Management of preterm labor

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Preterm labor and delivery continues to be one of the most serious problems in obstetrics, both medically and socioeconomically. The more classically used definitions of preterm delivery may not be useful in this era of advances in neonatal care. Similarly, the classically used criteria for “success” in tocolysis may obscure benefits from prolongation of gestation that does not meet these criteria. This article reviews the etiologic theories, risk factors, diagnostic techniques, and possible primary and adjunctive modes of therapy for preterm labor. The emphasis of these recommendations is on their clinical utility for the practicing obstetric care provider.

(Key words: preterm labor, tocolysis)

Preterm birth occurs in approximately 10% of pregnancies in the United States. Therefore, it is not only one of the most common obstetric complications, but also one of the most serious. After fetal anomalies, it is the leading cause of perinatal mortality, resulting in 70% of perinatal/neonatal losses. It is also one of the leading contributors to long-term morbidity, including mental retardation, developmental delay, cerebral palsy, seizure disorders, blindness, deafness, and non-neurologic disorders such as chronic pulmonary disease, and retinopathy of prematurity. This morbidity translates into a significant social problem, both for the families involved and for the cost in healthcare dollars, which has been estimated at greater than $2 billion annually.

Preterm birth is indicated for medical or obstetric problems in 20% to 30% of total early deliveries, thus leaving 75% as spontaneous deliveries. Of these spontaneous deliveries, approximately two thirds are due to spontaneous labor, and one third due to premature rupture of the membranes. Romero and associates have used the term preterm labor syndrome for a model in which the fetal membranes and decidua respond to an inflammatory insult (infectious, ischemic, traumatic, or allergic) by producing cytokines and then bioactive lipids (including prostaglandins) that stimulate contractions and release proteases that damage the membranes and decidua with a final result of cervical ripening, dilation, and possible rupture.

With a better understanding of the processes involved, obstetric care providers can determine which pregnancies are at risk for preterm labor and diagnose preterm labor in a timelier manner. Thus, preterm deliveries may become increasingly preventable.

Definition of preterm labor

The strict definition of preterm labor is delivery occurring before the 35th week of gestation. It is important to note that this definition is not related to fetal or neonatal size. Such confusion occurred because originally the American Academy of Pediatrics defined prematurity as a liveborn infant weighing 2500 g or less. Clearly, this criterion will include a significant proportion of small-for-gestational-age term infants, artificially increasing the number of premature neonates. In 1961, the World Health Organization added gestational age of less than 37 weeks to the criteria for prematurity, which has classically been the definition used. As the knowledge and technology in neonatal care have continued to improve, however, the functional definition of preterm delivery has declined. It is very unusual in a tertiary care center today for any significant morbidity or long-term sequelae to result from deliveries occurring (in a nonanomalous, healthy infant) after 35 weeks’ gestation. A more clinically useful definition, then, would be delivery occurring before the 35th week of gestation. This definition also provides a more useful end point for the treatment of preterm labor. For example, studies that fail to show efficacy of tocolytic treatment modalities may indicate that the inability to achieve 37 weeks’ gestational age is a treatment failure when, in practice, some significant prolongation of the pregnancy was actually achieved. For the purposes of this discussion, 35 weeks’ gestation will be used.

Risk factors for preterm labor

Unfortunately, early and accurate determination of who will deliver preterm has been very difficult. This effort has included attempts to assess risk, as more than half of preterm births occur in women who have no apparent risk factors. Possible factors that are associated with increased risk of preterm birth are shown in Figure 1.

Scoring systems for risk of preterm labor and delivery have been developed in an attempt to determine those women who will benefit from more intensive follow-up and possible treatment. The efficacy of such systems has not consistently been found to reduce the incidence of preterm birth.

More recently, interest has focused on the use of the following as possibly useful in the attempt to determine risk of preterm delivery:

- technologies such as home uterine activity monitoring (discussed in the following article in this supplement),
- biochemical markers such as salivary estriol or cervicovaginal fetal fibronectin (FFN), and
- anatomic markers such as endovaginal cervical evaluation of cervical length and membrane funneling as possibly useful tools in the attempt to determine preterm delivery risk.

Large trials, however, have not yet consistently shown the applicability of these modalities to the large “not at risk” population. When comparing previous risk evaluations and the newer technologies in determining preterm birth risk, the three findings most predictive of birth are:

- FFN in cervicovaginal secretions,
cervical length of less than 2.5 cm as measured by endovaginal sonography, and
previous spontaneous preterm birth before 35 weeks’ gestation.9

Determination and elimination of some risk factors are possible, including primary prevention with:
public health education regarding cessation of smoking and substance abuse, accessibility to regular prenatal care, stress avoidance, and workplace and environmental alterations

Secondary preventive measures are also possible, including evaluation for possible infection/colonization and appropriate treatment of genital tract organisms such as Chlamydia, Ureaplasma/Mycoplasma, and, most important, bacterial vaginosis.

