MATERNAL911®

Preterm Premature Rupture of Membranes (PPROM)

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Course Description:

Leaking fluid? We have problems! Preterm Premature Rupture of Membranes (PPROM) continues to be a leading cause of neonatal morbidity and mortality. This module will help to develop a knowledge base to further the care of a woman with PPROM.

Approximate Time to Complete: 45 minutes

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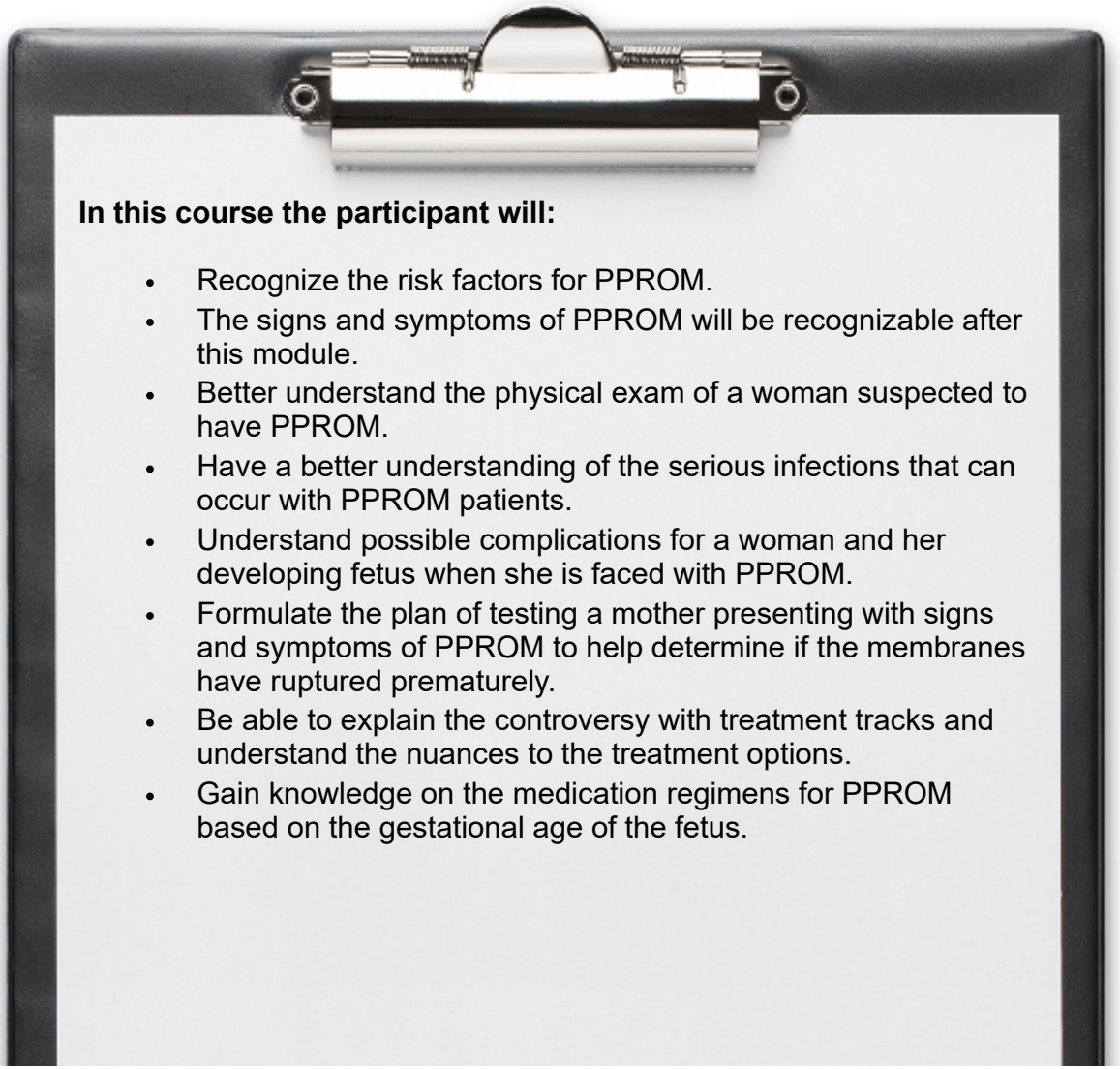

In this course the participant will:

- Recognize the risk factors for PPROM.
- The signs and symptoms of PPROM will be recognizable after this module.
- Better understand the physical exam of a woman suspected to have PPROM.
- Have a better understanding of the serious infections that can occur with PPROM patients.
- Understand possible complications for a woman and her developing fetus when she is faced with PPROM.
- Formulate the plan of testing a mother presenting with signs and symptoms of PPROM to help determine if the membranes have ruptured prematurely.
- Be able to explain the controversy with treatment tracks and understand the nuances to the treatment options.
- Gain knowledge on the medication regimens for PPROM based on the gestational age of the fetus.

Premature rupture of membranes (PROM)

Defined as membrane rupture before the onset of uterine contractions (also called pre-labor rupture of membranes)

Preterm PROM (PPROM)

PPROM before 37 weeks 0 days of gestation.

Occurrence of PPROM

PPROM occurs in 3% of pregnancies, but is responsible for or associated with about one-third of preterm births [1].

PPROM Risk Factors

- These risk factors are similar to those for preterm labor (PTL) (Table 1), but most patients have no identifiable risk factors.
- A history of PPROM in a previous pregnancy, genital tract infection, antepartum bleeding, and cigarette smoking have a particularly strong association with PPROM [2].

Bacturia	Fetal anomaly
Periodontal disease	Fetal growth restriction
Placenta previa	Environmental factors (i.e. heat, air pollution)
Occupational issues: • Upright posture • Use of industrial machines • Physical exertion • Mental or environmental stress-related work • Working conditions	Anemia (hemoglobin < 10g/dL)
	No partner
	Anxiety
	Depression
	Life events: • divorce, separation, death, etc
Previous preterm birth (PTB)	Abdominal surgery during pregnancy
Substance abuse	Multiple gestation
Smoking	Polyhydramnios
Maternal age (younger than 18 or older than 40)	Uterine anomaly
African - American race	DES induced uterine changes
Poor nutrition and low body mass index	History of second trimester abortion
Inadequate prenatal care	History of cervical surgery
Vaginal bleeding • Especially more than one trimester	Premature cervical dilation or effacement (shortened cervix)
Excessive uterine contractions	Lower level educational achievement
Placental Abruption	Genotype
Sexually transmitted infections (STI's)	Low socioeconomic status

Click on the table to view a larger version.

Risk Factors Table

Bacturia	Fetal anomaly
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Occupational issues: • Upright posture • Use of industrial machines • Physical exertion • Mental or environmental stress-related work • Working conditions	Anemia (hemoglobin < 10g/dL)
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	Life events: • divorce, separation, death, etc.
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PPROM Risk Factors

Previous PPROM

- PPROM when evaluated in studies has supported a strong risk for recurrence.
- For example, the Preterm Prediction Study, a large prospective study conducted by the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network, observed that women with a history of PPROM had a 13.5% rate of PPROM in a subsequent pregnancy compared to 4.1% in women with no such history [3].
- Others have reported recurrence rates at high as 32% [4].
- Women with a history of PPROM are at risk for recurrent PPROM or PTB without PPROM [5,6].

PPROM Risk Factors

Genital Tract Infection

- Genital tract infection is the single most common identifiable risk factor for PPROM.
- Three lines of epidemiologic evidence support this association:
  - Women with PPROM are significantly more likely than women with intact membranes to have pathogenic microorganisms in the amniotic fluid.
  - Women with PPROM have a significantly higher rate of histologic chorioamnionitis than those who deliver preterm without PPROM.
  - Lower genital tract infections, particularly bacterial vaginosis, has been associated with higher rates of PPROM than uninfected women [7].
  - There is a strong association between bacterial colonization of the lower genital tract and PPROM.
  - Lower genital tract microorganisms can colonize and produce phospholipases. The phospholipases stimulate prostaglandin production and can lead to uterine contractions.
  - The host's immune response to endocervical and fetal membrane bacterial invasion can lead to production of inflammatory mediators which will cause weakening of the fetal membranes and can cause PPROM [7].
  - The host's immune and inflammatory response can be genetically regulated and play a role in susceptibility and response to infections that are associated with PPROM.

PPROM Risk Factors

Antepartum bleeding

- When antepartum bleeding occurs in the first trimester, there is a statistically significant increase in the risk of PPROM [8].
- Bleeding in more than one trimester increases the risk of PPROM by 3-to-7 fold [2,9,10].

Cigarette smoking

- Among smokers, the risk of PPROM climbs by 2-to-4 fold compared to non-smokers [10].
- This risk continues after other treatment for PPROM has been provided, including infection.

PPROM is noted to have a classic presentation of a sudden gush of clear or pale yellow fluid from the vagina.

The problem is that many women describe intermittent or constant leaking of small amounts of fluid or just a sensation of wetness within the vagina or on the perineum.

On ultrasonography:

- Ultrasound findings show 50-70% of women with PPROM to have low amniotic fluid volume (AFV) on initial sonography [14].

Physical exam:

- Pathognomonic of PPROM is directly visualizing amniotic fluid coming out of the cervical canal or pooling in the vaginal fornix.
- During the direct visualization of the cervical os, if the amniotic fluid is not immediately visible, the woman can be requested to push on her fundus, Valsalva, or cough to provoke leakage of the amniotic fluid.
- A sterile speculum is utilized during the examination for patients who are not in active labor.
- The digital exam should be avoided and this avoidance may decrease the latency period (i.e. time from rupture to membranes to delivery) and increase the risk of intrauterine infection [11-13].
- Inspection of the cervix may reveal dilation, effacement and rarely, prolapsed fetal parts, prolapsed umbilical cord, or hour-glassing of the amniotic membrane outside of the cervical os.

1

2

3

- The majority of pregnancies with PPROM deliver within one week of membrane rupture.
- A randomized trial of PPROM at 24-32 weeks showed the median time to delivery of 239 group B streptococcal (GBS) negative women managed expectantly with prophylactic antibiotics was 6.1 days along with the following observations:
  - 27% delivered within 48 hours
  - 56% delivered within 7 days
  - 76% delivered within 14 days
  - 86% delivered within 21 days [15]

1

2

3

- Of interest, the duration of latency inversely correlates with gestational age at membrane rupture [16].
- Sealing of the membranes is associated with a more favorable outcome, however, cessation of fluid leakage is rare, except in women with PPROM related to amniocentesis [17].
- Unfortunately, the fetus and neonate are at greater risk of PPROM-related morbidity and mortality than the mother (**Table 2**).

