (30).

The pathophysiology of preterm premature rupture of membranes is multifactorial. Several mechanisms have been proposed, but the three most common ones are intrinsic fetal membrane weakness, infections, and genetics. In any given patient, more than one pathophysiologic process may be involved. The intrinsic weakness of the fetal membranes normally occurs near term and may involve one of the three mechanisms. First, the membrane cells undergo programmed cell death (apoptosis). Second, proteolytic enzymes called matrix metalloproteinase (MMP) break down the collagen, which is responsible for

the tensile strength of the membranes. Third, the proteins that bind and cross-link the collagen are altered leading to poor assembly of the collagen. In case of PPROM one or more of these three processes start earlier. In PPROM patients, chemical markers released from apoptosis and the inhibitors of matrix metalloproteinase enzymes have been found in high concentration in the amniotic fluid (31-33).

Infections are thought to be primarily responsible for the premature rupture of membranes, especially when it happens remote from term. The pathogens from lower genital tract infections and sexually transmitted diseases ascend into the cervical canal and cause local inflammation. This inflammation releases proteolytic enzymes including collagenase, elastase, and gelatinase that weaken the membranes and increase their susceptibility to rupture. Furthermore, the prostaglandins released as a result of inflammation cause uterine contractions and increase the shearing stress at the level of internal os of the cervix, leading to membrane rupture (32). Genes related to inflammation and collagen production, play a role in the predisposition of a woman to PPROM.

The clinical course of the pregnancies with PPROM depends upon the gestational age at membrane rupture. Preterm birth is the most frequent consequence of PPROM. Very small number of pre-viable PPROM pregnancies reach term. Approximately 50-60 percent of the pre-viable PPOM women deliver within one week of membrane rupture, 70-75 percent deliver within 2 weeks and 80-85 percent within 4 weeks (34). However, the duration of latency (time period between rupture of fetal membranes and the delivery of the fetus) varies with the gestational age of membrane rupture (35). Like many other studies, Farooqi et al. (36) demonstrated that there is an inverse relationship between the

latency period and the gestational age at PPROM, as shown in figure 2.2 below.

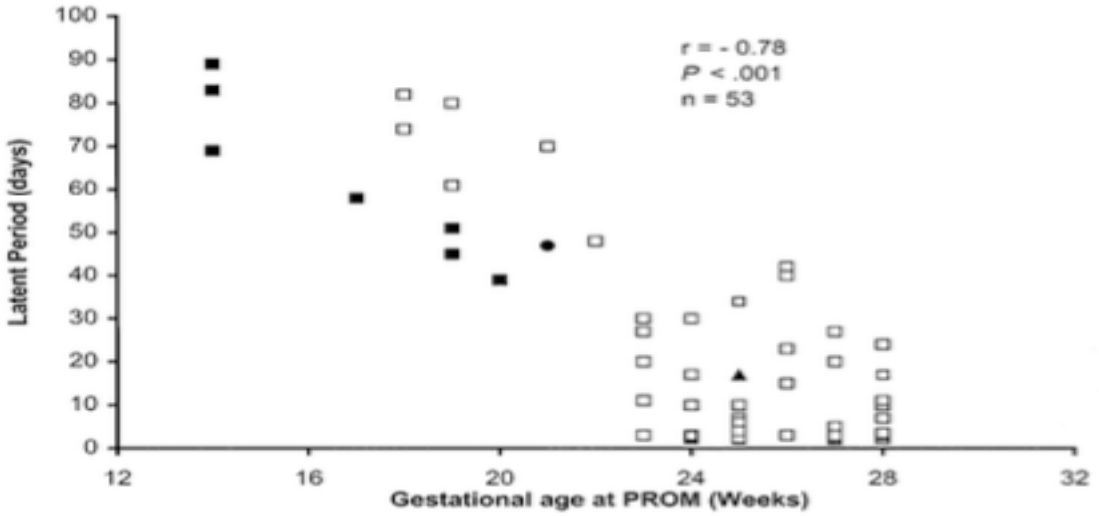

Figure 2.2: Relationship between latency period and gestational age at PPROM.
(Results of a study by Farooqi et al. Open square = neonatal survivors; solid square = deaths due to pulmonary hypoplasia; circle = death due to complication of prematurity; triangle = death due to congenital lethal anomaly)

Pre-viable PPROM results in a number of maternal and neonatal complications. Among maternal complications, chorioamnionitis is the most common, as rupture of fetal membranes allows the vaginal bacteria to enter into the womb. According to Gibbs criteria clinical chorioamnionitis is characterized by the presence of fever, maternal or fetal tachycardia, foul smelling vaginal discharge, uterine tenderness, and leukocytosis (37). In the studies published between 2000-2007, its incidence among pre-viable PPROM women varied between 31-46 percent (11-15). In addition to this, endometritis complicates one of every 10 and sepsis one of every 100 women suffering from pre-viable PPROM. Other maternal complications include preterm birth, cord prolapse, placental abruption, and retained placenta (2).

Neonatal complications are mainly associated with the extreme prematurity. The neonatal morbidity related to prematurity includes: intraventricular hemorrhage (IVH); necrotizing enterocolitis (NEC); sepsis, respiratory distress syndrome (RDS); bronchopulmonary dysplasia (BPD); and retinopathy of prematurity (ROP). The risk of these morbidities decreases and the neonatal survival rate improves with increasing gestational age at the delivery of fetus (1, 2, 6). Figure 2.3 is demonstrating the results of a prospective community based evaluation of 8,523 women, who gave birth between July 1997 and March 1998 at six hospitals in Shelby County, Tennessee. It showed that with every one-week increase in the gestational age at delivery of the fetus, the survival rate improved significantly, especially when delivery occurred before 32 weeks. For the neonatal morbidity, an opposite trend was observed (1).

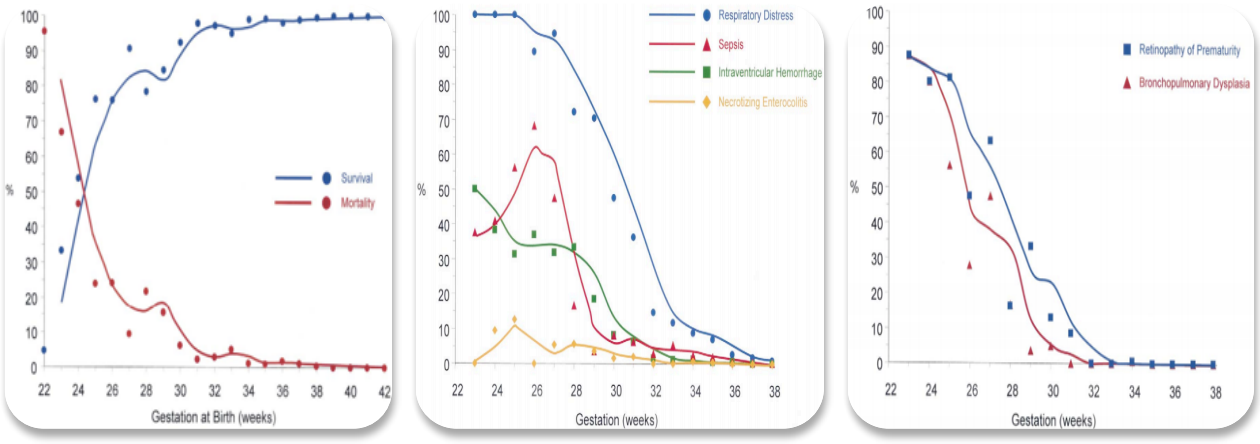

Figure 2.3: Neonatal survival and prematurity related morbidity by gestational age.
(Results of a prospective community based evaluation of 8523 women who gave birth between July 1997 and March 1998 at six hospitals in Shelby County, Tennessee)

Pre-viable PPROM neonates also suffer from the morbidities related to altered pulmonary development including pulmonary hypoplasia and pulmonary hypertension. An adequate amount of the amniotic fluid is essential for the normal fetal lung development,

which occurs in five stages: embryonic; pseudo glandular; canalicular; saccular; and alveolar (38).

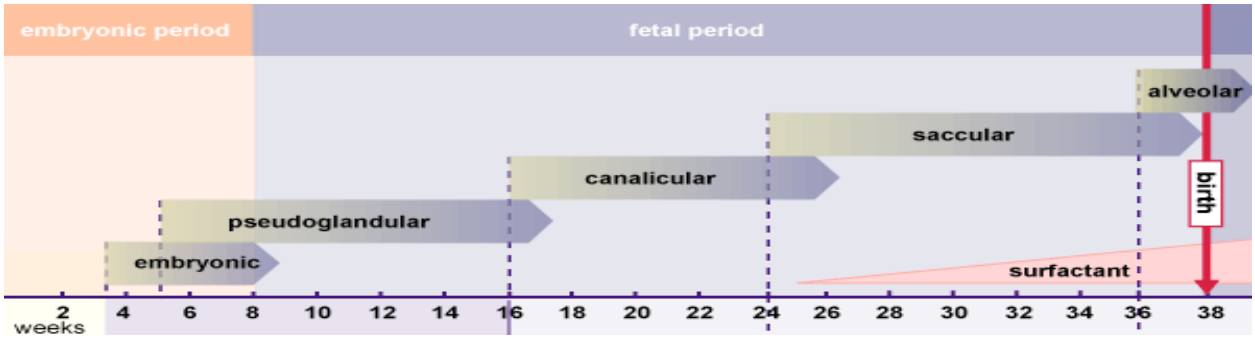

Figure 2.4: Stages of fetal lung development by gestational age

The canalicular phase of the lung development, characterized by the terminal bronchioles development, epithelial differentiation, and the air-blood barrier formation, occurs during 16-25 weeks of gestation (38). Decreased amount of amniotic fluid around the fetus during this critical period leads to decreased number of alveoli (pulmonary hypoplasia) and altered vascular resistance (pulmonary hypertension). Pulmonary hypoplasia is a lethal complication and occurs in 9-20 percent of the pre-viable PPROM neonates and the mortality rate in these neonates ranges between 50-100 percent (2). The risk of pulmonary hypoplasia increases, as the gestational age at membrane rupture decreases and duration of severe oligohydramnios increases (8, 39, 40).

Other neonatal complications associated with oligohydramnios resulting from pre-viable PPROM include potter syndrome like facial abnormalities and skeletal deformities. These occur due to asymmetrical outer growth of the fetus and its inability to freely move the limbs. Neurodevelopmental disabilities including cerebral palsy, mental retardation, delayed speech, and hearing and vision impairments are the long-term neonatal complications of pre-viable PPROM (36, 41).

PPROM also has a large impact on the national health care cost. It affects 120,000 pregnancies in the United States each year and is a major cause of consistently high preterm birth rate in the country (1). The preterm neonates have a very high mortality rate and the surviving preterm neonates bring economic burden to the society due to increased needs of NICU care, hospitalization and re-hospitalization. In 2007, the institute of medicine (IOM) in its comprehensive report called "Preterm birth, causes, consequences, and prevention" estimated that the annual societal economic burden associated with prematurity in the United States was 26.2 billion USD or 51,600 USD per premature infant for the year 2005 (42). These infants also pose financial and emotional burden to their parents and families.

After PPROM, membranes may reseal leading to the cessation of fluid leakage and re-accumulation of a normal volume of the amniotic fluid. This results in term deliveries and good perinatal outcomes. Beydoun and Yasin demonstrated that among pregnancies with documented resealing of PPROM, 78 percent delivered at term (43). Unfortunately membrane resealing after PPROM is an uncommon situation. The incidence of resealing after mid-trimester PPROM, was reported to be 9.7 percent by Schucker et al. (34) and 7.7 percent by Fortunato et al. (44). However, iatrogenic PPROM reseals more frequently and is associated with better pregnancy outcomes. A study by Gold et al. reported that 1.2 percent (7 out of 603) of the women undergoing genetic amniocentesis suffered from mid-trimester PPROM and all 7 of them demonstrated membrane resealing within one week of the procedure (45).

