**AN ADAPTED EVIDENCE-BASED CLINICAL PRACTICE GUIDELINE**

**ON**

**THE PREVENTION AND MANAGEMENT OF PRETERM LABOR**

**Overview**

This is an adapted evidence-based clinical practice guideline for the prevention and management of preterm labor.

**Guideline adapter**

**This guideline has been adapted by the Egyptian Universities Obstetrics & Gynecology Guideline Working Group (EUOBGYN-GWG).**

**Release date**

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**GUIDELINE ADAPTATION METHODOLOGY**

This guideline was produced in accordance with the ADAPTE methodology and procedure for the adaptation of evidence-based clinical practice guidelines published by the ADAPTE Group (Fervers B, et al., Adaptation of clinical guidelines: literature review and proposition for a framework and procedure. Int J Qual Health Care 2006; 18(3): 167-176).

**sources of the guideline**

**This guideline was adapted from:**

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**INTRODUCTION AND DEFINITIONS**

Preterm birth is commonly defined as labor occurring at gestational age between 20 and 37+0 completed weeks with subcategories of preterm birth based on weeks of gestational age. It is relatively common with a prevalence of 5 to 18% of births worldwide and is a leading cause of fetal morbidity and mortality.

* A woman who is presenting before 37+0 weeks of pregnancy reporting symptoms that might be indicative of preterm labor (such as abdominal pain), but no clinical assessment (including speculum or digital vaginal examination) has taken place is said to have **Symptoms suggestive of preterm labor**.
* **Suspected preterm labor** refers to a woman who is reporting symptoms of preterm labor and has had a clinical assessment (including a speculum or digital vaginal examination) that confirms the possibility of preterm labor but rules out established labor.
* **Diagnosed preterm labor** refers to a woman who is in suspected preterm labor and has had a positive diagnostic test (either cervical length measurement by ultrasound or performing fetal fibronectin test) for preterm labor.
* **Established preterm labor** occurs when there is progressive cervical dilatation from 4 cm with regular contractions

**RISK ASSESSMENT**

* Many factors have been associated with an increased risk of spontaneous PTB. However, there is a relative paucity of high-level research so that the cause of spontaneous preterm labor remains unidentified in up to half of all cases.

**Patient Characteristics**

* Age
  + Younger than 20 years
  + Older than 40 years
* Cigarette smoking: 13.6% are born preterm vs 8.1% of babies in non-smoking mothers
* High levels of psychological stress
* Late or no health care in pregnancy
* Low socio-economic status
* High or low body mass index (BMI)

**Medical and Pregnancy Related Conditions**

* Multiple births:
  + 66% of twins
  + 98.2% of all other multiples (triplets and higher order)
* Presence of fetal fibronectin in the vaginal secretions
* Short cervical length
* Previous PTB recurrence risk related to:
  + Gestational age of prior PTB
  + Approximately 30% of women who give birth between 20 and 31 weeks in a prior pregnancy will give birth before 37 weeks in a subsequent pregnancy and 10% of these will occur at a similar gestational age
  + Number of prior PTB
  + 15% recurrence risk with single prior PTB
  + 32% recurrence risk with two prior PTB
* Genital tract infections
  + Bacterial vaginosis risk of PTB doubled
* Urinary tract infections
* Vaginal bleeding
* Assisted reproduction associated with 2-fold increased risk of PTB
* Preterm prelab our rupture of membranes (PPROM)
* Surgical procedures involving the cervix
* Uterine anomalies
* Polyhydramnios/oligohydramnios
* Multiple gestation—60% of twins born preterm
* Chronic medical conditions
* Acute medical conditions (e.g. preeclampsia, antepartum hemorrhage)

**RISK REDUCTION**

**General Measures for Modifiable Risk Factors**

**Risk assessment and counseling**

* Perform a comprehensive review of all previous pregnancies because the most important historical risk factor is prior spontaneous PTB
* Counsel women about modifiable risk factors
  + Smoking cessation interventions
  + Optimization of control of underlying chronic diseases reduces risk
  + Lifestyle (e.g. balanced diet, activity limitations, stress management)
* Preform a psychosocial assessment and refer as appropriate to mental health services.

