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**REVIEW**

# Preterm Labor

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With its associated morbidity and mortality preterm delivery is still represents one of the major unsolved problems in Obstetrics and Gynecology. Aside from survival, another important issue is the quality of life of an immature, extremely low-birth weight infants. This update clinical review for preterm concludes only the clinical important points that can be truly applied for Thai-clinicians with the following aspects of preterm labor (PTL): definition, identification of high risk patients, prenatal care of high risk patients, and management of preterm labor.

## Definition

The causes of preterm delivery may be broadly divided into three groups. These are indicated preterm deliveries, premature rupture of membranes in preterm gestation, and preterm labor.

*Indicated preterm deliveries* are usually the result of various medical or surgical complications in mother or fetus that create an unfavorable intrauterine environment for the fetus or a dangerous environment for the mother. In these cases, the fetus is delivered to prevent morbidity or mortality of mother or fetus from occurring regardless of gestational age. These conditions commonly include severe preclampsia, chronic hypertension, diabetes, placenta previa, or placental abruption.[1]

*Premature rupture of membranes in preterm gestation* is used to denote spontaneous rupture of the fetal membranes before 37 weeks of gestation.[2]

*Preterm labor* means spontaneous labor with intact fetal membranes before 37 weeks of gestation. Herron and associates[3] (1982) require the following criteria to document preterm labor: Regular uterine contraction after 20 weeks or before 37 weeks of gestation, which are 5 to 8 minutes apart or less, and accompanied by one or more of the following: (1) progressive change in the cervix, (2) cervical dilatation of 2 cm or more, or (3) cervical effacement of 80 percent or more.

However, American College of Obstetricians and Gynecologists (1997) has proposed the following criteria to document preterm labor between 20 and 37 weeks' gestation:

1. Contractions occurring at a frequency of four in 20 minutes or eight in 60 minutes plus progressive change in the cervix
2. Cervical dilatation greater than 1 cm.
3. Cervical effacement of 80% or greater.

Threatened preterm labor is another word that may be diagnosed when there is documented uterine contraction but no evidence of cervical change.[4]

## Risk factors and predicting factors

To prevent preterm delivery, one must first correctly select women at the greatest risk for preterm delivery. Although the assessment of preterm risk status does not add any useful information and that it

is slightly better than conjecture,[5] it is still necessary for the physician to detect risk factors.

Factors most frequently associated with an increase risk for preterm birth are a history of a previous preterm, black race, multiple gestation, uterocervical anomalies and vaginal infection. History of preterm delivery is consistently the most important risk factor for subsequent preterm birth.[5,6,7] Approximately 30-50% of multiple gestations result in preterm delivery.[7] The average gestational age at delivery for twin gestations is 37 weeks, 33 weeks for triplet gestations, and 31 week for quadruplet gestations.[8,9] In addition, spontaneous preterm deliveries were associated with the extremes of maternal age.[6,10]

However, the risk may not be age itself but rather confounding factors associated with age. For example, young women have more sexual partners and vaginal infections. While older women may have more uterine irregularities, such as myomas.[6] Smoking has also been found to be significantly associated with preterm delivery in several studies.[10-12] There is an increasing body of evidence linking urinary tract infection,[13] intrauterine infections,[14] and vaginal microflora,[15] including bacterial vaginosis (BV) with an increased risk for spontaneous preterm labor.[16] A recent meta-analysis showed an association between untreated antepartum asymptomatic bacteriuria and a higher incidence of preterm birth / low birth weight delivery. The association was no longer present, however, if studies adjusted for socioeconomic and demographic variables.[13] Ureaplasma urealyticum has been isolated from the amniotic fluid of patients with preterm premature rupture of membranes and preterm labor with intact membranes.[17] Although most investigators agree that some patients with preterm labor have an infectious etiology, there are few data to support the routine use of amniocentesis in preterm labor with intact membranes and no clinical sign of infection. If an amniocentesis is use to diagnose intra-amniotic infection, a negative gram stain to exclude bacteria is most sensitive in ruling out infection prior to obtaining the culture results. Other tests to diagnose infection include elevated amniotic fluid white blood cell counts, low glucose levels of 10 mg/dl or less, and high interleukin levels.[6] In largest study involving more than 10000 women, those with BV diagnosed during the second trimester were 40% more likely than those without BV to have a premature infant with low birth weight.[16]