The management of pre-viable PPROM involves two options: (1) Termination of pregnancy or (2) Expectant management. In termination of pregnancy (TOP), dilatation and evacuation (D&E) or induction of labor (IOL) is done due to a high risk of maternal and neonatal complications and poor neonatal survival associated with pre-viable PPROM. In expectant management, the pregnancy is allowed to continue based on the fact that few pregnancies with pre-viable PPROM result in a healthy baby with no long-term sequelae. In this type of management, the suffering women are initially admitted in a hospital. They are given prophylactic antibiotics and monitored for the signs of infection, labor and vaginal bleeding. If there are no such signs, the patients are discharged with the advice of strict bed rest. They are counseled to report back to the hospital if they develop fever, vaginal bleeding, or uterine contractions. An ultrasound to assess the amniotic fluid volume and fetal growth is performed weekly. These patients are re-admitted at 24 weeks gestation. They are given corticosteroids for fetal lung maturity and kept admitted for feto-maternal monitoring till the delivery of the baby.

The choice between the two management options is a real challenge. These days, in order to practice evidence-based medicine, physicians follow the clinical practical guidelines (CPGs) to make medical decisions. These are, as defined by the Institute of medicine (IOM) Committee on Standards for developing Trustworthy Clinical Practical Guidelines, "…statements that include recommendations intended to optimize patient care. They are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options"(46).

Unfortunately, as mentioned in the previous chapter, there are no clear guidelines available for the management of PPROM at a pre-viable gestation. According to IOM committee, the experts develop CPGs on the basis of good quality systematic reviews. An UpToDate and methodologically sound systematic review on the risks and benefits associated with the two management options will be a step towards developing the guidelines for this critical condition.

CHAPTER 3: METHODS

I performed a systematic review of the published literature on the pregnancy outcomes following expectant management of preterm premature rupture of membranes before 24 weeks gestation (pre-viable PPROM), by applying the standards recommended by the Institute Of Medicine (IOM) Committee On Standards For Systematic Reviews of Comparative Effectiveness Research (19). According to this committee, following four steps are involved in conducting an effective systematic review,

- Initiating a systematic review
- Finding and assessing individual studies
- Synthesizing the body of evidence
- Reporting a systematic review

INITIATING A SYSTEMATIC REVIEW:

I started my study with a research question that was formulated using "the PICO model for clinical questions"

P = Population: Pregnant women having preterm premature rupture of membranes (PPROM) before 24 weeks gestation

I = Intervention: Expectant management

C = Comparison: none

O = Outcomes: neonatal survival to hospital discharge, and maternal and neonatal morbidity

My main research question was, "what are the pregnancy outcomes of the women suffering from preterm premature rupture of membranes before 24 weeks gestation following expectant management?"

FINDING AND ASSESSING INDIVIDUAL STUDIES:

The IOM committee recommends six standards to identify and assess the studies to be included in a systematic review. These are: I) conducting a comprehensive systematic search for evidence; II) taking action to address potentially biased reporting of research results; III) screening and selecting studies; IV) documenting the search; V) managing the data collection; and VI) critically appraising each study.

Search Strategy:

I searched PubMed database to identify the individual studies that would make the body of evidence of my review. To design my search strategy, I worked with Miss Linda Murphy, an experienced librarian at University of California Irvine, to ensure an accurate search. The database was accessed in August 2017 using the PubMed search strategy as shown in the table 3.1.

Table 3.1: Search strategy used to search PubMed database

Search	Query	Items found
#1	Pregnancy outcomes OR pregnancy outcome OR outcomes OR outcome OR neonatal outcome OR neonatal outcomes OR maternal outcomes OR maternal outcome	1933936
#2	Preterm premature rupture of membranes OR Premature rupture of membranes OR Preterm prelabour rupture of membranes OR preterm prelabor rupture of membranes OR Preterm premature rupture of fetal membranes OR Premature rupture of fetal membranes OR Preterm prelabour rupture of fetal membranes OR preterm prelabor rupture of fetal membranes OR Preterm premature rupture of amniotic membranes OR Premature rupture of amniotic membranes OR Preterm prelabour rupture of amniotic membranes OR preterm prelabor rupture of amniotic membranes OR prelabour rupture of membranes OR prelabor rupture of membranes OR prelabour rupture of amniotic membranes OR prelabor rupture of amniotic membranes OR prelabour rupture of fetal membranes OR prelabor rupture of amniotic membranes OR PPROM	9132
#3	Midtrimester OR midtrimesters OR mid-trimester OR second trimester OR second trimesters OR Pregnancy Trimester, Second OR pre-viable OR previable OR pre-viable gestation OR previable gestation OR before viability OR near viability OR before 24 weeks OR <24wk OR "24 weeks"	277598
#4	#1 AND #2 AND #3 Filters: published in the last 10 years; Humans; English	373

As, my plan was to review only the recent studies, published in the past ten years to report the outcomes of pre-viable PPROM under current/advanced neonatal and maternal healthcare, I applied the filter "published in the last ten years." Further, the search results were filtered for humans and English language only. In addition, I examined the reference lists of all the studies identified by the above mentioned search strategy to find the additional studies fulfilling the inclusion and exclusion criteria that were missed by the database search.

Eligibility Criteria:

For the selection of individual studies, I used following inclusion and exclusion criteria,

Inclusion Criteria:

Studies reporting the outcomes (maternal, neonatal) of pregnancies, complicated by preterm premature rupture of membranes before 24 weeks of gestation (pre-viable PPROM) were included

Exclusion Criteria:

Studies were excluded if they: a) were the review articles with no original data; b) were single case studies; c) studied pregnant women with a particular characteristic (for example, with oligohydramnios or cervical cerclage in situ); d) were conducted to evaluate the effect of a particular intervention (for example, antibiotics, steroids, Amniopatch, or Transabdominal Amnioinfusion) on perinatal outcomes; e) only included PPROM patients with prolonged latency period (more than 5 days, as these patients would have better pregnancy outcomes). The literature showed that some studies reported on pregnancy outcomes of mid-trimester PPROM (PPROM occurring at 14-28 weeks gestation) that in addition to women with PPROM at <24 weeks had also included women in whom rupture

of membranes occurred late in the second trimester (e.g., studies assessing outcomes of PPROM at 14-27 weeks, 18-26 weeks, etc.). Out of these, I excluded the studies that provided the aggregate data, from which the subjects having PPROM at < 24 weeks (viability limit) gestation could not be distinguished from those with PPROM occurring at a later gestation. I excluded these studies, as they would reflect better pregnancy outcomes due to higher gestational age at PPROM.

Study Selection:

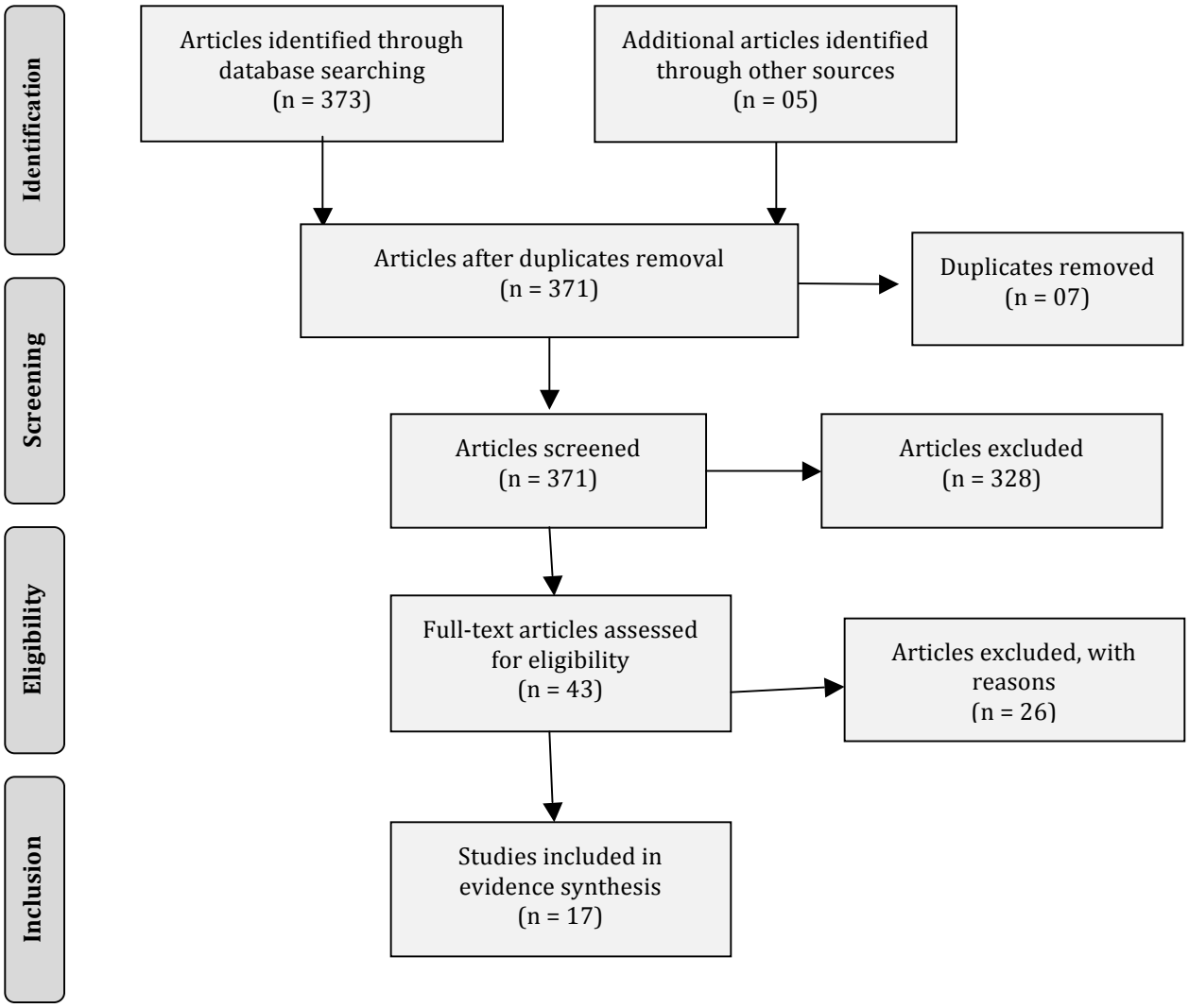

Figure 3.1: Flow chart showing the stages of study selection process

Using the search strategy mentioned in table 3.1 a total 373 articles were identified. After examining the reference lists of these 373 articles, another 5 studies were found. Figure 3.1 above demonstrates the whole process of study selection.

As recommended by the Committee on Standards for Systematic Reviews of Comparative Effectiveness Research, I used two-step approach for screening and selection of the articles. First, I screened the titles and abstracts of the studies identified in the original search and selected 43 articles that were studying the pregnancy outcomes in women with PPROM near the limit of fetal viability. Then, I retrieved the full text articles of these studies using University of California Irvine library system. After reading the full text articles, I excluded those studies that did not meet the inclusion and exclusion criteria.

A total 26 studies were excluded based on inclusion and exclusion criteria. Seven studies were excluded as they assessed the effect of a particular intervention (amnioinfusion, amniopatch, antibiotics & steroids) on PPROM outcomes (47-53). Dotters-Katz et al. did not provide the data on the maternal and fetal outcomes, we were interested in (54). Five studies only included women with prolonged latency period (55-59). Newman et al. only included those pre-viable PPROM women that delivered between 23-27 weeks (60). van Teeffelen et al. reported the perinatal outcomes of only those pre-viable PPROM pregnancies that continued beyond 22 weeks (61). Eight studies provided the aggregate data from which the data for the pregnancies with PPROM at less than 24 weeks gestation could not be distinguished (62-69). Three studies were conducted only in those pre-viable PPROM women, who had oligohydramnios (70-72). Finally, 17 studies were selected after full text articles review (73-89).

Assessment of Quality of Individual Studies:

To ensure inclusion of only quality studies in the systematic review, I assessed the quality of the 17 selected studies using Newcastle-Ottawa Quality Assessment Scale for Cohort Studies (90). All of them were of good quality according to this scale and were finally included in the systematic review.

SYNTHESIZING THE BODY OF EVIDENCE:

Study Variables:

The variables of my study included,

Primary outcome:

The neonatal survival to discharge following expectant management was the primary outcome of my research.

