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SUPPLEMENT ARTICLE

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FIGO good practice recommendations for preterm labor and preterm prelabor rupture of membranes: Prep-for-Labor triage to minimize risks and maximize favorable outcomes

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Abstract

Preterm labor occurs in around 10% of pregnancies worldwide. Once diagnosed, significant efforts must be made to reduce the likelihood of morbidity and mortality associated with preterm birth. In high-resource settings, access to hospitals with a neonatal intensive care unit (NICU) is readily available, whereas access to NICU care is limited in low- and middle-income countries (LMICs) and many rural settings. Use of FIGO's Prep-for-Labor triage method rapidly identifies low- and high-risk patients with preterm labor to enable clinicians to decide whether the patient can be managed on site or if transfer to a level II–IV facility is needed. The management steps described in this paper aim to minimize the morbidity and mortality associated with preterm labor and in the setting of preterm labor with preterm premature rupture of membranes (PPROM). The methods for accurate diagnosis of PPROM and chorioamnionitis are described. When the risk of preterm birth is high, antenatal corticosteroids should be administered for lung maturation combined with limited tocolysis for 48 hours to permit the corticosteroid course to be completed. Magnesium sulfate is also administered for fetal neuroprotection. Implementation of FIGO's Prep-for-Labor triage method in an LMIC setting will help improve maternal and neonatal outcomes.

KEYWORDS
antibiotics, chorioamnionitis, corticosteroids, magnesium sulfate, PPROM, preterm labor, tocolysis

1 | INTRODUCTION AND BACKGROUND EPIDEMIOLOGY

Preterm birth is defined as birth before 37 weeks of gestation or less than 259 days from the first day of a woman's last menstruation.[1,2] It is classified according to gestational age as extreme preterm (<28 weeks), very preterm (28^{+0} to 31^{+6} weeks), moderate preterm (32^{+0} to 33^{+6} weeks), and mild/late preterm (34^{+0} to 36^{+6} weeks) birth, with decreasing neonatal morbidity and mortality as gestational age increases. Mild/late preterm birth constitutes 60% of all preterm deliveries, moderate preterm 20%, very preterm 15%, and extreme preterm the lowest proportion at 5%.[3,4]

Defining when the patient is in preterm labor and whether preterm birth is anticipated requires an initial assessment of gestational age. An early trimester ultrasound provides the most precise information on gestational age. This implies that the patient was already followed from the first trimester in a clinical setting where such diagnostic tests are available. The last menstrual

*Complete list of members presented in Appendix A.

period has its limitations, including poor recall and menses continuing despite pregnancy. During the COVID-19 pandemic and its aftermath, particularly in LMICs and rural centers, precise ultrasound-based information is not readily available for patients presenting with suspected preterm labor. This is critical because both extensive diagnostics and therapeutic measures are based on knowledge of precise gestational age to minimize maternal and newborn morbidity and mortality and improve outcomes. Patient care can be further complicated when and if transfer to an integrated higher-level center (level II–IV) is feasible and realistic in a timely manner. FIGO's Prep-for-Labor triage method described in the present paper aims to bridge this gap by rapidly defining a pregnancy as high or low risk of preterm labor. By focusing on the high-risk patient, the low-risk patient can advance toward delivery with minimal intervention. As much clinical information as possible should be obtained, including accurate estimate of gestational age and presence or absence of preterm premature rupture of membranes (PPROM) or chorioamnionitis to help inform shared decision-making between the patient, her family, and the clinician. Practical measures available on site should be implemented, including low-cost and widely available antibiotics, corticosteroids, tocolytics, and magnesium sulfate infusion. Optimizing care may require ongoing communication and possible transfer in a timely manner to a level II–IV center where evidence-based management can take place. This article provides a summary of evidence-based management of preterm labor and PPROM, presented as good practice recommendations.

2 | PREVALENCE OF PRETERM BIRTH AND ASSOCIATED COMPLICATIONS

Preterm birth is the single most common cause of neonatal morbidity and mortality with 70%–75% of cases leading to neurodevelopmental disability.[2,5] In 2020 there were 13.4 million preterm births (9.9% of all births globally). For many regions the 2010–2020 rates remained stable; however, in Sub-Saharan Africa there was an increase of around 600000 preterm births between 2010 and 2020. Bangladesh (16.4%) and Malawi (14.5%) were among the countries with the highest preterm birth rates in 2020. India recorded the highest number of preterm births, at 3 million, followed by Pakistan (914000) and Nigeria (774000). By region, the highest preterm birth rates were in South Asia (13.2%) followed by Sub-Saharan Africa (10.1%), while the lowest rate came from Eastern and Southeastern Asia (6.8%). In Europe and North America, the rate is 7.9%. Finally, the death rate associated with preterm birth in Sub-Saharan Africa is 11%, while in Latin America, North America, and Europe it is only 3%. This reveals major differences in both preterm birth and survival rates among different regions, which must be addressed. Although improved standards of neonatal care have been introduced, disability rates in survivors have not significantly changed, therefore new practical measures urgently need to be introduced.[6–8]

The etiology of preterm labor is diverse, with spontaneous/idiopathic preterm labor accounting for 50% and preceded by PPROM (25%); the remaining 25% is iatrogenic (elective) preterm birth, indicated for specific maternal or/and fetal indications.[3–5] When elective, it is more practical to manage since the patient and site of care can be defined ahead of time, enabling effective management in the desired setting. Timely diagnosis and prompt management of preterm labor and PPROM are key to mitigating adverse outcomes. In these circumstances, access to higher-level care is necessary but is frequently not available in level I settings, therefore timely transfer to a higher-level center is crucial.

