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Review article

Management of preterm labor: Clinical practice guideline and recommendation by the WAPM-World Association of Perinatal Medicine and the PMF-Perinatal Medicine Foundation

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ABSTRACT

This practice guideline follows the mission of the World Association of Perinatal Medicine in collaboration with the Perinatal Medicine Foundation, bringing together groups and individuals throughout the world, with the goal of improving the management of preterm labor. In fact, this document provides further guidance for healthcare practitioners on the appropriate use of examinations with the aim to improve the accuracy in diagnosing preterm labor and allow timely and appropriate administration of tocolytics, antenatal corticosteroids and magnesium sulphate and avoid unnecessary or excessive interventions. Therefore, it is not intended to establish a legal standard of care. This document is based on consensus among perinatal experts throughout the world in the light of scientific literature and serves as a guideline for use in clinical practice.

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Rationale of this recommendation

Why was this guideline developed?

Preterm birth is a leading cause of perinatal morbidity and mortality worldwide. This guideline covers the care of women with signs/symptoms of preterm birth aiming to give recommendations to reduce both the risk of unnecessary treatment as well as the consequences of prematurity. Up until now, most guidelines have mainly focused on high-income countries or referral centers and present several discrepancies among them, especially in terms of the diagnostic tests that should be used or when to initiate treatment. The World Association of Perinatal Medicine (WAPM) and the Perinatal Medicine Foundation (PMF) found it necessary to develop a guideline that could be useful for all settings and worldwide adaptable according to local resources available.

How was this guideline developed?

In the development of this guideline, the Delphi consensus methodology was applied. This is a well-established method to reach consensus within a panel of experts in issues where current evidence is not strong. For this guideline, the panel consisted of 16 international perinatal medicine specialists, both obstetricians and neonatologists, active members of the WAPM, with extensive experience in the diagnosis and management of preterm labor and the management of premature birth, with an effort to achieve global coverage and thus ensure generalizability of the consensus definitions. At first, an online session was held with the participation of the 16 panelists. Prior to this meeting, a thorough scoping literature review had been performed to gather all the published evidence regarding this topic. During this online meeting, the main areas of controversy were discussed. Then, a series of questions were constructed based on the variations described in the literature and in clinical practice. These questions were sent to all panelists to review and comment. After considering all the feedback, the questions were sent, and anonymous replies were received. A level of agreement of 80% was agreed in advance for consensus to be reached and subsequent rounds of questions were conducted. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to classify the recommendations based on the robustness of existing evidence. For the strength of recommendation, the panel used an approach based on the directions suggested by the World Health Organization (WHO) for the development of clinical guidelines.

What does this guideline add to what is already known?

The present guideline provides evidence-based recommendations for the diagnosis and management of preterm labor in different settings. Furthermore, it provides some clarity within the most controversial/unresolved issues in literature through a Delphi approach by experts in the field from different regions of the world. More specifically, this guideline considers both secondary and tertiary care settings in low- and middle-income countries (LMIC) and high-income countries (HIC). This represents a significant improvement since the management of this pathology cannot be understood in the same way in all settings, as resources can vary widely, and the same intervention can be of use in one but not in another. On another note, although some guidelines put their focus on when to treat preterm labor, this one also remarks when it is reasonable to avoid unnecessary treatment. Given the growing body of evidence of the potential harms of steroids, a pillar in the management of preterm labor, and also considering the side effects of tocolytics, the current guideline adheres as to the principle of "first do no harm", emphasizing the importance of not only identifying patients at risk of preterm birth but also recognizing situations where it is unlikely for them to deliver soon, and treatment would not only be unnecessary but could potentially be harmful.

Introduction

Preterm birth, defined as delivery prior to 37 completed weeks, is a major contributor of perinatal mortality and morbidity across all health care settings, worldwide. It encompasses a broad spectrum of complications, ranging from morbidities such as intraventricular hemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity and cerebral palsy to perinatal death [1–7].

The burden of morbidity and mortality from preterm birth affects all healthcare settings but it disproportionately affects low and middle-income countries. There are approximately 15 million preterm births (10 % of all deliveries) annually worldwide, of which nearly 80 % (12 million births) occurred in Asia and sub-Saharan Africa [1]. Although preterm birth is any delivery prior to 37 completed weeks, most of these births (85 %) occur between 32^{+0} and 36^{+6} weeks' gestation. Multiple pregnancies contribute to a significant proportion of preterm births with 20 % of deliveries due to occurring because of multifetal gestations [1,2].

Preterm birth is subcategorized in spontaneous or medically indicated. The former is caused by the onset of contractions or/and rupture of membranes whereas in the latter, delivery is offered by health professionals when there is evidence that continuation of pregnancy poses an imminent risk to the mother and/or the fetus. Risk factors associated with spontaneous preterm labor (PTL) include extremes of maternal age, low socio-economic status, low or high BMI, uterine anomalies, substance use, suboptimal prenatal care and nutrition, history of previous PTL or cervical surgery, use of assisted reproduction technology (ART), urinary and vaginal infections, preterm premature rupture of membranes (PPROM) and amniotic fluid abnormalities [3,8–15].

