بسم الله الرحمن الرحيم

Guideline

Management of preterm labor

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Background and significance:

Preterm labor (PTL) defines as births at less than 37^{+0} weeks of gestation, includes all deliveries between 20^{+0} and 36^{+6} weeks. Late PTL is the delivery between 34^{+0} and 36^{+6} weeks and accounts for 70% of PTL [(1)]. The incidence of PTL has remained at 9% to 11% of all live births over the last 20 yrs.

Preterm birth is the leading cause of perinatal and infant mortality, a risk for specific diseases related to the immaturity include respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), bronchopulmonary dysplasia, patent ductus arteriosus, necrotizing enterocolitis (NEC), sepsis, apnea, and retinopathy of prematurity[(1)]. In addition to increased rates of cerebral palsy, neurosensory impairment, reduced cognition and motor performance, academic difficulties, and concerns relate to social behavior and criminality[(1)].

Purpose and scope:

This guideline has been developed to summarize up to date evidence for the management of patients presenting with preterm labour pain. Prevention of preterm delivery in asymptomatic high risk patients is not included in this guideline.

This guideline was developed by searching the recommended perinatology textbooks, recently published papers and international guidelines addressing this problem.

How PTL is diagnosed?

Diagnosis and treatment of PTL is challenging, because the sequence and timing of events that precede it are still not well understood. The traditional criteria (persistent uterine contraction (may be painful or painless) accompanied by dilation or effacement of the cervix or both)

are reasonably accurate at identifying women at risk for imminent delivery if the contraction frequency is six or more per hour and cervical dilation is 3 cm or greater or effacement is 80% or greater, or if membranes rupture or bleeding occurs. When lower thresholds for contraction frequency and cervical change are used, false-positive diagnosis is common, with sensitivity does not necessarily increase [(1)].
Women with symptoms whose cervical dilation is less than 2 cm or whose effacement is less than 80% present a diagnostic challenge with respect to identifying risk for imminent delivery.
Other symptoms including pelvic pressure, increased vaginal discharge, backache, and menstrual-like cramps occur commonly during normal pregnancy, they suggest PTL more by their persistence rather than their severity.

Is there any role of ultrasonography in diagnosis of PTL?

Diagnostic accuracy can be improved by transvaginal sonographic (TVS) measurement of cervical length. When performed by trained operators, cervical length analysis using TVS is safe, highly reproducible, and more predictive than transabdominal sonographic (TAS) screening which may be affected by maternal obesity, cervical position, or shadowing from the fetal presenting part, (American College of Obstetricians and Gynecologists, 2012b).
Cervical length of 30 mm or more by TVS suggests that PTL is unlikely despite symptoms [(1)].

That is the role of fetal fibronectin (fFN) testing?

This glycoprotein is produced by various cell types, including hepatocytes, fibroblasts, endothelial cells, and fetal amnion. Present in high concentrations in maternal blood and in amnionic fluid, it is thought to function in intercellular adhesion during implantation and in maintenance of placental adherence to uterine decidua.

fFN detection in cervicovaginal secretions before rupture of membrane was a possible marker for impending PTL. Is measured using an enzyme-linked immunosorbent assay, and values exceeding 50 ng/mL are considered positive [(2)].

A negative fFN test in women with symptoms before 34 weeks' gestation and cervical dilation of less than 3 cm can reduce the rate of false-positive diagnosis. However, in women with intact membranes, no bleeding, and cervical dilation less than 3 cm, the combination of a positive fibronectin test and a sonographic cervical length of less than 30 mm predicted increased risk for delivery within 48 hours (26%); the risk was less than 7% if only one or neither test is positive[(1)].

Unfortunately this test of fFN yet is not widely available in the country.

What are the management strategies?

Treatment of symptomatic PTL is directed at arresting labor long enough to allow administration of corticosteroids and to transfer the patient to an appropriate hospital which can provide neonatal intensive care; these two interventions have consistently been shown to reduce perinatal mortality and morbidity.