3 | DIAGNOSIS OF PPROM

Premature rupture of membranes (PROM) complicates 8%–10% of all pregnancies. When PROM occurs before 37 weeks of gestation, it is termed PPROM. PPROM complicates 2%–4% of singleton pregnancies and 7%–20% of twin pregnancies.[9,10] Early and accurate diagnosis of PPROM allows for prompt interventions to improve perinatal outcomes and reduce the risk of complications, including cord prolapse, placental abruption, chorioamnionitis, and neonatal sepsis.

PPROM is diagnosed clinically in most cases. Diagnosis is confirmed in 90% of patients with a typical sign of sudden gush and continuous leakage of fluid from the vagina.[11,12] Egress of amniotic fluid from the cervical canal or pooling of amniotic fluid in the vagina on sterile speculum examination confirms the diagnosis of PPROM.[13,14] During speculum examination, inspection for cervicitis and umbilical cord prolapse, as well as assessment of cervical dilatation and effacement should be done. Unless the patient is in labor or delivery is imminent, digital cervical examination is avoided since it increases the risks of chorioamnionitis, neonatal infection, and shortens latency. Cervical evaluation by speculum examination correlates well with digital examination findings.[15–17]

In clinically equivocal cases of PPROM, advanced diagnostics are used in only 10%–20% of cases since they are rarely available. Vaginal fluid tests assessing PPROM detect placental alpha microglobulin-1 (PAMG-1; Amnisure [Qiagen; Venlo, The Netherlands]) or insulin-like growth factor binding protein-1 (IGFBP-1; ActimPROM [Actim; Espoo, Finland]).[10,13,14,18] Palacio et al.[10] in their meta-analysis demonstrated that ActimPROM and AmniSure had comparable sensitivity (ActimPROM: 95.4% [95% CI, 93.1–97.0] vs AmniSure: 96.7% [95% CI, 94.8–98.0]; $P=0.352$) and negative predictive value (ActimPROM: 95.8% [95% CI, 93.7–97.3] vs AmniSure: 96.7% [95% CI, 94.7–98.0]; $P=0.548$). However, AmniSure had higher specificity (98.3% [95% CI, 96.7–99.2]) and positive predictive value (98.3% [95% CI, 96.7–99.2]) compared with ActimPROM (specificity 92.9% [95% CI, 90.4–94.8]; PPV 92.3% [95% CI, 89.5–94.4]; both $P<0.001$ vs AmniSure).[10] In the absence of amniotic fluid egress from the cervical canal and/or pooling of amniotic fluid in the posterior vaginal fornix, with negative PAMG-1 or IGFBP-1 tests, PPROM is improbable (>90%).[13]

Fern and nitrazine tests should be available in any setting. With detailed questioning, several factors can be ruled out, thereby reducing the high rates of false-negative or false-positive results. This involves evaluating for the presence of semen, cervical mucus, blood, cervicitis, vaginitis, alkaline urine, and topical antiseptics.[19–21] Erring on the side of caution has no adverse ramifications, whereas missing PPROM can have a significant negative impact. If feasible, for a patient with a high index of risk for PPROM based on the exam, transfer to a higher-level site should be pursued.

The following additional tests are available only in level II–IV settings. Fetal fibronectin, a highly sensitive but unspecific test for PPROM, is more useful as a predictor of preterm delivery than for diagnosis of PPROM.[14,22] Amniocentesis and instillation of indigo carmine dye into the amniotic cavity, which in the presence of PPROM is followed by the leakage of blue-stained fluid into the vagina within 20–30 minutes, is invasive, expensive, and carries the risk of iatrogenic PROM, placental abruption, infection, and miscarriage. Methylene blue dye is associated with fetal hemolytic jaundice, hemolytic anemia, hyperbilirubinemia, and methemoglobinemia. Therefore, amnio dye infusion is not routinely performed owing to ethical concerns.[9,23,24] Ultrasonographic documentation of oligohydramnios may be useful as an adjunct but is not diagnostic of PPROM. Ultrasonography is useful for assessing fetal well-being, and determining fetal position, placental location, estimated fetal weight, presence of any anomalies, and residual amniotic fluid volume.[14,21] A stepwise approach for diagnosing PPROM is given in Box 1. Several measures can provide diagnostic information, but these are not always available; therefore, more clinical, and secondary measures need to be used.