The diagnosis of bacterial vaginosis is made when three of four clinical criteria (vaginal pH> 4.5, amine odor with 10% KOH, vaginal cells heavily coated with bacilli (clue cells), few white cells with a mixed flora (as compared with the normal predominance of lactobacilli) on Gram staining of vaginal discharge. However, culture for G. vaginalis is not a recommended diagnostic method because it is not specific.[18] Because randomized clinical trials have reported that treatment of BV is effective in preventing preterm birth in women at high risk (previous preterm birth, weight <50 kg), Centers for Disease Control and Prevention recommends that women with BV diagnosed during pregnancy be treated with oral metronidazole 250 mg three times per day for seven days.[18] Alternative regimens include oral metronidazole 2 g in a single dose or clindamycin 300 mg twice daily for seven days. Nevertheless, clindamycin vaginal cream appears not to be as effective in reducing preterm birth in women with BV.[18,19]

Most studies have consistently reported a two-fold increase for preterm labor in women with syphilis infection. While the presence of Neisseria gonorrhoeae and Chlamydia trachomatis have been inconsistently associated with preterm delivery. There are conflicting data about an association of an increased risk for spontaneous preterm birth with group B streptococcus, human immunodeficiency virus, hepatitis B, and genital herpes simplex virus. Furthermore, the evidence supporting a causative link is poor.[20] The detection of Trichomonas vaginalis or candida had no significant association with preterm birth.[21] Surprisingly, there was an associated doubling in the risk of preterm births (19% vs 10.7%) in the trichomoniasis treatment group. That means routine

screening and treatment of women with asymptomatic Trichmonas vaginalis is not beneficial.[22]

For many decades, gold standard for the diagnosis of preterm labor was the documentation of cervical change by digital examination. This method proved to be neither diagnostic nor predictive and has cause investigators to develop newer methods of determining which women are at risk for preterm delivery. Concurrently, investigators rediscovered the cervix as a predictor for preterm birth using new technologies such as ultrasound. Iams and co-workers[23] used transvaginal ultrasound to measure the length of the cervix in 2915 women at approximately 24 weeks and again at 28 weeks. The mean cervical length at 24 weeks gestation was 34.0 ± 7.8 mm for nulliparous women and 36.1 ±8.4 mm in parous women. The mean cervical length at 28 weeks gestation was 32.6 ± 8.1 mm for nulliparous women and 34.5 ± 8.7 mm for parous women. The risk for preterm delivery significantly increases if the cervical length is 30 mm or less at 24 weeks gestation (6.19 relative risk for preterm delivery compared with those women with cervical length of 40 mm). The presence of cervical length >30 mm essentially rule out preterm labor. Of interest, the presence of cervical funneling was noted in 100% of patient who delivered preterm and was present in only 26% of patient who delivered at term.[24]

When the previous birth history is used with cervical length, the combination proves a more powerful predictor than either alone. The risk for preterm delivery increases with an earlier gestational age of the previous delivery and a shorter cervical length in the current pregnancy. One should also note that a term delivery in a previous pregnancy suggests a significantly lower risk for preterm delivery even if the cervical length is less than 25 mm (10$^{th}$ percentile).[23,25]

Listed here is a standard protocol of Colombo and Iams that can be used to measure the cervical length consistently,[26]

1. Ask the patient to void.
2. Insert the vaginal probe using direct visualization.
3. Identify bladder, amniotic fluid, and fetal presenting part. Be certain to identify any findings such as placenta previa or absence fetal heart motion.
4. Find the midline sagittal plane of the cervix and look in the proximal one-third of the image for the internal os.
5. Pull back the probe until the lightest touch provides a good image of the cervical canal.
6. Angle the probe slightly to get the best long axis of the cevix.
7. Measure the cervical length three times by placing the calipers appropriately and recording the distance between the internal os and external os.
8. Record the measurement of the best image and make a hard copy of the photo.
9. Record any evidence of funneling, dilatation, and membrane protrusion.
10. Apply gentle upward pressure on the lower uterine segment or transfundal pressure for approximately 15 seconds. Measure the cervix again in the same manner as described previously if it shortens or if a funnel becomes apparent.

Another diagnostic tool that can be used at the time of evaluation for preterm labor is evaluation of the vaginal mucous for the presence of fetal fibronectin (FFN). The initial clinical study of FFN suggested that it is commonly found in cervical and vaginal secretions during the first and early second trimester but it is rarely identified after 21 weeks gestation.[27]