Secondary Outcomes:

The secondary outcomes of my study were,

- Neonatal Morbidity following expectant management: including pulmonary hypoplasia, bronchopulmonary dysplasia (BPD), respiratory distress syndrome (RDS), neonatal sepsis, intra-ventricular hypoplasia (IVH), periventricular leukomalacia (PVL), necrotizing enterocolitis (NEC), retinopathy of prematurity (ROP), and limb contractures.
- Maternal Morbidity following expectant management: including chorioamnionitis, endometritis, maternal sepsis, cord prolapse, retained placenta, placental abruption, and caesarean delivery.
- The proportion of pre-viable PPROM women opting for the termination of their pregnancies (TOP) instead of expectant management

In addition, data was collected on:

- Factors influencing neonatal survival, maternal and the neonatal morbidity associated with pre-viable PPROM pregnancies, and to identify predictors for better outcomes for these pregnancies
- Factors influencing the affected parents' decision to opt for TOP instead of expectant management
- The latency period, which provided the information regarding the clinical course of the pregnancies suffering from pre-viable PPROM

Data Collection Process:

I thoroughly read each of the 17 studies selected for my review and collected the data for the basic characteristics of these studies and the primary and secondary outcomes of my research in the form of tables (as shown in the chapter 4).

Data Analysis:

The categorical variables of my paper including neonatal survival to discharge, maternal and neonatal morbidity, and TOP were presented in the form of number and percentage. The latency period, a continuous variable, was presented as mean or median.

Then, I combined the results of the included studies to provide the overall estimate of the impact of pre-viable PPROM on the pregnancy outcomes.

REPORTING THE REVIEW:

To report my review, I used the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist. This checklist provided 27 items that should be included in a well-conducted systematic review (91). This checklist is shown in the table 3.2.

Table 3.2: PRISMA Checklist

TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).
DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

CHAPTER 4: RESULTS

Basic Characteristics of the Studies:

The review included 17 articles (73-89), which reported the neonatal and maternal outcomes of 1,319 pre-viable PPROM women treated at the tertiary care centers in 10 developed countries following expectant management. The summary of the basic characteristics of all of these studies is shown in table 4.1. The selected studies varied in their inclusion and exclusion criteria. All of them assessed the pregnancy outcomes of only those PPROM women in whom membranes ruptured before 24 weeks gestation (pre-viable PPROM), with the exception of Esteves et al. (80) and van der Heyden et al. (84). These two studies also included the women with PPROM at higher gestations as well, but for this review, data was extracted only for the subjects with PPROM at <24 weeks, as I specifically wanted to report the outcomes associated with pre-viable PPROM. Half of the studies included only the singleton pregnancies (74, 77, 78, 80, 83, 86, 89); two studies only the twin pregnancies (76, 87); while rest of them had both (73, 75, 79, 81, 82, 84, 85, 88). Some studies included the patients with iatrogenic PPROM (75, 78, 84, 87, 88) and others excluded them. Majority of these studies excluded women with fetal anomaly, intrauterine fetal demise (IUFD), chorioamnionitis or active labor.

In these studies, the gestational age of the patients was established on the basis of either the last menstrual period (LMP) or the first trimester ultrasound. The diagnosis of PPROM was based on a typical history of fluid leakage and a sterile speculum examination confirmed by reduced amniotic fluid on ultrasound, a positive PROM test (Nitrazine test, Ferning test, Diamine oxidase test, Amni-Sure test, IGFBP-1 assay), or a combination of both. The patients were counseled regarding the risks and benefits of the expectant

management and allowed to choose between TOP and expectant management. However, the option for TOP was not available at the centers studied by Linehan et al. (74) and McLaughlin et al. (75).

Table 4.1: Basic characteristics of the included studies

Reference (PPROM, wk.)	Publication year (Study period) (Country)	Exclusion criteria	Expectantly Managed Women (fetuses)	No of twins	No of iatrogenic PPROM
Kibel et al. (20-24)	2016 (2004-2014) (Canada)	Major Fetal anomaly Termination of pregnancy Active labor/Chorioamnionitis Fetal distress Placental abruption	90(104)	14	-
Linehan et al. (14-23^{+6})	2016 (2007-2012) (Ireland)	Delivery within 24 hours of membranes rupture	42(42)	Nil	-
McLaughlin et al. (<24)	2016 (2007-2011) (Australia)	Termination of pregnancy	106(106)	-	5
Wagner et al. (<24)	2016 (2005-2015) (Germany)	Fetal anomaly Iatrogenic PPROM Multiple gestation	69(69)	Nil	Nil
Wagner et al. (<24)	2016 (2005-2015) (Germany)	Fetal anomaly Iatrogenic PPROM Monochorionic Twins Unclear chorionicity	27(54)	27	Nil
van der Marel et al. (<24) <20 wk. >20 wk.	2016 (2002-2011) (Netherland)	Fetal anomaly	121(125) 42(44) 79(81)	25*$^{\Phi}$	-
Esteves et al. (18-26) 18-20 20^{+1}-22 22^{+1}-24 24^{+1}-26	2016 (2005–2011) (Brazil)	Multiple gestation Fetal anomaly/ IUFD Termination of pregnancy Previous abortion attempts Signs of active labor Signs of infection	61(61) 16(16) 10(10) 14(14) 21(21)	Nil	-
van der Heyden et al. (13-27) 13-19^{+6} 20-23^{+6} 24-27	2013 (1994-2009) (Netherland)	Lethal Fetal anomaly Active labor Cervical insufficiency	305(336) 89(97) 96(101) 120(138)	25+3$^{\$}$ 08+0$^{\$}$ 05+0$^{\$}$ 12+3$^{\$}$	33

Reference (PPROM, wk.)	Publication year (Study period) (Country)	Exclusion criteria	Expectantly Managed Women (fetuses)	No of twins	No of iatrogenic PPROM
Verspyck et al. (14-24)	2013 (2000-2010) (France)	Fetal anomaly, Multiple gestation	83(83)	Nil	-
Acaia et al. (14-23^{+6})	2013 (2000-2009) (Italy)	Multiple gestation Active labor/chorioamnionitis Severe PV Bleeding Delivery within 24 hours	85(85)	Nil	27*
Hunter et al. (16-24)	2012 (2001-2007) (Australia)	Preterm labor before PPROM Fetal anomaly leading to TOP IUFD before PPROM	126(146)	20	-
Margato et al. (<24) 14-19 20-24	2012 (1996-2008) (Brazil)	-	31(32) 17(17) 14(15)	1 0 1	-
Storness-Bliss et al. (<24) AFI<1cm AFI≥1cm	2012 (2002-2011) (Canada)	Fetal anomaly/ IUFD Iatrogenic PPROM Multiple gestation Active labor/chorioamnionitis Delivery within 48 hours	22(22) 12 10	Nil	Nil
Deutsch et al. (18-23^{+6})	2010 (2000-2007) (USA)	Fetal anomaly, Termination of pregnancy, Active labor/chorioamnionitis Delivery within 12 hours	105(108)	3	
Zajicek et al. (13-20)	2010 (2003-2009) (Israel)	Termination of pregnancy	3(6)	All	1
Chauleur et al. (14-23^{+6}) Spontaneous Iatrogenic	2009 (1999-2004) (France)	-	25(29) 12(13) 13(16)	4	13
Manuck et al. (<24)	2009 (2001-2007) (Canada)	Fetal anomaly/ IUFD Termination of pregnancy Iatrogenic PPROM Multiple gestation Signs of chorioamnionitis Delivery within 12 hours	159(159)	Nil	Nil

* Based on total pre-viable PPROM women, undergoing either expectant or active management
Φ among co-twins, the data was recorded only for the twin, whose gestational sac was ruptured
$ Triplet pregnancies

The women who opted for expectant management were monitored for signs of infection and/or labor and their pregnancies were allowed to continue. In majority of these studies prophylactic antibiotics were routinely given except for two studies where antibiotics were only given if there was a clinical or a laboratory evidence of infection (82, 88). Patients were given corticosteroids once they reached the limit of fetal viability, i.e. 24 weeks. Tocolytics were used in three studies (78, 84, 85) for preterm labor in the absence of signs of chorioamnionitis, whereas, tocolytics were not used in the rest of the studies. Pregnancies were allowed to proceed as close to term as possible in most of the studies, however in some, (73, 76, 77, 80) patients were induced for delivery upon reaching 32-35 weeks of gestation.

Latency Period of pre-viable PPROM Pregnancies Following Expectant Management:

The latency period i.e. the interval between PPROM and delivery varied widely among the included studies. It was difficult for me to assess the overall latency period for all the subjects under study, as these studies used different approaches to present their data for the latency period ranging between mean ±SD to median (IQR) as demonstrated in the table 4.2. However, we can see that for the studies that presented the latency period as mean (73, 74, 79, 82, 83, 86, 87, 89), it varied between as small as 13 days in case of Linehan et al. to as large as 43 days in case of Storness-Bliss et al. In these studies, the GA at PPROM ranged between 14-22.6 weeks and the GA at delivery ranged between 20.7-28.8 weeks. On the other hand, for the studies presenting the latency period as median (75-77, 80, 81, 84, 85, 88), it ranged between 9-35 days. For these studies, GA at PPROM and delivery varied between 20.3-22.1weeks and 24.3-25.1 weeks, respectively.

Table 4.2: Latency Period of pre-viable PPROM women after expectant management

Reference (PPROM, wk.)	GA at PPROM (Weeks)	GA at Delivery (Weeks)	Latency period (Days)
Kibel et al. (20-24)[a]	22.6±1.0	24.8±2.6	15.3±18.3
Linehan et al. (14-23^{+6})[b]	18(15^{+5}-23^{+6})	20^{+5}(17^{+4} – 29^{+4})	13(1.1–85)
McLaughlin et al. (<24)[d]	22^{+1}(13^{+1}-23^{+6})	24^{+2}(17^{+4}-38^{+4})	09(0-157)
Wagner et al. (<24)[e] Delivered <24wk. Delivered >24wk.	 20.0(18.0 – 21.7) 22.3(20.1 – 23)	 21.4(19.3 – 22.6) 27.7(25.3 – 30.9)	 04(1.0 – 9.0) 49.5(24.3-74.5)
Wagner et al. (<24) [e] Delivered <24wk. Delivered >24wk.	20.4(17.9-22.4) 20.1(18.7-22.0) 22.1(17.9-23.4)	- 21.4(19.9-22.1) 26.4(25.4-30.0)	19.0(3.0-43.0) 1.5(0.0-8.0) 35.0(21.0-73.0)
van der Marel et al. (<24) [d] <20 wk. >20 wk.	20.3(12.4 – 23.9) 17.7(12.4 – 19.9) 22.5(20.0 – 23.9)	25.1 23.1(15.3 – 36.7) 25.3(21.0 – 35.9)	17.5 35(0 – 136) 12(0 – 103)
Esteves et al. (18-26) [d] 18-20 20^{+1}-22 22^{+1}-24	 - -	 21^{+6}(18^{+1}-30^{+0}) 22^{+6}(20^{+4}-30^{+7}) 25^{+5}(22^{+2}-28^{+6})	 19(1-77) 14(1-75) 16(1-44)
van der Heyden et al. (13-27)[e] 13-19^{+6} 20-23^{+6}	 - -	 24.1±6.8 26.1±3.4	 - -
Verspyck et al. (14-24)[c]	20.3	26.5	-
Hunter et al.[e¥] 16-20 20^{+1}-24	 19^{+2}(18^{+4}-19^{+6}) 22^{+4}(21^{+2}-23^{+3})	 21^{+5}(20^{+4}-27^{+1}) 23^{+5}(22^{+1}- 25^{+2})	 18(5-56) 7(2-14)
Margato et al. (<24)[b] 14-19[a] 20-24[a]	19(14-23) 16.9±1.67 22.1±1.5	24(16-39) 22±6 27±5.5	35(0-137) 39±40 40±34
Storness-Bliss et al. (<24)[c] AFI<1cm AFI≥1cm	18.5 18 19	25 22.9 27.5	43 32 57
Deutsch et al. (18-23^{+6})[c]	-	-	(5.5-24.3)
Zajicek et al. (13-20)[c]	14	28.8	15.3
Chauleur et al. (14-23^{+6})[d*] Spontaneous Iatrogenic	21(15-23^{+6}) 21+1(15-23^{+6}) 21(15-23^{+5})	 24(17-28^{+3}) 28(18^{+4}-39^{+1})	35(1-163) 23.5(1-94) 43(1-163)
Manuk et al. (<24)[a]	20.7±2.6	25.6±4.3	

a. Mean ± SD; b. mean (range); c. mean; d. median (range); e. median (IQR)
¥ Data was obtained only from singleton pregnancies
* Data was collected for all pre-viable PPROM women following either expectant management or TOP

The data of the included studies demonstrated that the duration of latency period has a strong association with the gestational age at membrane rupture. Two studies showed that the latency period was significantly longer for the women with early pre-viable PPROM (before 20 weeks) than those with late pre-viable PPROM (after 20 weeks)(81, 85). The study by Kibel et al. reported that the latency period decreased with increasing gestational age at rupture. For PPROM at 20, 21, 22, and 23 weeks the latency period was 22.9±28.3 days, 18.6±22.5 days, 18.3±18.0 days, and 10.5±13.3 days, respectively (73). Similar trend was noted in the studies conducted by van der Heyden et al. and Deutsch et al. (79, 84). However, this association between the latency period and the gestational age at PPROM was not found by Esteves et al., where this interval was 19, 14, and 16 for the women with PPROM at 18-20, 20-22, and 22-24 weeks of gestation, respectively ($p = 0.5$)(80).