BOX 1 Stepwise approach for diagnosis of PPROM

1. Sterile speculum examination demonstrates egress of amniotic fluid from cervix, vagina[13,14]
2. *LMIC setting: nitrazine test - use only as backup.* Must rule out interfering factors. Alternative vaginal fluid concentrations of urea and creatinine assess equivocal PPROM. When PPROM risk is high probability, consider patient transfer.
3. *High-resource setting*: use placental alpha microglobulin-1 (PAMG-1; Amnisure) or insulin-like growth factor binding protein-1 (IGFBP-1; ActimPROM) vaginal tests[10,13,14,18]
4. *Nitrazine, fern, or fetal fibronectin* can be used if other methods are not available[19–21]
5. *Digital cervical examination should not be performed* as it increases chorioamnionitis risk[15–17]
6. *Amniocentesis and dye instillation into the amniotic cavity is not recommended* [9,23,24]
7. *Ultrasonography* has a low predictive rate based on fluid pocket size[14,21]

4 | DETECTION OF INFECTION IN WOMEN WITH PPROM

A significant risk associated with PPROM is ascending bacterial invasion, which can result in chorioamnionitis (intra-amniotic infection) and postpartum infection. Clinical chorioamnionitis complicates 15%–25% of PPROM; combined with histologic chorioamnionitis, up to 40%–70% of PPROM cases are affected.[25–27] Once diagnosed, prompt treatment is needed. Diagnostic accuracy varies, which requires subsequent confirmation. Whereas some authors have defined clinical chorioamnionitis as the presence of any two of the clinical features, others have defined it as the presence of fever in addition to two other signs (uterine tenderness, maternal or fetal tachycardia, offensive/purulent vaginal discharge, leukocytosis).[26–29] Individual clinical features have variable sensitivity and low specificity for chorioamnionitis.[27,28,30]

Both cardiotocography and fetal biophysical profile have poor sensitivity for predicting infectious morbidity following PPROM.[31] Whereas initially Caloone et al.[32] reported that C-reactive protein is the best maternal marker for predicting histologic chorioamnionitis in women with PPROM, Sabogal et al.[33] found later that the test had low sensitivity (68.7%) and specificity (77.1%). Etyang et al.[34] recently demonstrated that C-reactive protein, procalcitonin, or interleukin 6 (IL6) tests are not useful for diagnosing histologic chorioamnionitis/funisitis in PPROM. It is therefore recommended that the parameters of clinical assessment (pulse rate, blood pressure, temperature, and clinical symptoms), white blood cell count, and cardiotocography should not be used in isolation, but in combination, to diagnose chorioamnionitis in women with PPROM.[13,35]

Group B streptococcus (GBS) is a leading cause of serious neonatal infectious morbidity and may be vertically transmitted to the fetus by ascending infection following PPROM. PROM greater than or equal to 18 hours has been identified as a risk factor for early-onset GBS.[36] Guidelines from the Royal College of Obstetricians and Gynaecologists (RCOG), American College of Obstetricians and Gynecologists (ACOG), and the Society of Obstetricians and Gynaecologists of Canada (SOGC) support obtaining vaginal fluid at diagnosis of PPROM to culture for GBS. GBS prophylaxis should be offered in case of a positive culture if expectant management of PPROM is considered.[14,35,37] Box 2 provides a diagnostic approach, in declining diagnostic accuracy, which is available in all care settings. This requires patient examination, especially vital signs as each has a predictive value.

5 | ANTIBIOTIC PROPHYLAXIS IN PPROM AND PRETERM LABOR

The use of antibiotics in cases of confirmed PPROM has been examined in multiple clinical trials with many patients, with discordant results. Data ranged from prenatal and neonatal outcome, while other studies examined antibiotic exposure during pregnancy and subsequent child health up to the age of 7 years. A Cochrane Review,

BOX 2 Presence of two or more symptoms is preferable for diagnosis of infection in women with PPROM

1. *Fever* (highest diagnostic accuracy; ≥100°F or 38°C) (seen in 95%–100% of cases)
2. *Maternal tachycardia* (>100/minute) (seen in 50%–80% of cases)
3. *Blood pressure* (hyper- or hypotensive requires prompt stabilization)
4. *Leukocytosis* (white blood cell count >12000–15000/mm^3) (seen in 70%–90% of cases)
5. *Fetal tachycardia* (>160/minute) (seen in 40%–70% of cases)
6. *Uterine tenderness*, *vaginal discharge* offensive/purulent (both seen in 4%–25% of cases)[27,28]

which included 22 trials involving 6872 women and newborns, confirmed that prophylactic use of antibiotics following PPROM significantly reduced chorioamnionitis (RR 0.66; 95% CI, 0.46–0.96), early delivery within 48 hours (average RR 0.71; 95% CI, 0.58–0.87) and 7 days of randomization (average RR 0.79; 95% CI, 0.71–0.89), neonatal infection (RR 0.67; 95% CI, 0.52–0.85), use of surfactant (RR 0.83; 95% CI, 0.72–0.96), oxygen therapy (RR 0.88; 95% CI, 0.81–0.96), and abnormal cerebral ultrasound scan prior to discharge from hospital (RR 0.81; 95% CI, 0.68–0.98). Overall use of antibiotics in confirmed PPROM cases led to 30%–40% reduction in rate of complications. There was no significant reduction in perinatal mortality.[38] This last point would support more attention given to early intervention during pregnancy prior to delivery, thereby reducing, when feasible, perinatal mortality as well as morbidity.