**Treatment of vaginosis**

* Bacterial vaginosis (BV) has been associated with increased risk of PTB
* Offer screening and treatment to women with previous PTB as there may be benefit.
* Routine screening and treatment for asymptomatic BV was not found to prevent PTB for the general population.
* The following is suggested to treat bacterial vaginosis after the first trimester of pregnancy. All regimens have equal effectiveness:
* Local vaginal application of 500–1000 mg metronidazole suppository for 7 days.
* Oral clindamycin 2 × 300 mg/day for 7 days.
* Intravaginal application of 5 g of 2 % clindamycin vaginal cream for 7 days

**Treatment of asymptomatic bacteriuria and urinary tract infection**

* + - Screen for and treat urinary tract infections (asymptomatic bacteriuria, cystitis, pyelonephritis) with antibiotics.
    - Urinary tract infection is associated with threatened preterm labor
    - Empirical antimicrobial treatments for asymptomatic bacteriuria will be required using an antibiotic regimen with either Nitrofurantoin (100 mg three times daily), amoxycillin (500 mg three times daily) for a week or Fosfomycin 3 grams orally as a single dose with 3 glasses of water. Treatment should be re-evaluated once culture and sensitivity results are available.

**Measures to Reduce Risks in Patients with History of Preterm Labor**

**Progesterone therapy**

* For singleton pregnancies recommend vaginal progesterone 200 mg from 16–36 weeks gestation for women with:
  + - An incidentally diagnosed shortened cervix (less than or equal to 25 mm) on TVCL measurement between 16–24 weeks
    - A prior spontaneous PTB between 20–34 weeks (with or without PPROM)
* For multiple pregnancy with a short cervix: conflicting evidence but some recommend its use.
* Do not use 17-α-hydroxy progesterone caproate because it is not as effective as vaginal progesterone and may increase the risk of neonatal adverse outcomes.

**Cervical length measurement**

* + - Recommend routine cervical length measurement to women during the mid-trimester (18–20 weeks) US scan.
    - Recommend serial ***transvaginal*** cervical length (TVCL) measurement for women ***with prior PTB*** every 2 weeks from 14–24 weeks gestation.
    - Use of a consistent technique for accurate measurement of cervical length.
    - Document cervical length in medical records and reports.

**Cerclage**

* + - If cervical length less than or equal to 10 mm, consider cervical cerclage, vaginal progesterone or a combination of both.
    - Consider cerclage for women with singleton pregnancy and history of:

Prior preterm birth or second trimester loss related to painless cervical dilation in the absence of labor or abruptio placentae

Prior cerclage due to painless cervical dilation in second trimester

TVCL less than 25 mm before 24 weeks with history of:

PPROM in previous pregnancy,

Cervical trauma/surgery, or

Prior spontaneous PTB before 34 weeks.

* + - If prophylactic cervical cerclage is used, ensure that a plan is in place for removal of the suture.
    - There is limited data about the effectiveness of rescue or emergency cerclage particularly beyond 24 weeks of gestation therefore individualize decisions.
    - Multiple dilation and evacuations or cervical surgery (e.g., cone biopsy, large loop excision of the transformation zone, laser ablation, diathermy) or other abnormalities (e.g., Mullerian anomaly) **are not** themselves an indication for cerclage
    - Not recommended for women with:
      * + Funneling of the cervix in the absence of cervical shortening to 25 mm or less
        + An incidentally identified short cervix without a history of spontaneous PTB or second trimester loss
        + Multiple pregnancy (and may be detrimental)

**CLINICAL ASSESSMENT OF PRETERM LABOR**

* This guideline is concerned with the management of preterm labor with intact membranes. For cases with rupture of membranes, refer to the concerned guideline.

