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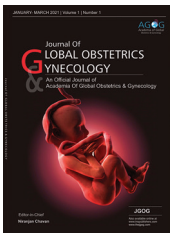

Premature Rupture of the Membranes: Current Thoughts and Concepts

Krishnendu Gupta

Department of Obstetrics and Gynaecology, Vivekananda Institute of Medial Sciences (VIMS), Kolkata, West Bengal, India

ABSTRACT

Premature rupture of membranes (PROM) refers to the rupture of fetal membranes before the onset labor. If rupture of membranes occurs before 37 weeks of gestation, it is known as preterm PROM (PPROM). PROM affects about 10% of all pregnancies. Preterm labor, PROM, and PPROM are amongst the more common and easily preventable causes of perinatal mortality and morbidity. Accurate and timely diagnosis is important for effective management to prevent severe maternal and fetal outcomes. In the last few years, the treatment of patients with preterm rupture of membranes has altered dramatically. This article reviews the published data to understand the current concepts in the evaluation and management of PROM.

Key words: Chorioamnionitis, Pregnancy, Preterm birth

INTRODUCTION

Premature rupture of membranes or pre-labor rupture of membranes (PROM) refers to the rupture of fetal membranes before the onset of labor.[1] It affects about 10% of all pregnancies.[1] Term PROM occurs at term, more than 37 weeks of gestation. If membrane rupture occurs before 37 weeks of gestation, it is referred to as preterm PROM (PPROM). The incidence is about 3%. It is responsible for about 30–40% of all preterm births.

IMPORTANT DEFINITIONS

- Low birth weight (LBW): Neonates weighing 1500–2500 g
- Very low birthweight: Neonates weighing 1000–1499 g
- Extremely low birthweight: Neonates weighing 500–999 g

In 1960, if a baby was born with birth weight of less than 1000 gm, the risk of death was 95%. Because of the advancement of medical science, in 2007 it was the opposite, which showed survival rate of >95%.

Corresponding Author:
Dr. Krishnendu Gupta, Department of Obstetrics and Gynaecology, Vivekananda Institute of Medial Sciences (VIMS), Kolkata, West Bengal, India.
E-Mail: krisim007@gmail.com

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PPROM: PATHOPHYSIOLOGY

Fetal membranes are bound together by different layers of extracellular matrix, composed of the amnion and chorion.[4] Matrix is the key factor that defines the elasticity and of the fetal membranes.[4] Any process that weakens the matrix, increases the chance of PROM.

PPROM: RISK FACTORS

- Infection is the greatest risk factor
- Previous history of PROM (Recurrence rate: 21%)
- History of antepartum hemorrhage, multiple pregnancies, polyhydramnios mechanical distension
- In urban areas, hazards of smoking and drug abuse are well-known
- Cervical incompetence (insufficiency)
- Iatrogenic: cerclage operation, amniocentesis, fetoscopy.

PPROM: INFECTION

- Bacterial proteases potentially decrease the strength and elasticity of the membranes. They produce phospholipases which stimulate the release of prostaglandins formed from arachidonic acid leading to premature uterine contractions[4]
- This infection which causes the host immune response to release cytokines and mediators which weaken the membranes

which damage the matrix and causes release of matrix metalloproteinases (MMPs)[3]

- MMPs are a family of enzymes that are released from the extracellular matrix and decrease membrane strength by increasing collagen degradation
- Increased risk of PPROM is seen in women infected with gonorrhea, trichomonas, chlamydia. Group B streptococcus (GBS) should be treated carefully: *Streptococcus agalactiae, Gardnerella vaginalis*
- Doctors should remember that if the sign of clinical infection is 1–2% and subclinical infection is as high as 40% and if not treated, then it may cause problem. Hence, it is necessary to diagnose and treat the infection as early as possible.

PPROM: HOW TO DIAGNOSE?

- History of leakage of liquor amnii per vagina (PV)/dribbling PV
- Per speculum (P/S) examination: To visualize the leakage of liquor/dribbling
- Valsalva maneuver such as coughing to visualize the leakage well when not clearly evident
- Avoid per vaginal/digital examination to prevent ascending infection
- Examination of escaping fluid by biochemical tests to confirm the diagnosis.

PPROM: TESTS

- Nitrazine paper test
- Fern test
- Nile blue sulfate test
- Others: Indigo-carmine test, Detection of fetal fibronectin
- New: Amniotic leak detection kit/pad (AminoSense™)- Worn in a panty liner. If there is a leak or discoloration it becomes blue and if after an hour or after drying the color remains blue, then it can be concluded that it is a kind of amniotic fluid and not the urine.