Amoxycillin and/or erythromycin antibiotic regimens for PPROM have been recommended by different obstetrics and gynecology societies, with minor variations in strength and length of administration when combined and/or used alone. Based on the findings of the Maternal–Fetal Medicine Units Network Trial by Mercer et al.,[39] ACOG recommends a 7-day course of antibiotic regimen consisting of intravenous ampicillin (2 g every 6 hours) and erythromycin (250 mg every 6 hours) for 48 hours followed by oral amoxicillin (250 mg every 8 hours) and erythromycin base (333 mg every 8 hours) for 5 days.[14] RCOG recommends oral erythromycin 250 mg four times daily for a maximum of 10 days or until the woman is in established in labor (whichever comes first).[35] This recommendation is based on the results of the ORACLE 1 trial.[40]

The ORACLE 1 trial randomly assigned 4826 women with PPROM to receive erythromycin only, co-amoxiclav only, erythromycin plus co-amoxiclav, or placebo. There was less neonatal death, chronic lung disease, and major cerebral abnormality among infants born to women who were administered erythromycin only. Erythromycin was also associated with reduction in delivery at 7 days after randomization, reduction in neonatal treatment with surfactant, decrease in oxygen dependence at 28 days of age and older, and fewer positive neonatal blood cultures. Although co-amoxiclav only and co-amoxiclav plus erythromycin were associated with prolongation of pregnancy, they were also associated with a significantly increased risk of neonatal necrotizing enterocolitis.[40]

SOGC recommends the use of either of two regimens: (1) intravenous ampicillin 2 g every 6 hours and intravenous erythromycin 250 mg every 6 hours for 48 hours followed by oral amoxicillin 250 mg every 8 hours and oral erythromycin base 333 mg every 8 hours for 5 days; or (2) oral erythromycin 250 mg every 6 hours for 10 days.[28,37] The French National College of Gynecologists and Obstetricians (CNGOF) recommends that amoxicillin, third-generation cephalosporins, and erythromycin can each be used individually or erythromycin and amoxicillin can be combined for a period of 7 days.[41] CNGOF also recommends that if the vaginal fluid sample taken at diagnosis of PPROM is positive, adaptation of the antibiotic prophylaxis to the culture and antibiotic susceptibility testing should be considered; prophylactic antibiotics should be discontinued if the vaginal sample is negative.[41]

A systematic review of 14 randomized controlled trials (RCTs) including 6559 women by Kenyon et al.[42] recommended the use of penicillin and erythromycin for PPROM, but suggested the latter as the antibiotic of choice on the strength of available evidence that more women were included in trials using erythromycin and, thus, the results were more robust. Co-amoxiclav is contraindicated in women with PPROM owing to its association with neonatal necrotizing enterocolitis.[14,35,37,42]

Data on long-term outcomes of children whose mothers were prescribed antibiotics in the ORACLE 1 trial were published in 2008 and revealed that antibiotics had little effect on the health of the children at 7 years of age.[43] However, long-term follow-up of children whose mothers participated in the ORACLE II trial of antibiotics for preterm labor in the presence of intact membranes revealed that antibiotics were associated with an increased risk of functional impairment and cerebral palsy among the children at 7 years of age.[44] Erythromycin (with or without co-amoxiclav) was associated with a statistically significant increase in the proportion of children with any level of functional impairment, from 38.3% to 42.3%. Similarly, there was a statistically significant increase in the proportion of children with cerebral palsy from 1.7% to 3.3% associated with erythromycin, and from 1.9% to 3.2% with co-amoxiclav.[44] This evidence lends credence to the recommendation that antibiotics should not be given unless the diagnosis of PPROM is confirmed.[35,44] Findings of the ORACLE II trial of 6421 women showed that antibiotics did not prolong pregnancy or improve neonatal outcomes in women in spontaneous preterm labor with intact membranes and no evidence of infection.[45] Prophylactic antibiotic use is therefore not recommended in this category of women.[45] Overall the risk is increased by overuse of any antibiotic with long-term negative ramifications for children of patients who have intact membranes. This reinforces that PPROM diagnosis must be accurate before considering any antibiotic use. As recently reported, use of erythromycin increased the congenital malformations rate by 50%.[46] Data for the second

BOX 3 Antibiotic prophylaxis only for women with confirmed PPROM

1. *Antibiotics* only with confirmed PPROM – risk to child with use of erythromycin[35,43]
2. *No antibiotics* when spontaneous preterm labor with intact membranes or no infection[45]
3. *PPROM confirmed*. Erythromycin 250 mg every 6 hours up to 10 days or until established labor (whichever comes first)[13,35]
4. *Erythromycin allergy or contraindicated*. Intravenous ampicillin 2 g every 6 hours followed by oral amoxicillin 250 mg every 8 hours for 5 days[35]
5. *Infection with PPROM or with intact membranes confirmed*. Combined ampicillin and erythromycin can be administered.
6. *Positive cultures*. Adapt treatment to antibiotic susceptibility[41]
7. *Avoid amoxicillin–clavulanate* as it increases the risk of neonatal necrotizing enterocolitis[14,35,37,41]

trimester were not able to provide a definitive conclusion and only showed a slight increase in the rate of genital anomalies.[46] On the other hand, penicillin use throughout pregnancy is safe. At this point, based on the extensive PPROM clinical data generated, erythromycin is still considered to be safe to use in pregnancy after the first trimester since PPROM is in general a late second- or third-trimester event. In general, the severity of the case dictates the patient management. This ranges from PPROM to active labor, from prophylaxis to actual infection, and from single to combined antibiotics based on case severity. A team management approach should be involved in this critical decision-making process since an error in judgment can have significant negative consequences for the affected child—almost doubling the rate of cerebral palsy. Antibiotics must be used carefully in cases of PPROM as prophylaxis versus infection treatment. Types of antibiotics and their uses are given in Box 3.