The latency period in pre-viable PPROM women also seems to have an association with oligohydramnios and multiple gestations. Storness-Bliss et al. demonstrated that the mean latency to delivery was significantly lower for oligohydramnios group (32 vs. 57 days, $P=0.014$) than the non-oligohydramnios group, although the gestational age at rupture was similar in both groups (18 vs. 19 weeks) (83). On the basis of two similar studies (one on singleton and the other on dichorionic diamniotic twin pregnancies) conducted by Wagner et al., they stated that the latency period following pre-viable PPROM appeared to be smaller for the dichorionic twin pregnancies compared to their singleton counterparts (76, 77).

Two of the included studies showed that the women suffering from iatrogenic PPROM delivered at a later gestational age than those with spontaneous PPROM (84, 88). Chauleur et al. compared the iatrogenic and spontaneous cohorts having pre-viable PPROM at similar gestations (21^{+1} vs. 21, p = 0.68). They demonstrated that both, the gestational age at delivery (28 vs. 24 p =0.05) as well as the latency period (43 vs. 23.5 p = 0.08) were higher in the iatrogenic cohort. However, in this study the difference in latency period between two groups was not statistically significant, which might be attributable to the small sample size of the study leading to type II error (88).

Neonatal Survival to Discharge after expectant management:

This was the primary outcome of my study. In my review, I studied 1,355 fetuses that suffered from pre-viable PPROM and underwent the expectant management. Among them, 899 (66.3%) neonates were born alive. 342 of these live born neonates died during their stay in ICU. Hence, the overall neonatal survival to discharge rate was **41.1 %** (557/1355). For the studies that studied only the singleton pregnancies, the survival to discharge rate was **44.6 %** (266/596). The table 4.3 below is demonstrating the data on the neonatal survival for the studies included in my review.

Several factors have been described in these studies present at the time of admission to a medical facility, which can be used to predict the neonatal survival rate of pre-viable PPROM pregnancies. These include gestational age at PPROM, oligohydramnios, the etiology of PPROM either iatrogenic or spontaneous, and the C-reactive protein level on the first day of presentation. These factors may assist obstetricians in counseling of these women.

Table 4.3: Neonatal survival after expectant management of pre-viable PPROM

Reference (PPROM, wk.)	No of Fetuses (n)	Total Live born n (%)	Survival to Discharge n (%)
Kibel et al. (20-24)	104	66 (63.5)*	51 (49.0)
Linehan et al. (14-23^{+6})	42	10 (23)	2(4.76)
McLaughlin et al. (<24)	106	75(70.7)	39(37)
Wagner et al. (<24)	69	40(58)*	38(55)
Wagner et al. (<24) PPROM Twins Non-PPROM Twins	54 27 27	34(63) 17(63) 17(63)	31(57.4) 15(55) 16(59)
van der Marel et al. (<24) <20 wk >20 wk	125 44 81	87(69.6) 24(54.5) 63(77.8)	48 (38.4) 10 (22.7) 38 (46.9)
Esteves et al. (18-24) 18-20 20^{+1}-22 22^{+1}-24	30 16 10 14	22(73.3) 4(25.0) 5(50.0) 13(92.8)	11(36.7) 3(18.7) 2(20.0) 6(42.8)
van der Heyden et al. (13-23^{+6}) 13-19^{+6} 20-23^{+6}	198 97 101	121(61.1) 50(51.5) 71(70.3)	67(33.8) 28 (28.9) 39 (38.6)
Verspyck et al. (14-24)	83	46 (55.4)	38$^{\Phi}$ (45.8)
Acaia et al. (14-23^{+6})	85	49(57.6)	42$^{\Phi}$ (49.4)
Hunter et al. ¥ (16^{+0}-24^{+0}) 16^{+0}-20^{+0} 20^{+1}-24^{+0}	106 24 82	57(53.8) 09(38) 48(58)	36(34) 04 (17) 32(39)
Margato et al. (<24) 14-19 20-24	32 17 15	18(56.2) 07(41.2) 11(73.3)	11 (34.4) 03 (18) 08 (53)
Storness-Bliss et al. (<24) AFI<1cm AFI≥1cm	22 12 10	22 12 10	07(31.8) 01 (8.3) 06(60.0)
Deutsch et al. (18-23^{+6})	108	98(90.7)	28 (25.9)
Zajicek et al. (13-20)	6	5(83.3)	5(83.3)
Chauleur et al. (14-23^{+6}) Spontaneous Iatrogenic	29 13 16	17(59) 06(46.1) 11(68.7)	14 (48) 03(23.1) 11(68.7)
Manuk et al. (<24)	159	112(70.4)	89 (56)
Overall survival for PPROM <24 weeks	**1,355**	**899(66.3)**	**557(41.1)**
Survival for PPROM <24 weeks for studies with singleton pregnancies only	596	376(63.1)	266(44.6)

* Does not include neonates delivered at <24 weeks and were alive
$^{\Phi}$ Survival beyond neonatal period
¥ Data obtained only from singleton pregnancies

The gestational age at which the membranes rupture is the single most important factor that determines the neonatal survival to discharge. Most of the included studies showed that the survival to discharge rate improved significantly with increasing gestational age at PPROM (78, 80, 84). van der Marel et al. (85) studied a cohort of 125 fetuses. They demonstrated that the neonatal survival to discharge was significantly better in women with PPROM at >20weeks than those with PPROM at <20 weeks (46.9 vs. 22.7 %, p = 0.008). This association remained significant after adjusting for the potential confounders in a multivariable analysis (adjusted OR: 9.78, 95% CI: 1.85-51.66). Similar association of improved survival with PPROM at >20 weeks was demonstrated by two other studies as well (81, 82). According to Hunter et al., "The adjusted hazard ratio for survival to discharge was 0.42 times lower for the early (<20 weeks) pre-viable PPROM group compared with the late (>20 weeks) pre-viable PPROM group (95% CI: 0.21–0.83, p = 0.012)" (81). Kibel et al. and Deutsch et al. reported that the improved survival was significantly associated with the gestational age at PPROM >22 weeks (73, 79).

Oligohydramnios seems to be the second most important predictor of neonatal survival to discharge. This association has been described by four studies included in our review (78, 81, 83, 89). In 2012, Storness-Bliss et al. compared the perinatal outcomes between pre-viable PPROM women with oligohydramnios with those without oligohydramnios. They reported that the take home baby rate was seven times lower in the oligohydramnios group compared to the other group (8.3% vs. 60 %, P = 0.02)(83). Hunter et al. demonstrated that amniotic fluid index level is a poor predictor (area under ROC: 0.649, 95% CI:0. 532–0.766) of neonatal survival to discharge (81). Acaia et al. study showed that the oligohydramnios was a significant predictor of neonatal survival to

discharge (p = 0.041)(78). Another study showed that among the neonates admitted to ICU, presence of anhydramnios was frequently encountered in those who died during their stay in ICU than those who survived (53% vs. 32%, P = .014)(89). However, a recent study did not find any significant association between oligohydramnios and neonatal survival (73).

Two studies described a positive association between iatrogenic etiology of PPROM and neonatal survival (78, 88). Chauleur et al. reported that the survival to discharge rate was significantly better in the iatrogenic PPROM group than the spontaneous PPROM group (69% compared to 23%)(88). One of the reviewed studies also reported that the CRP level within 24 hours of admission was a significant predictor of poor neonatal survival to discharge (78).

Furthermore, some other factors that are not present at the time of presentation of pre-viable PPROM patients to a hospital facility, but can predict the neonatal survival once the baby is born, have also been described by some studies. Three studies demonstrated that gestational age at delivery was significantly associated with neonatal survival to discharge (73, 78, 89). Two studies described the latency period to be a predictor of neonatal survival (73, 81). McLaughlin et al. reported that the birth weight of a newborn was significantly associated with its survival during the neonatal period (p = 0.031)(75).

Neonatal Morbidity:

Almost all of the included studies provided data on the neonatal morbidity. The data on pulmonary hypoplasia, the neonatal morbidity that is specifically associated with the pre-viable PPROM, is shown in table 4.4. This data showed that among the neonates born alive after pre-viable PPROM, the rate of the pulmonary hypoplasia varied between 0.0-16.3%.

Table 4.4: Pulmonary hypoplasia in pre-viable PPROM

Reference	(n)*	Pulmonary Hypoplasia$
Linehan et al.	10	1(10.0)
McLaughlin et al.	75	6(8.0)
Wagner et al.	40	2(5.0)
van der Heyden et al.	121	11(9.1)
Verspyck et al.	46	2(4.3)
Acaia et al.	49	8(16.3)
Margato et al.	32	4(12.5)
Zajicek et al.	05	0(0.0)
Manuk et al.	112	14(12.5)
Total~	490	44(9.8)

*No of neonates born alive in all studies except by Margato et al., where it is total no of fetuses following expectant management
~ Does not include Margato et al. data
$ All values are number (percent)

The gestational age at PPROM and AFI levels have been described as factors in predicting the risk of pulmonary hypoplasia in neonates delivered after pre-viable PPROM. One study reported that the gestational age at PPROM was significantly lower in the neonates suffering from pulmonary hypoplasia than those who did not experience this morbidity (18.9 vs. 20.9 weeks, P =0.006). In this study the rate of pulmonary hypoplasia was 13% among live born neonates. The data demonstrated that the rate of pulmonary hypoplasia decreased by 21% with every one-week increase in the PPROM gestational age (89). The study by Margato et al. demonstrated that 12.5% pre-viable PPROM fetuses developed pulmonary hypoplasia and all were born to mothers with PPROM at <20 weeks gestation (82). Manuck et al. reported that 71% of the pre-viable PPROM neonates with pulmonary hypoplasia had oligohydramnios during their intrauterine life.

The data on the rest of the neonatal morbidities is shown in table 4.5. There was a variation among studies in evaluating this outcome. Most of the studies assessed the morbidity among neonates that were born alive or admitted to NICU (74, 76, 77, 85, 86, 88, 89). However, some studies observed this outcome among neonates that survived beyond early neonatal (84) or neonatal period (78), or till the hospital discharge (73, 75, 80, 87).