Despite the significant progress in perinatal care, the rate of spontaneous PTL leading to preterm birth has remained relatively unchanged in the past decades [16]. At the same time, there is difficulty in establishing a universal approach in diagnosing true PTL as women often report symptoms resembling PTL, leading to unnecessary admissions and treatment [17]. In fact, a large proportion of women receiving tocolytics and antenatal corticosteroids for symptoms of PTL eventually deliver at term. Thus, a large observational register-based study found that 44% of neonates exposed to antenatal corticosteroids were delivered at term [18]. In another retrospective cohort of preterm neonates, 50% of women presenting with vaginal bleeding or preterm rupture of membranes, 38.5% of women with asymptomatic cervical changes and 16.5% of women with contractions received corticosteroids but eventually delivered later than 7 days [18,19]. In a retrospective study of steroids administration in cases with anticipated spontaneous or medically indicated preterm delivery at 34^{+0} to 36^{+6} weeks, only 5% of women in spontaneous cases and 23% of women in medically indicated cases delivered within 2–7 days; 20% of spontaneous and 30% of medically indicated went on to deliver at term [20]. Finally, a recent study in the United States showed that only 55% of pregnancies that had received steroids delivered in the optimal timeframe; notably, of the ones delivering beyond the optimal timeframe, 85% were treated due to threatened preterm labor [21]. Apart from the burden for the healthcare systems, this unnecessary treatment may carry significant risks for both the mother and the offspring as tocolytics and especially steroids are

potent drugs that may carry short- and long-term risks [22]. Thus, in a Finnish population-based study, there was a 30% increase in mental and behavioral disorders in term neonates that had previously been exposed to steroids (HR: 1.47; 95% CI: 1.36–1.69) [23].

Therefore, it is crucial first, to balance the risk to benefit ratio across the preterm period and second, develop algorithms that will effectively guide clinicians in predicting true PTL and offer management according to the infrastructure in each setting. The WAPM in collaboration with the PMF recognized the importance of addressing the issue of appropriate management of PTL and proceeded to propose an up-to-date guideline, based on the best available evidence, acknowledging, at the same time, the significant differences that may exist in various settings.

Definition of preterm labor and birth

It is generally accepted that prematurity refers to the period preceding 37^{+0} gestational weeks [24]. Prematurity may be subcategorized to extremely preterm ($<28^{+0}$ weeks), very preterm ($28^{+0} - 31^{+6}$ weeks), moderate preterm ($32^{+0} - 33^{+6}$ weeks) and late preterm neonates ($34^{+0} - 36^{+6}$ weeks) [3]. The earlier limit of preterm birth may vary in different settings, ranging from 20^{+0} to 24^{+0} weeks, based on the gestational age from which active neonatal support is offered in each setting [24].

There are apparently two major considerations in managing PTL, both originating from its definition. The term “preterm” refers to the gestational age limits within which PTL treatment should be indicated; the term “labor” pertains to defining the phase of labor at which true PTL should be diagnosed. Regarding the first parameter of gestational definition of prematurity, there is significant variation in recommendations from professional bodies regarding the lower gestational threshold at which maternal and neonatal intervention is recommended, reflecting disparities in infrastructure between healthcare settings, for example in centers where there is availability of neonatal intensive care versus those which are in resource poor settings in low-middle income countries. Therefore, our guideline includes recommendations that can be customized in both above-mentioned settings as most of the burden of prematurity is in the latter [25,26]. Therefore, the WAPM recommends that the earlier gestational cut-off is individualized in each setting, according to local neonatal facilities and protocols; in high income settings, by consensus, the suggested cut-off is 22^{+0} weeks, whereas in other settings such as those with limited neonatal infrastructure the cut-off may be 24^{+0} or even 26^{+0} weeks of gestation in very resource-poor settings [22].

On the other end of the spectrum, the upper gestational limit in terms of maternal and neonatal intervention is also debated, especially in light of recent evidence which questions the risk/benefit ratio of treatment and interventions such as tocolysis, corticosteroids and magnesium sulphate, at late prematurity, i.e. at 34^{+0} to 36^{+6} weeks [27–30]. Therefore, the WAPM recommends that the later gestational cut-off is also individualized in each setting, according to local neonatal facilities and protocols; by consensus, the suggested cut-off is 34^{+0} weeks, until further evidence regarding risk/benefit ratio of treatment and interventions is available for the gestational window between 34^{+0} and 36^{+6} weeks.