The largest body of data on FFN in women without symptoms whom were screened during prenatal care comes from National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network Preterm prediction Study; 3073 women were generally enrolled in the study, which examined a large number of potential markers for risk of preterm delivery. Beginning at 22 to 24 weeks, cervical and vaginal specimens were collected for FFN analysis every 2 weeks until 30 weeks gestation. FFN had a strong predictive usefulness for preterm delivery, with two important patterns emerging from data analysis. First, FFN was more useful as a predictor for early preterm delivery (<28 weeks gestation) than later preterm delivery (<35 weeks

gestation). Second, FFN was more predictive of preterm delivery soon after testing (eg, delivery within 7 days or within 14 days) than of preterm delivery remote from testing. The results showed a small PPV (eg, 17% risk for delivery within 4 weeks after a positive test result) and it is clear that performing FFN testing only once during pregnancy has a lower sensitivity than serial testing.[28] The value of FFN screening of pregnant women remains uncertain because no available interventation has demonstrated efficacy in reducing preterm delivery risk among women with positive FFN results. For this reason, routine FFN screening of women at low-risk is not recommended. Screening of women at high-risk may identify a subgroup of women who are at low risk for recurrent preterm delivery. The suggested FFN collection protocol will be discussed later.

## Prenatal care for high-risk women

Women identified as being at increased risk for preterm labor should be triaged to a special prenatal program. They must be taught to recognize the early signs of preterm labor, such as an increase and change in vaginal discharge, a bloody show, increased uterine contractions, and pelvic clamps, leakage of amniotic fluid, and pelvic fullness and backache. If any of these signs develops, the woman must contact her health care provider for evaluation. This early symptom recognition education program is importance and should be reinforced at each prenatal visit. Because breast stimulation and orgasm cause uterine contractions, at risk women should be encouraged to decrease sexual stimulation during pregnancy. They should also increase their resting time or avoid strenuous exercise or work.[6] Cervical sonography combined with FFN screening of high-risk women, such as previous preterm delivery, may be especially valuable. Identifying a low-risk for preterm delivery reassures the patient and physician, may allow her reasonably to continue working or caring her family, and reduces unnecessary medical resource expenditures. If a woman at high -risk has a positive screening test result, further management must be based on the clinical condition. In some cases, prophylactic steroid therapy may be warranted.

## Diagnosis

The diagnostic of preterm labor is perhaps one of the most difficult and important tasks facing clinician today. The diagnosis of preterm labor is based on the clinical assessment of uterine contractility and cervical changes. The more difficult diagnosis involves patients having regular contractions but only minimal cervical dilatation. Evidence from placebo-controlled trials of tocolytics demonstrates that between 25% and 75% of pregnant women suspected of having preterm labor (in control and placebo group) will go on to delivery at term without intervention.[29]

Because uterine contractions alone can be misleading, Herron and associates (1982) require the criteria mentioned before to document preterm labor (PTL).[3, 30] Most will agree that a patients at less that 37 weeks' gestation with regular contractions and cervical dilatation of 3 cm and effacement of 80% should be considered to have preterm labor without waiting for cervical change.[6] On the other hand, if the diagnosis of preterm is missed, an early delivery could occur without treatment. The earlier the patient is in gestation, the more aggressive management should be in evaluation.[6]

In addition to painful or painless uterine contraction, symptoms such as pelvic pressure, menstrual -like clamps, watery or bloody vaginal discharge and pain in the low back have been empirically associated with impending preterm birth. The importance of these signs and symptoms has been emphasized by some investigators did not find these to be meaningful in the prediction of preterm birth. These only appeared within 24 hours of preterm labor. Thus, these are late warning signs of preterm birth.[30] Iams et al.[31] (1994) evaluate 60 patients who had symptoms of preterm labor between 24-34 weeks gestation and who had been treated with parenteral tocolysis. 100% of the women who delivered preterm, the initial cervical length

detected by vaginal ultrasound was less than 30 mm. In contrast, cervical dilatation of 2 cm or more, or effacement of 50% or more detected by digital examination, were predictive of preterm birth in only 62 percent and 83 percent respectively. Timor-Tritsch et al.[24] evaluated 70 patients between 20-35 weeks gestation who had symptoms of preterm labor. In their study, the 19 patients were noted to deliver before 37 weeks gestation. The mean cervical length in the subset that delivered preterm was 16.9 ± 1.6 mm, which was significantly different from the subset that delivered at term, with cervical length was 31.9 ± 1.3 mm. The presence of cervical length >30mm essentially rule out preterm labor. Interestingly, the presence of cervical funneling was noted in 100% of patient who delivered preterm and was present in only 26% of patients who delivered at term.