PPROM: ROLE OF ULTRASOUND (USG)

- The role of USG is not only to diagnose the leak of urine but also liquor or amniotic fluid volume/index
- Assessment of the cervix: length dilatation of the cervical os, funneling (if any)
- Assessment of the fetus: gestational age, heart rate, and presentation
- Placenta: Localization.

PPROM: MATERNAL COMPLICATIONS

- Infection: Chorioamnionitis (13–60%) Puerperal sepsis

Chorioamnionitis (clinical/acute): Presence of pyrexia and presence of any two of the following-.Maternal and fetal tachycardia, uterine tenderness, foul-smelling vaginal discharge, maternal leukocytosis.

- Abruptio placentae (4–12%)

Because of all these complications, there is an increased incidence of cesarean section.

PPROM: FETAL AND NEONATAL COMPLICATIONS

- Prematurity
- Infection: neonatal septicemia
- Fetal asphyxia: oligohydramnios, cord compression, or cord prolapse
- Fetal pulmonary hypoplasia (more common if PROM <26 weeks of gestation)
- Musculoskeletal deformity because of the cramping of the uterus (due to chronic oligohydramnios): limb, talipes, craniofacial defects
- Respiratory distress syndrome
- Cerebral palsy (CP) (Extremely important)[4]

$MgSO_4$ ROLE: EARLY OBSERVATIONAL DATA

In the 1980's Van de Bor, Leviton studies showed decreased rates of intraventricular hemorrhage (IVH) and CP in very low birthweight (VLBW) infants born to women with preeclampsia who were given $MgSO_4$. In the early 1990's, a study by Kuban demonstrated that.

VLBW infants exposed to $MgSO_4$ for tocolysis also had decreased rates of IVH. In 1996, Grether *et al.*, showed lower rate of CP in VLBW infants exposed to $MgSO_4$. As per the above studies, it could be concluded that exposure to MgSO4 can be beneficial.

PPROM: ROLE OF $MgSO_4$

Magnesium sulfate is used in women at risk of preterm birth for neuroprotection of the fetus. Antenatal administration of $MgSO_4$ in imminent preterm birth protects the offspring from the risk of developing CP.

INDICATIONS

"Imminent preterm birth" which includes:

1. Preterm labor with or without PPROM
2. Planned preterm birth for fetal or maternal indication.

HOW DOES $MgSO_4$ WORK?

It works in one of the four ways.

1. $MgSO_4$ decreases neuronal injury by "down regulation" of excitatory stimuli. Damaged neurons are sensitive to the excitatory neurotransmitter glutamate, but the blocking of N- methyl-D-aspartate receptors by magnesium prevent the influx of calcium that causes cell death[4,5]

2. The vasoactive properties of magnesium minimize the hypoxic-ischemic damage by the resulting increased cerebral blood flow due to cerebral vasodilatation[5]
3. $MgSO_4$ has been shown to prevent neuronal injury by reducing both oxygen free radicals and proinflammatory cytokines[5]
4. Magnesium may directly reduce the neuronal loss as it has anti-apoptotic (programmed cell death).[5]
   It imparts the best protection to the preterm birth that occurs within 24–32 weeks of gestation.

DOSE

- $MgSO_4$ is administered as a 4 g IV loading dose over 30 min, followed by a 1 g/h maintenance infusion until birth[6]
- For planned preterm birth, it is started ideally within 4 h before birth, as a 4-g IV loading dose over 30 min, followed by a 1 g/h maintenance dose until birth[7]
- $MgSO_4$ is discontinued if delivery is no longer imminent, or a maximum of 24 h of therapy has been given
- When $MgSO_4$ is given for fetal neuroprotection, other tocolytic(s) is/are usually discontinued, as magnesium sulfate itself acts as a tocolytic. Based on this, it is found that it has role in preventing CP.

$MgSO_4$ FOR NEUROPROTECTION: HOW TO ADMINISTER

Loading dose and Maintenance dose- 1 ampoule of $MgSO_4$ contains 1 gm in 2 mL (50% solution).

Initial: 4 g IV over 30–60 min.

Dilute 4 amps of $MgSO_4$: 8 mL+12 mL of normal saline (NS) = 20 mL; Infuse 20 mL in 30–60 min.

Maintenance: 1 g IV per hour for 24 h.

Dilute 10 amps $MgSO_4$: 20 mL + 30 mL of NS = 50 mL; infuse 5 mL/h for 24 h. Check for any signs of $MgSO_4$ toxicity.

$MgSO_4$: CLINICAL EVIDENCE

Study by Doyle *et al.*, in Cochrane Database of Systemic Reviews 2009, concluded that the neuroprotective role of antenatal magnesium sulfate therapy given to women at risk of preterm birth for the preterm fetus is now established.