Table 2: Complications with PPROM

Pregnancy Complications	Potential Consequences for Offspring	Potential Maternal Consequences
Intrauterine infection	Neonatal sepsis Long-term neurodevelopmental abnormalities, particularly cerebral palsy	Postpartum endometritis
Umbilical cord Compression	Fetal asphyxia	Cesarean delivery
Oligohydramnios	Limb restriction deformities and pulmonary hypoplasia (primarily with severe oligohydramnios in the early to mid second trimester), occurring rarely when membranes rupture occur after 23 weeks.	
Fetal malrepresentation		Cesarean delivery
Umbilical cord prolapse	Fetal asphyxia	Cesarean delivery
Placental abruption	Fetal asphyxia	Cesarean delivery Coagulopathy
Preterm birth	Morbidity of prematuraty	

1

2

3

- The morbidity associated with prematurity varies with gestational age and is higher in the setting of chorioamnionitis [18].
- There is an increased risk of neurodevelopmental impairment when the fetus is exposed to intrauterine inflammation [19].
- About one-third of PPROM patients develop potentially serious infections, such as intraamniotic infection (chorioamnionitis and funisitis), endometritis, or septicemia.
- Endometritis occurs more often following a cesarean than a vaginal delivery.
- Infection occurs at a higher rate the earlier the gestational age [19, 20].

Increased risk of placental abruption and prolapsed umbilical cord occurs with PPROM.

- Placental abruption occurs in 2 to 5% of pregnancies complicated by PPROM [21-24].
- Placental abruption risk increases even further with an increase of 7-9 fold in PPROM pregnancies when intrauterine infection or oligohydramnios is present [22, 23].
- Placenta abruption may be the event that either causes PPROM or the consequence of PPROM.

It is common to have fetal malpresentation and reduced AFV at a preterm gestational age.

- The cord prolapse risk is especially high, up to 11% in one study [25], when both non-vertex fetal presentation occurs with PPROM.
- This malpresentation may also increase the risk of abruption, infection, and fetal death in utero [26].

When PPROM occurs early, is severe and with prolonged oligohydramnios, it can be associated with pulmonary hypoplasia, facial deformation, and orthopedic abnormalities.

- These complications are much more likely when membrane rupture occurs under 23 weeks of gestation.

Risks of PPROM

- Nitrazine
- Ferning
- Ultrasonography
- Instillation of Indigo Carmine
- AmniSure vs Actim PROM
- AmniSure
- Actim PROM
- fFN

- Generally, the diagnosis of PPROM occurs clinically and is based on the visualization of amniotic fluid in the vagina of a woman who presents with a history of leaking fluid.
- When the diagnosis is uncertain, laboratory tests are utilized.

Click each term to the left to learn more about diagnosing PPROM.

Nitrazine

Ferning

Ultrasonography

Instillation of Indigo Carmine

AmniSure vs Actim PROM

AmniSure

Actim PROM

fFN

- After visualization, if PPROM is not obvious, the diagnosis can be confirmed by testing the pH of the vaginal fluid utilizing nitrazine paper or a like pH indicator product.
- The typical pH range of amniotic fluid is 7.0 to 7.3 and much higher compared to normal acidic vaginal pH of 3.8 to 4.2 [27].
- In up to 5% of testing, a false negative or false positive result occurs.
- The false negative results can occur when leaking is intermittent or the amniotic fluid is diluted by other vaginal secretions.
- On the other hand, false positive results may occur in the presence of alkaline vaginal fluids, such as blood, seminal fluid, or soap.
- When the urine has infection of proteus species, the pH of the urine may be elevated near 8.0.

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- Another confirmatory test is the presence of aborization, also called ferning.
- To view the arborization, fluid is obtained from the posterior vagina fornix in a woman suspected of having PPROM, swabbing this onto a glass and allowing it to dry for at least ten minutes.
- The dried amniotic fluid produces a delicate ferning pattern, in contrast to the thick and wide arborization pattern of dried cervical mucus.
- False positive fern testing may occur by well estrogenized cervical mucus or a fingerprint on the microscope slide.
- Insufficient amniotic fluid transferred from the swab to the slide or heavy contamination with vaginal discharge or blood can lead to false negative results.

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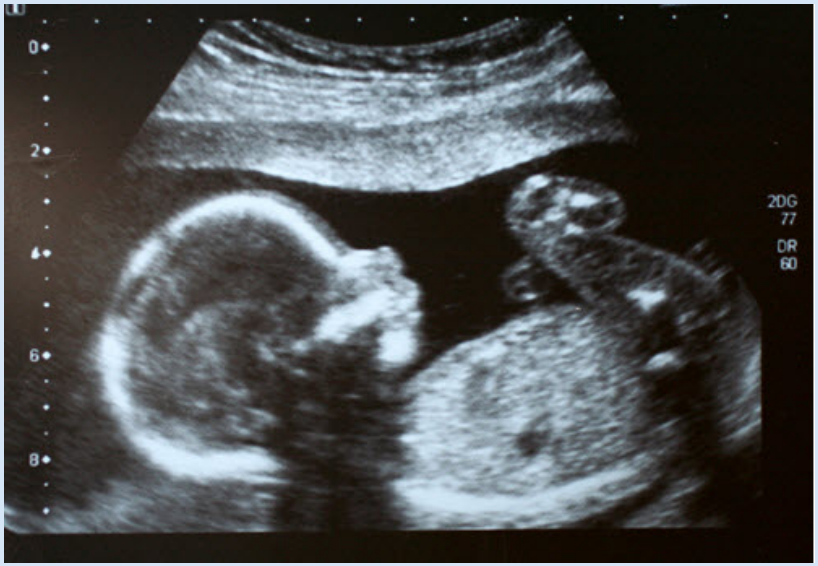
- In equivocal cases, ultrasound can be performed to look for a reduction in AFV.



- Nitrazine
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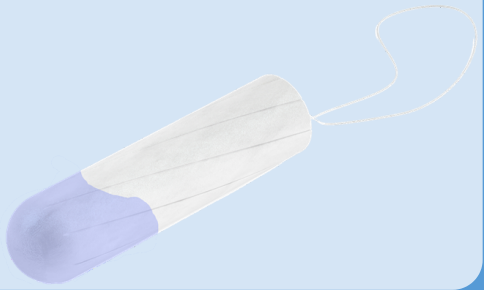
- When there is continued uncertainty of PPROM, instillation of indigo carmine into the amniotic cavity may lead to a definitive diagnosis.
- Utilizing ultrasound guidance, 1 mL of indigo carmine in 9 mL of sterile saline is injected transabdominally into the amniotic fluid.
- A tampon is placed in the vagina.
- When the tampon is removed it is examined for blue staining, typically about 20 minutes later, and if present PPROM is confirmed.
- Of note, the maternal urine will also turn blue so this finding should not be confused with leaking of amniotic fluid.
- Alternatives to indigo carmine include sodium fluorescein and phenolsulfonphthalein where available.



Nitrazine

Ferning

Ultrasonography

Instillation of Indigo Carmine

AmniSure vs Actim PROM

AmniSure

Actim PROM

fFN

- There are commercially available tests for diagnosing ROM, two of which are:
  - Amnisure, which is placental alpha microglobulin-1 protein assay (PAMG-1)
  - Actim PROM, an insulin growth factor binding protein 1 (IGFBP-1)
- A meta-analysis from 2013 of prospective observational or cohort studies investigating AmniSure was more accurate than Actim PROM for diagnosing ROM in all patient populations (i.e. known or unknown rupture status) [30].
- A subsequent randomized trial reported similar findings [31].

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- AmniSure (placental alpha microglobulin-1 protein assay) is a rapid slide test using immunochromatography methods to detect trace amounts of placental alpha microglobulin-1 protein in vaginal fluid.
- A significant advantage to AmniSure testing is that the testing is not affected by semen or trace amounts of blood.
- There is a commercially available kit that is obtained by the provider at the point of care.
- The kit has a sterile swab, which is inserted into the vagina for one minute, then placed into a vial containing a solvent for one minute and then an AmniSure test strip is dipped into the vial.
- The result is revealed by the presence of one or two lines within the next 5-10 minutes:
  - No visible line is an invalid result
  - One visible line is a negative result
  - Two visible lines is a positive result
- The sensitivity ranged from 94.4-98.9% with a specificity range of 87.5-100% in large studies {32-36].
- There were three false positives in one study and the authors hypothesized these had occurred due to a small leak that sealed over [33].
- The cost of the test is relatively high, often limiting the use to cases where the diagnosis remains uncertain after physical exam with ferning and nitrazine testing.

Nitrazine

Ferning

Ultrasonography

Instillation of Indigo Carmine

AmniSure vs Actim PROM

AmniSure

Actim PROM

fFN

- In problematic cases, the identification of insulin-like growth factor 1 (IGFBP-1) may be of value in confirming the diagnosis of PPROM.
- This protein, insulin-like growth factor binding protein 1, is secreted by decidual and placental cells. It has a very high concentration in amniotic fluid compared to other body fluids.
- The method is easy to use with a immunochromotography dipstick method (Actim PROM), and is available in some countries for use at the bedside to detect IGFBP-1 in vaginal secretions.
- This test is popular in Europe, but is not widely used in the United States.
- Two blue lines on the dipstick indicate a positive test.
- The test is not affected by the presence of infected vaginal secretions, urine, semen, or small amounts of blood.
- This test is most accurate when performed as soon as possible after PROM.
- Sensitivity ranges form 95-100% in detecting ruptured membranes with specificity ranging from 93-98%, and positive predictive values approach 98% [35, 37-40].
- This test is very helpful in identifying women likely to deliver within seven days.

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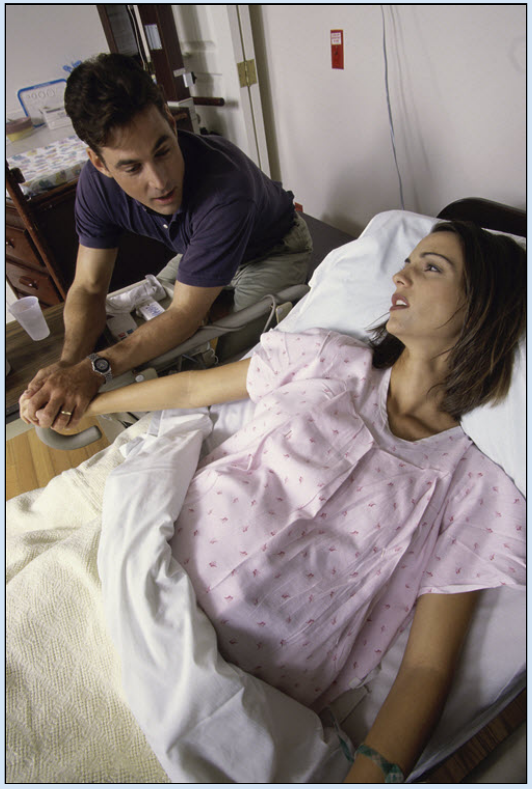
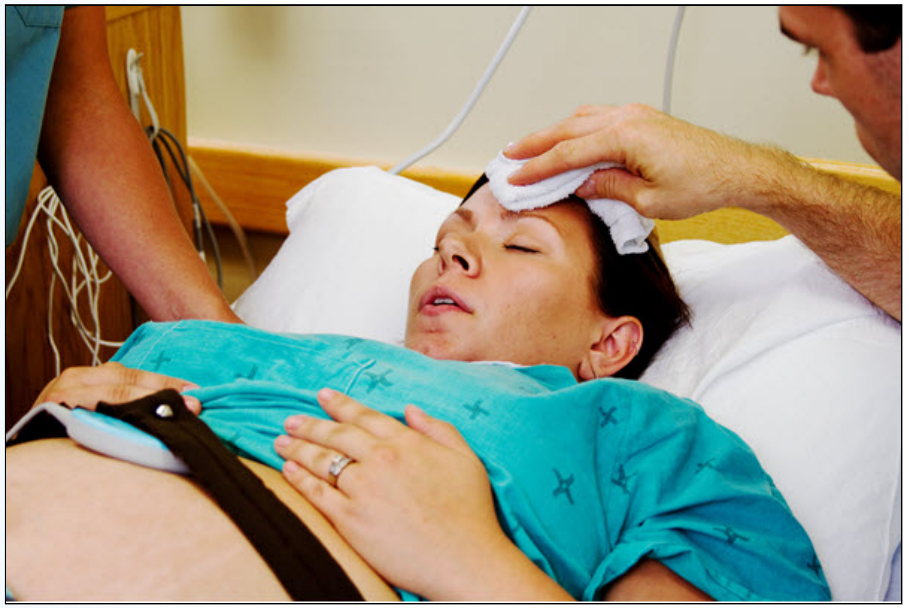