**Diagnosis**

**Review history**

* Medical
* Surgical
* Obstetric
* Psychosocial and lifestyle
* Refer to the section on Risk factors associated with preterm birth

**Symptoms**

* **Contractions characterized by:**
* Pelvic pressure
* Lower abdominal cramping
* Lower back pain
* Vaginal loss (mucous, blood or fluid)
* Regular uterine activity

**Physical examination**

* Vital signs
* Abdominal palpation to assess uterine tone, contractions, fetal size and presentation
* Sterile speculum examination to:
* Confirm/exclude rupture of membranes
* Visualize cervix/membranes
* Assess liquor (e.g. clear, meconium stained, bloody)
* Collect high vaginal swab for microscopy culture and sensitivity (MC&S)
* Perform test for the presence of fetal fibronectin (if not contraindicated)
* Collect combined low vaginal and anorectal swab for Group B streptococcus (GBS).
* Sterile digital vaginal examination
* Assess cervical dilatation and effacement by sterile digital vaginal examination unless confirmed by speculum examination or contraindicated due to:
  + - * Ruptured membranes
      * Suspected placenta previa

**Fetal surveillance**

* Fetal heart rate (FHR)
* Continuous CTG
* Consider gestational age (interpret with caution if less than 28 weeks gestation)
* Ultrasound examination for fetal growth and wellbeing
* Fetal number, presentation, liquor volume and placenta localization

**Laboratory investigations**

* In addition to vaginal swabs, obtain midstream specimen of urine for bacteriology and C&S

**Cervical length measurement**

* Recommend TVCL measurement to women with suspected preterm labor (where available and by a trained ultra-sonographer)
* Consider therapeutic interventions when the TVCL is measured at less than 25 mm

**Fetal Fibronectin testing**

* Value
* To determine likelihood of birth within 48 hours for women who are 30+0 weeks pregnant or more
* Quantitative fFN testing can:
  + - Quantify the likelihood of PTB
    - Assist with risk assessment and planning
    - Avoid unnecessary interventions
    - Identify women for targeted interventions
    - Provide reassurance to health care providers and the woman
* Indications
* Symptoms suggestive of preterm labor between 22+0- and 36+0-weeks’ gestation and
* Intact membranes and
* Cervical dilatation less than or equal to 3 cm or if transvaginal ultrasound measurement of cervical length is indicated but is not available or not acceptable
* Contraindications
* Cervical dilatation more than 3 cm
* Ruptured membranes
* Cervical cerclage in situ
* Presence of soaps, gels, lubricants or disinfectants
* Relative contraindications
* Visual evidence of moderate or gross bleeding
* Within 24 hours of coitus
* Procedure
* Speculum examination prior to any examination or manipulation of the cervix or vagina
  + Use only sterile water as a lubricant
  + Obtain the sample for testing from the posterior fornix of the vagina
* Results
* fFN < 50 ng/mL(negative)
  + Low risk of birth within 7–14 days
  + False negative result may occur due to:
* Use of lubricant with speculum examination
* Intravaginal disinfectants
* fFN >50 ng/mL (positive)
  + view the woman as being in diagnosed preterm labor and offer treatment
  + False positive may occur as a result of recent:
* Coitus
* Digital vaginal examination
* Transvaginal ultrasound
* Bleeding
* NB:
* If there is no transvaginal ultrasound measurement of cervical length or fetal fibronectin testing, offer treatment consistent with her being in diagnosed preterm labor.
* Do not use transvaginal ultrasound measurement of cervical length and fetal fibronectin testing in combination to diagnose preterm labor