The American College of Obstetricians and Gynecologists (ACOG) Committee guideline in 2010 which without any change has been reaffirmed in 2020 with their opinion on magnesium sulfate given before anticipated preterm birth for neuroprotection.[8]

The Royal College of Obstetricians and Gynecologists (RCOG) took a Scientific Impact Paper in 2011 speaking positively for magnesium sulfate. The paper showed that magnesium sulfate given to mothers shortly before delivery reduces the risk of CP and protects against gross motor dysfunction in those infants who are delivered preterm. The effect may be greatest at early gestations and is not associated with adverse long-term fetal or maternal outcome. Women should be advised of an increase in minor adverse effects associated with the medication.[9]

Nguyen *et al.*, conducted a study in the Cochrane Database of Systemic Reviews 2013 for determining the role of magnesium sulfate for women at term for neuroprotection of the term fetus.[10] They found that there is currently insufficient evidence of the efficacy and safety of magnesium sulfate when administered to women for neuroprotection of the term fetus. There has been recent evidence for the use of magnesium sulfate for neuroprotection of the preterm fetus. Hence, magnesium sulfate can be given to preterm, for term gestation the studies are inadequate.

The Royal College of Physicians of Ireland 2015 Clinical practice guideline which is currently under revision showed the beneficial role of magnesium sulfate in preterm labor in fetal neuroprotection.

PPROM/PROM: CLINICAL EVIDENCE

The decision to prescribe antibiotics for women with PROM is not clear-cut. Co-amoxiclav has increased risk of neonatal necrotizing enterocolitis, thus should be avoided in women at risk of preterm delivery. Another paper by Tchirikov *et al.*, clearly shows which antibiotic can be used.

Erythromycin is the choice of antibiotic for PPROM as per the evidence available [Table 1].

PPROM: MANAGEMENT

The data from ACOG 2016, 2017 on the management of PPROM by gestational age categories are mentioned in Table 2.

Single corticosteroid course may be considered Tocolytics: no consensus

Antimicrobials may be considered

- The combination of birthweight, gestational age, and sex provides the best estimates of chances of survival and should be considered in individual cases.[11]

PPROM RECOMMENDATIONS

RCOG Green-top guideline no. 73., June 2019 stated that-

- The diagnosis of spontaneous rupture of the membranes is made mainly by the combination of maternal history and a sterile speculum examination (Grade D)
- If on speculum examination, no amniotic fluid is seen, clinicians should consider performing an insulin-like growth factor-binding protein1 or placental alpha microglobulin-1 test of vaginal fluid for further management (Grade B)
- Following the diagnosis of PPROM, an antibiotic (preferably erythromycin) should be given for 10 days or until the labor is established (whichever is earliar) (Grade A)

Table 1: Antibiotics in PPROM: Review

Organization	Antibiotics	Comment
ACOG (USA)	Penicillin Ampicillin (alternative) Erythromycin (up to 32% resistance) Clindamycin	Not commended Only if the isolate is susceptible 04 sensitive 5 Mio. E. I initial, then 2.5 Mio. E. I 4 h until delivery
DGGG (Germany)	Penicillin G Mezlocillin, piperacillin, clindamycin, ampicillin, erythromycin or cefazolin (alternative)	
RANZCOG (Australia and New Zealand)	Ampicillin/amoxicillin and erythromycin Erythromycin (alternative single use IAP regime for GBS colonized women: penicillin or alternative ampicillin IV; with penicillin allergy clindamycin and erythromycin after sensitivity testing because of resistants! Alternative cefazolin or vancomycin (20 mg/kg N every 8 h - maximum 2 g)	(for PPROM 2 g IV 6 h and then 250 mg PO 8 h for 5 days: 250 mg 532 weeks) PO 6 h for 48 h, then 500 mg PO 8 h for 5 days) 250 mg PO every 6 h for 10 days
RCOG (UK)	Penicillin Erythromycin (may be used if allergic to penicillin) IAP regime for GBS colonized women: benzylpenicillin (3 g IV and 1.5 g 4-h until delivery) or clindamycin (900 mg IV 8-h) if allergic to penicillin; alternative vancomycin by resistant	For 10 days
SOGC (Canada)	Ampicillin erythromycin (alone if allergic to penicillin) IAP regime for GBS colonized women: penicillin G 5 million units IV, then 2.5 million 4 h instead of ampicillin or cefazolin (2 g IV then 1 g IV 8 h) if penicillin allergic but not at risk of anaphylaxis or erythromycin (500 mg I every 6 h) or clindamycin (900 mg IV every 8 h) if penicillin allergic and at risk of anaphylactic shock	2 g IV every 6 h for 48 h and amoxicillin 250 mg PO and/or every 8 h for 5 days 250 mg I every 6 h for 48 h following by 333 mg PO every 8 h for 5 days or 250 mg PO every 6 h for 10 days

Table 2: Management of PPROM by gestational age[11]