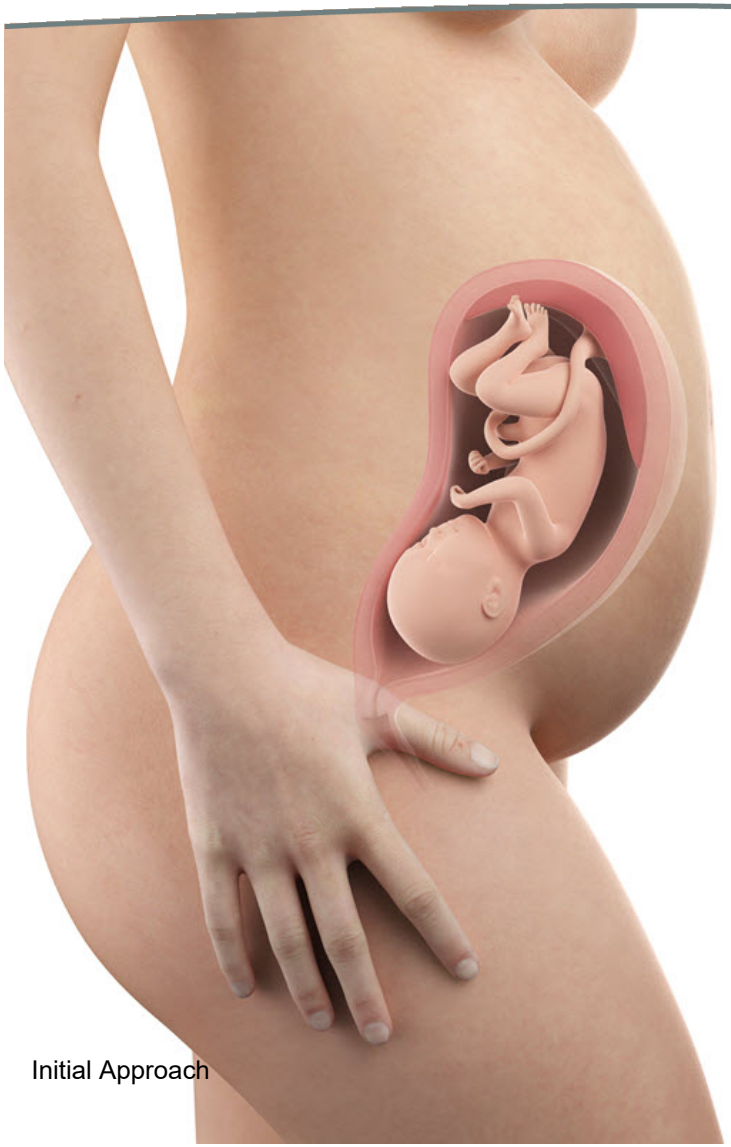
A negative fetal fibronectin result strongly supports the absence of membrane rupture.

A positive result only indicates disruption of the interface between chorion and decidua, which can occur with intact membranes [41].

- There are other causes of vaginal wetness:
  - Urinary incontinence
  - Vaginal discharge
  - Perspiration
  - When the clinical and laboratory findings for PPROM are negative, these other causes should be considered.
  - A mild reduction in amniotic fluid volume, by ultrasound findings, is non-specific and related to many etiologies other than PPROM.
- Highly suggestive of PPROM is the finding on ultrasound of anhydramios or severe oligohydramnios, combined with a characteristic history.
  - Although, renal agenesis, obstructive uropathy, or severe utero-placental insufficiency may be the etiology to marked reductions in amniotic fluid volume.

- Some of the most controversial issues in perinatal medicine come from contentions in treating PPROM.
- Points of contention include:
  - Expectant management versus intervention
  - Use of tocolytics
  - Duration of administration of antibiotic prophylaxis
  - Timing of administration of antenatal corticosteroids
  - Methods of testing for maternal/fetal infection
  - Timing of delivery
  - Treatment of women from 23-37 weeks gestation who have PPROM will be reviewed.
  - Treatment of previable PPROM and ROM at term are topics beyond the scope of this program.





Initial Approach

PPROM management in women is based upon consideration of several factors, which are assessed at presentation:

- Gestational age
- Presence or absence of maternal and/or fetal infection
- Presence or absence of labor
- Fetal presentation
- Fetal well-being
- Fetal lung maturity
- Cervical status by visualization using a sterile speculum
- Availability of neonatal intensive care unit (NICU)

Assessment

- Nitrazine and fern
- Placental alpha microglobulin-1 protein assay (AmniSure)
- Once confirmed PPROM then consider
  - Complete blood count
  - Culture for Neisseria gonorrhoeae, Chlamydia trachomatis, Trichomonas vaginalis, and bacterial vaginosis
- Fetal lung maturity testing
  - Lamellar body count in amniotic fluid
  - Lecithin:sphingomyelin (L/S) ratio
- Rectovaginal culture for GBS
- Ultrasound to determine
  - Fetal growth
  - Fetal position
  - Residual AFV
  - Fetal anatomy
- Biophysical profile (BPP)
- Cardiotocography monitoring, also known as non-stress test (NST), for recording of fetal heart rate (FHR) and uterine contraction pattern.

- A key factor in managing PPROM is whether to induce labor, perform a cesarean, or manage expectantly.
- An immature fetus may benefit by prolonging the pregnancy which could result in significant reduction in gestational aged-related morbidity. However, this benefit needs to balance with the risks of PPROM associated complications and their sequelae (Table 2).
- When intratuterine infection, abruptio placentae, nonreassuring fetal testing, or high risk of cord prolapse is present or suspected, then expeditious delivery of these women is appropriate.
- With each of these situations, fetal well-being can quickly deteriorate during expectant management and there are no therapeutic interventions available other than delivery.
- When these complications are absent, interventions leading to delivery are not indicated, until 34 weeks, then proceeding with delivery is appropriate.
- An algorithm to manage women with PPROM at 26-37 weeks is shown (Algorithm 1).
- Several aspects of management will be discussed; however, a detailed analysis of the nuances in managing women with PPROM is beyond the scope of this program.

Table 2: Complications with PPROM

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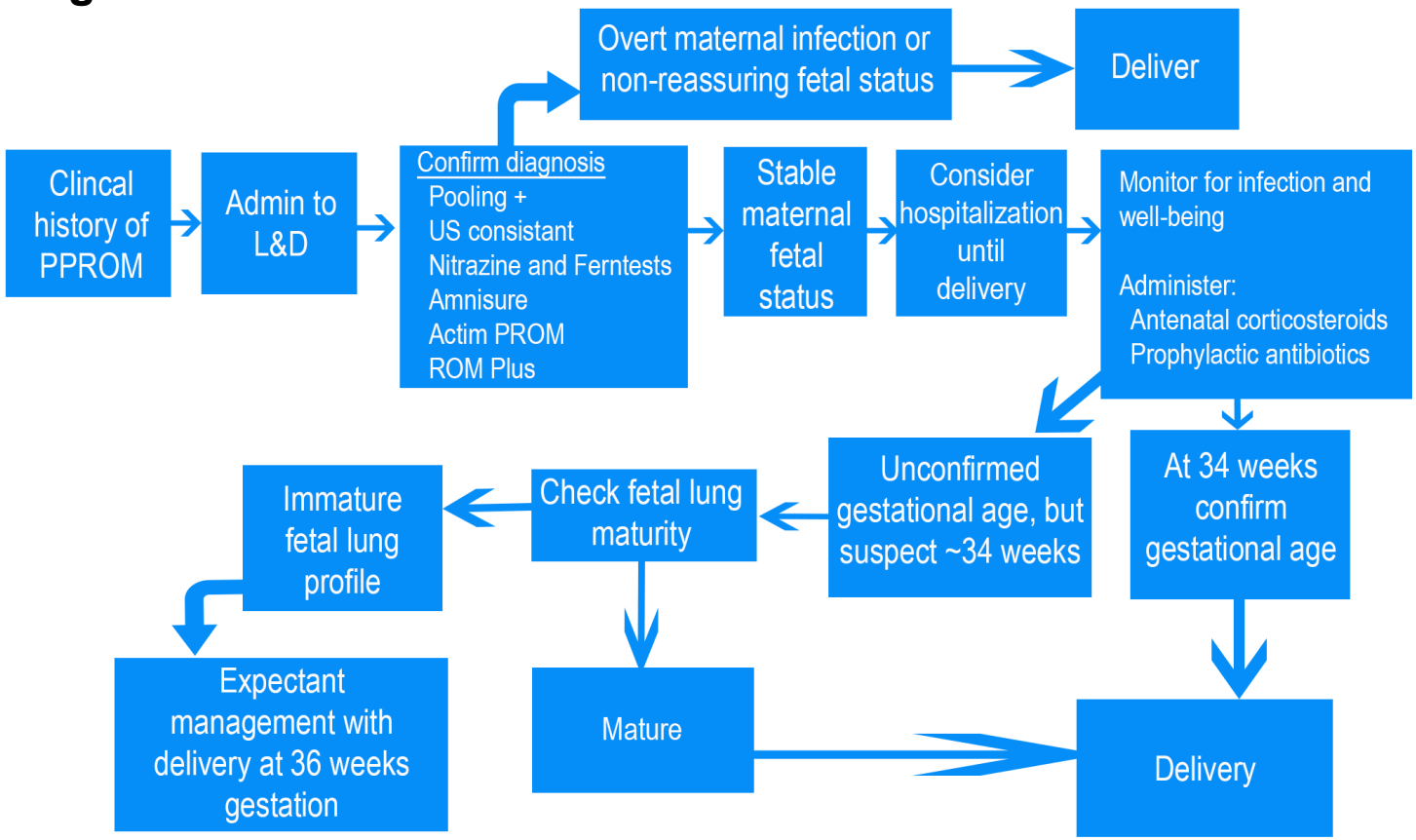
Preterm birth	Morbidity of prematuraty	

Algorithm: Managing PPROM 23-34 Weeks gestation



- The optimal time to intervene varies by facility and depends on the balance between morbidity related to prematurity and morbidity related to complications from PPROM.
- American College of Obstetricians and Gynecologists (ACOG) suggests delivery of all patients at 34 weeks 0 days gestation [42].
- Between 28-37 weeks gestation, meta analysis of randomized trials and subsequent randomized trials, have not provided conclusive evidence favoring induction or expectant management of women with PPROM [43-46].
- The data is limited for analysis due to heterogeneity among the trials.
- Examples are fetal lung maturity not being consistently determined and thus not a factor in selecting patients who may or may not benefit from expectant management.
- Another example that could not be assessed is the administration of prophylactic antibiotics because there was not a standard practice and patient level data was not analyzed.
- The last concern involves the power of the trials; the trials have been underpowered to detect meaningful measures of neonatal and maternal morbidity.