Another diagnostic tool that can be used at the time of evaluation for preterm labor is evaluation of the vaginal mucus for the presence of fetal fibronectin (FFN). The presence of fetal fibronectin, defined as ≥ 50 ng/ml, in the vaginal mucus is suggestive of the disruption on the matrix between the chorion and the decidual cavity.[24] There are several potential confounding factors that could decrease the accuracy of FFN testing. The presence of more than a minimal amount of blood, may create a false-positive test result because of the presence of FFN in plasma.[32] Amniotic fluid contains fibronectin and its presence in the cervicovaginal secretions will cause a false-positive result. Recent intercourse and recent digital examination may cause a false-positive test results.[27] Listed here is a suggested protocol of Andersen that can be used to measure FFN consistently.[33]

1. Perform sterile speculum examination before digital examination or vaginal or perineal ultrasound.
2. Lubricate speculum, if necessary, only with water.
3. Fibronectin evaluation is confounded by:
   *Bleeding (moderate or heavy): false-positive result*
   *Ruptured membranes: false-positive result*
   *Intercourse within 24 hours: false-positive result*
   *Digital cervical examination within past 24 hours: false-positive result*
   *Lubricant (eg, Surgilube or K-Y): false-negative result*
   *Soaps or disinfectants (eg, Betadine, hexachlorophene): false-negative result*
4. Using the Dacron polyester swab from the sampling kit, swab cervical or vaginal mucus, leaving swab in place for approximately 10 seconds.
5. Transfer swab to buffer solution and cap tube for transport. If immediate transport is not possible, specimen may be refrigerated (2-6 degree celcius) but must be tested within 3 days.

The most striking finding was the strong negative predictive value (NPV) of a negative FFN result for delivery with in next 7 days (NPV 99.5%) and within next 14 days (NPV 99.2%). That means the major clinical utility of FFN testing appears to be its ability to identify women who are unlikely to delivery in the 7-14 days after the onset of preterm labor symptoms. If FFN testing is positive, the clinician should consider what therapy would be effective in patients with preterm labor. Corticosteroid therapy is indicated in most patients between 24-34 weeks of gestation.[34,35]

## Management in the patients with symptoms

If FFN testing is available, speculum should be performed before manual cervical examination in all suspected preterm labor cases, and a vaginal pool and cervical specimen were collected for FFN evaluation. In 1995, the Food and Drug Administration (FDA) approved a commercial enzyme-linked immunosorbent assay (ELISA) to identify FFN. The majority of data concerning FFN testing are based on the ELISA assay. Recently, FDA FFN in vaginal secretions and in1998, the FDA approved an automated test for rapid semiquantitative identification of approved a rapid FFN testing device (Tli system). This moderately complex device allows qualitative FFN testing in the hospital with results in about 1 hour, depending on the laboratory protocol.[33] Testing for an infectious etiology is important in the initial assessment and includes culture of vaginal and cervical secretions and a midstream specimen of urine, a full blood count

and c-reactive protein estimation.[4] Too often, women who have frequent contractions are treated with oral or even parenteral medication without waiting for overt cervical change, or other definitive evidence of labor. This practice reduces contraction frequency by does nothing to establish the diagnosis of PTL and often leads to unnecessary oral prophylaxis of recurrent contractions in otherwise normal pregnancy. To aid in the accurate the diagnosis of PTL, several investigators have suggested the use of cervical ultrasound to more adequately assess the state of cervix.[26] After a careful clinical appraisal of maternal and fetal condition, preliminary investigation should be performed. Ultrasonography can be used to ascertained fetal number, estimate fetal weight, check fetal morphology and presentation, measure the volume of amniotic fluid and identify the placental site. It can also be used to assess fetal well-being. Iams suggests that the patients with contractions whose cervix is effaced at least 80% and dilated more than 2 cm should be treated without waiting for additional information.[36] While a retrospective study of 209 patients with PTL suggested that for patients whose initial digital examination was 2 cm or less, there was no change in gestational outcome if treatment was initiated only obvious change in dilatation. An initial examination showing dilatation of 3 or more cm. was associated with failed tocolysis.[37]

Not all preterm labors are treated. If the fetus is dead or has major congenital anomalies incompatible with life, or if the mother has medical problems such as severe preclampsia requiring early delivery and the fetus is already viable, then the labor is not treated and the infant is delivered. The patient population suitable for medical management is small. Excluded from it are: (1) women with PROM, (2) women with serious maternal or fetal diseases, such as abruption, chorioamnionitis, preclampsia - HEELP syndrome, fetal distress, and major congenital anomalies incompatible with life, (3) and women who present in advanced labor with more than 5 cm of cervical dilatation.[6]

The first therapeutic approach to diagnosed preterm labor is admission to the hospital to attempt to increase uterine blood flow and improve the intrauterine environment, quieting the uterus. This is done by using two measures: bed rest on the side and maternal hydration. A women in preterm labor can be quickly hydrated with a bolus of 500 ml of balanced electrolyte solution, such as Ringer's lactate solution, administered intravenously over the 30-minute period. While uterine contractions frequently stop.[6] However, there are no conclusive investigations on the benefit of bed rest to prevent preterm birth[38] and there are no evidence that hydration as an independent factor is effective. It is always an uncontrolled covariant and currently a common initial management of preterm labor is ensuring maternal hydration.[39]