As previously indicated, more recent attention has focused on methods of screening in the general population, such as evaluation of salivary estriol. Estriol is one of the three major placental estrogens, and the level is increased in a surge-like fashion that precedes labor by several weeks. Estriol levels can be reliably measured in saliva, and studies have indicated that such measurement has possible usefulness in determining pregnancies at risk for preterm labor.9

Diagnosis of preterm labor
Classically, the diagnosis of preterm labor has included the findings of preterm uterine contractions (frequently defined as at least one every 10 minutes lasting 30 seconds) and one or more of the following:
progressive cervical change,
cervical dilation of at least 2 cm,
cervical effacement of 80% or greater.

There exist, however, significant problems with these criteria in trying to diagnose true preterm labor. Among the most concerning is that the symptoms of preterm labor are nonspecific and can include pelvic pressure, menstrual-like cramps, increase in vaginal discharge, and backache. All these symptoms can occur in a normal pregnancy. These contractions can be painless in up to 50% of instances, and if felt at all are often described only as tightening or a feeling of the baby “balling up.” It is common for a patient to be admitted with advanced cervical dilation, and tocolytic monitoring reveals regular uterine activity with contractions lasting up to 60 seconds. Yet, the patient is unaware of uterine activity until she is made aware of the contractions. Other patients present with a palpably long, closed cervix, yet they have premature rupture of the membranes and deliver a short time after being evaluated. Multiparas may have contractions every 5 minutes for 10 weeks with the cervix dilated 2 cm to 3 cm for many weeks, and then eventually need induction for postdate delivery. The difficulty, then, in accurately diagnosing preterm labor is the high prevalence of the symptoms and signs of preterm labor among normal healthy women and the imprecision of the digital examination of the cervix.2

These concerns have led to the treatment of a large number of women who are not actually in preterm labor (a false-positive diagnosis) as well as the omission of treatment in a significant number of women who are actually in preterm labor but do not show the typical signs or symptoms expected for the diagnosis (a false-negative diagnosis). Therefore, greatly needed is a method of early, reliable, noninvasive, office-based, accurate diagnosis of preterm labor, which unfortunately does not exist. The importance of earlier, accurate diagnosis cannot be underestimated.

If the physician waits for regular contractions of which the patient is aware, progressive cervical change, or rupture of the membranes, it is likely that the diagnosis of preterm labor will be valid, but it is unlikely that the therapy will be successful. Methods are available, however, to improve the accuracy of our diagnosis at earlier stages of the labor process. The two most studied of these methods are identification of cervicovaginal FFN and endovaginal assessment of cervical length.

Fetal fibronectin
Fetal fibronectin is an extracellular matrix protein that is present in the fetal membranes and maternal decidua. It is not normally present in the cervicovaginal secretions after 20 weeks’ gestation, but it does begin to be found near term as the onset of labor approaches. It is thought that any significant disruption or inflammation of this membrane-decidual interface can result in the release of FFN into cervicovaginal secretions, where it may be identified. Studies have repeatedly shown that the utility of this test is the negative predictive value for preterm delivery (within 7 days of the test) of up to 98.2%.10 This value means that 1.8% of patients who tested negative for FFN did deliver within 7 days of the test. Therefore, care must be taken to not “ignore” these patients when there is concern for possible preterm labor, but a negative FFN test. A recent study found that 40% of pregnant women testing negative for FFN ultimately delivered preterm.11

Cervical length
Although digital examination of the cervix is largely imprecise, ultrasound evaluation of cervical length and membrane status can provide useful and reproducible information. Abdominal ultrasound attempts at cervical evaluation are significantly affected by body habitus and bladder filling, which, however, do not affect endovaginal imaging. Thus, an appropriate endovaginal image can be obtained in more than 95% of patients. Iams and colleagues8 found that cervical lengths of greater than 30 mm at 24 weeks’ gestation had a negative predictive value of 97.4% for preterm birth. Further, as cervical length decreases, the positive predictive value and sensitivity for preterm delivery increase (25.7% and 23%, respectively, for cervical length less than 20 mm).8 These patterns also hold true for the presence or absence of membrane descent in the cervical canal (funneling). The utility

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**Checklist**

**Major risk factors**
- Multiple gestation
- Polyhydramnios
- Uterine anomaly
- Cervical dilation > 2 cm at 32 weeks
- Two or more second-trimester abortions
- Prior preterm delivery
- History of cervical surgical procedure (cone biopsy, loop electrosurgical excision procedure)
- Cocaine or amphetamine use
- Major abdominal surgery after the first trimester

**Minor risk factors**
- Bleeding after 12 weeks’ gestation
- Pyelonephritis
- Smoking more than 10 cigarettes per day
- One second-trimester abortion
- More than two first-trimester abortions

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Figure 1. Risk factors associated with preterm delivery.
of this test is also mainly in the negative predictive value for at-risk patients. An advantage of this test is that as the cervical length decreases to less than 20 mm, it may be helpful in determining who may benefit from further observation or initiation of treatment, even if no ongoing symptoms exist.