Administration of Antenatal Corticosteroids
Antibiotic Therapy
Prophylaxis
Drug Regimen
Chemoprophylaxis for GBS
Tocolysis
Supplemental Progesterone
Hospitalization versus Home Care
Maternal Monitoring
Fetal Monitoring

- When women have a gestation between 23-34 weeks, and have been diagnosed with PPROM, then a course of corticosteroids should be given.
- Two systematic reviews of randomized trials [47,48] provide data supporting antenatal glucocorticoid treatment showing reduced neonatal death, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC), and duration of neonatal respiratory support without an increase in either maternal nor neonatal infection rates.
- Mean risk reduction for these adverse events ranged from 30 to 60 percent.
- The use of rescue therapy is controversial as available data on potential benefits and harms are not definitive in this setting [49-51].
- It is reasonable to provide a single dose of "rescue" therapy if the woman is clinically estimated to be at high risk of delivery within the next seven days, at least two weeks have passed since the initial course of antenatal corticosteroids, and the initial course was given under 28 weeks gestation.
- The research is inconsistent regarding the effect of PPROM on fetal pulmonary maturation.
- The discordance may be due to failure to adjust for factors affecting neonatal respiratory function such as:
  - Mode of delivery
  - Presence or absence of labor
  - Gestational age
  - Duration of latency
  - Comorbidities [52]

Click each term to learn more.

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- The indication for antibiotics are to prolong latency and to reduce the risk of early onset neonatal GBS infection, when present.

Click each term to learn more.

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- Infection may be both a cause and consequence of PPROM, thus making antibiotics a key component to her treatment regimen.
- Spontaneous PTL may be caused by the infection and may be the indication to proceed with medically - indicated preterm delivery.
- Goals of antibiotic therapy include reduction in frequency of maternal and fetal infection, thereby delaying the onset of preterm labor, and prolonging latency and the need for preterm birth.
- Studies underscore the importance of reducing infection by suggesting a relationship between chorioamnionitis, duration of membrane rupture, and development of cerebral palsy or neurodevelopment delay.
- Compared with placebo or no treatment, antibiotic use was associated with significant reductions in:
  - Chorioamnionitis
  - Babies born within 48 hours
  - Neonatal infection
  - Use of surfactant
  - Neonatal oxygen therapy
- Prophylactic antibiotics are given for seven days when the women is less than 34 weeks of gestation at the time of membrane rupture.
- Targets of antibiotic therapy include:
  - Ampicillin and Amoxicillin
    - group B streptococcus
    - many aerobic gram-negative bacilli

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- Targets of antibiotic therapy include:
  - Ampicillin and Amoxicillin
    - group B streptococcus
    - many aerobic gram-negative bacilli
    - some anaerobes
  - Azithromycin
    - Ureaplasma for chorioamnionitis with PPROM
    - Chlamydia trachomatis (cause of neonatal conjunctivitis and pneumonitis)

Click each term to learn more.

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Fetal Monitoring

- The optimal regimen is not clear, but a regimen with reasonable activity against major pelvic pathogens should be utilized [53].
- A seven day course of antibiotic prophylaxis is recommended for all women with PPROM who are managed expectantly.
- A current preference is Ampicillin 2gm intravenous (IV) every six hours for 48 hours followed by Amoxicillin 500mg po TID or 875mg po BID for an additional five days.
- In addition, one dose of azithromycin 1 gm po is recommended upon diagnosing PPROM.
- Targets of antibiotic therapy involve:
  - Ampicillin and Amoxicillin for:
    - group B streptococcus
    - many aerobic gram negative bacilli
    - some anaerobes
  - Azithromycin for:
    - mycoplasm (an important cause of chorioamnionitis with PPROM)
    - Chlamydia trachomatis (cause of neonatal conjunctivitis and pneumonitis)
    - abnormal cerebral ultrasound prior to hospital discharge
- The regimen discussed is similar to the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network trial.
  - This trial studied antibiotic therapy for reduction of infant morbidity after PPROM with IV ampicillin 2g every 6 hours and erythromycin 250mg every 6 hours for 48 hours FOLLOWED by oral amoxicillin 250mg every 8 hours and erythromycin 333mg every 8 hours for five days [16]. This is recommended by ACOG.
  - Due to the ease of administration, improved gastrointestinal tolerance, favorable cost profile and similar efficacy, azithromycin is recommended in lieu of a multiple-day course of erythromycin.
  - In a retrospective study, the two regimens ampicillin + erythromycin versus ampicillin +

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Administration of Antenatal Corticosteroids
Antibiotic Therapy
Prophylaxis
Drug Regimen
Chemoprophylaxis for GBS
Tocolysis
Supplemental Progesterone
Hospitalization versus Home Care
Maternal Monitoring
Fetal Monitoring

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  - Due to the ease of administration, improved gastrointestinal tolerance, favorable cost profile and similar efficacy, azithromycin is recommended in lieu of a multiple-day course of erythromycin.
  - In a retrospective study, the two regimens ampicillin + erythromycin versus ampicillin + azithromycin, were reviewed in women with PPROM and resulted in similar pregnancy and neonatal outcomes [54]:
    - Length of latency
    - Mean birth weight
    - Rates of chorioamnionitis
    - Cesarean delivery
    - Low Apgar score
    - Neonatal sepsis
    - Neonatal respiratory distress syndrome (RDS)

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Administration of Antenatal Corticosteroids
Antibiotic Therapy
Prophylaxis
Drug Regimen
Chemoprophylaxis for GBS
Tocolysis
Supplemental Progesterone
Hospitalization versus Home Care
Maternal Monitoring
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- GBS chemoprophylaxis is indicated when GBS test results are positive or unknown and delivery is imminent. It is generally not given when women have had recent negative results, within the prior five weeks.
- For women GBS colonized, in labor at the time of admission or who go into labor within 48 hours of admission, IV portion of the regimen described (ampicillin 2gm IV Q 6hr for 48 hours) should provide adequate treatment.
- The regimen of IV ampicillin followed by oral amoxicillin, combined with azithromycin, is usually given for seven days.
- Once the seven day regimen is complete, the antibiotics should be discontinued. For a woman with culture positive GBS, specific prophylaxis for GBS should be resumed when the patient goes into subsequent labor [55].
- If the woman has a history of high risk for penicillin allergy, it is suggested she be given:
  - Azithromycin 1 gram orally upon admission, plus
  - Clindamycin 900mg IV every 8 hours for 48 hours, plus
  - Gentamicin 5mg/kg actual body weight IV every 24 hours for two doses, followed by
  - Clindamycin 300mg orally every eight hours for five days. This regimen is appropriate for patients with a positive GBS culture and laboratory-documented GBS susceptibility to clindamycin
- If the women has a low-risk penicillin allergy, antibiotic therapy suggested is a one time oral dose of azithromycin 1g and cefazolin 1g IV Q 8 hours for 48 hours, followed by cephalexin 500mg orally four times daily for five days. These drugs provide coverage for both GBS and Escherichia coli, which are two major causes of neonatal infection.
- If the woman is at high risk for anaphylaxis and GBS is resistant to clindamycin, per lab results, the following treatment regimen is recommended
  - Azithromycin 1 gram orally upon admission, PLUS
  - Vancomycin 20mg/kg every 8 hours (maximum single dose is 2 grams) for 48 hours
- Algorithm's are available for GBS prevention from the Centers for Disease Control and Prevention

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Administration of Antenatal Corticosteroids
Antibiotic Therapy
Prophylaxis
Drug Regimen
Chemoprophylaxis for GBS
Tocolysis
Supplemental Progesterone
Hospitalization versus Home Care
Maternal Monitoring
Fetal Monitoring

- Tocolysis has a principal indication in the setting of PPROM, in order to delay delivery 48 hours, allowing for administration of corticosteroids.
- In general, tocolysis should not be administered beyond 48 hours.
- Tocolysis is not indicated when women are found to have advanced labor > 4 cm dilated or in those with findings to suggest the presence of subclinical or overt chorioamnionitis.
- Tocolysis is also contraindicated with non-reassuring fetal status, abruptio placentae, and significant risk of cord prolapse such as fetal malpresentation and dilated cervix.

Click each term to learn more.

Administration of Antenatal Corticosteroids
Antibiotic Therapy
Prophylaxis
Drug Regimen
Chemoprophylaxis for GBS
Tocolysis
Supplemental Progesterone
Hospitalization versus Home Care
Maternal Monitoring
Fetal Monitoring

- There is no evidence to suggest supplemental progesterone extends the latent period in women with PPROM or provide other benefits.
- However, for women on supplemental progesterone due to a prior pregnancy with preterm delivery, related to PTL or PPROM, discontinuing the progesterone upon diagnosis of PPROM would be appropriate.

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Administration of Antenatal Corticosteroids
Antibiotic Therapy
Prophylaxis
Drug Regimen
Chemoprophylaxis for GBS
Tocolysis
Supplemental Progesterone
Hospitalization versus Home Care
Maternal Monitoring
Fetal Monitoring

- Women with PPROM and a viable fetus warrant hospitalization from the time of diagnosis until delivery, with very few exceptions.
- Once PPROM is diagnosed, the woman's activity is limited to using the bathroom and sitting up in a bedside chair.
- All pregnant women hospitalized and placed on bedrest should undergo thromboprophylaxis with sequential compression devices [56].
- Women with additional risk factors for deep venous thrombosis (DVT) should receive prophylactic doses of enoxaparin (Lovenox), 1mg/kg/day. Enoxaparin (Lovenox) should be discontinued 48 hours prior to delivery.
- When weight gain occurs during pregnancy, intermediate dose anticoagulation adjustment can be made. American College of Physicians [75] and ACOG [76] recommend enoxaparin 40mg twice daily, some experts use an alternate dose of enoxaparin at 1mg/kg.