Regarding the second parameter, defining “labor” could be challenging even at term. The definition proposed by the WHO recognizes two stages: the “latent” as a period of time characterized by painful uterine contractions and variable changes of the cervix, including some degree of effacement and slower progression of dilatation up to 5 cm for first and subsequent labors and the “active” as a period of time characterized by regular painful uterine contractions, a substantial degree of cervical effacement and more rapid cervical dilatation from 5 cm until full dilatation, for first and subsequent labors [31]. However, this definition was based on studies carried out on term pregnancies [32] and does not take into account the relative cervical dilatation compared to fetal head circumference at preterm gestations (e.g., the definition of full dilatation is 10 cm at term and therefore, the 5 cm cut-off proposed by the WHO is reflective of a term gestation, whereas at 24 to 27 weeks, full dilatation of the cervix relative to fetal head size maybe reached at earlier cervical dilatations as the maximum fetal head diameter is only 6–8 cm). Therefore, for the purposes of this guideline, the WAPM, by consensus, recommends a more pragmatic cut-off of latent/active phase of labor at the cervical dilatation of 3 cm, until further evidence is available.

Establishing a universal definition for PTL is of paramount importance to avoid unnecessary (due to Braxton Hicks contractions, or other causes) admissions in the labor ward, as these may lead to unnecessary interventions and resource use. There is a variation in the literature with regards to the terminology and MeSH terms used to define women presenting with symptoms of preterm labor, with some studies using ‘suspected’ and others using the term ‘threatened’ [24]. This guideline uses the term threatened PTL to include all women presenting with such symptoms, which will include those with non-specific symptoms and false PTL as well as those which will progress to true PTL.

In threatened PTL, the aim is to recognize signs of labor, neither too early resulting in the woman not delivering within 7 days, nor too late allowing insufficient time for patient transfer and, if deemed necessary, administration of magnesium sulfate and corticosteroids. As the first stage of spontaneous labor from admission to full dilatation in a nulliparous at term lasts a median of 8.5 hours [32], we would be already too late to achieve maximum effect of ACS, unless tocolysis is effective. In fact, if the woman is in the active phase, at a preterm gestation, with a dilatation of >3 cm, the available time may be even less. On the other hand, it could be difficult to correctly recognize the latent phase at its very onset, i.e., before changes in the cervix develop and, if waiting for those changes, precious time might be lost. Ultimately, it is impossible to effectively intervene only in cases undergoing true PTL while avoiding unnecessary interventions in all cases that eventually will not undergo PTL if left untreated. Inevitably, by applying strict criteria for diagnosing true labor, a large proportion of cases will not receive adequate treatment. This became apparent in the ALPS study, where, although cases that were expected to deliver in less than 24 hours were excluded from randomization (constituting 31.7% of screened, twice the number of the randomized), 38.3% of randomized women still delivered within 24 hours, before a second dose of steroids could be administered [27]. If the criteria are less strict, as is currently the situation in most settings, a large proportion of women will unnecessarily receive tocolytics and ACS and eventually deliver more than seven days later or even at term, with the long-term adverse neurodevelopmental outcomes, as mentioned earlier [23].

Recommendation

PTL is defined as labor occurring before 37^{+0} weeks.

The suggested earlier and later gestational limits as thresholds for treatment and interventions are 22^{+0} and 33^{+6} weeks respectively, in high income settings, and should be individualized depending on resources and infrastructure.

Diagnosis of preterm labor

The determination of the exact gestational age is crucial for the accurate diagnosis of PTL. The WAPM recommends accurate dating of pregnancy based on first trimester fetal crown rump length at

11–13 weeks or fetal head circumference for those booked later, acknowledging that the latter is less accurate. In settings without access to ultrasound, the last menstrual period should be used if the woman is certain of her dates and reports regular menstrual cycles, whereas if the dates are unknown or the cycle irregular, the use of the fundal-symphysis height is the only available option for dating [33,34].

Established (true) preterm labor

Women in PTL typically present with painful uterine contractions, abdominal/low back pain, pelvic pressure, vaginal leakage/discharge or a combination of the above. Physical examination may demonstrate cervical effacement and/or dilatation [24]. The diagnosis of PTL is based on the confirmation of regular uterine contractions (manual palpation or by cardiotocography) that produce changes to the cervix [24]. In the literature, there is a wide range of cut-offs used for the minimum frequency of contractions that are required for the definition of 'established' or 'true' PTL. In a *meta*-analysis of studies on PTL, the threshold ranged from 4 to 12 contractions per hour and most studies did not mention a minimum duration of observation [35]. This guideline uses the term established PTL for consistency throughout this document to imply labor beyond which delivery is considered inevitable.

By consensus, a minimum of 6 contractions per 30 min is proposed as an acceptable threshold of frequency and duration of observation and constitutes one of the two necessary criteria for immediate diagnosis. The uterine contractions should be regular and lead to cervical changes. These changes may be confirmed by visualization of the cervix with a speculum examination or by digital examination to assess cervical dilatation and effacement. In most published data a dilatation of ≥3 cm (in some ≥2 cm) was used as a cut-off for the diagnosis of PTL requiring management [24]. The WAPM, by consensus, recommends a cut-off of ≥3 cm as the second of the necessary criteria for the diagnosis of established PTL.

Recommendation

The diagnosis of established PTL is based on confirmation of regular contractions (manually or by cardiotocography) that produce changes to the cervix. The combination of ≥6 contractions per 30 min (1/5min) and cervical dilatation of ≥3 cm are necessary for the diagnosis of established PTL.