With the advent of these additional technologies, clinicians have an increased capability not only of avoiding treatment in those patients whose risk of preterm delivery is found to be low, but also of earlier initiation of treatment in those patients who have continually increasing risk.

**Treatment of preterm labor**

Some general principles exist in managing patients with preterm labor. Therapy becomes less aggressive as gestational age increases. Full maternal involvement with therapy decisions is essential. Ongoing reassessment of whether treatment continues to be indicated should be done, balancing a healthy respect not only for the possible benefits for the fetus, but also for the risks to an otherwise healthy mother.

If, after identification of risk and appropriate diagnostic evaluation, treatment appears warranted, the decision process involves several components:

- Do any contraindications to tocolysis exist? (Figure 2).
- Does the severity of the problem warrant hospitalization?
- Are adjunctive modes of therapy indicated?
- How long should treatment continue?

**Tocolytic therapy**

The majority of tocolysis is initiated with in-hospital therapy. Initial evaluation includes evaluation of maternal clinical status, membrane status, complete blood cell count, urinalysis, group B β-hemolytic *Streptococcus* status, and other tests as indicated. Fetal status should be ascertained by non-stress test or biophysical profile, and if not recently done, include evaluation of fetal growth and amniotic fluid. Unless the patient is dehydrated, excessive fluid boluses should not be given to try to decrease contractions, because this measure will have only a temporary effect in true preterm labor and increases the risk of pulmonary edema. Maternal risks from tocolysis as well as the anticipated benefits are thoroughly reviewed. Clearly, the earlier the gestational age, the greater the fetal risk, and therefore the greater the maternal risk to which we may choose to expose her in order to benefit the fetus. The goal is not to stop all uterine activity, but to safely suppress it to the point that labor does not progress.

Therapy usually is initiated with intravenous magnesium sulfate (MgSO₄), which acts to suppress myometrial activity, likely through calcium antagonism at the motor end plate. Initial dosing is 4 g to 6 g over a 15-minute interval, followed by a continuous infusion at a rate of 1 g/h to 3 g/h. To avoid excessive fluid and free water (increasing risk of pulmonary edema), higher concentrations are used (such as 40 g of MgSO₄ in 1000 mL of lactated Ringer’s solution). Serum magnesium levels are not measured as long as urine output is adequate and deep tendon reflexes remain present. Magnesium sulfate may take several hours to begin to significantly suppress uterine activity. Therapy is continued for at least 48 hours, after which the patient is reevaluated to determine if she is stable enough to be switched to other tocolytics. Infusion of MgSO₄ is continued as long as needed in situations where significant risk of delivery continues to exist. Careful attention is paid to maternal pulmonary and volume status to avoid pulmonary edema. In addition to the known problems with adverse patient tolerance of the muscle relaxant symptoms, significant ileus can develop. These problems can, on occasion, be serious enough to warrant discontinuation of use of the agent. If consideration is given to long-term use, a peripherally inserted central catheter is placed for the patient’s comfort.

In patients who have extreme risk of delivery with significant prematurity (less than 30 weeks’ gestation), a second agent can be used if needed after a complete and thorough discussion of both the possible maternal risks involved and of the limited large-scale trials. Indomethacin is a common second agent and works through inhibition of the cyclooxygenase system, decreasing prostaglandin synthesis. The dose is 50 mg to 100 mg initially, then 25 mg to 50 mg every 6 to 12 hours. Although oral and rectal routes are most common, vaginal dosing has been shown to potentially be more efficacious. The most common maternal risk is of gastric irritation, and this risk is significantly reduced by taking the drug with food and by using a gastric protector such as sucralfate (1 g orally before each dose). Fetal risks are that of decreased amniotic fluid and closure of the ductus arteriosus (both are under the control of prostaglandins). If therapy is continued for longer than 48 hours, fetal status must be followed up weekly with evaluation of amniotic fluid volume and Doppler ultrasonography of the ductus arteriosus. If the mother remains stable with adequate suppression for at least 48 hours, we consider a switch to other agents.