## Tocolytic drugs

It has been postulated that tocolytic therapy may be less effective in the setting of advanced cervical dilatation. The clinician then is faced with the concept that early aggressive treatment of preterm labor will enhance successful treatment. Thus, starting the medication before true labor is established has result in overuse of tocolytics.[40] The long-term use of tocolytic agents offers no prophylactic advantage after the acute parenteral treatment of preterm labor with tocolytic agents. The most probable reason for the failure is that the blood concentration of the drug seldom achieves therapeutic levels.[6] Maintenance oral tocolytic therapy does not decrease uterine activity, reduce the rate of recurrent preterm labor or preterm birth, nor improve perinatal outcome.[41] If the initial selected tocolytic agent is unsuccessful or cannot tolerate in the suppression of PTL then an alternative agent may be considered. However, after an initial 48 hours of labor suppression by intravenous tocolysis, some workers have continued oral tocolytic agents until 34 to 37 weeks' gestation.[4]

## Betamimetics

Betamimetics are structurally related to epinephrine, and norepinephrine and include ritodrine, turbutaline, albuterol, fenoterol, hexoprenaline, and

salbutamol. Terbutaline and salbutamol are common β - agonist drug used by many Thai-physicians for prevent preterm labor. It can be administered in intravenous, oral, and subcutaneous forms. Oral β - agonist therapy has convincingly been shown to be ineffective, and parenteral therapy can only delay delivery for no more than 48 hours. Only ritodrine has been approved (1980) by the food and Drug Administration to treat preterm labor.[2] Finally, Macones and colleagues used meta-analysis to assess the available data on the efficacy of oral β - agonist therapy and found no benefits.[42]

***Dosage and administration***

**Salbutamol:**

The mean concentration of salbutamol in serum during intravenous infusion was twice as high as the peak concentration during oral treatment. The serum concentration was not correlated to maternal weight, height or duration of pregnancy. After discontinuation of intravenous treatment, serum concentrations remain high for at least one day and obviously clinical effect achieved continues for several hours after intravenous therapy. It used to be recommended that the first tablet can be taken 4 to 6 hours after stopping infusion. The therapy may be continued with 4 mg of salbutamol orally at 4-hour intervals for at least 10 days.[43] However, intermittent treatment should be the best in term of the effect on inhibition of uterine activity. Continuous prophylactic oral treatment by betamimetics cannot be recommended because leads to receptor down-regulation and a decreased clinical effect.[44] Intravenous administration is employed in some centers with wide variation of dosage. Beginning at 2.0 to 12 µg/min diluted in normal saline and increasing by 2.5 to 6 µg/min every 10 minutes upto a maximum of 30-50 µg/min until labor stopped or maternal pulse reach 140-160 beats per minute.[43-45] Infusion was continued for 12 hours with 12-24 µg/min after uterine contraction ceased.

**Terbutaline:**

Terbutaline is an off-label-used betamimetic and can be administered in intravenous, oral, and subcutaneous forms. The intravenous route is seldom used because of significant increase in the risk for pulmonary edema. The oral route has been clearly shown to be ineffective.[46] The most common dosing regimen is 0.25 mg subcutaneously every 20 minutes to 3 hours, stopping the dose for pulse greater than 120. A rapid onset of 3 to 5 minutes is seen after subcutaneous administration. However, the efficacy of subcutaneous terbutaline has yet to be established.[46] Intravenous administration is also employed in some centers, beginning at 2.5 µg/min and increasing by 2.5 µg/min every 20 minutes in a manner similar to ritodrine until a maximum of 17.5 to 20 µg/min is reached.[4]

***Maternal Side effects of betamimetics***

The notable side effects of betamimetics are cardiopulmonary (tachycardia, hypotension, arrhythmias, myocardial ischemia, pulmonary edema) and metabolic (hyperglycemia, hypokalemia). Patients may also have tremor, palpitations, nervousness, or restless develop.[46]

One of the most serious complications of β - agonist therapy is pulmonary edema. Multiple gestations, polyhydramnios, excessive fluid administration (especially with physiologic solutions), anemia, and hypertension are associated with increased risk for development of pulmonary edema during therapy.[47,48] It is uncommon for pulmonary edema to occur in the first 24 hours of therapy, with more than 90% of reported cases occurring after24 hours of treatment.[46]