Table 4.5: Neonatal morbidity after expectant management of pre-viable PPROM*

Reference	n	BPD	RDS	Sepsis	IVH	PVL	NEC	ROP	Contractures	Hospital stay (days)	Intact Survival
Kibel et al.[a]	51	11 (21.6)	-	7 (13.7)	-	-	3 (5.9)	6[£] (11.8)	15 (29.4)	63	27 (53)
Linehan et al. [b]	10	-	7 (70.0)	3 (30.0)	3 (30.0)	-	2 (20.0)	-	-	35	0 (0)
McLaughlin et al.[a]	39	19 (47)	-	17 (43.6)	0[£] (0.0)	0 (0.0)	1 (2.6)	2[£] (5.1)	-	-	-
Wagner et al.[b]	40	13 (32.5)	-	-	-	1 (2.5)	3 (7.5)	7[¥] (17.5)	-	67	22 (55)
Wagner et al. [b] PPROM twins	17	5 (29.4)	-	-	1 (5.9)	1 (5.9)	6 (35.5)	3 (17.6)	-	72	7 (41.2)
Non-PPROM twins	17	0 (0)	-	-	1 (5.9)	0 (0.0)	1 (5.9)	3 (17.6)	-	72.5	12 (70.6)
van der Marel et al. [c]	68[$]	25/60 (41.7)	39/66 (59.1)		5/68 (7.3)		4/67 (6.0)	7/43 (16.2)	14/66 (21.2)	46	
<20 wk.	18[$]	7/18 (38.9)	12/18 (66.7)	-	0/18 (0.0)	-	0/17 (0.0)	0/9 (0.0)	10/17 (58.8)	30	-
>20 wk.	50[$]	18/42 (42.9)	27/48 (56.2)		5/50 (10.0)		4/50 (8.0)	7/34 (20.6)	4/49 (8.2)	56	
Esteves et al. [a]											
(18-24)	11	-	-	-	-	-	-	-	-	-	3(27.3)
18-20	3	-	-	-	-	-	-	-	-	-	1(33.3)
20-22	2	-	-	-	-	-	-	-	-	-	1(0.5)
22-24	6	-	-	-	-	-	-	-	-	-	1(16.67)
van der Heyden et al.[e]	69	10 (14.5)	20 (29.0)	05 (7.2)	08 (11.6)		02 (2.9)		-		44 (63.8)
(13-23[+6])	28	3 (10.7)	3 (10.7)	1 (3.6)	0 (0.0)	-	1 (3.6)	-		-	24 (85.7)
13-19[+6]	41	7 (17.1)	17 (41.5)	4 (9.8)	8 (19.5)		1 (2.4)				20 (48.8)
20-23[+6]											
Verspyck et al. [b]	44[$]	14/29 (48.3)	32/44 (72.7)	-	0/31[£] (0.0)	0/31 (0.0)	3/31 (9.7)	0/35[¶] (0.0)	8/35 (22.9)	-	-
Acaia et al.[d]	42	7 (16.7)	11 (26.2)	6 (14.2)	3 (7.1)	-	6[¥] (14.2)	3[£] (7.1)		25	23 (54.8)
Margato et al.[f]	32	-	-	7 (21.9)	3 (9.4)	-	-	-	-	-	-

Reference	n	BPD	RDS	Sepsis	IVH	PVL	NEC	ROP	Contractures	Hospital stay (days)	Intact Survival
Deutsch et al.	45	12 (26.7)	-	31 (68.9)	10 (22.2)	-	5 (11.1)	10 (22.2)	-	-	-
Zajicek et al.[a]	5	-	5 (100)	-	-	-	-	-	2 (40.0)	-	-
Chauleur et al.[b]	17	4 (23)	12 (71)		5 (29)						9 (52.9)
Spontaneous	6	1 (16)	6 (100)	-	1 (16)	-	-	-	-	284	2 (33.3)
Iatrogenic	11	3 (27)	6 (54)		4 (36)					172	7 (63.6)
Manuk et al.[c]	112	-	-	15 (13.4)	47 (42.0)	-	12 (10.7)	-	8 (7.1)	82	43 (38.4)
Total	**619**	**120/ 426 (28.2)**	**94/ 253 (37.1)**	**91/ 400 (22.7)**	**86/ 499 (17.4)**	**2/ 144 (1.4)**	**48/ 540 (8.9)**	**41/ 329 (12.5)**	**47/ 269 (17.5)**		**190/ 386 (49.2)**

*All variables are no (%) except hospital stay
a. Based on neonates survived to discharge b. Based on live born neonates c. Based on neonates admitted to ICU d. Based on survivors beyond neonatal period e. Among neonates alive 7 days after birth (early neonatal period) f. among total neonates with expectant management
$ Different variables were obtained from different total no of neonates as the data was not available for certain no of neonates
£. ≥ stage III ¶. > Stage II ¥. > Stage I

The respiratory morbidities were most frequently observed including RDS (37%) and BPD (28%). Sepsis, IVH, and joint contractures were also observed in a significant proportion of studied neonates (22.7%, 17.4%, and 17.5%, respectively). Other less common morbidities were NEC, ROP and PVL.

Overall, 49 percent neonates survived without a major morbidity (intact survival). Seven studies tried to find out the factors associated with intact survival by analyzing the data (73, 77, 79, 80, 84, 85, 89). These studies considered gestational age at PPROM, latency

period, oligohydramnios, chorioamnionitis, twin pregnancy, GA at delivery, and birth weight in their analysis.

Studies demonstrate that the gestational age at birth was significantly associated with intact neonatal survival (77, 80, 89). Wagner et al. demonstrated that gestational age at the time of delivery was the only factor that was significantly associated with survival without a major morbidity in a multivariable analysis (adjusted OR: 2.09, 95% CI: 1.20-3.63). The survival without a major morbidity was 8.3%, 58.3%, and 87.5% for the pre-viable PPROM fetuses delivering at gestations <26 weeks, 26-29^{+6} weeks, and ≥ 30 weeks, respectively (77). Esteves et al. also observed a similar association (80). Another study demonstrated that gestational age at birth was the single most important predictor of neonatal survival without major morbidity among neonates admitted to ICU (89).

Six articles studied the association between gestational age at PPROM and intact survival. Four of them reported that there was no association between these two variables, and no significant improvement in neonatal morbidity was observed with increasing gestational at PPROM (77, 79, 84, 85). However, Kibel et al. and Manuck et al. found a positive association between these two variables (73, 89).

No other factor was demonstrated to contribute towards the intact survival. The study by Wagner et al. showed that although latency period was associated with improved survival without major morbidity in a univariate model (un-adjusted OR: 1.081, 95%CI: 1.044-1.119), but this association did not remain significant when other covariates were considered in a multivariate analysis (adjusted OR: 0.999, 95%CI: 0.943-1.059)(77). Similarly, another study reported that the latency period >7 days was associated with survival without major morbidity in a multivariable analysis (73). The reason might be that

this study did not consider gestational age at delivery as a covariate in its multivariable analysis, despite the fact that it was significantly associated with the outcome in the univariate model of this study. Manuck et al. demonstrated that anhydramnios is a poor predictor of intact neonatal survival (sensitivity: 43%, specificity: 64%)(89). Other studies reported that the association of an/oligohydramnios with intact survival was not statistically significant (73, 77).

Long Term Neonatal Morbidity:

Only few of the included studies reported on the long-term morbidity among the surviving neonates. The data of these studies is shown in table 4.6.

Table 4.6: Neonatal Long-term morbidity

Reference	Follow-up period (Months)	No of fetuses (n)	Long -term Neonatal Morbidity
Kibel et al.	18–21	43	10 (23.3)
Linehan et al.	48	02	01 (50)
Acaia et al.	24	42	08(19)
Zajicek et al.	18	05	02(40)
Chauleur et al.	66	14	05(35.7)
Total		**106**	**26(24.5)**

Kibel et al. performed neurodevelopmental assessment of 43 surviving neonates at 18-21 months. It was reported that 10 of these neonates had neurological impairments (73). Two neonates survived to hospital discharge in Linehan et al. study (74). One of them had necrotizing enterocolitis (NEC) and died at 8 weeks of life and the other had chronic lung disease (CLD) at the time of discharge but was alive and healthy at 4 years of age. In the study by Acaia et al. the surviving neonates were followed at 2 years of age. Three children had some serious neurological problems requiring support and five had minor problems including recurrent bronchitis and inability to gain normal weight (78). Out of the five neonates that survived to discharge in the study by Zajicek et al. two had minor lower limb defects at 18 months of age (87). Chauleur et al. followed the 14 surviving neonates at 4-7 years (median: 5.5 years) of age and reported that the long-term sequelae were present in 5(35.7%) of them.

Three children had slow psychomotor development and two had patent ductus arteriosus (one of these two suffered from pulmonary hypertension)(88).

Maternal Outcomes:

The maternal outcomes of 749 pre-viable PPROM pregnancies following expectant management are shown in table 4.7. The data of the included studies demonstrated that almost half (49.3%) of the pre-viable PPROM women suffered from clinical chorioamnionitis after expectant management. Cesarean mode of delivery (33%), placental abruption (30%), and retained placenta (20%) were also frequently observed in these women. Other less common morbidities include endometritis, cord prolapse, and sepsis.

There was no significant predictor of maternal morbidity described in these studies. A study by Storness-Bliss et al. compared the rate of maternal complications of pre-viable PPROM women with oligohydramnios to those without oligohydramnios. The results of this study showed that although the rate of chorioamnionitis was higher in the oligohydramnios group than the other group (70% vs. 50%), but the difference was not statistically significant (p=0.63). The study also reported that there was no significant difference between two groups regarding other maternal complications including endometritis, placental abruption, retained placenta and sepsis (83). None of other 16 studies commented on the relationship between oligohydramnios and maternal complications.

Deutsch et al. studied the effect of the gestational age at PPROM on maternal complications. They reported that the rate of chorioamnionitis and endometritis did not differ based on the gestational age at PPROM. However, the rates of placental abruption and cord prolapse were significantly higher at earlier gestational ages of PPROM (79).

Table 4.7: Maternal morbidity after expectant management of pre-viable PPROM*

Reference (PPROM, wk.)	No of wo-men	Chorioamnionitis		Endom etritis	Sepsis	Cord prolapse	Retained placenta	Placental Abruption	Cesarean Delivery
		Clini-cal	Histo-logical						
Kibel et al. (20-24)	90	44 (49)	-	-	5 (5.5)	6 (6.7)	-	18 (20)	37 (41.1)
Linehan et al. (14-23^{+6})	42	5 (12)	22 (52)	-	1 (2.4)	-	9 (21)	1 (2.4)	-
McLaughlin et al. (<24)	106	46 (43)	90 (85)	-	-	-	-	-	38 (36)
Acaia et al. (14-23^{+6})	85	27 (32)	32 (38)	-	8 (9.4)	-	-	4 (4.7)	28 (32.9)
Hunter et al. ¥ 16^{+0}-20^{+0} 20^{+1}-24^{+0}	106 24 82	58 (55) 13 (54) 45 (55)	77 (73) 15 (63) 62 (76)	-	-	10 (9) 1 (4) 9 (11)	-	-	21(20) 4 (17) 17 (21)
Margato et al. (<24)	31	22 (71)	9 (29.0)	1 (3.2)	2 (6.5)	-	-	1 (3.2)	-
Storness-Bliss et al. (<24) AFI<1cm AFI≥1cm	22 12 10	13 (59.1) 8(70) 5(50)	-	1 (4.5) 1(9) 0(0)	0 (0) 0 0	-	4 (18.2) 2(20) 2(22)	11 (50.0) 5(45) 6(63)	-
Deutsch et al. (18-23^{+6})	105	68 (64.8)	-	20 (19.0)	1 (0.9)	6 (5.7)	-	26 (24.8)	23 (21.9)
Zajicek et al. (13-20)	3	1 (33.3)	0 (0.0)	-	-	-	-	-	2 (66.6)
Manuk et al. (<24)	159	85 (53.5)	-	8 (5.0)	0 (0.0)	-	-	97 (61.0)	68 (42.8)
Total	**749**	**369/ 749 (49.3)**	**230/ 373 (61.7)**	**30/ 317 (9.5)**	**17/ 534 (3.2)**	**22/ 301 (7.3)**	**13/ 64 (20.3)**	**158/ 534 (29.6)**	**217/ 654 (33.2)**

*All variables are no (%)
¥ Data obtained only from singleton pregnancies

A study comparing pre-viable PPROM women following expectant with those opting active management reported that the rate of maternal complications was not significantly different between two groups (p=0.693)(85).

Termination of Pregnancy (TOP):

Out of 17 studies included in our review, 2 were conducted at the centers where the option to opt for the TOP was not available (74, 75). The data of the 11 studies on proportion of pre-viable PPROM women opting for TOP instead of expectant management is shown in the table 4.8. Three studies did not provide the data on this variable. van der Heyden et al. reported that 2 percent (6/311) of the women opted for TOP among women with PPROM at 13-27 weeks gestation, but they did not provide separate data for TOP among 185 women with PPROM at <24 weeks (84).