If significant risk continues, terbutaline sulfate therapy is infused via a continuous subcutaneous pump. Advantages of the continuous subcutaneous pump include administration of lower total daily doses and programmable drug bolus and basal rates requiring no intervention by the patient. Terbutaline is a β-agonist and works through increasing cyclic adenosine monophosphate. It can also be given by intermittent subcutaneous injection, 0.25 mg every 3 hours. Large oral doses or continuous intravenous infusion has been found to result in tachyphylaxis to the drug effect (possibly through receptor site saturation), limiting the effectiveness of these dosing methods. Significant care is taken to assess maternal cardiac status before using β-agonist therapy to avoid myocardial ischemia through increased cardiac work or initiation of...
Adjunctive modes of therapy
Of the adjunctive modes of therapy available, corticosteroid administration is the most important. Although some debate exists about whether single- versus multiple-dose courses are best, there is no question that antenatal corticosteroid therapy reduces mortality, respiratory distress syndrome, and intraventricular hemorrhage in preterm infants. This therapy extends from 24 to 34 weeks and is additive to the benefits of surfactant use. Although treatment 24 or more hours before delivery has the greatest beneficial effect, duration of less than 24 hours can still be protective. Consequently, corticosteroids are used in essentially all patients in preterm labor who are at significant risk for delivery. The dose is 12 mg of betamethasone intramuscularly and is repeated in 12 to 24 hours. If betamethasone therapy is continued, the dose is generally 12 mg intramuscularly every week. Contraindications are choioamnionitis with sepsis and uncontrolled diabetes with actual or significant risk of ketoacidosis. Antibiotic therapy is started with the initiation of tocolysis in cases of known group B Streptococcus colonization, or pending culture results if the patient’s status is unknown. Cultures are taken by use of separate swabs from the outer third of the vagina and rectum, and selective growth medium is used in the laboratory. In the absence of other risk factors (prolonged premature rupture of membranes, presence of a cerclage, advanced dilation), treatment is stopped after 1 week or if culture status is negative. Amniocentesis is done if there is clinical concern of possible intra-amniotic infection for such reasons as an isolated increased temperature or white blood cell count, uterine tenderness, fetal tachycardia, or persistent contractions despite adequate tocolysis. Amniotic fluid is analyzed with Gram’s stain, culture, and measurement of glucose level. In specific circumstances in which a significant possibility exists that cervical incompetence is contributing to the contractions and cervical changes, cerclage is occasionally considered. This decision, however, is never made lightly, and cerclage is not a replacement for appropriate diagnosis and tocolytic treatment. Outpatient therapy is considered when patients have remained stable on initial tocolysis and do not have factors that would prohibit home follow-up, such as advanced dilation, high-order multiple gestation, or inability to change successfully to oral or subcutaneous therapy. As a general rule, patients who require more than one mode of therapy for tocolysis are rarely discharged. Those patients whose preterm labor is controlled on subcutaneous terbutaline, oral indomethacin, or oral nifedipine therapy can be discharged to home bed rest and pelvic rest if they understand the need for compliance, have adequate transportation to office visits, and are in a social situation that allows compliance.

Very few patients can attain the same degree of rest at home as they can in the hospital. Home uterine activity monitoring is considered in patients with a worrisome history such as previous preterm delivery at home or rapid labors. These patients are seen weekly as outpatients to assess cervical status and to measure FFN if indicated. Weekly antenatal testing is done, as are evaluations of serial fetal growth and amniotic fluid volume.

Comment
The goal of any modality of treatment of preterm labor should be safe prolongation of gestation to achieve fetal benefit from corticosteroid administration and increasing gestational age. Because treatment is solely for fetal benefit and potentially places the mother at risk, constant reassessment of the benefits versus risk is important. It should never become “us against the uterus.” Given this dictum, the goal is any increase in gestational age successful in decreasing neonatal risk, especially in the 24- to 30-week range of an otherwise healthy infant. “Success” is not defined as achieving term status, but as determining who is truly at risk and appropriately intervening to gain whatever gestational age safely possible. Any decrease in neonatal morbidity and mortality is therefore a “success” to the baby and the family.

A further benefit to this intervention is the decrease in healthcare costs, both initially for admission to the neonatal intensive care unit (NICU) and possibly long-term care if handicaps occur. The cost of initial therapy to prevent preterm delivery (even if in the hospital) pales in comparison to the NICU and long-term care costs. Thus, a more appropriate way to evaluate therapeutic efficacy is not in actual gestational age achieved, but of days or weeks of gestation gained and the resultant decrease in morbidity or mortality, and therefore costs.

References

Hole and Tressler • Management of preterm labor
Preterm birth is associated with significant neonatal mortality and morbidity nationwide. Multiple strategies have been used to attempt to reduce the incidence of preterm births, and none have been entirely successful. The current review contains assessment of recent literature and home uterine activity monitoring. It also makes some suggestions about how and when this diagnostic modality may be used in current obstetric practice.

(Key words: home uterine activity monitoring, preterm birth, pregnancy)