6 | CORTICOSTEROID USE IN PPROM AND PRETERM LABOR

The use and value of antenatal corticosteroid administration has been widely studied since its introduction over 30 years ago. The research aimed to define the specific gestational age where treatment is utilitarian, presence/absence of preterm labor and/or PPROM, and presence or absence of chorioamnionitis. Data demonstrated that use in women with PPROM or in established preterm labor reduces the risks of respiratory distress syndrome, intraventricular hemorrhage, neonatal necrotizing enterocolitis, NICU admissions, systemic infections in the first 48 hours of life, and neonatal death.[35] Steroids do not increase the risks of chorioamnionitis, puerperal sepsis, or maternal death.[47–49] Many guidelines recommend that antenatal corticosteroids are offered to all women who are in established preterm labor or with PPROM between 24^{+0} and 33^{+6} weeks.[13,14,35,50,51]

Use of antenatal corticosteroids beyond that gestational age, namely late preterm (34^{+0} to 36^{+6} weeks), has been debated even though births at that gestational age are associated with increased neonatal morbidity, respiratory distress syndrome, and mortality compared with term deliveries.[52,53] However, the utility of antenatal corticosteroids was confirmed in this gestational age group. The Antenatal Late Preterm Steroids (ALPS) trial, a multicenter double-blind placebo-controlled randomized trial conducted in 17 centers and including 2831 women, demonstrated that administration of betamethasone to women at risk for late preterm delivery significantly reduced rates of respiratory distress syndrome, stillbirth, and neonatal death within 72 hours of delivery. As expected, neonatal hypoglycemia was increased in the betamethasone group versus the placebo group (24.0% vs 15.0%; RR 1.60; 95% CI, 1.37–1.87; $P < 0.001$). Rates of other neonatal and maternal complications were not increased with betamethasone.[54] Similarly, a systematic review and meta-analysis of six trials (including the ALPS trial) including 5698 women also demonstrated benefits of steroids in reducing respiratory distress syndrome in late preterm infants.[55] Based on this evidence, antenatal corticosteroids should also be considered for women between 34^{+0} and 36^{+6} weeks who are in confirmed preterm labor or with PPROM.

Currently, both NICE and RCOG recommend that antenatal corticosteroids should be considered in women between 22 and 35^{+6} weeks—one week less than used in the ALPS study in patients with established labor or with PPROM.[13,35] Use of antenatal corticosteroids below 22 weeks, before viability, is currently not recommended as evidence is lacking to support a recommendation.[13,14]

Corticosteroids should be administered to women with PPROM or in confirmed preterm labor irrespective of whether they are carrying a singleton or multiple pregnancy.[50] Although there is paucity of data on the risks, there is clear benefit of antenatal corticosteroid administration in multiple pregnancy, especially those at risk for preterm birth.[47,56]

The WHO does not recommend use of antenatal corticosteroids in women with chorioamnionitis since it analyzes worldwide data from many settings where advanced maternal and newborn care is not available.[50] In contrast, in high-resource settings, two systematic reviews and meta-analyses of eight studies by Been et al.[57] and Amiya et al.[58] suggest that antenatal corticosteroids may be safe and effective in reducing adverse neonatal outcomes in women with chorioamnionitis who have PPROM or are in established preterm labor. Given the immunosuppressive effects of corticosteroids, the risk of exacerbating maternal infection is higher in LMICs, where the baseline risk of pre-existing maternal infectious morbidity is greater than in high-resource countries. There is need for RCTs and more robust evidence to guide practice on antenatal corticosteroid administration in women with chorioamnionitis who are at risk of preterm birth.[50,57,58] At this point, antenatal corticosteroids should not be

used unless the hospital is level II–IV, with a care team that is available for managing these complex cases.

Considering antenatal corticosteroid administration at 22–36^{+6} weeks, any exposure—even for few hours—may be of benefit in reducing respiratory distress syndrome for women with PPROM or who are in established preterm labor. This is the case even if total protection (i.e. 48-hour exposure before preterm birth) is not completed prior to birth.[50] This is because the optimal benefits of antenatal corticosteroids are already seen 24 hours after administration, and are maximal at 48 hours; therefore, delaying preterm birth until this time point is optimal, if feasible and safe. There is strong evidence to support the safety of a single repeat course of antenatal corticosteroids in women in preterm labor or with PPROM if 7 days have passed after the initial course and there is a high risk of preterm birth in the next 7 days.[50,59,60] This is because the optimal benefits of antenatal corticosteroids last for 7 days.[48] More than two courses is not recommended owing to the deleterious effects of multiple corticosteroid doses on fetal growth and neurodevelopment.[13,61]