Table 4.8. Pre-viable PPROM women opting for TOP

Reference (PPROM, wk.)	Total no of pre-viable PPROM women	Women opting for TOP no(%)
Kibel et al. (20-24)	115	11(9.6)
Wagner et al. (<24)	101	32(31.7)
Wagner et al. (<24)	29	02(6.9)
van der Marel et al. (>24) <20 >20	160 74 86	39(24.4) 32(43.2) 07(8.1)
Verspyck et al. (14-24)	94	11(11.7)
Acaia et al. (14-23+6)	132	47(35.6)
Hunter et al. (16-24)	143	17(11.8)
Margato et al. (<24) 14-19 20-24	36 20 16	05(13.9) 03(15.0) 02(12.5)
Storness-Bliss et al. (<24) AFI<1cm AFI≥1cm	31 18 13	09(29.0) 06(33.3) 03(23.1)
Deutsch et al. (18-23^{+6})	133	28(21.0)
Chauleur et al. (14-23+6) Spontaneous Iatrogenic	38 22 16	13(34.2) 10(45.5) 03(18.7)
Total	**1,012**	**214(21.1)**

Overall, 21.1% (214/1012) of pre-viable PPROM women opted for the TOP. The decision to choose active management (TOP) was influenced by three major factors: gestational age at PPROM, amniotic fluid index (AFI) levels, and iatrogenic cause of PPROM.

Two studies demonstrated that the women who chose to electively terminate their pregnancies had significantly earlier gestation at PPROM than those opting for expectant management (77, 81). Similarly, all the women opting for TOP in the study by van der Heyden et al. had gestational at PPROM <20 weeks (84). van der Marel et al. compared the TOP rate between women with pre-viable PPROM at <20 weeks and >20 weeks. The rate was 43 percent in <20 weeks group compared to only 8 percent in the other group (p= <0.001)(85).

Three studies reported that among women opting for termination of pregnancy, oligo/anhydramnios was a more frequent finding (77, 78, 88). Chauleur et al. demonstrated that 45.5 percent of the spontaneous pre-viable PPROM women opted for TOP compared to 18.7 percent of the iatrogenic pre-viable PPROM women (88). Similarly, Acaia et al. reported that Amniocenteis as a cause of PPROM was less frequent in TOP group than in expectant management group (6% vs. 29%, p=0.002)(78). The study by Hunter et al. showed that there was no difference in the rate of TOP between singleton and multiple pre-viable PPROM pregnancies (p=0.469)(81).

Summary of Results:

The neonatal survival to discharge rate was 41.1%. Among surviving neonates, 49.2% had no major morbidity. Respiratory morbidity was the most commonly observed neonatal morbidity. 37% neonates suffered from respiratory distress syndrome, 28% from broncopulmonary dysplasia, and 9.8% from pulmonary hypoplasia. Sepsis occurred in 22.7% neonates. 49.3% pre-viable PPROM women developed chorioamnionitis. Other common maternal morbidities included cesarean delivery (33%) and placental abruption

(30%). The predictors for better neonatal survival to discharge included later gestational age at PPROM, absence of oligohydramnios, iatrogenic etiology of PPROM, and the C-reactive protein (CRP) level <1mg/dl on the first day of presentation. Later gestational age at delivery was associated with lower neonatal morbidity. There was no significant predictor for maternal morbidity. Overall, 21.1% of pre-viable PPROM women opted for the TOP instead of expectant management.

CHAPTER 5: DISCUSSION

Discussion of Study Results:

The aims of my study were: to assess maternal and neonatal outcomes associated with the pre-viable PPROM pregnancies following the expectant management; to describe the predictors of better outcomes of these pregnancies; and to find out the proportion of pre-viable PPROM women who opt for TOP instead of expectant management. The major findings of my review are as follows.

Pregnancy Outcomes:

Out of 1,355 pre-viable PPROM fetuses studied in my review, 66.3% (899) were born alive. Majority of them were preterm and therefore admitted to NICU. The average duration of hospital stay for these neonates ranged between 25 days to 7 months among different studies. Out of these 899 live born neonates, 342 died before they were discharged form the hospital. The main causes of neonatal death during NICU stay described in the reviewed articles included extreme prematurity, pulmonary hypoplasia, bronchopulmonary dysplasia, respiratory distress syndrome, neonatal sepsis, and grade-IV intraventricular hemorrhage (73-75, 78). Hence, the overall neonatal survival to discharge rate was 41.1% after expectant management. This rate was 44.6% for the studies that included only singleton pregnancies.

The most common neonatal morbidities observed in my study were of respiratory origin. 37% neonates developed respiratory distress syndrome, 28% bronchopulmonary dysplasia, and 9.85% pulmonary hypoplasia. The data of the individual studies demonstrated that the rate of pulmonary hypoplasia ranged between 0.0-16.3% among live born neonates. However, this rate does not seem to be a proper estimate of the exact

incidence of pulmonary hypoplasia after pre-viable PPROM. The methods used to diagnose the pulmonary hypoplasia in the included studies were inconsistent. The diagnostic methods included clinical diagnosis, based on the difficulty in ventilating the newborn with respiratory failure; radiological diagnosis, based on the chest X-ray with reduced lung expansion; and histological diagnosis, based on a low lung-to-body-weight ratio on autopsy. In addition, the studies that diagnosed the condition based on histological criteria did not perform autopsy of all dead neonates. This may have resulted in underestimation of pulmonary hypoplasia rate.

Other neonatal morbidities that were commonly observed in my study include sepsis, intraventricular hemorrhage, and joint contractures (22.7%, 17.4%, and 17.5%, respectively). Furthermore, retinopathy of prematurity, necrotizing enterocolitis, and periventricular leukomalacia were reported in 12.5%, 8.9%, and 1.4% neonates, respectively. Among the surviving neonates that were followed up during their childhood, every fourth child had some long-term consequence. The neurological impairment was the most frequent finding. Other long-term sequelae reported in the reviewed articles include developmental problems, limb defects, chronic bronchitis, patent ductus arteriosus, pulmonary hypertension, and chronic lung disease.

Around 50% neonates survived without a major morbidity. However, there was also a controversy in the definition of survival without major morbidity among different studies. Nine studies presented the data regarding this variable. The presence of any of the following: BPD; IVH; PVL; and ROP, was considered as a major morbidity by most of the studies. The studies also variably included in this list one or more of the following: NEC; RDS; sepsis; and pulmonary hypoplasia.

In our study, approximately half (49.3%) of the pre-viable PPROM women developed chorioamnionitis after expectant management of their pregnancies. Other reported maternal morbidities include cesarean mode of delivery, placental abruption, retained placenta, endometritis, cord prolapse, and sepsis.

Predictors for Better Pregnancy Outcomes:

Many factors have been described in the reviewed studies, which can predict the neonatal survival and other pregnancy outcomes of pre-viable PPROM women. These factors can help the physicians to counsel the suffering parents about their chances of taking home a live and healthy baby and assist the parents to choose either expectant management or TOP.

The predictors of neonatal survival to discharge include GA at PPROM, oligohydramnios, the etiology of PPROM either iatrogenic or spontaneous, and the C-reactive protein (CRP) level on the first day of presentation. The gestational age at PPROM is a strong predictor of neonatal survival. The survival rate increases with increasing GA at PPROM. The take home baby rate is particularly better when the membranes rupture after 20 weeks gestation. The presence of oligohydramnios is associated with lower survival rate but Hunter et al. reported that it is a poor predictor of neonatal survival with area under ROC curve 0.649. The neonatal survival rate is better when PPROM is iatrogenic and the CRP level is < 1mg/dl during first 24 hours of admission. Among the live born neonates, survival to hospital discharge rate is higher for those who have higher gestational age at delivery, higher birth weight, and prolonged latency period.

The factors that predict pulmonary hypoplasia include GA at PPROM and the level of amniotic fluid surrounding the fetus. Early gestational age at membrane rupture

(particularly <20 weeks) and the presence of oligohydramnios (AFI<2cm) are associated with a higher rate of this morbidity. The risk of pulmonary hypoplasia decreases markedly with every week increase in the gestational age at PPROM and every unit increase in amniotic fluid volume.

The rates of neonatal morbidities other than pulmonary hypoplasia are not dependent on the GA at PPROM or oligohydramnios. The only predictor of these neonatal morbidities is GA at the time of the delivery of the baby. The higher gestational age at birth leads to a larger proportion of the PPROM neonates without a major morbidity. The risk of long-term morbidity is higher among the pre-viable PPROM neonates experiencing some major morbidity immediately after birth.

No significant predictor of maternal morbidity has been observed in our review. Oligohydramnios is generally thought to have an association with chorioamnionitis. Storness-Bliss et al. demonstrated that although the rate of chorioamnionitis was higher in the PPROM women with oligohydramnios than those without oligohydramnios (70% vs. 50%), but the difference was not statistically significant (p=0.63). This inability to demonstrate a significant difference might be a result of type II error as the sample size of the study was very small (n=22). Future studies with large sample size are required to better describe the association between oligohydramnios and maternal morbidity.

Proportion of Pre-viable PPROM Women Opting for TOP:

Overall, 21.1% of pre-viable PPROM women opted for the TOP instead of expectant management when both options were available in the hospital.

The pre-viable PPROM women with lower GA at the time of membrane rupture and those with oligohydramnios are more prone to opt for TOP. On the other hand, the pre-viable PPROM women with iatrogenic PPROM choose TOP less frequently.

Effect of Advanced Care on The Pregnancy Outcomes:

My hypothesis was, "the perinatal outcomes of the pre-viable PPROM pregnancies have improved over the past few decades due to advances in maternal (routine use of prophylactic antibiotics, monitoring for the signs of infection, immediate delivery in case of chorioamnionitis) and neonatal care (antenatal corticosteroids, surfactant therapy, nitric oxide inhalation, mechanical ventilation)". So, I expected a higher neonatal survival rate and lower neonatal and maternal morbidity in my review than those reported previously in the reviews published in 2001 by Dewan and Moris (92) and 2009 by Waters and Mercer (2).

The neonatal survival rate (41.1%) of my study was higher than that reported by Dewan and Moris (21%). Contrary to my expectation, this rate was lower than that of Waters and Mercer review (44.9%).

The relatively higher survival rate (44.9% vs. 41.1%) reported by Waters and Mercer could be explained by three factors. First, the survival outcome in Waters and Mercer's review was 'perinatal survival' (i.e. survival till the neonatal period or 28 days of life) but in my review, it was 'survival to hospital discharge'. Table 4.5 shows that the average neonatal hospital stay was more than 28 days in almost all of the included studies. Thus, the survival rate of my review would have been greater, if I had considered perinatal survival as an outcome instead of survival to hospital discharge. Second, out of 6 studies from which survival rate was calculated in Waters and Mercer's review, 2 were studying

only those PPROM pregnancies that continued beyond 2 weeks following PPROM (prolonged PPROM). These pregnancies were prone to have better neonatal survival, leading to overestimation of survival rates. If these studies were excluded from the Waters and Mercer's meta-analysis, the survival rate would be 36.9%, markedly lower than my review's survival rate. A third reason for this unexpected higher survival rate is that in Waters and Mercer's review, TOP option was available in case of all of the included studies. But in my review, 2 studies (including one with lowest survival rate of only 5%) were conducted at the centers where the option of TOP was not available. The women who opted for TOP were usually those who expected lower survival rate. The survival rate of my review would be greater if TOP were available in all of the included studies.

Due to improved ventilation techniques and better respiratory support, the rates of respiratory morbidities including respiratory distress syndrome (37), bronchopulmonary dysplasia (28), and pulmonary hypoplasia (9.8) were much lower in my review than those reported in 2001 and 2009 reviews. In 2009 review, the reported rates of respiratory distress syndrome, bronchopulmonary dysplasia, and pulmonary hypoplasia were 65.7 percent, 29.1 percent, and 19.2 percent, respectively. The review published in 2001 showed that among pre-viable PPROM neonates, respiratory distress syndrome rate was 67-75 percent.

Despite significant improvements in the maternal care, maternal morbidity has not declined. The rate of chorioamnionitis (49 percent) in my review was much higher than 37% reported by Waters and Mercer's. This was surprising as I was expecting a relatively lower rate of chorioamnionitis due to routine use of prophylactic antibiotics in pre-viable PPROM. One potential explanation of this unexpected higher rate may be due to more

women opting for the expectant management compared to 10 years ago. However, the rate of serious maternal complications, i.e. sepsis (3.2 percent) was low and no maternal death was reported.