Stepwise approach for the management of threatened PTL

Women presenting with threatened PTL may either progress and develop established PTL or their symptoms may subside thus allowing discharge and continuation of pregnancy. The following section outlines the recommendations for observation of women with threatened PTL and the investigations that can be carried out that may allow for accurate stratification of those that are likely to progress to established PTL and may consequently require treatment or interventions, and those who can be reassured and safely discharged. The management of women with threatened PTL is marked by considerable ambiguity and variations in recommendations and protocols, due to significant diversity in the presenting symptoms of threatened PTL, with some experiencing subtle symptoms such as mild back ache while others presenting with painful/palpable uterine contractions. For them all, there is considerable variability in the sensitivity and specificity of the recommended investigations for threatened PTL leading to ambiguity in clinical management. This guideline summarizes the evidence to date along with a flow chart of management to aid clinical management in a uniform fashion.

The main diagnostic tools available for management include a combination of clinical, biophysical and biochemical assessments. These include the observation of the frequency of uterine contractions and demonstrable changes in the cervix as assessed by either a speculum or a digital vaginal examination, the measurement of CL and the qualitative or quantitative assessment of fetal fibronectin (fFN), placental alpha-microglobulin-1 (PAMG-1) or phosphorylated insulin-like growth factor-binding protein-1 (phIGFBP-1) [17,36–38]. The assessment of uterine contractions and cervical dilatation has been described above in this document.

The CL may be assessed sonographically by the transvaginal, transabdominal or transperineal technique; the transvaginal approach (TVUS) is the gold standard method [39–42]. In a *meta*-analysis of studies in women with symptoms of PTL, using the CL measurement for triage, a CL ≤20 mm or ≤15 mm identified a large proportion of women that delivered within 7 days; overall, only 11 % of symptomatic women delivered within 7 days; a CL <15 mm (10 % of women) predicted 60 % of these cases (90 % specificity) and a CL <20 mm predicted 75 % of these cases (80 % specificity). Importantly, in symptomatic women at <34 weeks, a CL >15 mm had a negative predictive value of 96 %, i.e. these women may be reassured that the chance of delivering in the next 7 days is only 4 %; also, this negative predictive value did not improve significantly if the cut-off of CL was set at 20 or 25 mm [35]. A more recent Cochrane review examined the effect of the knowledge of CL measurement in singletons with symptoms of PTL. In the knowledge groups, delivery occurred four days later (mean difference 0.64 weeks, 95 % CI 0.03 to 1.25; 3 trials, 290 women); the results were inconclusive for other outcomes and the evidence was low-quality [37].

The biochemical markers used in management of threatened PTL include fFN, phIGFBP-1 and PAMG-1. The first (fFN) is an extracellular matrix glycoprotein concentrated between the decidua and the trophoblast, found normally in very low levels in cervico-vaginal secretions. Levels ≥50 ng/mL have been associated with increased risk of spontaneous preterm birth [36]. PAMG-1 is a human protein in the amniotic fluid that is also present in very low levels in the cervico-vaginal secretions; a cut-off level of 5 ng/ml is usually used to detect preterm labor [43]. PhIGFBP-1 is a protein produced by the decidua that may appear in the cervical secretions if uterine contractions disrupt the chorio-decidual interface [44]. In the prediction of preterm birth within 7 days in women with signs and symptoms of PTL, the positive predictive value of PAMG-1 was significantly higher than that of phIGFBP-1 or fFN whereas other diagnostic accuracy measures did not differ. As prevalence affects the predictive performance of a diagnostic test, use of a highly specific assay for a low-prevalence syndrome such as PTL may reduce unnecessary treatment significantly [45–47].

In settings where both CL measurement and biomarkers are available, a contigent approach that may be chosen for symptomatic women with universal CL assessment and additional biomarker testing in selected cases [45]. According to this approach, if CL < 15 mm, admission and treatment is advised, whereas if CL > 30 mm reassurance is offered and, if CL is 15–30 mm, biomarker testing (fFN or PAMG-1) allows further triage. Notably, PAMG-1 testing has been found to be particularly accurate in predicting PTL within a week in patients with symptoms of PTL and a CL of 15–30 mm [48,49].

Recently, a multivariable application has been proposed for the prediction of preterm birth in symptomatic women, with promising results both in development and validation cohorts; the area under the curve for preterm birth prediction within one week was 0.96 and the negative predictive value close to 100 % [50].

The WAPM, recommends that a period of observation of at least 2 h is offered in all women presenting with threatened PTL to allow further management which may be either reassurance and discharge from the hospital, or further assessment. In low resource settings, further assessment involves the recording of contraction frequency and a new examination for cervical dilatation. No consensus could be reached as to whether at the end of initial observation CL measurement should be obligatory in LMIC settings. In settings with more resources, further assessment may include sonographic CL measurement, biomarker assessment or both. When CL measurement is available, a cut-off of 15 mm is, by consensus, recommended as threshold for discharge in the absence of any clinical symptoms of labor. If only biomarker assessment

is available, then a negative test in the absence of any other symptoms would be a recommendation for discharge. If both tests are available, a CL between 15 and 30 mm should be followed up with the biomarker assessment with further management depending on the latter.