**Assess the Need for Admission**

* Consider admission for reassessment and/or therapeutic interventions if any of the following:
* Cervical dilation (painless or painful)
* TVCL changes and/or less than 25 mm (if measured)
* fFN test greater than or equal to 50 ng/mL
* Cervical change over 2–4 hours
* Ruptured membranes
* Contractions regular and painful
* Further observation or investigation indicated
* Other maternal or fetal concerns
* Consider discharge If fFN less than 50 ng/mL and admission not otherwise indicated if:
* Maternal vital signs within normal parameters
* Normal FHR/CTG relevant to gestational age
* No signs of chorioamnionitis
* Contractions infrequent/irregular
* No/minimal cervical change
* If Admission Is Not Indicated, Provide the woman with information that:
* Aids her recognition of the signs and symptoms of preterm labour
* Identifies risk reduction measures appropriate to the circumstances (e.g. fluids)
* Provides instruction about when to seek clinical advice
* Arrange follow-up:
  + - * If fFN 0-9 ng/mL routine follow-up as per usual model of care
      * If fFN 10-49 ng/mL return for medical review within 7 days

**MANAGEMENT OF PRETERM LABOR**

* Tocolysis and steroids are the main strategies to manage preterm labor.
* Consider in-utero transfer to a center with higher neonatal service capabilities. Discuss with the women and family the conditions of transfer including limited resuscitation if birth occurs en route. Adequate assessment of the women should be done before transfer. Transfer decisions should be coordinated between obstetric and neonatology teams on both sides.

**Planning of Care**

* All women requiring admission:
* Admit for observation
* Offer analgesia
* Administer corticosteroids (vide infra)
* Commence tocolysis if delay of birth indicated and no contraindications
* Measure TVCL if resources available
* Communicate with multidisciplinary team as relevant to the circumstances (e.g. neonatology consultation, social worker referral, an aesthetic involvement)
* Discuss plan for ongoing care with the woman in a manner that supports informed choice
* Document plan of care in the health record
* Clinical reassessment as required
* If labor is established or birth appears imminent, and gestational age is less than 34 weeks, commence Magnesium Sulfate for neuroprotection of the fetus

**Antenatal corticosteroids**

**Antenatal corticosteroids beneficial effects**

* Significant reduction in rates of
* Neonatal death
* Respiratory distress syndrome and respiratory support measures
* Intraventricular hemorrhage (IVH)
* Necrotizing enterocolitis
* Intensive care admissions and systemic infections in the first 48 hours of life
* Beneficial effects are demonstrated regardless of membrane status.
* Antenatal corticosteroids are most effective in reducing RDS in pregnancies that deliver 24 hours after and up to 7 days after administration of the second dose of corticosteroids.

**Indications**

* All women between 24 - 34+6 weeks of gestation who are at risk of PTB within 7 days whether it is a singleton or multiple pregnancy.
* If gestational age is < 24 weeks with a risk of preterm birth within 7 days, administration is linked to a family's decision regarding resuscitation. Due consideration should be given to local limits of fetal viability (i.e. the NICU capabilities) when determining the lowest limit of gestational age at which steroids should be administered.
* Women undergoing planned cesarean delivery at 37–38.6 week's gestation.
* Consider the use of antenatal corticosteroids in patients with:
  + Multiple gestations reduced to a singleton gestation on or after 14 0/7 weeks of gestation,
  + Patients with fetal anomalies,
  + Patients who are expected to deliver in <12 hours
  + Do Not offer antenatal corticosteroids in late preterm pregnant patients with pregestational diabetes mellitus, given the risk of worsening neonatal hypoglycemia.
  + Do not use antenatal corticosteroids for fetal lung maturity in pregnant patients with a low likelihood of delivery before 35 weeks of gestation.
  + Patients at risk for late preterm delivery (35 -36+6 weeks) should be thoroughly counseled regarding the potential risks and benefits of antenatal corticosteroid administration and be advised that the long-term risks remain uncertain.

**What to give and dosage intervals**

1. **Betamethasone**: two 12-mg doses of betamethasone I.M. 24 hours apart, **OR**
2. **Dexamethasone**: four 6-mg doses I.M. at 12 hours intervals.