Study Implications:

The study demonstrates that the perinatal outcomes of the pre-viable PPROM pregnancies following expectant management have improved over the past two decades. Currently, about 41% pre-viable PPROM neonates do survive and half of them are without any major morbidity. Although maternal morbidity is still high, but serious maternal morbidities are rare. In the light of these findings, women may be counseled for expectant management particularly when PPROM occurs after 20 weeks gestation and oligohydramnios is absent. Another clinical implication is that as the neonatal survival has improved due to advancements in maternal and neonatal care, all pre-viable PPROM women should be managed at tertiary care facilities with higher level of NICU care.

Study Limitations:

My study has some limitations. Due to limited resources, the review did not include the studies published in non-English language. Publication bias might also be present, as some studies may have not been published due to negativity of the results. Furthermore, there are potential sources of bias both within and across the studies that may have affected the accuracy of our results.

<u>Bias Within Studies:</u>

Sample size for most of the included studies was very small that might have led to type-II error in the data analysis. This was due to low incidence of the pre-viable PPROM i.e. only 0.4%. All studies were retrospective in nature. These studies were conducted at tertiary

care referral centers. So, pre-admission selection bias might also exit. 15 of the 17 studies offered TOP at their centers and excluded these women while analyzing the data for the 'outcomes after expectant management of pre-viable PPROM pregnancies'. Most of the women opting for TOP were those who had risk factors (oligohydramnios and early gestational age at PPROM) for a lower neonatal survival. Thus, their exclusion may have resulted in overestimation of the survival rate. In addition, all of the reviewed studies had long study periods. It was ≥7 years for most of them. The management protocols change over the time. This might be a potential source of bias.

Bias Across Studies:

The range of the GA of the included patients varied across the studies. For example, five studies included the patients having PPROM at 14-24 weeks gestation and others at <24, 20-24, 16-24, 18-24, or 13-20 weeks. This is a source of bias, as the gestational age at PPROM is a major factor in determining the PPROM outcome. The operational definitions of many study variables (chorioamnionitis, pulmonary hypoplasia, survival without major morbidity, etc.) varied widely across the included studies. The studies also differed in their exclusion of twin pregnancies, TOP, and iatrogenic PPROM that may have affected the outcome. The expectant management protocols regarding prophylactic antibiotics use, tocolytics use, GA to start neonatal resuscitation, and patients monitoring were not uniform across the studies. Furthermore, although all of the studies have been conducted at the tertiary care centers of well-developed countries, but the level of neonatal ICU care would have been varied widely across them.

Suggestion for Future Research:

In future, a prospective study with large sample size should be conducted. The study should include all the patients with PPROM at ≤24 weeks. The patients with multiple gestation and iatrogenic PPROM should also be included and then sub-population analysis should be performed. To achieve a large sample size in short duration of time, the study should be conducted at multiple health centers of the country with same management protocols. All the neonates should undergo long-term follow-up at 4-5 years of age to assess the long-term sequelae of the pre-viable PPROM. This multicenter study will provide the local, accurate, and up-to-date data regarding the perinatal outcomes of pre-viable PPROM pregnancies.

Conclusion:

The survival rate of pre-viable PPROM is poor, but it is not zero. 4 of every 10 affected neonates do survive and half of them are without any major morbidity. Maternal morbidity is still high, but serious maternal morbidities are rare.

REFERENCES:

1. Mercer BM. Preterm premature rupture of the membranes. Obstetrics & Gynecology 2003;101(1):178-93.
2. Waters TP, Mercer BM. The management of preterm premature rupture of the membranes near the limit of fetal viability. Am J Obstet Gynecol 2009 Sep;201(3):230-40.
3. Beckmann C. *Obstetrics and Gynecology* Chapter 22: Premature Rupture of Membranes. 6 ed. Baltimore, MD: Lippincott Williams & Wilkins; 2010.
4. Paumier A, Gras-Leguen C, Branger B, Boog G, Roze JC, Philippe HJ, et al. [Premature rupture of membranes before 32 weeks of gestation: prenatal prognosis factors]. Gynecol Obstet Fertil 2008 Jul-Aug;36(7-8):748-56.
5. Alexander JM, Cox SM. Clinical course of premature rupture of the membranes. Seminars in Perinatology; 1996: Elsevier; 1996. p. 369-74.
6. Kilbride HW, Thibeault DW. Neonatal complications of preterm premature rupture of membranes: pathophysiology and management. Clinics in perinatology 2001;28(4):761-85.
7. Nimrod C, Varela-Gittings F, Machin G, Campbell D, Wesenberg R. The effect of very prolonged membrane rupture on fetal development. Am J Obstet Gynecol 1984 Mar 01;148(5):540-3.
8. Kilbride HW, Yeast J, Thibeault DW. Defining limits of survival: lethal pulmonary hypoplasia after midtrimester premature rupture of membranes. American journal of obstetrics and gynecology 1996;175(3 Pt 1):675-81.
9. Taylor J, Garite TJ. Premature rupture of membranes before fetal viability. Obstet Gynecol 1984 Nov;64(5):615-20.
10. Moretti M, Sibai BM. Maternal and perinatal outcome of expectant management of premature rupture of membranes in the midtrimester. Am J Obstet Gynecol 1988 Aug;159(2):390-6.
11. Xiao Z, André P, Lacaze-Masmonteil T, Audibert F, Zupan V, Dehan M. Outcome of premature infants delivered after prolonged premature rupture of membranes before 25 weeks of gestation. European Journal of Obstetrics & Gynecology and Reproductive Biology 2000;90(1):67-71.
12. Grisaru-Granovsky S, Eitan R, Kaplan M, Samueloff A. Expectant management of midtrimester premature rupture of membranes: a plea for limits. Journal of perinatology 2003;23(3):235-9.
13. Falk SJ, Campbell LJ, Lee-Parritz A, Cohen AP, Ecker J, Wilkins-Haug L, et al. Expectant management in spontaneous preterm premature rupture of membranes between 14 and 24 weeks' gestation. Journal of perinatology 2004;24(10):611-6.
14. Dinsmoor MJ, Bachman R, Haney EI, Goldstein M, MacKendrick W. Outcomes after expectant management of extremely preterm premature rupture of the membranes. American journal of obstetrics and gynecology 2004;190(1):183-7.
15. Muris C, Girard B, Creveuil C, Durin L, Herlicoviez M, Dreyfus M. Management of premature rupture of membranes before 25 weeks. Eur J Obstet Gynecol Reprod Biol 2007 Apr;131(2):163-8.
16. Shah DM, Kluckow M. Early functional echocardiogram and inhaled nitric oxide: usefulness in managing neonates born following extreme preterm premature rupture of membranes (PPROM). Journal of paediatrics and child health 2011;47(6):340-5.
17. Sackett DL, Rosenberg WM, Gray JM, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. British Medical Journal Publishing Group; 1996.
18. Ehsanipoor R. Practice Bulletin No. 172: Premature rupture of membranes. Obstetrics and Gynecology 2016;128(4):e165-e77.
19. Institute of Medicine Committee on Standards for Systematic Reviews of Comparative Effectiveness R. In: Eden J, Levit L, Berg A, Morton S, editors. Finding What Works in Health Care: Standards for Systematic Reviews. Washington (DC): National Academies Press (US)
Copyright 2011 by the National Academy of Sciences. All rights reserved.; 2011.
20. Underwood MA, Gilbert WM, Sherman MP. Amniotic fluid: not just fetal urine anymore. J Perinatol 2005 May;25(5):341-8.
21. Moore R, Mansour J, Redline R, Mercer B, Moore J. The physiology of fetal membrane rupture: insight gained from the determination of physical properties. Placenta 2006;27(11):1037-51.
22. Waters TP, Mercer B. Preterm PROM: prediction, prevention, principles. Clinical obstetrics and gynecology 2011;54(2):307-12.
23. Lewi L, Van Schoubroeck D, Van Ranst M, Bries G, Emonds M-P, Arabin B, et al. Successful patching of iatrogenic rupture of the fetal membranes. Placenta 2004;25(4):352-6.
24. Ferianec V, Krizko Jr M, Papcun P, Sviteková K, Cizmar B, Holly I, et al. Amniopatch–possibility of successful treatment of spontaneous previable rupture of membranes in the second trimester of pregnancy by transabdominal intraamiotic application of platelets and cryoprecipitate. Neuroendocrinology Letters 2011;32(4):449-52.

25. Tabor A, Madsen M, Obel E, Philip J, Bang J, Gaard-Pedersen Br. Randomised controlled trial of genetic amniocentesis in 4606 low-risk women. The Lancet 1986;327(8493):1287-93.
26. Dolinger MB, Donnenfeld AE. Therapeutic amniocentesis using a vacuum bottle aspiration system. Obstetrics & Gynecology 1998;91(1):86-91.
27. Ville Y, Van Peborgh P, Gagnon A, Frydman R, Fernandez H. [Surgical treatment of twin-to-twin transfusion syndrome: coagulation of anastomoses with a Nd:YAG laser, under endosonographic control. Forty four cases]. J Gynecol Obstet Biol Reprod (Paris) 1997;26(2):175-81.
28. Harrison MR, Mychaliska GB, Albanese CT, Jennings RW, Farrell JA, Hawgood S, et al. Correction of congenital diaphragmatic hernia in utero IX: fetuses with poor prognosis (liver herniation and low lung-to-head ratio) can be saved by fetoscopic temporary tracheal occlusion. Journal of pediatric surgery 1998;33(7):1017-23.
29. Deprest JA, Van Ballaer PP, Evrard VA, Peers KH, Spitz B, Steegers EA, et al. Experience with fetoscopic cord ligation. European Journal of Obstetrics & Gynecology and Reproductive Biology 1998;81(2):157-64.
30. Medina TM, Hill DA. Preterm premature rupture of membranes: diagnosis and management. Am Fam Physician 2006;73(4):659-64.
31. French JI, McGregor JA. The pathobiology of premature rupture of membranes. Seminars in perinatology; 1996: Elsevier; 1996. p. 344-68.
32. Kelly T. The pathophysiology of premature rupture of the membranes. Current Opinion in Obstetrics and Gynecology 1995;7(2):140-5.
33. Mercer BM. Preterm Premature Rupture of the Membranes. *Glob. libr. women's med*; 2008.
34. Schucker JL, Mercer BM. Midtrimester premature rupture of the membranes. Seminars in perinatology; 1996: Elsevier; 1996. p. 389-400.
35. Lamont RF. Recent evidence associated with the condition of preterm prelabour rupture of the membranes. Curr Opin Obstet Gynecol 2003 Apr;15(2):91-9.
36. Farooqi A, Holmgren PÅ, Engberg S, Serenius F. Survival and 2-year outcome with expectant management of second-trimester rupture of membranes. Obstetrics & Gynecology 1998;92(6):895-901.
37. Gibbs RS, Castillo MS, Rodgers PJ. Management of acute chorioamnionitis. American journal of obstetrics and gynecology 1980;136(6):709-13.
38. Warburton D, El-Hashash A, Carraro G, Tiozzo C, Sala F, Rogers O, et al. Lung organogenesis. Curr Top Dev Biol 2010;90:73-158.
39. Nimrod C, Varela-Gittings F, Machin G, Campbell D, Wesenberg R. The effect of very prolonged membrane rupture on fetal development. American journal of obstetrics and gynecology 1984;148(5):540-3.
40. Vergani P, Ghidini A, Locatelli A, Cavallone M, Ciarla I, Cappellini A, et al. Risk factors for pulmonary hypoplasia in second-trimester premature rupture of membranes. American journal of obstetrics and gynecology 1994;170(5):1359-64.
41. Clark EA, Varner M. Impact of preterm PROM and its complications on long-term infant outcomes. Clinical obstetrics and gynecology 2011;54(2):358-69.
42. Butler AS, Behrman RE. Preterm birth: causes, consequences, and prevention: National Academies Press; 2007.
43. Beydoun SN, Yasin SY. Premature rupture of the membranes before 28 weeks: conservative management. Am J Obstet Gynecol 1986 Sep;155(3):471-9.
44. Fortunato SJ, Welt SI, Eggleston MK, Jr., Bryant EC. Active expectant management in very early gestations complicated by premature rupture of the fetal membranes. J Reprod Med 1994 Jan;39(1):13-6.
45. Gold RB, Goyert GL, Schwartz DB, Evans MI, Seabolt LA. Conservative management of second-trimester post-amniocentesis fluid leakage. Obstetrics & Gynecology 1989;74(5):745-7.
46. Institute of Medicine Committee on Standards for Developing Trustworthy Clinical Practice G. In: Graham R, Mancher M, Miller Wolman D, Greenfield S, Steinberg E, editors. Clinical Practice Guidelines We Can Trust. Washington (DC): National Academies Press (US)
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47. Myrick O, Dotters-Katz S, Grace M, Manuck T, Boggess K, Goodnight W. Prophylactic Antibiotics in Twin Pregnancies Complicated by Previable Preterm Premature Rupture of Membranes. AJP Rep 2016 Jul;6(3):e277-82.
48. Roberts D, Vause S, Martin W, Green P, Walkinshaw S, Bricker L, et al. Amnioinfusion in preterm premature rupture of membranes (AMIPROM): a randomised controlled trial of amnioinfusion versus expectant management in very early preterm premature rupture of membranes--a pilot study. Health Technol Assess 2014 Apr;18(21):1-135.
49. van Teeffelen AS, van der Ham DP, Willekes C, Al Nasiry S, Nijhuis JG, van Kuijk S, et al. Midtrimester preterm prelabour rupture of membranes (PPROM): expectant management or amnioinfusion for improving perinatal outcomes (PPROMEXIL - III trial). BMC Pregnancy Childbirth 2014 Apr 04;14:128.