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Administration of Antenatal Corticosteroids
Antibiotic Therapy
Prophylaxis
Drug Regimen
Chemoprophylaxis for GBS
Tocolysis
Supplemental Progesterone
Hospitalization versus Home Care
Maternal Monitoring
Fetal Monitoring

- Women with PPROM need to be monitored for signs of infection. Unfortunately, there is not a consensus as to the best approach for these women.
- At minimum, routine parameters such as maternal temperature, uterine tenderness and contractions, and maternal and fetal heart rate should be monitored.
- Markers for inflammation and infection may be periodically ordered but have not proven useful [57].
- It is controversial for the woman to undergo amniocentesis for gram stain, culture, leukocyte esterase, and glucose.
- An amniocentesis is not recommended to screen for amniotic infection in an asymptomatic woman.
- The amniocentesis may be indicated when the clinical diagnosis of chorioamnionitis is uncertain and more information is needed for treatment versus expectant management.
- In at least 50% of patients, the amniotic fluid sample is insufficient for the woman to undergo amniocentesis, thus the diagnosis of chorioamnionitis will have to be based clinically with indirect testing such as an abnormal peripheral white blood cell count (WBC) and physical exam.
- Diagnosis and management of intraamniotic infection is beyond the scope of this program.

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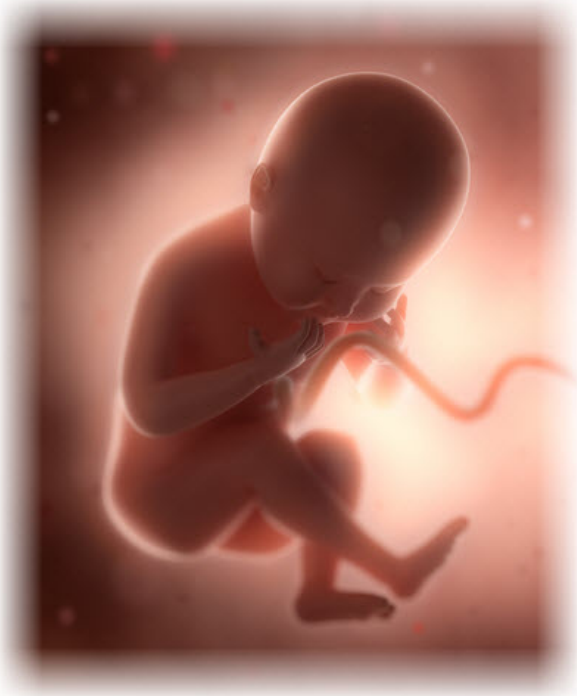
Administration of Antenatal Corticosteroids
Antibiotic Therapy
Prophylaxis
Drug Regimen
Chemoprophylaxis for GBS
Tocolysis
Supplemental Progesterone
Hospitalization versus Home Care
Maternal Monitoring
Fetal Monitoring

- Fetal surveillance is generally employed such as kick counts, NSTs, and BPP. These provide the woman and clinician some assurance of fetal well-being.
- Recommendations to perform a daily NST are reasonable.
  - When the NST is non-reassuring, then a BPP is obtained.
  - When attempting to predict fetal infection, these tests (NST, BPP) do not have good sensitivity with NST at 39% and BPP at 25 percent [58].
- The optimum type and frequency of testing does not have a consensus.
- A low AFV is associated with an increased risk of fetal umbilical cord compression and shorter latency, but the value of NST's or the BPP score for predication of adverse fetal/neonatal outcome is low [15].
- Fetal umbilical cord doppler surveillance, similarly, is not useful for predicting fetal status in PPROM either [59-61].

Click each term to learn more.

The fetus/neonate is at greater risk of PPROM-related morbidity and mortality than the mother.

- Neonatal sepsis can occur from intrauterine infection with long term neurodevelopmental abnormalities, particularly cerebral palsy.
- Umbilical cord compression can lead to fetal asphyxia.
- Limb restriction deformities and pulmonary hypoplasia may result from the oligohydramnios; primarily with severe oligohydramnios in early to mid second trimesters.
  - When membranes rupture occurs after 23 weeks, these complications are rare.
- Umbilical cord prolapse may lead to fetal asphyxia.
- Abruptio placentae may also lead to fetal asphyxia.
- Preterm birth may lead to
  - Respiratory abnormalities
  - Intraventricular hemorrhage (IVH)
  - Necrotizing enterocolitis (NEC)
  - Retinopathy of prematurity
  - Patent ductus arteriosus (PDA)



Click the arrows below to view the slides.

Women with HSV, HIV, or Cerclage

- Controversy exists with the expectant management of women with PPROM and genital herpes simplex virus (HSV) or human immunodeficiency virus (HIV) and opinions regarding the best course of action diverge widely.
- These issues are beyond the scope of this program.

Click the arrows below to view the slides.

Meconium Stained Fluid

- In term and preterm women with PROM, studies showed those with meconium stained amniotic fluid have higher rates of both overt and subclinical chorioamnionitis and positive amniotic fluid cultures [61-63].
- When meconium is released it predisposes to infection by enhancing growth of bacteria and lowering phagocytic capacity of neutrophils [64].
- It is possible; however, that the meconium-like staining could actually be pigment staining associated with decidual hemorrhage such as from abruption.
- Women with PPROM and meconium-stained amniotic fluid should be evaluated for signs of chorioamnionitis.
- Meconium in isolation is not an indication for intervention. So no action is needed in the absence of these signs.

Click the arrows below to view the slides.

Tissue Sealants

- Neither the safety nor the efficacy has been established for tissue sealants. However, there are some case reports of a variety of tissue sealants (i.e. fibrin glue, gelatin sponge) showing some success in stopping leakage.

Click the arrows below to view the slides.

Amnioinfusion

- Pregnancy outcomes were studied in a 2014 systematic review and meta-analysis comparing women who received antepartum transabdominal amnioinfusion to those who underwent usual care for PPROM in the third trimester. The five trials had n = 241 pregnancy women.
- Very small trials with low to moderate quality have shown transabdominal amnioinfusion resulting in statistical reductions in neonatal death, sepsis, infection, and pulmonary hypoplasia but the data for each outcome was limited.
- Better understanding is needed on peri-natal outcome regarding whether amnioinfusion is beneficial in PPROM. More and better information is needed about the effects of specific amnioinfusion protocols:
  - Selection of patients such as gestational age at membrane rupture
  - Other interventions with type, dose, and duration of antibiotics along with use of corticosteroids
  - Amnioinfusion in women with PPROM is not indicated until further research is available to support a change in practice.

Click the arrows below to view the slides.

Diagnosis and Treatment of Overt Infection

- When there is maternal fever with associated leukocytosis, maternal and fetal tachycardia, uterine tenderness, and malodorous discharge, overt chorioamnionitis can be clinically diagnosed.
- Subclinical chorioamnionitis diagnosis requires amniocentesis to identify microorganisms in the amniotic fluid with gram stain and culture along with documenting an abnormally low amniotic fluid glucose concentration.
- In some countries, evaluation of infection can be performed using a rapid test for interleukin-6 (IL-6). This is the most sensitive marker for microbial invasion of the amniotic sac.
- Women who develop overt infection require therapy with therapeutic, rather than prophylactic antibiotics.
- Of note, women with PPROM with an identifiable genital tract infection such as gonorrhea, chlamydia, or bacterial vaginosis (BV), that would not be eliminated with prophylactic antibiotic regimen, should receive antibiotics specifically targeting the infection.

- Magnesium sulfate for neuroprotection
  - Magnesium sulfate is given prior to delivery according to standard clinical protocols for fetal neuroprotection in women at gestational ages of at least 24 weeks but less than 32 weeks at risk of imminent delivery.
- Timing of delivery for expectantly managed pregnancies
  - The approach to timing delivery is based on weeks gestation.


Gestation at 24 - 32 Weeks


Gestation at 32w0d - 33w6d

Gestation at 34 Weeks+

24 - 32 Weeks

- When there is no evidence of chorioamnionitis or fetal compromise, then expectant management is appropriate.
- Administer corticosteroids
- Antibiotics, broad spectrum, are given and GBS prophylaxis at delivery, if indicated
- Generally, prematurity is the greatest risk to the fetus with uncomplicated PPROM at less than 34 weeks of gestation.
- It is appropriate to manage pregnancies at this gestational age expectantly in the absence of complications:
  - Infection
  - Abruption
  - Cord prolapse
  - Unstable fetal presentation
  - Nonreassuring fetal assessment
- If delivery becomes evident, consideration to start magnesium for neuroprotection may be warranted.

Delivery Cont'd


Gestation at 24 - 32 Weeks


Gestation at 32w0d - 33w6d

Gestation at 34 Weeks+

32w0d - 33w6d

- When fetal lung maturity can be documented or there is evidence of an intraamniotic infection clinically or on amniocentesis, then delivery is indicated.
- Otherwise, expectant management with delivery at 34 weeks.
- Adminster corticosteroids if there is evidence of fetal lung immaturity or fetal lung status is unknown.
- Administer broad spectrum antibiotics and GBS prophylaxis, if indicated.