Other interventions directed for reducing neonatal and infant morbidity and mortality include pre-delivery administration of antibiotics and fetal neuro-protectants.

Uses of tocolysis in women presented with PTL.

Use of a tocolytic drugs is associated with a prolongation of pregnancy for up to 7 days, but with no significant effect on preterm birth and no clear effect on perinatal or neonatal morbidity and mortality[(3)]. These few days gained would be beneficial for completing a course of corticosteroids or in utero transfer to place providing reasonable neonatal care.

Any contraindication for prolonging pregnancy is a contraindication to tocolytic therapy; for example, known lethal congenital or chromosomal malformation, intrauterine infection, severe pre-eclampsia, placental abruption, advanced cervical dilatation and evidence of fetal compromise or placental insufficiency. Relative contraindications include mild haemorrhage due to placenta praevia, non-reassuring cardiotocograph, fetal growth restriction and multiple pregnancy [(3)].

Although no medications are currently approved for tocolysis by the US Food and Drug Administration (FDA), calcium channel blockers, β-agonists, and non-steroidal anti-inflammatory drugs (NSAIDs) have been used in practice for this purpose within FDA guidelines that allow physicians to prescribe medications for off-label use[(1)]. Ritodrine (β-agonists) and Atosiban (oxytocin receptors antagonist) are licensed in the UK for the treatment of threatened PTL[(3)].

Nifedipine and Atosiban have comparable effectiveness in delaying birth for up to seven days, and β-agonists reduce the risk of giving birth within 48 hours[(3)]. Compared with β-agonists, nifedipine has an advantages of being orally administered, lower price and is associated with improvement in neonatal outcome (less neonatal RDS, NEC and IVH), although long-term data are not available[(3)].

Indomethacin is the Cyclo-oxygenase (COX) enzymes inhibitor most commonly used for tocolysis. COX inhibitor might be effective tocolytics with fewer fetal side effects, however, Short-term use of NSAIDs in the third trimester of pregnancy is associated with a significant increase in the risk of premature ductal closure[(3)].

Nitroglycerine has been compared with other tocolytics and there was no clear impact on birth before 32–34 weeks of gestation [(3)]. Although there is no clear evidence that magnesium sulphate reduces the risk of preterm birth, but should administered to women considered at risk of preterm birth for 24 hours to reduce the risk of cerebral palsy[(3)].

β-agonists have a high frequency of adverse effects (palpitations, tremor nausea/ vomiting, chest pain ,dyspnea), however, nifedipine, atosiban and the COX inhibitors have fewer adverse effects, and they occur less frequently than for β-agonists[3].

Despite both nifedipine and atosiban have been widely used, there is no specific evidence for the role of tocolytic drugs in PTL in multiple pregnancy. A series of case reports have suggested an association between nifedipine use in multiple pregnancy and pulmonary oedema (this association was not confirmed in a prospective study), so atosiban may be preferable [3].

There is insufficient evidence for maintenance tocolytics following threatened PTL, and should not recommend.

Once a decision is made to use a tocolytic drug, the best choice of drug would be the most effective available drug with the fewest adverse effects. The available evidence should be discussed with the woman and her partner and their preferences taken into consideration in determining her care.

Recommended dose regimens for tocolytic drugs

The suggested dose of nifedipine is an initial oral dose of 20 mg followed by 10–20 mg three to four times daily, adjusted according to uterine activity, for up to 48 hours. A total dose above 60 mg appears to be associated with a three- to four-fold increase in adverse events[3].

As indomethacin is well absorbed orally, the usual regimen is a 50-mg oral loading dose followed by 25-50 mg every 6 hours. This therapy is generally limited to 48 hours and to pregnancies before 32 weeks' gestation [1].