**NOTICE:**

* Accelerated dosing i.e., dosage intervals shorter than those outlined previously (as when labor is imminent) is not associated with additional benefits.
* If the risk of PTB persists seven or more days after initial course, repeat dose(s) are associated with less respiratory distress and fewer serious health problems in the first few weeks after birth. ***A single additional dose*** of corticosteroids may be given (Rescue dose): 12 mg of betamethasone or dexamethasone.
* Do not give more than 2 courses of maternal corticosteroids for preterm birth.
* In cases with early preterm labor with diabetes mellitus, monitor blood sugar during the intake of corticosteroids. Do Not offer antenatal corticosteroids to patients with late preterm labor with pregestational diabetes mellitus, given the risk of worsening neonatal hypoglycemia

**Tocolysis**

**Indications**

* Recommended when a 48-hour delay in birth will benefit the newborn
* Tocolytic drugs may delay birth and allow:
* Administration of corticosteroids
* Administration of Magnesium Sulfate for neuroprotection
* In-utero transfer to an appropriate level facility
* Tocolysis is not associated with a clear reduction in perinatal mortality or serious neonatal morbidity
* No evidence to support the use of prophylactic tocolytic therapy after contractions have ceased
* There is limited evidence about the use of tocolytics in the setting of PPROM
* Tocolysis with PPROM before 34 weeks is associated with:
* A lower risk of birth within 48 hours
* An increased risk of chorioamnionitis without significant maternal or neonatal benefit

**Contraindications**

* Maternal contraindications to tocolysis (agent specific)
* Any condition where prolongation of pregnancy is contraindicated including but not limited to:
* In-utero fetal death
* Lethal fetal anomalies
* Suspected fetal compromise
* Maternal bleeding with hemodynamic instability
* Severe preeclampsia
* Placental abruption
* Chorioamnionitis

**Types of tocolytic agents**

**Nifedipine**

* Nifedipine is the tocolytic of choice. It is a calcium channel blocker that relaxes smooth muscle
  + **Doses:**
* Nifedipine 20 mg oral (2 of 10 mg capsules)
* If contractions persist after 30 minutes repeat Nifedipine 20 mg oral
* If contractions persist after a further 30 minutes repeat Nifedipine 20 mg oral
* If BP stable, Nifedipine 20 mg oral every 6 hours for 48 hours
* Maximum dose is 160 mg/day
* Further maintenance therapy is ineffective
  + NB: Do not use sustained release formulation
  + **Contraindications**
* If there are contraindications to Nifedipine use alternate tocolysis
* Maternal hypotension or cardiac disease (preload-dependent cardiac lesions)
* Previous adverse reaction to calcium channel blockers.
* Concomitant use with Magnesium Sulfate may increase effects of nifedipine and the risk of hypotension so use cautiously with Magnesium Sulfate
  + **Observation**
* BP, pulse and respiratory rate every thirty minutes for first hour, then hourly for four hours
* Temperature every four hours
* Review frequency in accordance with clinical circumstances

**Inhibitors of prostaglandin synthesis (Indomethacin)**

* Potent inhibitor of uterine contractility by inhibiting cyclo-oxygenase (COX) enzyme but limited high level evidence with few adequate trials.
* Risks for the fetus and neonate include:
* Constriction of the fetal ductus arteriosus (increased risk with advancing gestational age; the effects are transient and reversible with short term administration; longer administration may lead to pulmonary hypertension in the fetus and neonate)
* Alteration of fetal, especially cerebral, blood flow
* Reduced renal function (may result in oligohydramnios)
* Necrotizing enterocolitis
* Because of the potential adverse fetal and neonatal effects, consider use of Indomethacin only where:
* Gestational age is less than 32+0 weeks
* There is failure to achieve tocolysis with other tocolytic regimens
* Contraindications to other tocolytics exist (e.g., cardiac disease)
* With Indomethacin administration, ensure close monitoring of fetal wellbeing

**Betamimetics**

* This category of medications **should not** be offered for tocolysis due to significant adverse side effects including reports of maternal death from pulmonary oedema.

**Magnesium Sulfate**

* Magnesium sulfate is not used for tocolysis, if magnesium sulfate is being used in the context of preterm labor for fetal neuroprotection and the patient still is experiencing preterm labor, a different agent could be considered for short-term tocolysis.