Gestation at 24 - 32 Weeks


Gestation at 32w0d - 33w6d

Gestation at 34 Weeks+

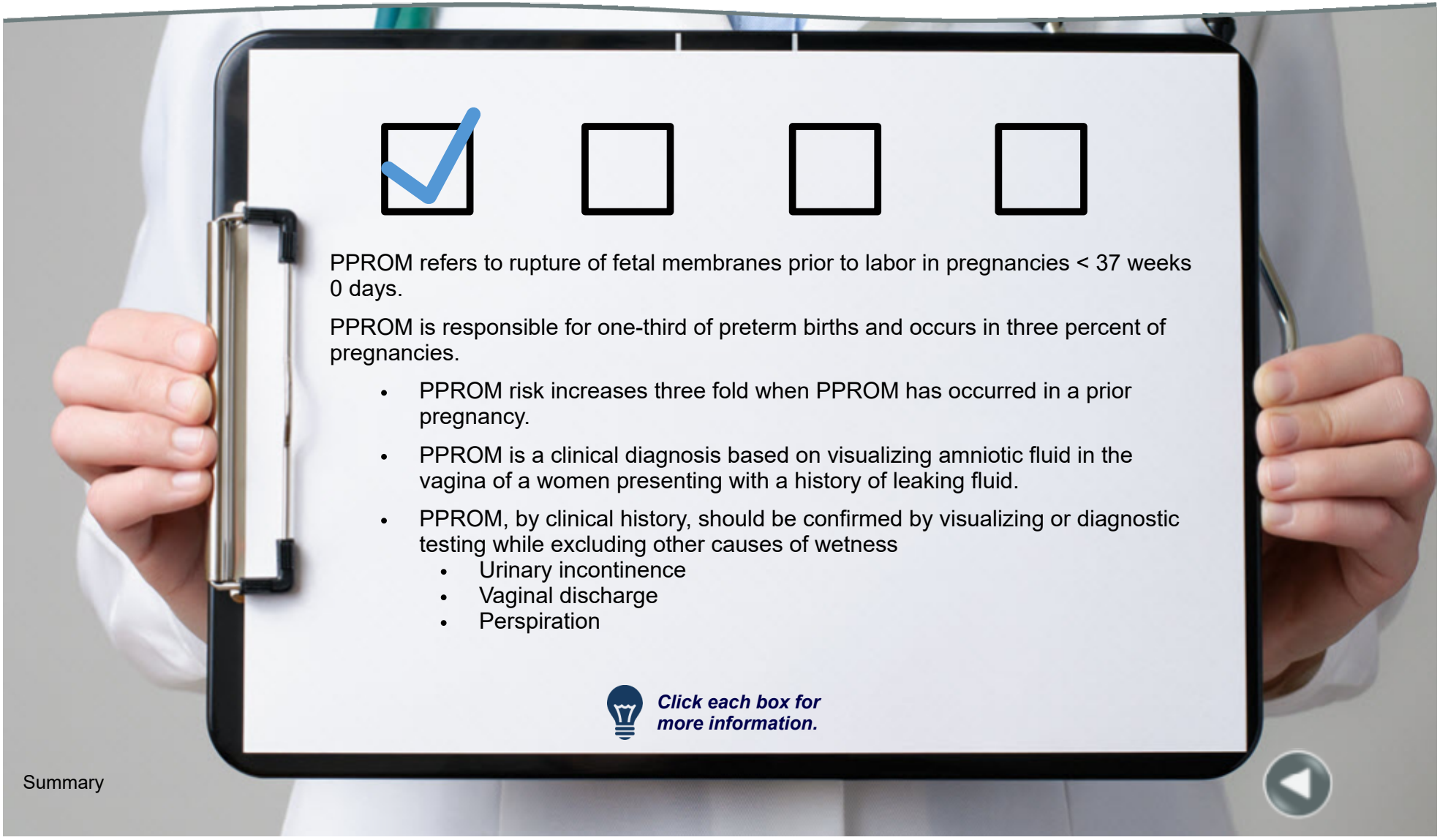
34 Weeks +

- When the pregnancy reaches 34 weeks, usually labor is induced without testing for fetal lung maturity.
- However, if there is uncertainty about the patient's gestational age, attempting to aspirate amniotic fluid from the vaginal vault to test for fetal lung maturity, is reasonable.
- Use of the lamellar body count as the initial screen for fetal lung maturity is appropriate.
- If this test is immature, performing a lecithin/sphingomyelin (L/S) ratio is a common next step.
- When testing shows a low risk of neonatal respiratory problems, initiating delivery is appropriate because the risks of prematurity are small when compared to the risk of developing maternal or fetal complications during expectant management [67].
- When fluid can not be aspirated or testing suggests a high risk of neonatal respiratory problems, continuing management expectantly until 36 weeks (by estimate) is appropriate; delivery without resampling at this time is appropriate.
- The woman who develops clinical evidence of infection or abruption, PTL or non-reassuring fetal well being would be indication for earlier delivery
- In summary the plan for gestations 34 weeks 0 days or greater is:
  - Delivery
  - Corticosteroids are not indicated
  - GBS prophylaxis begun on admission and continued until delivery unless she is known to have negative GBS status.

- In the situation where there are no contraindications to labor and vaginal birth, most women will deliver by spontaneous or induced vaginal delivery [68].
- Cesarean delivery is performed for standard indications; otherwise, labor is induced.
- At this point, performing a digital cervical exam is indicated to determine whether cervical ripening has occurred.
- Oxytocin is administered for induction when the cervix is found to be favorable, according to standard protocols.
- Once cervical ripening is adequate, the use of oxytocin over prostaglandins is favored since oxytocin is more easily titrated.

Unfavorable cervix

- With an unfavorable cervix, it may be advantageous to utilize misoprostol since it is effective for inducing labor as well.
- Fifteen randomized trials of women with term PROM underwent a meta-analysis and reported the rate of vaginal delivery in 12 and 24 hrs was similar after administration of misoprostol or oxytocin [69].
- Is it unknown whether misoprostol was advantageous in the subgroup of women with an unfavorable cervix since it was not evaluated.
- The optimum dose and route of misoprostol administration have not been determined.
- Prostaglandin E2 is a reasonable alternative [70].
- There is minimal information on the safety of mechanical methods of cervical ripening in PROM [71].
- Some methods are not utilized due to concerns of introduction of a foreign body may increase infection, such as Foley bulb for cervical ripening, so this method is typically avoided.



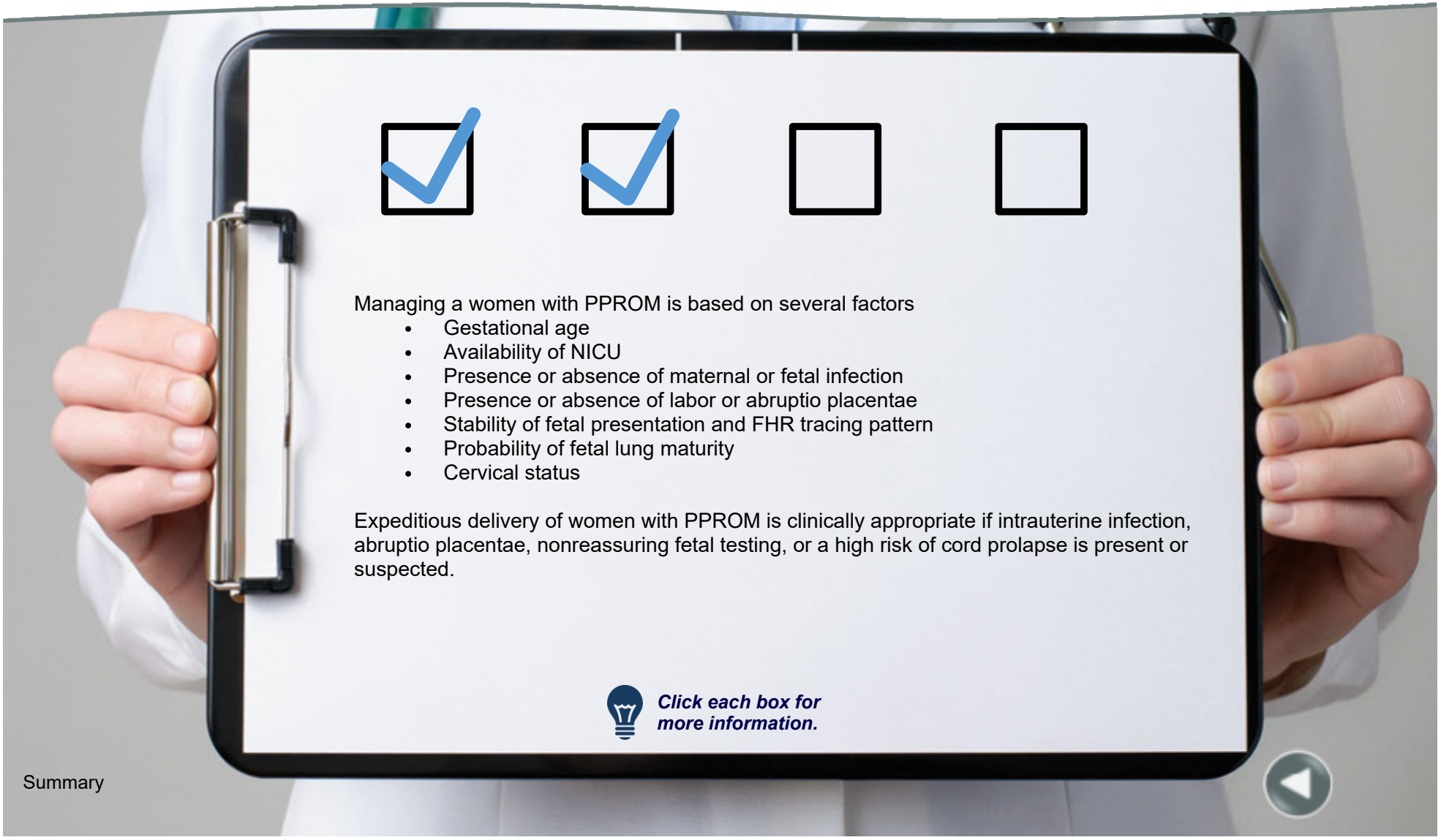
PPROM refers to rupture of fetal membranes prior to labor in pregnancies < 37 weeks 0 days.

PPROM is responsible for one-third of preterm births and occurs in three percent of pregnancies.

- PPROM risk increases three fold when PPROM has occurred in a prior pregnancy.
- PPROM is a clinical diagnosis based on visualizing amniotic fluid in the vagina of a women presenting with a history of leaking fluid.
- PPROM, by clinical history, should be confirmed by visualizing or diagnostic testing while excluding other causes of wetness
  - Urinary incontinence
  - Vaginal discharge
  - Perspiration

Click each box for more information.

