Premature Labor, Part II: Management

Dwenda K. Gjerdingen, M.D.

Abstract: ***Background:*** **As the second paper in a two-part series on preterm labor, this article discusses the management of preterm labor as it relates to risk reduction, tocolytic therapy, corticosteroids, and antibiotics.**

Methods: **Published literature on the management of preterm labor was reviewed by searching MEDLINE files from 1983 to the present, using the terms "preterm labor," "premature labor," "preterm labor and antibiotics," "tocolytic agents," "tocolysis," "betamethasone," and "premature rupture of membranes." Additional references were obtained by cross-referencing bibliographies from available articles.**

Results and Conclusions: **Effective management of preterm labor and birth begins with an assessment and reduction of risks for all pregnant women. In addition, pregnant women should be screened and appropriately treated for urologic and gynecologic infections (e.g., syphilis, gonorrhea, *Chlamydia*, and bacterial vaginosis). Women who are at high risk for preterm birth should be enrolled in a preterm birth prevention program that includes frequent contact with health professionals, patient education about the signs and symptoms of preterm labor, home monitoring, and regular cervical examinations. For women who develop preterm labor that does not require immediate delivery, recommended management strategies include reduced activity, early tocolytic therapy, corticosteroids for up to 34 weeks' gestation (both for women with intact and ruptured membranes), and antibiotics for known infections. Early studies also suggest that prophylactic antibiotics can be beneficial for women with idiopathic preterm labor or preterm premature rupture of membranes. (J Am Board Fam Pract 1992; 5:601-15.)**

Preterm births constitute the most predominant cause of neonatal morbidity and mortality in this country, and this problem continues to grow in spite of our technological advances. As discussed in Part I of this series,[1] our attempts to address the problem of preterm births have been stymied by our incomplete understanding of the etiology and pathophysiology of preterm labor and birth. As a result, our efforts to manage preterm labor have been frustrated, as they focus more on "cures" than on "causes." Further, because our management strategies are based on incomplete information, clinicians do not agree on techniques for managing preterm labor, and their practices vary considerably. This variable management has been documented in a report on a national survey about obstetricians' management of preterm labor by Taslimi, et al.,[2] which showed wide variations in criteria for diagnosing preterm labor and in choices of tocolytic agents, use of amniocentesis, and use of corticosteroids.

This paper presents a protocol for managing preterm labor based on a recent review of the literature as it relates to risk reduction, conservative treatment measures, and the use of tocolytics, corticosteroids, and antibiotics.

Risk Reduction

Risk factors for preterm birth include several demographic, socioeconomic, and medical variables, many of which were described in Part I of this review.[1] Although a number of these factors are not easily changed, others — particularly lifestyle characteristics and health practices — can be altered. By addressing such issues as the use of cigarettes and recreational drugs, work responsibilities, nutrition, and sexual practices, important causes of preterm labor can be eliminated, which is the ultimate goal in management.

Recent studies have reported that 22 to 38 percent of pregnant women smoke throughout pregnancy,[3] an unfortunate finding, considering the problems that can result from prenatal cigarette use: preterm labor, low-birth-weight infants, placenta previa, abruptio placentae, spontaneous

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From the Department of Family Practice and Community Health, University of Minnesota, Minneapolis. Address reprint requests to Dwenda K. Gjerdingen, M.D., 590 Park Street, #310, St. Paul, MN 55103.

abortion, and premature rupture of membranes.[1,3,4] Many women wisely stop smoking during pregnancy, and reports from smoking cessation trials indicate that cessation rates are higher when women are given assistance in stopping.[4] Among the smoking cessation methods that are currently available for pregnant women are those sponsored by the American Lung Association: *Because You Love Your Baby*,[3] and *A Pregnant Woman's Self-Help Guide to Quit Smoking*.[5] The use of other recreational drugs can also heighten a woman's risk for preterm delivery[1]; therefore, physicians who practice obstetrics should investigate expectant mothers' use of cigarettes and illicit drugs and assist in their discontinuing these substances whenever possible.

A woman's work responsibilities can also increase her risk for preterm delivery, especially if the work is heavy, tiring, or requires long hours. Freda, et al.[6] recently evaluated the relation of women's time at work to the preterm birth rate in 173 New York women who were at risk for preterm labor. For these women, working more than 30 hours per week corresponded to the greatest risk of having a preterm delivery; moreover, when long working hours, commuting, and heavy lifting were associated with symptoms of preterm labor, women who decreased these activities were more likely to deliver at term.