Recommendation

In cases of threatened PTL, a stepwise approach should be implemented which includes a period of observation of at least 2 h, with or without hospital admission. In low-resource settings contractions and cervical dilatation will guide further management. In high-resource settings, further stratification of risk using either CL, biomarkers such as fFN or PAMG or a combination of all above should be offered.

Hospital discharge and expectant management should be offered based on:

Low-resource settings: discontinuation of contractions and no increase in cervical dilatation.

High resource settings:

1. only CL available: CL ≥15 mm.
2. Only biomarker (fFN or PAMG) available: negative test.
3. Both CL and biomarker available: CL >30 mm or CL 15–30 mm and negative biomarker

Management of preterm labor

Tocolysis

In cases considered high-risk of delivering preterm within the next 7 days, the administration of antenatal corticosteroids improves perinatal and long-term outcomes for the offspring and, therefore, should be initiated as soon as possible [22,25]. As steroids act more efficiently when given ≥48 h (but less than seven days) before birth, tocolysis is also recommended with the intention to delay delivery for at least 48 h [51,52]. Tocolysis may also serve to allow for the time needed for in-utero transfer to appropriate level neonatal centers. Beyond that time frame, tocolysis should be discontinued, as it has been shown that it offers no benefit; studies comparing placebo to different tocolytics, i.e., oral betamimetics [53], magnesium sulphate [54], calcium channel blockers [55] or oxytocin receptor antagonists [56] showed that, although continuing tocolytic treatment may postpone delivery for up to seven days, this does not appear to improve outcomes. It should be noted that tocolytic agents are not without risks [23,57,58]. Despite the lack of evidence on the benefit of maintenance tocolysis, a recent study from Germany has shown that 80 % of clinicians offer this treatment for threatened preterm labor, also contrary to their national guideline [59].

As tocolytics should only be used to allow time for the action of steroids or transfer to an appropriate level neonatal care setting, a further episode of threatened preterm labor within less than 2 weeks should not be treated using tocolytics. If administered more than 2 weeks before, in case of the gestational age still being below 34^{+0} weeks, tocolytics may be used once more for up to 48 hours to allow the administration of a new course of steroids. Moreover, if transfer is needed, repeated tocolysis may also be considered.

Tocolytics and steroids are generally recommended for PTL from viability up to $<34^{+0}$ weeks of gestation; there is inconsistency on the optimal lower gestational age; in a study of 6,925 multiple-birth infants at $\geq 22^{+0}$ gestational weeks, extremely preterm infants showed benefit from antenatal steroids [60]. Tocolysis should be avoided in certain cases, including severe bleeding, chorioamnionitis, severe preeclampsia/eclampsia requiring immediate delivery, lethal fetal anomalies, fetal death or non-reassuring fetal status. In cases with PPROM without evidence of maternal infection, tocolytic treatment may be used.

Calcium channel blockers, (i.e. nifedipine, 10–30 mg loading dose and 10–20 mg/4–8 h; maximum 180 mg/day), may be used as the first line tocolytic treatment. A *meta*-analysis showed that nifedipine offers advantages compared to other tocolytics [61]. A Cochrane review concluded that these agents have less maternal adverse effects and lower rates of serious neonatal morbidity compared to betamimetics and less admissions to the neonatal intensive care unit compared to oxytocin receptor antagonists [55]. Oxytocin receptor antagonists are an acceptable alternative as they have less side effects, compared to the other tocolytics [55,62,63]. Betamimetics, on the other hand, are no longer considered first line options for tocolysis due to their increased risk of life-threatening adverse reactions [53]. Finally, combinations of tocolytic agents should be avoided, as there are insufficient data regarding their safety and effectiveness [64].

Recommendation

Treatment with tocolytic drugs is recommended up to 33^{+6} weeks with the aim to prolong pregnancy up to 48 h for the administration of antenatal corticosteroids or transfer to a tertiary center.

Calcium channel blockers (nifedipine) or oxytocin receptor antagonists should be offered as first-line agents.

Combinations of tocolytic agents should not be used until more data are available.

Maintenance tocolysis (beyond 48 h) is not recommended until more data are available.

Corticosteroids

Antenatal corticosteroids are administered for fetal lung maturation in cases where preterm birth is imminent [51,52]. The WAPM has recently published a clinical practice guideline on the use of antenatal corticosteroids (Table 1). Briefly, a single course is recommended between 24^{+0} and 33^{+6} weeks of gestation in case of high risk of preterm delivery within the following 7 days. A course may be considered from as early as 22^{+0} weeks based on local limits of viability. The effect of the treatment is optimal if birth occurs after at least 24 h (ideally 48 h) but no more than seven days following the first dose and it is of no benefit at all if that happens in more than 14 days [22]. A Cochrane review and *meta*-analysis of 30 studies clearly demonstrated that this treatment

Table 1
WAPM Summary of recommendations on the use of antenatal corticosteroids.