Gestational Age	Management
34 weeks or more	Plan delivery: Labor induction unless contraindicated Group B Streptococcal prophylaxis Single corticosteroid course up to $36^{6/7}$ weeks
32 weeks to 33 completed weeks	Expectant management Group B Streptococcal prophylaxis Single corticosteroid course Antimicrobials to prolong latency[11]
24 weeks to 31 completed weeks	Expectant management Group B Streptococcal prophylaxis Single corticosteroid course Tocolytics: no consensus Antimicrobials to prolong latency Magnesium sulphate for neuroprotection may be considered
Before 24 weeks	Patient counseling Expectant management or induction of labor Group B Streptococcal prophylaxis is not recommended

- Women who have PPROM between 24+0 and 33+6 weeks' gestation should be offered corticosteroids; steroids can be considered up to 35+6 weeks' gestation (Grade A).
- A combination of clinical assessment, maternal blood tests (C-reactive protein and white cell count) and fetal heart rate can be used to diagnose chorioamnionitis in women with PPROM; these parameters cannot not be used in isolation[12] (Grade D) as one parameter is not sufficient
- Women whose pregnancy is complicated by PPROM after 24+0 weeks' gestation and who have no contraindications to continuing pregnancy should be offered expectant management until 37+0 weeks; timing of birth should be discussed with each woman on individual basis with careful consideration of the patient preference and ongoing clinical assessment (Grade A).[13] A discussion is important, in every guideline the patient or the couple must be involved in the plan of the management because not only of the risk involved to the baby but also the cost involved is extremely important
- In women who have PPROM and are in established labor or having a planned preterm birth within 24 h, intravenous magnesium sulphate should be offered between 24+0 and 29+6 weeks of gestation (Grade A).[13]

CONCLUSION

Accurate diagnosis of PROM in term and preterm pregnancies is important for gestational-age-specific intervention and management. Early detection and diagnosis of PPROM are of utmost importance. It is also vital to identify potential risk factors for PPROM. Single most important risk factor being infection.

The use of Co-amoxiclav should be avoided. As per the available evidence, erythromycin is the antibiotic of choice for PPROM. Magnesium sulfate should be offered for fetal neuroprotection.

REFERENCES

1. Dayal S, Hong PL. Premature rupture of membranes. In: Stat Pearls. Stat Pearls Publishing; 2021.
2. Manohari SG. Active Versus Expectant Management in Women with Preterm Premature Rupture of Membranes between 34 and 37 Weeks of Gestation. Chennai: Stanley Medical College; 2010.
3. Medical Informatics and Evidence Based Medicine; 2016. Available from: https://www.studylib.net/doc/7486163/medical-informatics-and-evidence-based-medicine [Last accessed on 2022 Jan 16].
4. Available from: https://www.ranzcog.edu.au/publications/o-g_pdfs/o&g-winter-2010/mgso4_preterm%20birth_walker.pdf [Last accessed on 2022 Jan 16].
5. Available from: https://www.media.sogc.org/covid19/26thed_manual_en.pdf [Last accessed on 2022 Jan 16].
6. Merrill L. Magnesium sulfate during anticipated preterm birth for infant neuroprotection. Nurs Womens Health 2013;17:42-51.
7. Doyle LW, Crowther CA, Middleton P, Marret S, Rouse D. Magnesium sulphate for women at risk of preterm birth for neuroprotection of the fetus. Cochrane Libr 2009;1:CD004661.
8. Magnesium Sulphate to Prevent Cerebral Palsy following Preterm Birth; 2022. Available from: http://www.docplayer.net/1481043-Magnesium-sulphate-to-prevent-cerebral-palsy-following-preterm-birth.html [Last accessed on 2022 Jan 16].
9. Nguyen TM, Crowther CA, Wilkinson D, Bain E. Magnesium sulphate for women at term for neuroprotection of the fetus. Cochrane Libr 2013;2:CD009395.
10. Compendio ACOG, Scribd; 2022. Available from: https://www.scribd.com/document/228802200/compendio-acog [Last accessed on 2022 Jan 16].
11. OnMedica. Many Women Whose Waters Break Early Can Safely Continue Pregnancy, Wilmington Healthcare; 2020. Available from: https://www.onmedica.com/posts/63088-many-women-whose-waters-break-early-can-safely-continue-pregnancy?badge_id=1069-news [Last accessed 2022 Jan 16].
12. Thomson AJ, Royal College of Obstetricians and Gynaecologists. Care of women presenting with suspected preterm prelabour rupture of membranes from 24+0 weeks of gestation: Green-top Guideline No. 73: Green-top Guideline No. 73. BJOG 2019;126:e152-66.
13. Available from: http://www.medind.nic.in/jaq/t05/i2/jaqt05i2p118.pdf [Last accessed on 2022 Jan 16].

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