A suggested dose of atosiban is an initial bolus dose of 6.75 mg over 1 minute, followed by an infusion of 18 mg/hour for 3 hours, then 6 mg/hour for up to 45 hours (to a maximum of 330 mg)[3].

For magnesium sulfate begins with a loading dose of 4 - 6 g in a 10% to 20% solution given over 30 minutes, followed by a maintenance dose of 1-2 g/hr. Intravenous fluids are restricted to 125 mL/hr. Fluid

status should be followed closely in addition to deep tendon reflexes and vital signs, including respiratory rate, should be recorded hourly [(1)]. Serum therapeutic level is 5-8 mg/dl.

Published protocol for terbutaline is subcutaneous administration, with a usual dosage of 0.25 mg every 4 hours [(1)].

Uses of corticosteroids in PTL

Corticosteroids are associated with a significant reduction in rates of neonatal death, RDS and IVH [(4)]. A single course of antenatal corticosteroids should be offered to women between 24^{+0} and 34^{+6} weeks of gestation, and for pregnancies affected by fetal growth restriction between 24^{+0} and 35^{+6} weeks who are at risk of preterm birth. However, can be considered also for women between 23^{+0} and 23^{+6} weeks of gestation at risk of PTL, but this decision should be made at a senior level taking all clinical aspects into consideration[(4)].

Corticosteroids are most effective in reducing respiratory distress in women deliver 24 hours and up to 7 days after administration of the second dose, however, still should be given even if delivery is expected within 24 hrs.

Diabetes mellitus is not a contraindication to antenatal corticosteroid treatment for fetal lung maturation. Yet, these women should have additional insulin according to an agreed protocol and be closely monitored. Caution should be exercised when giving corticosteroid therapy to women with systemic infections including sepsis and tuberculosis [(4)].

The regimens are either two doses of betamethasone 12 mg intramuscular (IM) 24 hrs apart or four doses of dexamethasone 6 mg IM 12 hrs apart [(4)].

Weekly repeat courses of antenatal corticosteroids are associated with a reduction in weight and head circumference and should not be recommended. Repeated dose should only be considered with caution in those pregnancies where the first course was given at less than 26^{+0} weeks and another obstetric indication arises later in pregnancy[(4)].

Corticosteroids can suppress both fetal activity and heart rate variability; this should be mentioned to the patient and put in mind when interpreting a fetal trace [4].

Is there is any role for rescue cerclage in patient presented with symptoms of PTL?

Rescue cerclage may be suggested for women presenting with relatively minor symptoms whom found to have membrane bulging through the cervix when examined. The decision should be individualized; taking into account the gestation at presentation, and a senior obstetrician should be involved in making the decision [5].
Insertion of a rescue cerclage may delay delivery by 5 weeks on average compared with expectant management and may also be associated with a two-fold reduction in the chance of delivery before 34 weeks gestation. However, advanced dilatation of the cervix (> 4cm) or membrane prolapse beyond the external os appears to be associated with a high chance of cerclage failure [5].

Is there is any role of antibiotics in the management of women presented with PTL?

Because preterm infants have an increased risk for neonatal group B streptococcal (GBS) infection compared to term infants, intrapartum prophylaxis with penicillin is recommended[1]. On the other hand, antibiotic therapy for women with preterm labor and intact membranes has not been effective in prolongation of pregnancy or reducing morbidity, so, should be limited for prophylaxis of GBS transmission or treatment of a specific pathogen (e.g. urinary tract infection)[1].
Recommended dose for prevention of GBS is 3 g intravenous benzyl penicillin be given as soon as possible after the onset of labour followed by 1.5 g 4-hourly until delivery. Clindamycin 900 mg should be given intravenously 8-hourly to those allergic to benzyl penicillin[6]. Vancomycin is an alternative agent in cases of

clindamycin resistance. Broad-spectrum antibiotics such as ampicillin should be avoided if possible due to raise concerns regarding increased rates of Gram-negative neonatal sepsis [6].

References:

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