A Cochrane systematic review of 12 trials (1557 women and 1661 infants) evaluating antenatal corticosteroids for preterm birth included 10 trials (1159 women and 1213 infants).[62] Dexamethasone efficacy was comparable to betamethasone. However, the drug dosing was different; in six of the 10 trials, two doses of 12 mg intramuscular betamethasone 24 hours apart was compared with four doses of 6 mg intramuscular dexamethasone 12 hours apart.[62] The latter regimen is recommended by both SOGC and the NIH Consensus Development Panel.[51,63] In both cases the intramuscular route is the recommended route for antenatal corticosteroid administration.[62,64] Owing to its lower cost and wider availability, dexamethasone should be available for patient care at any site, where such a simple measure can make a major difference in newborn outcome. Use of antenatal corticosteroids to mature fetal lungs is a mainstay for preterm fetus management. The indications for and use of antenatal corticosteroids are described in Box 4, with the emphasis on gestational age.

BOX 4 Antenatal corticosteroids in PPROM or proven preterm labor

1. *Antenatal corticosteroids at 24^{+0}–33^{+6} weeks* with PPROM or established preterm labor singleton/multiple pregnancy[13,14,35,50,51]
2. *Antenatal corticosteroids at 22^{+0}–23^{+6} and 34^{+0}–36^{+6} weeks* with PPROM or established preterm labor depend on practice/setting[13,14,53,55]
3. *No antenatal corticosteroids below 22 weeks* before viability. Verify by ultrasound[13,14]
4. *Antenatal corticosteroids for PPROM or preterm labor.* Start even with risk of incomplete course completion[9,50]
5. *No antenatal corticosteroids in LMIC settings* with chorioamnionitis, PPROM, and proven preterm labor. Major increase in maternal/fetal risk
6. *Antenatal corticosteroids in high-resource settings* with chorioamnionitis, PPROM, and proven preterm labor. Risk/benefit based on multidisciplinary/patient decision.
7. *Antenatal corticosteroids repeat after 7 days* with PPROM or proven preterm labor if preterm birth does not occur and there is a high risk of preterm birth in the next 7 days[50,59,60]
8. *Maximum of two courses of antenatal corticosteroids* with PPROM or those at risk of preterm birth[13,61]
9. *LMIC setting*: Four doses of 6 mg intramuscular dexamethasone given 12 hours apart, widely accessed/cheap medication with PPROM and proven preterm labor
10. *High-resource setting*: Either two doses of 12 mg intramuscular betamethasone given 24 hours apart or four doses of 6 mg intramuscular dexamethasone given 12 hours apart[62–64]

7 | TOCOLYSIS IN PPROM AND PRETERM LABOR

Optimally, early identification of a patient at risk of being in preterm labor and significantly delaying delivery toward fetal maturity could make a major difference in outcome. Based on that assumption, several studies have been carried out to confirm this hypothesis. However, the results are equivocal—some are effective but with limits.

A systematic review of 18 RCTs evaluating tocolytics for preterm labor showed that they were associated with a significant reduction in the likelihood of delivery within 24 hours and 7 days, but increased the risk of maternal complications including palpitations, nausea, tremor, chorioamnionitis, hyperglycemia, hypokalemia, and the need to discontinue treatment in women in preterm labor.[65] Tocolytics had no significant effect on perinatal mortality and other adverse perinatal outcomes including respiratory distress syndrome, intraventricular hemorrhage, neonatal necrotizing enterocolitis, patent ductus arteriosus, neonatal sepsis, seizures, hypoglycemia, and low birth weight.[65] NICE recommends tocolytics for women less than 34 weeks pregnant who are in preterm labor with intact membranes.[13] The use of tocolytics in this setting is limited to prolonging pregnancy up to 48 hours to allow for corticosteroid administration, initiation of antibiotics, and/or maternal/in utero fetal transfer to an appropriate level II–IV healthcare setting.[9,21,41]

The use of tocolytics in women with PPROM is controversial. WHO, RCOG, and ACOG do not recommend tocolysis for women with PPROM.[14,35,50] On the other hand, CNGOF considers there is insufficient evidence to recommend for/against the use of tocolysis for PPROM.[41] Practice also differs among specialists.[66] A Cochrane

review of eight trials that included 408 women assessed the potential benefits and harms of tocolysis in women with PPROM, and reported that compared to no tocolysis, tocolysis increased latency by 73 hours (95% CI, 20.21–126.03), decreasing birth rate within 48 hours (RR 0.55; 95% CI, 0.32–0.95) but not perinatal mortality.[67] Furthermore, tocolysis was associated with increased 5-minute Apgar score of less than seven (RR 6.05; 95% CI, 1.65–22.23) and increased need for neonatal ventilation (RR 2.46; 95% CI, 1.14–5.34). In women at less than 34 weeks of gestation with PPROM, tocolytic therapy significantly increased the risk of chorioamnionitis (RR 1.79; 95% CI, 1.02–3.14). Overall, tocolytic treatment in women with PPROM is not recommended, since it increases maternal chorioamnionitis without significantly benefitting neonatal outcomes.[67]