**Antibiotics**

* Routine administration of prophylactic antibiotics to women in threatened preterm labor with intact membranes and without evidence of infection is not recommended
* If preterm labor does not commence and no other indications, then with:
* Intact membranes, cease antibiotics
* If membranes are ruptured: as prophylaxis for intrauterine infection, offer women with PPROM oral erythromycin 250 mg 4 times a day for a maximum of 10 days or until the woman is in established labour (whichever is sooner).
* If preterm labor ensues or there is imminent risk of PTB, give intrapartum antibiotic prophylaxis for prevention of Early onset Group B streptococcal disease irrespective of GBS status or membrane status.

**Magnesium Sulfate for neuroprotection**

* Offer intravenous magnesium sulfate for neuroprotection of the baby to women between 24+0 and 33+6 weeks of pregnancy who are in established preterm labor or having a planned preterm birth within 24 hours.
* When birth is planned, commence administration as close to four hours prior to birth as possible. Best effect when given for at least four hours within the six hours prior to birth
* If birth is expected to occur within four hours, commence MgSO4 immediately, as there may still be benefit from administration.
* In situations where urgent birth is necessary, do not delay birth to administer MgSO46
* Give a 4 g intravenous bolus of magnesium sulfate over 15 minutes, followed by an intravenous infusion of 1 g per hour until the birth or for 24 hours (whichever is sooner).
* If birth does not occur after giving MgSO4 and PTB (less than 30 weeks’ gestation) again appears imminent (planned or expected within 24 hours), a repeat dose of MgSO4 may be considered at the discretion of the obstetrician.

**Observations and fetal surveillance**

* CTG until contractions cease (relative to gestation)
* There is an absence of evidence that using cardiotocography improves the outcomes of preterm labor for the woman or the baby compared with intermittent auscultation.
* A normal cardiotocography trace is reassuring and indicates that the baby is coping but an abnormal trace does not necessarily indicate that fetal hypoxia or acidosis is present.
* Fetal scalp electrodes and fetal blood sampling should not be used before 34 weeks.
* Explain different fetal monitoring options to the woman (and her family members) or specifically emphasize on the limited evidence about the usefulness of specific features to suggest hypoxia or acidosis in preterm babies using electronic fetal monitoring.
* Involve a senior obstetrician in discussions about whether and how to monitor the fetal heart rate for women who are between 24+0 and 25+6 weeks pregnant

**MODE OF PRETERM BIRTH**

* There is insufficient high-quality evidence about whether mode of birth affects neonatal morbidity and outcomes.
* For Singleton presenting with the vertex: Recommend vaginal birth unless there are specific contraindications to vaginal birth or maternal conditions necessitating CS
* For Breech Presentation:
* ≥ 26+0 weeks: The evidence regarding optimal mode of birth for preterm breech is conflicting and unclear due to a lack of high-quality studies
* Base decisions on individual circumstances and maternal preferences
* CS is not generally recommended where vaginal birth is imminent
* ≤ 25+6 weeks gestation (vertex or breech): CS for fetal indications alone is not generally recommended.
* Discuss the general benefits and risks of caesarean section and vaginal birth with women in suspected, diagnosed or established preterm labor
* Discuss implications of decision with the woman
* Preterm CS is usually technically more difficult to perform and is not without risk to the baby as the lower segment is usually not well formed
* A classical incision may be required with risks to future pregnancies including scar dehiscence, uterine rupture, placental adherence and maternal death
* Early consultation with anesthetic team required
* **Timing of cord clamping for preterm babies** (born vaginally or by caesarean section)
* If a preterm baby needs to be moved away from the mother for resuscitation, or there is significant maternal bleeding: consider clamping the cord as soon as possible.
* If the baby and mother are stable: Wait for 60 seconds, but no longer than 3 minutes, before clamping the cord.
* Position the baby at or below the level of the placenta before clamping the cord.