Summary

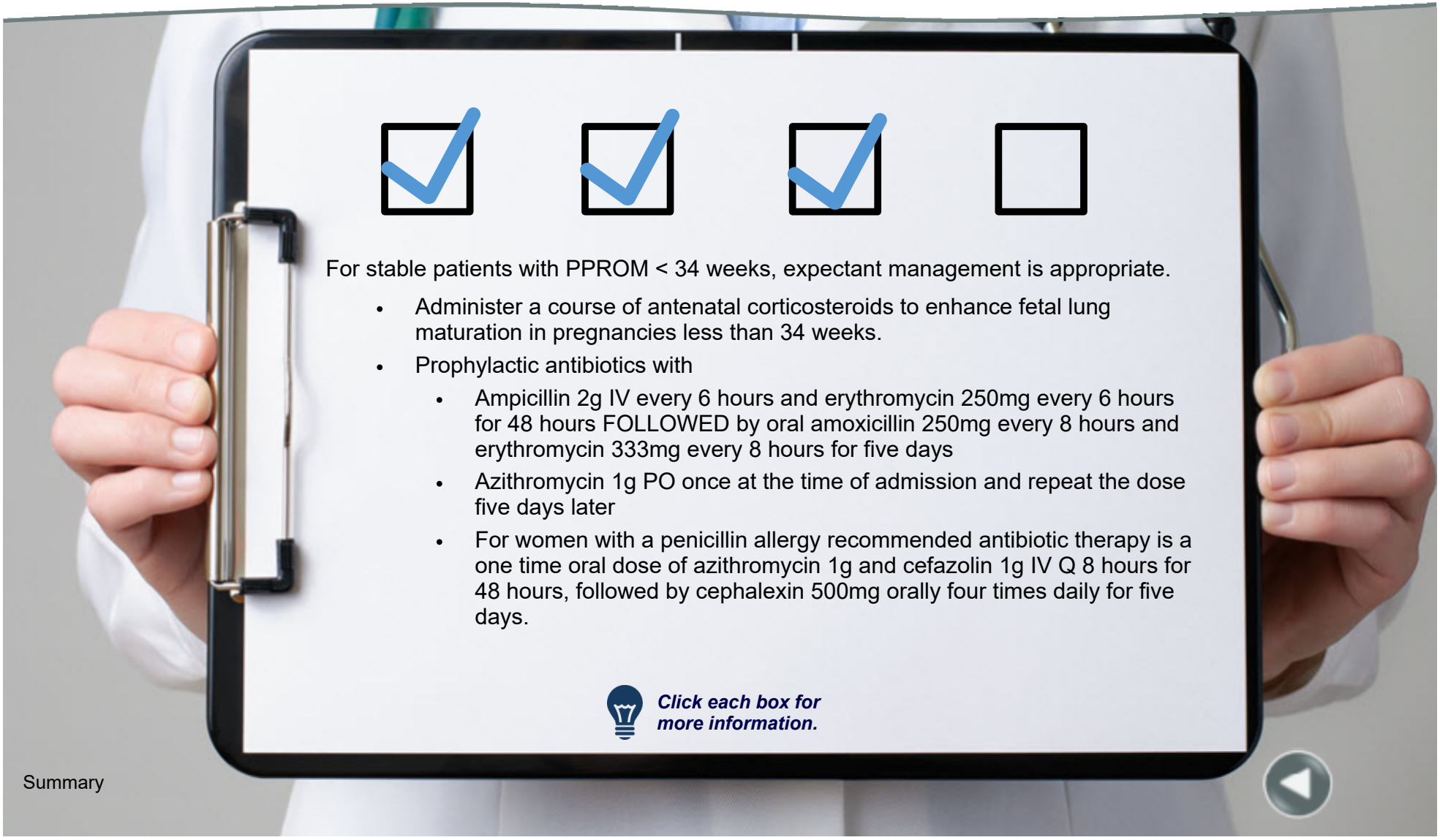


Managing a women with PPROM is based on several factors

- Gestational age
- Availability of NICU
- Presence or absence of maternal or fetal infection
- Presence or absence of labor or abruptio placentae
- Stability of fetal presentation and FHR tracing pattern
- Probability of fetal lung maturity
- Cervical status

Expeditious delivery of women with PPROM is clinically appropriate if intrauterine infection, abruptio placentae, nonreassuring fetal testing, or a high risk of cord prolapse is present or suspected.

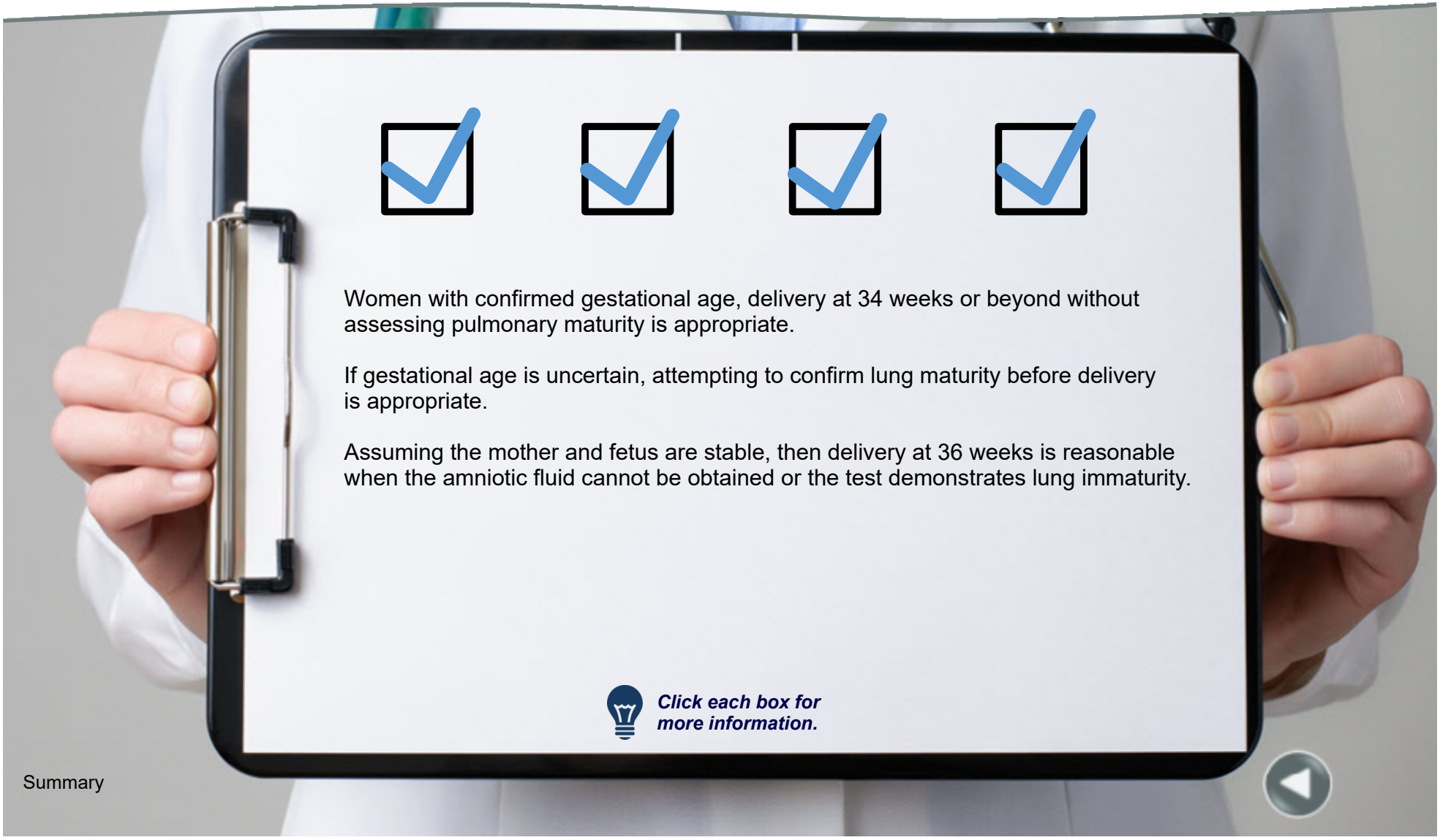
Click each box for more information.



For stable patients with PPROM < 34 weeks, expectant management is appropriate.

- Administer a course of antenatal corticosteroids to enhance fetal lung maturation in pregnancies less than 34 weeks.
- Prophylactic antibiotics with
  - Ampicillin 2g IV every 6 hours and erythromycin 250mg every 6 hours for 48 hours FOLLOWED by oral amoxicillin 250mg every 8 hours and erythromycin 333mg every 8 hours for five days
  - Azithromycin 1g PO once at the time of admission and repeat the dose five days later
  - For women with a penicillin allergy recommended antibiotic therapy is a one time oral dose of azithromycin 1g and cefazolin 1g IV Q 8 hours for 48 hours, followed by cephalexin 500mg orally four times daily for five days.

Click each box for more information.



Women with confirmed gestational age, delivery at 34 weeks or beyond without assessing pulmonary maturity is appropriate.

If gestational age is uncertain, attempting to confirm lung maturity before delivery is appropriate.

Assuming the mother and fetus are stable, then delivery at 36 weeks is reasonable when the amniotic fluid cannot be obtained or the test demonstrates lung immaturity.

Click each box for more information.

Congratulations!

You have successfully completed this module.

Click on the above 'X' to take the post-test for this course.
If you do not attain a passing score after two attempts at the post-test the entire program must be repurchased.

1. Callaghan Creanga AA, Kukllina EV. Severe maternal morbidity among delivery and postpartum hospitalisations in the US. Obstet Gynecol 2012; 120: 1029

2. Rattray DD, O'Connel CM, Baskett TF. Acute disseminaqted intrqavascular coagulation in obstetrics: a tertiary centre population review (1980 to 2009). J Obstet Gynaecol Can 2012; 34:341.

3. Erez O, Novack L, Beer-Weisel R, et al. DIC score in pregnant women-- a population based modification of the International Society on Thrombosis and Hemostasis score. PLoS One 2014; 9:e93240.

4. Gilbers WM, Danielsen B. Amniotic fluid embolism: decreased mortality in a population-based study. Obstet Gynecol 1999; 93:973.

5. Sibai BM, Ramdan MK, Usta I, et al. Maternal Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). Am J bstet Gynecol 1993; 169: 1000.

6. Earez O, Mastrolia SA, Thachil J. Disseminated Intravascular coagulations in pregnancy: insights in pathophysiology, diagnosis and management. Am J Obstet Gynecol 2015.

7. Bonnar J, Prentice CR, McNicol GP, Douglas AS. Haemostatic mechanism in the uterine circulation during placental separation. Br Med J 1970; 2:564.4.

8. Bonnar J, McNicol GP, Douglas AS. Coagulation and fibrinolytic mechanisms during and after normal childbirth. Br Med J 1970; 2:200.

9. Levi M. Disseminated intravascular coagulation (DIC) in pregnancy and the peri-partum period. Thromb Res 2009; 123 Supple2:263.

10. Takai H, Kondoh E, Sato Y, et al. Disseminated intravascular coagulation as the presenting sign of gastric cancer during pregnancy. J Obstet Gynaecol Res 2011; 37:1717.

11. Morimatsu Y, Matsubara S, Hirose N, et al. Acute promyelocytic leukemia: an unusual cause showing prolonged disseminated intravascular coagulation after placental abruption. Arch Gynecol Obstet 2008; 277:267.

12. Lockwood CJ, Murk W, Kayisli UA, et al. Progestin and thrombin regulate tissue factor expression in human term decidual cells. J Clin Endocrinol Metab 2009; 94:2164.

13. Lockwood CJ, Paidas M, Murk WK, et al. Involvement of human decidual cell-expressed tissue factor in uterine hemostasis and abruption. Thromb Res 2009; 124:516.

14. Hossain N, Paidas MJ. Disseminated intravascular coagulation. Semin Perinatol 2013; 37:257.

15. Gando S. Microvascular thrombosis and multiple organ dysfunction syndrome. Crit Care Med 2010; 38:S35.

16. Abbassi-Ghanavati M, Greer LG, Cunningham FG. Pregnancy and laboratory studies: a reference table for clinicians. Obstet Gynecol 2009; 114:1326.

17. Levi M, de Jonge E, van der Poll T, ten Cate H. Disseminated intravascular coagulation. Thromb Haemost 1999; 82:695.

18. Murphy N, Broadhurst DI, Khashan AS, et al. Gestation-specific D-dimer reference ranges: a cross-sectional study. BJOG 2015; 122:395.

19. Liu J, Yuan E, Lee L. Gestational age-specific reference intervals for routine haemostatic assays during normal pregnancy. Clin Chim Acta 2012; 413:258.