When tocolysis is indicated, nifedipine and atosiban (if nifedipine is contraindicated) are recommended as first-line tocolytic agents.[68,69] APOSTEL III, a multicenter RCT that compared nifedipine and atosiban for tocolysis in women with threatened preterm birth, found that both drugs were equally effective in prolonging pregnancy over 7 days, with similar perinatal outcomes except for a modest reduction in NICU admission with nifedipine.[68] One Cochrane review (38 trials, 3550 women) assessed maternal, fetal, and neonatal outcomes of calcium channel blockers (CCBs) administered as tocolytic to women in preterm labor. Among 35 trials (involving 3275 women) that compared CCBs (mainly nifedipine) with other tocolytic agents, the superiority of nifedipine over other tocolytic agents was demonstrated.[70] There is considerable variation in nifedipine regimen for tocolysis but the most common used in most trials for acute tocolysis is an initial oral dose of 10–30 mg immediately followed by 10–20 mg given every 4–8 hours until contractions cease or up to 48 hours.[50] Betamimetics are not recommended for tocolysis owing to their frequent cardiovascular adverse effects, which could be life threatening.[69,71]

There is no evidence of any additional benefit of combining different classes of tocolytics compared with using a single agent. The use of a combination of different tocolytics is therefore not recommended. In case of initial failure with a particular tocolytic, another tocolytic belonging to a different class may be offered.[50,69] Overall, 48-hour tocolysis for preterm labor enables maximal efficacy of antenatal corticosteroids. In contrast, in patients with PPROM, tocolysis is not recommended as it increases the risk for maternal and newborn infection. Box 5 describes tocolysis application while antenatal corticosteroids are administered, up to 48 hours, and the type and methods of use.

BOX 5 Tocolysis for women in proven preterm labor or with PPROM

1. *LMIC setting*: <34 weeks tocolysis and antenatal corticosteroids when in preterm labor, intact membranes, viable singleton/twins. Coordinate timely transfer to level II–IV facility[9,13,21,41]
2. *High-resource setting*: <34 weeks tocolysis and antenatal corticosteroids for patients with singleton/twins in preterm labor with intact membranes
3. *All facilities*: <34 weeks with PPROM no tocolysis when the chorioamnionitis risk is high.[41,65] Multidisciplinary/patient decision when preterm labor and PPROM is not complicated
4. *Tocolysis only for 48 hours* provides maximal benefit by antenatal corticosteroids[41]
5. *Tocolysis with nifedipine* (widely available) 10–30 mg immediately followed by 10–20 mg every 4–8 hours until contractions cease or up to 48 hours (whichever comes first)[49,68,69]
6. *If nifedipine is contraindicated*, offer atosiban for tocolysis[68,69]
7. *No betamimetics*. Use has severe cardiovascular adverse effects[70,71]
8. *Single tocolytic*. Avoid any agent combination[49,69]
9. *Tocolysis failure*. Use another tocolytic from a different class.[69]

8 | MAGNESIUM SULFATE FOR FETAL NEUROPROTECTION IN PPROM AND PRETERM LABOR

The fetal neuroprotective effects of antenatal magnesium sulfate therapy administered to women in preterm labor or with PPROM is now established.[72-74] A Cochrane review (5 trials, 6145 infants) demonstrated that administration of magnesium sulfate to women with PPROM and/or in preterm labor expected to deliver within 24 hours significantly reduces the risks of cerebral palsy (RR 0.68; 95% CI, 0.54–0.87) and motor dysfunction (RR 0.61; 95% CI, 0.44–0.85) in the offspring.[74] Different dosing regimens were used in the five trials included in the review namely: (1) intravenous 4 g over 20 minutes, then 1 g/hour maintenance infusion until delivery or up to 24 hours, whichever came first (no repeat treatment course) (ACTOMgSO4 study); (2) intravenous 4 g over 10–15 minutes, then 1 g/hour maintenance infusion for 24 hours or intravenous 4 g over 10–15 minutes followed by intramuscular 5 g into each buttock, then 5 g every 4 hours intramuscular for 24 hours or intravenous 4 g over 10–15 minutes followed by intramuscular 2.5 g into each buttock, then intramuscular 2.5 g every 4 hours for 24 hours (Magpie Trial); (3) intravenous 4 g over 30 minutes (no repeat treatment) (Premag Trial); (4) intravenous 4 g bolus (no repeat treatment) (MAGNET Trial); and (5) intravenous 6 g over 20–30 minutes, followed by a maintenance infusion of 2 g/hour. If delivery had not occurred after 12 hours and was no longer considered imminent, the infusion was discontinued and resumed when delivery threatened. If at least 6 hours had passed since magnesium sulfate was discontinued and delivery was again considered imminent, another loading dose was given (BEAM Trial).[75] There is insufficient evidence to recommend any one regimen over another.[72,75] However, owing to concerns about toxicity,

the minimum effective dose should be administered and most guidelines recommend an intravenous loading dose of 4 g administered slowly over 20–30 minutes, followed by a maintenance infusion of 1 g/hour continued until delivery or up to a maximum duration of 24 hours if delivery does not occur within 24 hours.[13,76,77] There is not enough evidence to support a recommendation for a repeat course of magnesium sulfate for fetal neuroprotection after an initial course has been administered.[72,76]

When magnesium sulfate is administered, women should be monitored for clinical signs of toxicity by recording maternal pulse, blood pressure, respiratory rate, oxygen saturation, deep tendon reflexes, and urine output at least four-hourly.[77] The maintenance dose of magnesium sulfate should be discontinued if patellar reflexes are absent, the respiratory rate is less than 12 per minute, the diastolic blood pressure drops more than 15 mmHg below the baseline, or urine output is less than 100 mL/4 hours. Calcium gluconate should always be available for treatment of magnesium sulfate toxicity.