(1) A course of ACS should be considered between 22^{+0} and 23^{+6} gestational weeks in women at high risk of PTB within the next seven days. The decision should be based on local standards regarding periviable neonatal support, availability of neonatal facilities, following appropriate consultation with the parents.
(2) A single course of ACS should be administered between 24^{+0} and 33^{+6} gestational weeks in women at high risk of PTB within the next seven days.
(3) A single course of ACS is not routinely recommended between 34^{+0} and 36^{+6} gestational weeks in women at high risk of PTB within the next seven days, because of the current uncertainty regarding the benefit to risk ratio.
(4) Either betamethasone (two doses of 12 mg IM in a 24 h interval) or dexamethasone (four doses of 6 mg IM at 12 h intervals) may be administered for fetal lung maturation.
(5) Repeated doses of ACS following an initial course of ACS are not recommended. A single rescue course of ACS is not routinely recommended. It may be administered up to 33^{+6} gestational weeks in women at high risk of PTB within the next seven days when a course of ACS has been administered at least 14 days before.
(6) ACS are not routinely recommended before scheduled cesarean section at term, because of the current uncertainty regarding the benefit to risk ratio. In the absence of other indications, a scheduled cesarean section should not be performed before 39+0 weeks of gestation.
(7) In multiple pregnancies, ACS should be administered at the same dosage and indications as in singleton pregnancies.
(8) In obese women, ACS should be administered at the same dosage and indications as in women without obesity.
(9) A single course of ACS is recommended at the time of diagnosis of PPROM when gestational age criteria are met.
(10) In cases complicated with FGR, ACS should be administered at the same dosage and indications as in appropriate for gestational age fetuses.
(11) In diabetic women, ACS should be administered at the same dosage and indications as in women without diabetes. Close monitoring of the maternal blood glucose levels is recommended for women with diabetes in the following days after the administration of ACS. After the administration of ACS, screening with glucose tolerance test should be delayed for at least one week.

achieves a significant reduction in prematurity-related serious adverse outcomes [65].

Recommendation

Please refer to the respective WAPM guideline [22]. A summary is shown in Table 1.

Magnesium sulfate

Magnesium sulfate offers fetal neuroprotection when administered for at least 4 h in cases delivering before 32 gestational weeks [52]. A Cochrane review showed that this treatment significantly reduces the risk of cerebral palsy or substantial gross motor dysfunction in the offspring [28]. Nevertheless, a recent randomized clinical trial, failed to show improvement in child survival free of cerebral palsy at 2 years, following administration of intravenous magnesium sulfate prior to preterm birth at 30 to 34 weeks [66]. In small for gestational age fetuses, below the 5th centile, this treatment may be considered up to 33^{+6} gestational weeks. The recommended regimen includes a 4 g IV bolus dose delivered over 15 to 30 min followed by an IV infusion of 1 g/hour until delivery or for up to 24 h.

Recommendation

Magnesium sulfate for fetal neuroprotection is recommended up to 31^{+6} gestational weeks and may be considered up to 33^{+6} gestational weeks in small for gestational age fetuses, below the 5th centile.

The proposed regimen consists of 4 g IV bolus dose given over 15–30 min followed by a maintenance IV infusion of 1 g/hour until delivery or for up to 24 h.

Prophylactic antibiotics

Prophylactic antibiotic therapy is not routinely recommended for women in PTL with intact membranes and no signs of infection. In a Cochrane review, the use of antibiotics in PTL reduced maternal infection but no benefit was achieved on perinatal outcomes; on the contrary, an increase in neonatal mortality was observed in cases that received antibiotics compared to placebo [67]. Furthermore, according to the ORACLE II study, treatment with erythromycin in cases of spontaneous PTL with intact membranes was associated with a higher risk of functional impairment of the offspring at 7 years of age [68]. A limitation of these studies was that they did not assess amniotic fluid for infection. There are ongoing studies that investigate the potential benefit of antibiotics for microbial invasion or inflammation of the amniotic fluid [69]. Antibiotic treatment is clearly indicated in cases with PPROM, clinical chorioamnionitis or Group B Streptococcus colonization.

Recommendation

Prophylactic antibiotic therapy is not routinely recommended in PTL with intact membranes in the absence of infection.

Activity restriction

Activity restriction is not advised for PTL prevention; however, the evidence is limited. A secondary analysis found that this prophylactic measure increased the rate of preterm birth in asymptomatic nulliparous women with a short cervix compared to normal activity (OR: 2.37; 95 % CI: 1.60–3.53) [70]. A more recent randomized controlled trial found that in singleton pregnancies with arrested preterm labor, activity restriction (including pelvic rest, no sexual intercourse, and reduction of work), did not reduce the preterm birth rate < 37 weeks [71]. Women should be advised against it as there is no proven benefit; on the contrary, there are several associated risks, including venous thrombosis, muscle atrophy, symptoms of musculoskeletal and cardiovascular deconditioning, self-blame feelings and increased patient and healthcare costs [72].