20. Hypertension in pregnancy: Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol 2013; 122:1122.

21. Bell SF, Rayment R, Collins PW, Collis RE. The use of fibrinogen concentrate to correct hypofibrinogenaemia rapidly during obstetric haemorrhage. Int J Obstet Anesth 2010; 19:218.

22. Harrity C, Johnson S, et al. The efficacy of fibrinogen concentrate compared with cryoprecipitate in major obstetric haemorrhage-- an observational study. Transfus Med 2012; 22:344.

23. Sharma SK, Vera RL, Stegall WC, Whitten CW. Management of a postpartum coagulopathy using thrombelastography. J Clin Anesth 1997; 9:243.

24. Huissoud C, Carrabin N, Audibert F, et al. Bedside assessment of fibrinogen level in postpartum haemorrhage by thrombelastometry. BJOG 2009; 116:1097.

25. Miall FM, Deol PS, Barnes TA, et al. Coagulation status and complications of pregnancy. Thromb Res 2005; 115:461.

26. Bracey A. Guidelines for Massive Transfusion, American Association of Blood Banks, Bethesda, MD 2005.Technical Manual, 16th ed, American Association of Blood Banks, Bethesda, MD 2008.

27. Charbit B, Mandelbrot L, Samain E, et al. The decrease of fibrinogen is an early predictor of the severity of postpartum hemorrhage. J Thromb Haemost 2007; 5:266.

28. Ahmed S, Harrity C, Johnson S, et al. The efficacy of fibrinogen concentrate compared with cryoprecipitate in major obstetric haemorrhage-- an observational study. Transfus Med 2012; 22:344.

29. Sagraves SG, Toschlog EA, Rotondo MF. Damage control surgery-- the intensivist's role. J Intensive Care Med 2006; 21:5.

30. Dildy GA, Scott JR, Saffer CS, Belfort MA. An effective pressure pack for severe pelvic hemorrhage. Obstet Gynecol 2006; 108:1222.

31. Martí-Carvajal AJ, Comunián-Carrasco G, Peña-Martí GE. Haematological interventions for treating disseminated intravascular coagulation during pregnancy and postpartum. Cochrane Database Syst Rev 2011; CD008577.

32. Nelson DB, Yost NP, Cunningham FG. Hemostatic dysfunction with acute fatty liver of pregnancy. Obstet Gynecol 2014; 124:40.

33. Rotondo MF, Zonies DH. The damage control sequence and underlying logic. Surg Clin North Am 1997; 77:761.

34. Lee SE, Park JS, Norwitz ER, et al. Measurement of placental alpha-microglobulin-1 in cervicovaginal discharge to diagnose rupture of membranes. Obstet Gynecol 2007; 109:634.

35. Abdelazim IA, Makhlouf HH. Placental alpha microglobulin-1 (AmniSure(®) test) for detection of premature rupture of fetal membranes. Arch Gynecol Obstet 2012; 285:985.

36. Marcellin L, Anselem O, Guibourdenche J, et al. [Comparison of two bedside tests performed on cervicovaginal fluid to diagnose premature rupture of membranes]. J Gynecol Obstet Biol Reprod (Paris) 2011; 40:651.

37. Abdelazim IA, Makhlouf HH. Placental alpha microglobulin-1 (AmniSure(®) test) for detection of premature rupture of fetal membranes. Arch Gynecol Obstet 2012; 285:985.

38. Birkenmaier A, Ries JJ, Kuhle J, et al. Placental α-microglobulin-1 to detect uncertain rupture of membranes in a European cohort of pregnancies. Arch Gynecol Obstet 2012; 285:21.

39. Akercan F, Cirpan T, Kazandi M, et al. The value of the insulin-like growth factor binding protein-1 in the cervical-vaginal secretion detected by immunochromatographic dipstick test in the prediction of delivery in women with clinically unconfirmed preterm premature rupture of membranes. Eur J Obstet Gynecol Reprod Biol 2005; 121:159.

40. Darj E, Lyrenäs S. Insulin-like growth factor binding protein-1, a quick way to detect amniotic fluid. Acta Obstet Gynecol Scand 1998; 77:295.

41. Erdemoglu E, Mungan T. Significance of detecting insulin-like growth factor binding protein-1 in cervicovaginal secretions: comparison with nitrazine test and amniotic fluid volume assessment. Acta Obstet Gynecol Scand 2004; 83:622.

42. Gaucherand P, Salle B, Sergeant P, et al. Comparative study of three vaginal markers of the premature rupture of membranes. Insulin like growth factor binding protein 1 diamine-oxidase pH. Acta Obstet Gynecol Scand 1997; 76:536.

43. ACOG practice bulletin. Premature rupture of membranes. Obstet Gynecol 2013; 122:918.

44. van der Ham DP, van der Heyden JL, Opmeer BC, et al. Management of late-preterm premature rupture of membranes: the PPROMEXIL-2 trial. Am J Obstet Gynecol 2012; 207:276.e1.

45. Al-Mandeel H, Alhindi MY, Sauve R. Effects of intentional delivery on maternal and neonatal outcomes in pregnancies with preterm prelabour rupture of membranes between 28 and 34 weeks of gestation: a systematic review and meta-analysis. J Matern Fetal Neonatal Med 2013; 26:83.

46. Buchanan SL, Crowther CA, Levett KM, et al. Planned early birth versus expectant management for women with preterm prelabour rupture of membranes prior to 37 weeks' gestation for improving pregnancy outcome. Cochrane Database Syst Rev 2010; :CD004735.

47. van der Ham DP, Vijgen SM, Nijhuis JG, et al. Induction of labor versus expectant management in women with preterm prelabor rupture of membranes between 34 and 37 weeks: a randomized controlled trial. PLoS Med 2012; 9:e1001208.

48. Roberts D, Dalziel S. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev 2006; :CD004454.

49. Harding JE, Pang J, Knight DB, Liggins GC. Do antenatal corticosteroids help in the setting of preterm rupture of membranes? Am J Obstet Gynecol 2001; 184:131.

50. Gyamfi-Bannerman C, Son M. Preterm premature rupture of membranes and the rate of neonatal sepsis after two courses of antenatal corticosteroids. Obstet Gynecol 2014; 124:999.

51. Crowther CA, McKinlay CJ, Middleton P, Harding JE. Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. Cochrane Database Syst Rev 2011; :CD003935.

52. Yang SH, Choi SJ, Roh CR, Kim JH. Multiple courses of antenatal corticosteroid therapy in patients with preterm premature rupture of membranes. J Perinat Med 2004; 32:42.

53. Shimokaze T, Akaba K, Banzai M, et al. Premature rupture of membranes and neonatal respiratory morbidity at 32-41 weeks' gestation: A retrospective single-center cohort study. J Obstet Gynaecol Res 2015.

54. ACOG Committee Opinion No. 445: antibiotics for preterm labor. Obstet Gynecol 2009; 114:1159.

55.Pierson RC, Gordon SS, Haas DM. A retrospective comparison of antibiotic regimens for preterm premature rupture of membranes. Obstet Gynecol 2014; 124:515.

56. Verani JR, McGee L, Schrag SJ, Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep 2010; 59:1.

57. Abdul Sultan A, West J, Tata LJ, et al. Risk of first venous thromboembolism in pregnant women in hospital: population based cohort study from England. BMJ 2013; 347:f6099.

58. Tita AT, Andrews WW. Diagnosis and management of clinical chorioamnionitis. Clin Perinatol 2010; 37:339.

59. Lewis DF, Adair CD, Weeks JW, et al. A randomized clinical trial of daily nonstress testing versus biophysical profile in the management of preterm premature rupture of membranes. Am J Obstet Gynecol 1999; 181:1495.

60. Leo MV, Skurnick JH, Ganesh VV, et al. Clinical chorioamnionitis is not predicted by umbilical artery Doppler velocimetry in patients with premature rupture of membranes. Obstet Gynecol 1992; 79:916.

61. Abramowicz JS, Sherer DM, Warsof SL, Levy DL. Fetoplacental and uteroplacental Doppler blood flow velocity analysis in premature rupture of membranes. Am J Perinatol 1992; 9:353.

62. Carroll SG, Papaioannou S, Nicolaides KH. Doppler studies of the placental and fetal circulation in pregnancies with preterm prelabor amniorrhexis. Ultrasound Obstet Gynecol 1995; 5:184.

63. Romero R, Hanaoka S, Mazor M, et al. Meconium-stained amniotic fluid: a risk factor for microbial invasion of the amniotic cavity. Am J Obstet Gynecol 1991; 164:859.

64. Duff P. Premature rupture of the membranes in term patients. Semin Perinatol 1996; 20: 401.

65. PG, Hannah ME, Myhr TL, et al. International Multicentre Term Prelabor Rupture of Membranes Study: evaluation of predictors of clinical chorioamnionitis and postpartum fever in patients with prelabor rupture of membranes at term. Am J Obstet Gynecol 1997; 177:1024.

66. Clark P, Duff P. Inhibition of neutrophil oxidative burst and phagocytosis by meconium. Am J Obstet Gynecol 1995; 173:1301.

67. Hofmeyr GJ, Eke AC, Lawrie TA. Amnioinfusion for third trimester preterm premature rupture of membranes. Cochrane Database Syst Rev 2014; 3:CD000942.

68. Kacerovsky M, Musilova I, Hornychova H, et al. Bedside assessment of amniotic fluid interleukin-6 in preterm prelabor rupture of membranes. Am J Obstet Gynecol 2014; 211:385.e1.

69. Melamed N, Ben-Haroush A, Pardo J, et al. Expectant management of preterm premature rupture of membranes: is it all about gestational age? Am J Obstet Gynecol 2011; 204:48.e1.

70.Kunze M, Hart JE, Lynch AM, Gibbs RS. Intrapartum mangement of premature rupture of membranes: effect on cesarean delivery rate. Obstet Gynecol 2011; 118: 1247.

71.Lin MG, Nuthalapaty FS, Carver AR, et al. Misoprostol for labor induction in women with term premature rupture of membranes: a meta-analysis. Obstet Gynecol 2005; 106:593.

72.ACOG Committee on Practice Bulletins -- Obstetrics. ACOG Practice Bulletin No. 107: Induction of labor. Obstet Gynecol 2009; 114:386.

73.Wolff K, Swahn ML, Westgren M. Balloon catheter for induction of labor in nulliparous women with prelabor rupture of the membranes at term. A preliminary report. Gynecol Obstet Invest 1998; 46:1.

74. Quist-Nelson J, Parker P, Mokhtari N, Di Sarno R, Saccone G, Berghella V. Progestogens in singleton gestations with preterm prelabor rupture of membranes: a systematic review and metaanalysis of randomized controlled trials. Am J Obstet Gynecol. 2018;219(4):346.

75. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, Vandvik PO, American College of Chest Physicians. VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):e691S.

76. American College of Obstetricians and Gynecologists Women's Health Care Physicians. ACOG Practice Bulletin No. 138: Inherited thrombophilias in pregnancy. Obstet Gynecol. 2013;122(3):706.