There is no consensus on the upper gestational age limit for magnesium sulfate administration for fetal neuroprotection. Whereas the WHO and ACOG recommend magnesium sulfate for all women at risk of imminent preterm birth before 32 weeks of gestation for prevention of cerebral palsy, NICE recommends that magnesium sulfate should be offered even before 30^{+0} weeks and considered between 30^{+0} and 33^{+6} weeks, while the SOGC guidelines recommend administration before 34 weeks.[13,14,50,78] All the women in the 2009 Cochrane review were administered magnesium sulfate at less than 34 weeks of gestation. The number needed to treat to prevent one case of cerebral palsy was low at all gestational ages below 34 weeks.[74] Therefore, magnesium sulfate is recommended for fetal neuroprotection for all women with PPROM or who are in established preterm labor from viability to 33^{+6} weeks of gestation regardless of singleton or multiple pregnancy. Box 6 describes the utility of magnesium sulfate for neuroprotection, specifically defines the gestational age to be used, methods of administration, and safeguards needed to minimize risk of toxicity.

BOX 6 Magnesium sulfate for fetal neuroprotection in women with established preterm labor or PPROM

1. *Magnesium sulfate to all above 23 weeks* with established preterm labor or PPROM at risk of imminent preterm birth within 24 hours (singleton/twins)
2. *LMIC setting simplified magnesium sulfate*: intravenous 4 g slowly over 20–30 minutes, followed by intramuscular 5 g into each buttock, then 5 g given intramuscularly into alternate buttocks every 4 hours for 24 hours
3. *High-resource setting*: Intravenous loading dose 4 g slowly over 20–30 minutes, followed by 1 g/hour continued infusion until delivery or up to 24 hours. Requires monitoring[71]
4. *Discontinue magnesium sulfate* after 24 hours if delivery does not occur[71]
5. *No repeat magnesium sulfate* for fetal neuroprotection after an initial course[72,75]
6. *Magnesium sulfate monitoring*: Clinical toxicity signs, maternal pulse, blood pressure, respiratory rate, oxygen saturation, deep tendon reflexes, urine output at least four-hourly using a foley balloon[77]
7. *Magnesium sulfate maintenance. Stop if signs of toxicity.* Absent patellar reflexes, respiratory rate less than 12/minute, diastolic blood pressure drops more than 15 mm Hg below baseline, or urine output is less than 100 mL/4 hours. Calcium gluconate should always be available to treat magnesium sulfate toxicity.

9 | HOME VERSUS HOSPITAL CARE FOR WOMEN WITH PPROM

Dussaux et al.[78] in a retrospective study of 90 women with PPROM who received outpatient care and 324 women who received hospital care observed no major complications related to home care. They recommended an RCT to confirm the safety of home care for women with PPROM.[78] Carlan et al.[79] in their RCT randomized 67 patients with PPROM to receive either home or hospital care. There was no significant difference in clinical characteristics and perinatal outcomes between the two groups. However, only 18% of the women met the criteria for home care.[80] A Cochrane review to assess planned home versus hospital care for PPROM included two small trials of 118 women but lacked sufficient statistical power to detect meaningful differences between the two groups.[80] There is therefore insufficient evidence to recommend home care for women with PPROM. This is strengthened because it is difficult to predict latency and complications such as infection, umbilical cord compression, cord prolapse, and placental abruption.[9] However, realistically, in a primary setting (similar to home care) with limited staff and tools, when the ability to transfer to a higher-level setting is not possible, onsite management should be maximized based on the widely available safe medications, which can, in some cases, make a major difference in maternal and newborn outcomes. There is insufficient evidence to recommend home care of women with PPROM.

10 | CONCLUSION

Preterm labor rates remain high and there are no demonstrated preventive measures. In many cases, preterm labor is associated with PPROM, complicating management and suitability of care, primarily in LMICs and remote rural areas. Good practice recommendations are presented with a stepwise approach to diagnose preterm labor, PPROM, and identify risks of chorioamnionitis, which enables the judicious use of antibiotics. Furthermore, steps are provided for

effective tocolysis to enable administration of antenatal corticosteroids combined with magnesium sulfate for maximizing neuroprotection. Applying such an integrated approach will significantly improve maternal and newborn outcomes.

AUTHOR CONTRIBUTIONS

Eytan R. Barnea conceived the article. Akaninyene Eseme Ubom prepared the first draft, which was revised by Eytan R. Barnea and Manu Vatish.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

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APPENDIX A

FIGO CHILDBIRTH AND POSTPARTUM HEMORRHAGE COMMITTEE

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