50. Richter J, Henry A, Ryan G, DeKoninck P, Lewi L, Deprest J. Amniopatch procedure after previable iatrogenic rupture of the membranes: a two-center review. Prenat Diagn 2013 Apr;33(4):391-6.
51. Kwak HM, Choi HJ, Cha HH, Yu HJ, Lee JH, Choi SJ, et al. Amniopatch treatment for spontaneous previable, preterm premature rupture of membranes associated or not with incompetent cervix. Fetal Diagn Ther 2013;33(1):47-54.
52. Miyazaki K, Furuhashi M, Yoshida K, Ishikawa K. Aggressive intervention of previable preterm premature rupture of membranes. Acta Obstet Gynecol Scand 2012 Aug;91(8):923-9.
53. Clerici G, Porcaro G, Kanninen T, Di Renzo GC. The role of serial amnioinfusions in the management of previable pre-term premature rupture of membranes. J Obstet Gynaecol 2011 May;31(4):345-7.
54. Dotters-Katz SK, Panzer A, Grace MR, Smid MC, Keku JA, Vladutiu CJ, et al. Maternal Morbidity After Previable Prelabor Rupture of Membranes. Obstet Gynecol 2017 Jan;129(1):101-6.
55. Lee JY, Ahn TG, Jun JK. Short-Term and Long-Term Postnatal Outcomes of Expectant Management After Previable Preterm Premature Rupture of Membranes With and Without Persistent Oligohydramnios. Obstet Gynecol 2015 Nov;126(5):947-53.
56. Brumbaugh JE, Colaizy TT, Nuangchamnong N, O'Brien EA, Fleener DK, Rijhsinghani A, et al. Neonatal survival after prolonged preterm premature rupture of membranes before 24 weeks of gestation. Obstet Gynecol 2014 Nov;124(5):992-8.
57. Soylu H, Jefferies A, Diambomba Y, Windrim R, Shah PS. Rupture of membranes before the age of viability and birth after the age of viability: comparison of outcomes in a matched cohort study. J Perinatol 2010 Oct;30(10):645-9.
58. Palacio M, Cobo T, Figueras F, Gomez O, Coll O, Cararach V, et al. Previable rupture of membranes: effect of amniotic fluid on pregnancy outcome. Eur J Obstet Gynecol Reprod Biol 2008 Jun;138(2):158-63.
59. Everest NJ, Jacobs SE, Davis PG, Begg L, Rogerson S. Outcomes following prolonged preterm premature rupture of the membranes. Arch Dis Child Fetal Neonatal Ed 2008 May;93(3):F207-11.
60. Newman DE, Paamoni-Keren O, Press F, Wiznitzer A, Mazor M, Sheiner E. Neonatal outcome in preterm deliveries between 23 and 27 weeks' gestation with and without preterm premature rupture of membranes. Arch Gynecol Obstet 2009 Jul;280(1):7-11.
61. van Teeffelen A, van der Heijden J, van der Ham D, Schaaf JM, van Kuijk S, Ravelli AC, et al. The Relation between Duration of Ruptured Membranes and Perinatal Outcome in Patients with Midtrimester Prelabor Rupture of Membranes. Am J Perinatol 2015 Oct;32(12):1112-8.
62. Wong LF, Holmgren CM, Silver RM, Varner MW, Manuck TA. Outcomes of expectantly managed pregnancies with multiple gestations and preterm premature rupture of membranes prior to 26 weeks. Am J Obstet Gynecol 2015 Feb;212(2):215.e1-9.
63. Manuck TA, Varner MW. Neonatal and early childhood outcomes following early vs later preterm premature rupture of membranes. Am J Obstet Gynecol 2014 Sep;211(3):308.e1-6.
64. Al Riyami N, Al-Ruheili I, Al-Shezaw F, Al-Khabori M. Extreme preterm premature rupture of membranes: risk factors and feto maternal outcomes. Oman Med J 2013 Mar;28(2):108-11.
65. Al-Riyami N, Al-Shezawi F, Al-Ruheili I, Al-Dughaishi T, Al-Khabori M. Perinatal Outcome in Pregnancies with Extreme Preterm Premature Rupture of Membranes (Mid-Trimester PROM). Sultan Qaboos Univ Med J 2013 Feb;13(1):51-6.
66. Patkai J, Schmitz T, Anselem O, Mokbat S, Jarreau PH, Goffinet F, et al. Neonatal and two-year outcomes after rupture of membranes before 25 weeks of gestation. Eur J Obstet Gynecol Reprod Biol 2013 Feb;166(2):145-50.
67. Azria E, Anselem O, Schmitz T, Tsatsaris V, Senat MV, Goffinet F. Comparison of perinatal outcome after pre-viable preterm prelabour rupture of membranes in two centres with different rates of termination of pregnancy. Bjog 2012 Mar;119(4):449-57.
68. Pristauz G, Bader AA, Schwantzer G, Kutschera J, Lang U. Assessment of risk factors for survival of neonates born after second-trimester PPROM. Early Hum Dev 2009 Mar;85(3):177-80.
69. Pristauz G, Bauer M, Maurer-Fellbaum U, Rotky-Fast C, Bader AA, Haas J, et al. Neonatal outcome and two-year follow-up after expectant management of second trimester rupture of membranes. Int J Gynaecol Obstet 2008 Jun;101(3):264-8.
70. Canda MT, Sezer O, Ozturk C, Demir N. Expectant management of preterm premature rupture of membranes remote from term with exiguous amniotic fluid and a prolonged latency period: report of two cases. Clin Exp Obstet Gynecol 2012;39(2):247-8.
71. Williams O, Michel B, Hutchings G, Debauche C, Hubinont C. Two-year neonatal outcome following PPROM prior to 25 weeks with a prolonged period of oligohydramnios. Early Hum Dev 2012 Aug;88(8):657-61.

72. Williams O, Hutchings G, Debieve F, Debauche C. Contemporary neonatal outcome following rupture of membranes prior to 25 weeks with prolonged oligohydramnios. Early Hum Dev 2009 May;85(5):273-7.
73. Kibel M, Asztalos E, Barrett J, Dunn MS, Tward C, Pittini A, et al. Outcomes of Pregnancies Complicated by Preterm Premature Rupture of Membranes Between 20 and 24 Weeks of Gestation. Obstet Gynecol 2016 Aug;128(2):313-20.
74. Linehan LA, Walsh J, Morris A, Kenny L, O'Donoghue K, Dempsey E, et al. Neonatal and maternal outcomes following midtrimester preterm premature rupture of the membranes: a retrospective cohort study. BMC Pregnancy Childbirth 2016 Jan 29;16:25.
75. McLaughlin LM, Gardener GJ. Neonatal outcomes after prelabour rupture of membranes before 24 weeks' gestation. J Paediatr Child Health 2016 Jul;52(7):722-7.
76. Wagner P, Sonek J, Mayr S, Abele H, Goelz R, Hoopmann M, et al. Outcome of dichorionic diamniotic twin pregnancies with spontaneous PPROM before 24 weeks' gestation. J Matern Fetal Neonatal Med 2016 Sep 08:1-5.
77. Wagner P, Sonek J, Mayr S, Abele H, Goelz R, Hoopmann M, et al. Outcome of pregnancies with spontaneous PPROM before 24+0 weeks' gestation. Eur J Obstet Gynecol Reprod Biol 2016 Aug;203:121-6.
78. Acaia B, Crovetto F, Ossola MW, Nozza S, Baffero GM, Somigliana E, et al. Predictive factors for neonatal survival in women with periviable preterm rupture of the membranes. J Matern Fetal Neonatal Med 2013 Nov;26(16):1628-34.
79. Deutsch A, Deutsch E, Totten C, Downes K, Haubner L, Belogolovkin V. Maternal and neonatal outcomes based on the gestational age of midtrimester preterm premature rupture of membranes. J Matern Fetal Neonatal Med 2010 Dec;23(12):1429-34.
80. Esteves JS, de Sa RA, de Carvalho PR, Coca Velarde LG. Neonatal outcome in women with preterm premature rupture of membranes (PPROM) between 18 and 26 weeks. J Matern Fetal Neonatal Med 2016;29(7):1108-12.
81. Hunter TJ, Byrnes MJ, Nathan E, Gill A, Pennell CE. Factors influencing survival in pre-viable preterm premature rupture of membranes. J Matern Fetal Neonatal Med 2012 Sep;25(9):1755-61.
82. Margato MF, Martins GL, Passini Junior R, Nomura ML. Previable preterm rupture of membranes: gestational and neonatal outcomes. Arch Gynecol Obstet 2012 Jun;285(6):1529-34.
83. Storness-Bliss C, Metcalfe A, Simrose R, Wilson RD, Cooper SL. Correlation of residual amniotic fluid and perinatal outcomes in periviable preterm premature rupture of membranes. J Obstet Gynaecol Can 2012 Feb;34(2):154-8.
84. van der Heyden JL, van der Ham DP, van Kuijk S, Notten KJ, Janssen T, Nijhuis JG, et al. Outcome of pregnancies with preterm prelabor rupture of membranes before 27 weeks' gestation: a retrospective cohort study. Eur J Obstet Gynecol Reprod Biol 2013 Sep;170(1):125-30.
85. van der Marel I, de Jonge R, Duvekot J, Reiss I, Brusse I. Maternal and Neonatal Outcomes of Preterm Premature Rupture of Membranes before Viability. Klin Padiatr 2016 Mar;228(2):69-76.
86. Verspyck E, Bisson V, Roman H, Marret S. Adverse respiratory outcome after premature rupture of membranes before viability. Acta Paediatr 2014 Mar;103(3):256-61.
87. Zajicek M, Yagel S, Ben-Ami M, Weisz B, Keselman L, Lipitz S. Outcome of twin pregnancies complicated by early second trimester rupture of membranes in one sac. Twin Res Hum Genet 2010 Dec;13(6):604-8.
88. Chauleur C, Rochigneux S, Seffert P, Chene G, Billiemaz K, Collet F. Neonatal outcomes and four-year follow-up after spontaneous or iatrogenic preterm prelabor rupture of membranes before 24 weeks. Acta Obstet Gynecol Scand 2009;88(7):801-6.
89. Manuck TA, Eller AG, Esplin MS, Stoddard GJ, Varner MW, Silver RM. Outcomes of expectantly managed preterm premature rupture of membranes occurring before 24 weeks of gestation. Obstet Gynecol 2009 Jul;114(1):29-37.
90. *Wells G*, *Shea B*, *O'Connell D*, *Peterson J*, *Welch V*, *Losos M*, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2014 [cited 2017 May]; Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp
91. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj 2009 Jul 21;339:b2535.
92. Dewan H, Morris JM. A systematic review of pregnancy outcome following preterm premature rupture of membranes at a previable gestational age. Aust N Z J Obstet Gynaecol 2001 Nov;41(4):389-94.