Hyperglycemia with a maximum value at 8 hours after infusion has been observed with betamimetic therapy. Potassium replacement is not required unless serum potassium decreases to less than 2.5mEq/L. The maximal decrease in serum potassium levels is usually 0.6-1.5 mEq, which occurs approximately 2 to 3 hours after infusion. Serum potassium levels normalized after 10 to 20 hours of infusion.[46]

***Fetal side effects of betamimetics***

During ritodrine infusion, the average fetal heart rate increase was from 0 to 9 beats per minute. Neonatal hyperbilirubinemia and hypocalcaemia have also been reported. Administration of certain β - agonists has been related to increased intraventricular hemorrhage when compared with magnesium sulfate and no treatment.[46]

## Contraindications

β - agonists should be used with great caution. They should be avoided in patients with cardiac arrhythmia, poorly controlled thyrotoxicosis, and poorly controlled diabetes mellitus.[46]

## Magnesium sulfate

Magnesium sulfate appeared to be more effective with less cervical dilatation on admission. Gestation was prolonged at least 48 hours in 87% of patients with cervical dilatation < 2 cm, in 62% with cervical dilatation of 3 to 5 cm.[49] There are many studies found that tocolysis with magnesium sulfate to be successful, inexpensive and relatively nontoxic.[49-51] However, there was a randomized controlled studies of the tocolytic properties of magnesium sulfate in humans reported by Cox and co-workers . No benefits for such therapy were found.[52]

***Dosage and administration***

Magnesium sulfate must be administered intravenously to achieve therapeutic levels. A 4-g to 6-g bolus over the course of 20 minutes, followed-up by an infusion of 4 to 6 g per hour is standard dosing regimen.[46] The bolus usually consists of 6 g of intravenous magnesium sulfate administered in 250 mg of solution over a 30-minute period; the infusion is then maintained at 2 to 4 g per hour.[6]

Steere and Petrie[50] concluded that intravenously administered magnesium sulfate, 4 g given as a loading dose followed by a continuous infusion of 2 g/hr, will usually arrest labor. Individual titration to uterine quiescence and maternal side effect are recommended. Because magnesium sulfate is excreted in the urine, dosing should be adjusted for any evidence of renal impairment and maternal serum levels should be assessed. Beginning to reduce the infusion rate is recommended once the serum level exceeds 8 mg/dl.[46]

***Maternal side effects***

Flushing, lethargy, headache, muscle weakness, diplopia, dryness of mouth, nausea, emesis, shortness of breath, and pulmonary edema have been reported. Adverse effects may be minimized by closely monitoring urinary output, deep tendon reflexes, pulse, respiratory rate, and pulmonary auscultation. Loss of patellar reflexes are seen at serum levels of 8 to 12 mg/dl, but respiratory difficulty and cardiac arrest are not seen until serum levels are 15 to 17 mg/dl and 30 to 35 mg/dl, respectively. On rare occasions, hypotension and loss of responsiveness can be seen with normal doses and nontoxic serum magnesium concentrations. Calcium gluconate 1 g administered as a bolus intravenous infusion can be used to reverse untoward side effects.[46]

***Neonatal side effects***

Neonate may show lethargy and hypotonia. Respiratory depression is possible, but uncommon. Demineralization was reported in 50% of infants whose mothers were treat with magnesium for more than 7 days.[53] After magnesium sulfate tocolysis, 50% of fetus had non-reactive of non-stress tests and only 18% demonstrated fetal breathing movement. No effect was seen on fetal tone, movement, and amniotic fluid volume.[54]

***Contraindications***

Patients with myasthenia gravis or evidence of marginal cardiac compensation should not receive magnesium sulfate. Caution should be taken when administering magnesium sulfate to women with renal disease.[46]

## Calcium Channel Blockers

There have been several studies of nifedipine

tocolysis, and these have been comprehensively reviewed by Childress and Katz. In all studies, nifedipine was as successful or better than ritodrine in stopping preterm contractions without adverse fetal effect. Maternal side effects were much worse with ritodrine.[55] A randomized, multicenter trial showed nifedipine postponed delivery longer than ritodrine did.[56] Overall, when calcium channel blockers have been compared with ritodrine or magnesium sulfate, they have shown equal or superior results in regard to delaying delivery.[2,46]

Currently, nifedipine is most often used as a tocolytic agent. Dosage regimens vary from 10 to 20 mg every 4 to 6 hours orally, while other use up to 40 mg (10 mg every 15 minutes) sublingually in the first hour, followed by 60 to 160 mg per day of slow-release nifedipine.[6]

***Dosage and administration***

Most administered an initial loading dose of 30 mg nifedipine, followed by 10-mg to 20-mg orally every 4 to 6 hours. Different loading dose regimens included:

1. 10 mg sublingual every 20 minutes for up to three doses (some studies would administer up to four doses for a maximum of 40 mg).
2. 10 mg sublingual with 20 mg oral.
3. 30 mg oral.