Recommendation

Activity restriction is not recommended to prevent PTL.

Mode of delivery

PTL at any gestational age should not be considered an indication for cesarean delivery, as this approach is not protective for the neonate. Thus, planned immediate cesarean section or vaginal delivery for PTL were associated with similar incidence of birth injury (RR: 0.56; 95 % CI: 0.05–5.62), asphyxia (RR: 1.63; 95 % CI: 0.84–3.14), perinatal death (RR: 0.29; 95 % CI: 0.07–1.14) or postpartum hemorrhage (RR: 3.69; 95 % CI: 0.16–83.27). In fact, vaginal delivery appeared protective for maternal infections (RR: 2.63; 95 % CI: 1.02–6.78) [73]. Therefore, vaginal delivery is considered safe for both singleton and twin preterm fetuses with vertex presentation [74]. Notably, vaginal birth after previous cesarean delivery is not contraindicated in cases of PTL [75].

Cesarean delivery may be offered for preterm breech presentation. A systematic review concluded that it is associated with lower neonatal mortality compared to vaginal delivery (RR: 0.63; 95 % CI: 0.48–0.81) [76]. Cesarean delivery may also be opted in certain cases of severe early fetal growth restriction with an estimated fetal weight below 1,500gr or in twins with a non-vertex presenting fetus [77].

Operative vaginal delivery is not generally recommended before 34^{+0} weeks, however, if applied, low forceps delivery should be preferred over vacuum extraction; a large cohort study (40,764 neonates) found that the risk of neonatal injury was lower with forceps [78]. There is no sufficient data regarding the safety of operative vaginal delivery at 34^{+0} to 36^{+0} gestational weeks [79].

Recommendation

PTL is not an indication for routine cesarean delivery.

Vaginal birth is the gold standard method for both singleton and twin preterm fetuses with vertex presentation.

Vaginal birth after previous cesarean delivery is not contraindicated in cases of PTL.

Operative vaginal delivery is not recommended before 34^{+0} weeks, however, if necessary, low forceps delivery is preferred over vacuum extraction.

Intrapartum fetal monitoring

Fetal monitoring during PTL includes fetal heart rate examination, fetal scalp electrode or fetal blood sampling. Both external cardiotocography or intermittent auscultation are available options for intrapartum assessment of fetal well-being. A Cochrane review concluded that the use of antepartum cardiotocography does not improve perinatal outcomes, however, most included studies lacked power. There was also insufficient data to allow comparison of term versus preterm cases [80]. There is limited evidence for recommending

one over the other and local protocols should be used, especially prior to 26^{+0} weeks; Electronic fetal monitoring should be considered after 26^{+0} weeks, to assess intrapartum fetal well-being.

Recommendation

Monitoring of fetal wellbeing during an established PTL using cardiotocography or intermittent auscultation should follow local protocols especially prior to 26^{+0} weeks, with consideration for electronic fetal monitoring after this gestational window.

Timing of cord clamping and prevention of hypothermia

Delaying umbilical cord clamping for at least of 30–60 s, for a maximum of 180 s, is recommended in preterm neonates. Delayed cord clamping in preterm infants is associated with lower incidences of neonatal death, transfusion for anemia, intraventricular hemorrhage and necrotizing enterocolitis [81]. However, no clear benefit on neuromotor development has been observed after discharging from the neonatal intensive care units. There is insufficient evidence to show what duration of delay clumping is best, therefore, current recommendations support not clamping the cord immediately after birth. In cases of severe maternal bleeding or need for immediate neonatal resuscitation, cord milking and rapid clamping may be preferable [81].

Current practices of routine thermal care for preterm infants immediate after birth such a warm temperature in the delivery room, drying of neonate, and radiant warmers or incubators are often inadequate in preventing heat loss in preterm infants. Therefore, the addition of a polyethylene bag or a portable thermal nest to standard care reduces the incidence and duration of hypothermia at birth [82].

Recommendation

Delaying umbilical cord clamping for at least 30–60 s in preterm neonates is recommended as in term neonates.

Placement of the neonate in a polyethylene bag during this period significantly reduces the risk of hypothermia.