Onset of action after oral nifedipine is less than 20 minutes with peak plasma concentration in 1 hour and half-life of 1.5 to 3 hours. Onset appears somewhat faster with sublingual dose. Duration of action of a single dose can be as long as 6 hours, but no apparent cumulative effect occurs when administered orally every 6 hours. Elimination is mainly through the kidney (70%) and bowels (30%).[46]

***Maternal side effects***

When compared with ritodrine, maternal side effects are less frequent and severe. The most common side effects are flushing, headache, dizziness, and nausea.[57] Transient hypotension, described as a decrease in the systolic blood pressure of 15 mmHg and diastolic blood pressure of 10 mmHg, with an associated increase in maternal pulse of 10 beats per minute may occur. Close monitoring of maternal vital signs is recommended, as well as assuring adequate maternal hydration.[46]

***Neonatal side effects***

Calcium channel blockers can cross the placenta. Garcia-Velasco and Gonzalez addressed concerns regarding the effect on blood flow by Doppler analysis of umbilical artery flow of fetuses of mothers treated by nifedipine versus ritodrine. The result did not show any difference.[57]

***Contraindications***

Maternal hypotension, defined as a blood pressure less than 90 / 50 mmHg, is a contraindication to calcium channel blocker tocolysis. Concomitant use with magnesium sulfate should be avoided because of reports of neuromuscular blockade.[46]

## Prostaglandin Synthetase Inhibitors

In randomized studies, indomethacin prove to be equally efficacious in comparison with betamimetics and magnesium sulfate with regard to delay of delivery.[58,59]

***Dosage and administration***

Indomethacin is rapidly absorbed after oral administration with peak plasma concentration seen in 1 to 2 hours. Patients may initially be administered a 50-mg oral dose or 50 to100 mg dose rectally, followed by 25 mg orally every 4 to 6 hours up to 48 hours.

Treatment with all prostaglandin synthetase inhibitors is usually limited to 48 to 72 hours and pregnancy at 32 weeks or less because of concern of side effects such as oligohydramnios and premature constriction of the fetal ductus arteriosus.[6,46]

***Maternal side effects***

Prostaglandin synthetase inhibitors are well tolerated with minimal maternal side effects. The most

common side effects are mild nausea and heartburn.[46] Gastric bleeding, as well as alteration in bleeding time, thrombocytopenia, and asthma in susceptible patients can occur.[6] The maternal cardiovascular system is not affected. Maternal side effects are significantly less when compared with ritodrine and magnesium sulfate.[58, 59]

***Fetal side effects***

The incidence of ductal constriction is increased after 32 weeks of gestation, with rate up to 50% in some series. Other reported side effects include oligohydramnios from decreased renal blood flow, primary pulmonary hypertension, necrotizing enterocolitis with small bowel perforation, acute renal failure, and intracerebral hemorrhage in the newborn.[46]

***Contraindication***

Prostaglandin synthetase inhibitors should be avoided in patients with significant renal or hepatic impairment, active peptic ulcer disease, nonsteroidal anti-inflammatory drug-sensitive asthma, coagulation disorders, thrombocytopenia, or other sensitive to nonsteroidal agents.[46]

## Steroids

Antenatal corticosteroid therapy for fetal maturation reduces both mortality and morbidity rates, extended to a broad range of gestational ages (24 - 34 weeks), and is not limited by gender or race. Optimal neonatal benefit from a complete course of antenatal corticosteroid therapy starting at 24 hours after administration and lasting up to 7 days after initial course. Morbidity, RDS, and IVH are reduced even when corticosteroid treatment lasts for less than 24 hours, therefore, antenatal corticosteroid should be administered unless delivery is imminent.[60] The two preferred synthetic corticosteroids are betamethasone and dexamethasone. The effective doses of two compounds are: (1) betamethasone 12.0 mg administered intramuscularly every 24 hours for two doses and (2) dexamethasone 6.0 mg administered intramuscularly every 12 hours for four doses.

Significant improvement in neonatal outcome is limited when corticosteroids are administered to the women greater than 34 weeks gestation.[61] In preterm premature rupture of membranes at less than 30 to 32 weeks gestation in the absence of clinical chorioamnionitis, antenatal corticosteroids use is recommended because of the high-risk of IVH at these early gestational ages. There are inadequate evidences to establish clinical benefit beyond 7 days after antenatal corticosteroid therapy and the potential benefits or risks of repeated administration after 7 days are unknown.[61] Beneficial effects of antenatal corticosteroid therapy may extend beyond the 7-day window. To date, there are no published randomized controlled trials of the efficacy or safety of mutiple-course versus single-course antenatal corticosteroid therapy.[62] Clinical trials are in progress to assess potential benefits and risks of various regimens of repeat courses. Until data establish a favorable benefit-to-risk ratio, repeat courses of antenatal corticosteroids, including rescue therapy, should be reserved for patients enrolled in clinical trials.[63]

***Maternal side effects***

Potential adverse maternal side effects may include infection, hyperglycemia, pulmonary edema, and adrenal suppression. Maternal infection is a possible side effect of antenatal corticosteroid therapy that may be magnified with multi-course therapy. In Crowley's meta-analysis of evidence from randomized controlled trials of antenatal corticosteroid therapy, nine of the reviewed trials reported an increased risk for infection in mothers or an altered immunologic response to an infectious process. The pooled odds ratio was 1.15 (95% CI; 0.84-1.57) that suggests either an increase in maternal infection or no effect at all.[64] Antenatal betamethasone administration may cause transient maternal hyperglycemia in the gravida without diabetes and screening for gestational diabetes may be affected. Maternal pulmonary edema has not been reported in women receiving antenatal corticosteroids alone. The role of antenatal corticosteroids in the development of pulmonary edema is

unclear and more likely related to tocolytic agents and maternal fluid balance.[62]

***Contraindication***

Corticosteroid therapy is indicated for any woman at risk for preterm delivery, with few exceptions. Antenatal corticosteroid therapy should be avoided in insulin-requiring diabetes. Hyperglycemia may be magnified in the gestational or pregestational diabetes in women who present in preterm labor. When antenatal corticosteroids are administered to these women, hyperglycemia may necessitate an adjustment in insulin therapy. With poorly controlled diabetes, fetal hyperinsulinism may occur which blocks surfactant production by type II pneumocytes.

## Antibiotic

A definite association has been demonstrated between preterm labor and genital tract infection. Currently, the conclusion regarding the true benefits of antibiotics adjunctive therapy in treatment of preterm labor are inconsistence. The administration of antibiotic treatment to women with preterm labor for the purpose of pregnancy prolongations has not yet recommended. Treatment should be direct towards those with specific indications for treatment, such as urinary tract infection, GBS intrapartum prophylaxis, etc.[65] Premature infants are very susceptible to early Group B. Streptococcus (GBS) infections. In 1996 the Centers of Disease Control and Prevention along with the American College of Obstetricians and Gynecologists (ACOG), recommended ampicillin, 2 g intravenously in intrapartum period every 6 hours until delivery for women in labor prior to 37 weeks. Rectovaginal cultures for GBS should be obtained, an the antibiotic can be discontinued when the cultures come back negative.[3, 6]

## Intrapartum management

Whether labor is induced or spontaneous, abnormalities of fetal heart rate and uterine contractions should be sought, preferred by continuous electronic monitoring. In the absence of a relaxed of vaginal outlet, a liberal episiotomy for delivery is advantageous once the fetal head reaches the perineum. It is doubtful whether use of forceps in the most instances produces fewer traumas. A physician and staff proficient in resuscitative techniques and fully oriented to the specific problems of the case should be present at delivery.[3]

In conclusion, preterm delivery is one of the most common causes of infant mortality and morbidity in Thailand. Many researches have tried to establish clinical assessments of risk for preterm delivery, usually only minimal to moderate success. Nearly half of women with preterm deliveries have no identifiable clinical risk factor.[66] During the past 20 years, ultrasound assessment of the cervix has moved from a purely experimental research tool to a standard part of obstetrics diagnostic imaging. The presence of FFN in vaginal or cervical secretions before 35 weeks is a moderately good predictor of preterm delivery. The absence of FFN is a strong predictor that preterm delivery is unlikely within the next 7 to 14 days, with NPVs exceeding 99% in some studies. Tocolytic agents are effective in prolonging pregnancy. Clinical use of betamimetics is limited by the adverse maternal effects, most significantly cardiopulmonary complications. Magnesium sulfate became the first line tocolytic agent because it was shown to have similar efficacy with fewer adverse maternal side effects. A low-side effect profile makes calcium channel blockers an attractive alternative. When use earlier in gestation (<32 weeks) and for short duration (<48-72 hrs), prostaglandin synthetase inhibitors are an appropriate alternative agent. The use of antenatal steroids in conjunction with tocolytic agents theoretically have substantial benefits. The efficacy and safety of repeated courses of antenatal steroids has not been established. Conclusion regarding the true benefits of antibiotics as adjunctive therapy in treatment of preterm labor are inconsistent.

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