Conclusions

In women presenting with symptoms and signs raising the suspicion of PTL, the correct identification of patients experiencing true PTL should be aimed. The WAPM/PMF, supporting the approach of "first do no harm", proposes strict criteria for the diagnosis of established PTL and a stepwise approach in threatened PTL cases may be applied in different settings to distinguish transient uterine activity from true labor and reduce unnecessary interventions, quite common in current practice. The diagnosis should be based on the recognition of regular uterine contractions, at least 6 per 30 minutes (1 in 5 minutes), and the identification of associated cervical changes, namely a dilatation of at least 3 cm. In symptomatic women that do not fulfil the criteria for diagnosis of established PTL, existing data are supportive of using a combination of CL measurement and biomarkers, if available, to identify those at highest risk to deliver within seven days. This high-risk group will benefit from treatment with tocolytic drugs (calcium channel blockers or oxytocin receptor antagonists) for 48 hours to allow for the prompt administration and optimal effect of steroids (if $<34^{+0}$ weeks) and magnesium sulfate (if $<32^{+0}$ weeks), as well as transfer to a center with appropriate neonatology support. In undetermined cases, a period of observation, of at least two hours, for development of cervical changes, is recommended as a reasonable approach. The recommendations for the mode of delivery in PTL should be based on standard guidelines for intrapartum management, except at extreme preterm gestations when associated obstetric morbidity, parental wishes and neonatal infrastructure should be considered. However, certain exceptions exist, as cesarean section may be preferable in some cases (i.e., severe early fetal growth restriction or non-vertex twins) and instrumental deliveries are generally not recommended before 34^{+0} weeks. Finally, delayed cord clamping, and the use of thermoregulatory devices is advised.

Although PTL and preterm birth pose a major problem in perinatal medicine, there are still controversies regarding the optimal diagnostic approach and effective management. The WAPM/PMF encourages research in all relevant undetermined issues. New algorithms that may include more variables to increase the accuracy in the prediction of preterm birth within the next seven days in a cost-effective manner and would also be flexible in performing in different settings are especially needed.

Table 2
Summary of statements and recommendations.

Recommendation/Statement	Strength	Level of evidence
1. PTL is defined as labor occurring before 37^{+0} weeks. The suggested earlier and later gestational limits as thresholds for treatment and interventions are 22^{+0} and 33^{+6} weeks respectively, in high income settings, and should be individualized depending on resources and infrastructure.	Conditional	Low
2. The diagnosis of established PTL is based on confirmation of regular contractions (manually or cardiotocography) that produce changes to the cervix. The combination of ≥6 contractions per 30 min (1/5min) and cervical dilatation of ≥3 cm are necessary for the diagnosis of established PTL.	Conditional	Low
3. In cases of threatened PTL, a stepwise approach should be implemented which includes a period of observation of at least 2 h, with or without hospital admission. In low-resource settings contractions and cervical dilatation will guide further management. In high-resource settings, further stratification of risk using either CL, biomarkers such as fFN or PAMG or a combination of all above should be offered. Hospital discharge and expectant management should be offered based on: Low-resource settings: discontinuation of contractions and no increase in cervical dilatation High resource settings: only CL available: CL ≥15 mm Only biomarker (fFN or PAMG) available: negative test Both CL and biomarker available: CL >30 mm or CL 15–30 mm and negative biomarker	Conditional	Moderate
4. Treatment with tocolytic drugs is recommended up to 33^{+6} weeks with the aim to prolong pregnancy up to 48 h for the administration of antenatal corticosteroids or transfer to a tertiary center. Calcium channel blockers (nifedipine) or oxytocin receptor antagonists should be offered as first-line agents. Combinations of tocolytic agents should not be used until more data are available. Maintenance tocolysis (beyond 48 h) is not recommended until more data are available.	Strong	Moderate
5. The treatment with antenatal corticosteroids should follow the relevant WAPM guideline.	Strong	Moderate
6. Magnesium sulfate for fetal neuroprotection is recommended up to 31^{+6} gestational weeks and may be considered up to 33^{+6} gestational weeks in small for gestational age fetuses, below the 5th centile. The proposed regimen consists of 4 g IV bolus dose given over 15–30 min followed by a maintenance IV infusion of 1 g/hour until delivery or for up to 24 h.	Strong	Moderate
7. Prophylactic antibiotic therapy is not routinely recommended in PTL with intact membranes in the absence of infection.	Strong	Low
8. Activity restriction is not recommended to prevent PTL.	Strong	Moderate
9. PTL is not an indication for routine cesarean delivery. Vaginal birth is the gold standard method for both singleton and twin preterm	Strong	Low

(*continued on next page*)

Table 2 (*continued*)

Recommendation/Statement	Strength	Level of evidence
fetuses with vertex presentation. Vaginal birth after previous cesarean delivery is not contraindicated in cases of PTL. Operative vaginal delivery is not recommended before 34^{+0} weeks, however, if necessary, low forceps delivery is preferred over vacuum extraction.		
10. Monitoring of fetal wellbeing during an established PTL using cardiotocography or intermittent auscultation should follow local protocols prior to 26^{+0} weeks, with consideration for electronic fetal monitoring after this gestational window.	Conditional	Low
11. Delaying umbilical cord clamping for at least 30–60 s in preterm neonates is recommended as in term neonates. Placement of the neonate in a polyethylene bag during this period significantly reduces the risk of hypothermia.	Strong	Moderate

Table 3
Grading of recommendations.

Grading of recommendations*
The quality of evidence was graded as
(i) very low
(ii) low
(iii) moderate
(iv) high
The strength of recommendation was defined as
(i) Strong
(ii) Conditional
* Based on GRADE [83] and WHO [84].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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