If certain work characteristics are associated with a greater risk for preterm delivery, it would be important to discover which work interventions might decrease the risk. Two French investigations addressed this question. In a study carried out in 50 factories on a total of 1168 pregnancies, "episodes of sick leave" prescribed to pregnant workers especially for fatigue, without pathological reasons, were associated with a lower preterm birth rate.[7] Papiernik and Keith[8] observed the effects of a work-reduction program on 321 twin pregnancies and found that when work leaves were prescribed early in pregnancy, at approximately 20 to 24 weeks' gestation, the rate of low-birth-weight infants was lower. The total cost of preventing preterm births in this study was calculated to be one-third of the long-term costs associated with lack of prevention. Another study comparing outcomes for 78 Swedish women with twin gestations who were prescribed prophylactic leaves of absence beginning at an average of 27.5 weeks' gestation and 78 control women with twin gestations who did not take leaves found no differences in length of gestation or birth weight.[9] Therefore, it is not clear whether routine leaves of absence for certain high-risk groups are beneficial, and additional studies are needed.

Other health practices, such as the use of nutritional supplements, could be important in preventing preterm births. In a recent randomized, double-blinded controlled clinical trial of calcium supplementation in 190 indigent pregnant women, participants who were treated with 2 g of elemental calcium daily had a lower incidence of preterm delivery (7.4 versus 21.1 percent) and low birth weight (6.4 versus 17.9 percent).[10] While the value of good prenatal nutrition is generally recognized, the contribution of specific nutritional deficiencies to the preterm birth rate requires further study.

A woman's sexual practices also can heighten her risk for preterm birth, as seen in an earlier discussion about the association between sexually transmitted diseases and preterm labor.[1] Consequently, information about the pregnant woman's sexual practices should be obtained at an early prenatal visit, and advice to reduce her risk for such infections should be offered. Such advice would include limiting relationships to a single trusted partner, using barrier contraceptives, and contacting her physician with any symptoms of infection. Data from a recent study by Freda, et al.[6] of 173 women also suggest that, for women at risk for preterm delivery, reductions in overall sexual activity during pregnancy can help decrease their chances of an early delivery.

Finally, the role of social support in preterm birth prevention should be considered. Although it seems likely that such factors as help with housework and childcare, transportation, and emotional support would lessen the possibility of a premature birth for high-risk women, little information is readily available concerning these issues. In a brief review of three studies by Bryce, et al.,[11] who looked at the value of enhanced prenatal support services consisting primarily of prenatal home visits, no distinct benefits were seen in preterm birth rates. Their report indicates that other studies on antenatal support are underway.

In conclusion, several lifestyle and health factors that can contribute to preterm birth — smoking, use of recreational drugs, demanding work,

nutrition, and sexual practices — can potentially be altered to reduce a woman's risk for preterm labor. Physicians should make it a priority to address these issues with each pregnant patient.

Conservative Measures of Treatment

Preterm labor has traditionally been treated with conservative measures, such as bed rest, sedation, and hydration. Sedation and hydration have also been used in the recent past by several clinicians to define the patients in so-called real premature labor: only those women who continued to have contractions after these treatments were considered to be truly in preterm labor and were treated as such.[12] Sedation and hydration have since fallen into disfavor in many institutions for several reasons. Hydration has been reported by some to be ineffective in stopping preterm labor,[13] and it could lead to respiratory complications if tocolytic agents are subsequently used.[14] Sedatives can also complicate the resuscitation of the newborn if given too close to the time of delivery.[14]

Although sedation and hydration might not be useful in the treatment of preterm labor, bed rest continues to be a mainstay of therapy, despite the paucity of recent investigations about its efficacy. A 1985 study on bed rest in preterm labor looked at a unique obstetric group: women with twin gestations. Saunders, et al.[15] randomly allocated 212 women with twin pregnancies to receive either bed rest in the hospital from 32 weeks' gestation until delivery or to be part of a control group in which hospital admission was offered selectively (usually 5 weeks later). The results were surprising — preterm delivery was more common in the early bed rest group than in the control group (30.4 versus 18.7 percent). Most women with the diagnosis of preterm labor do not have such extensive periods of bed rest, and they seem to benefit from the shorter periods of bed rest often prescribed during in-hospital treatment or from the reduced activity commonly recommended after discharge from the hospital. Additional studies are needed, however, to document the efficacy of bed rest or partial limitation of activity and their recommended duration.

Several other modalities, in addition to bed rest, are currently being used to treat preterm labor or its associated complications: tocolytic medications, corticosteroids, and antibiotics. These therapeutic agents are discussed below.

Tocolytic Therapy

For the majority of women in preterm labor, it is desirable to prolong gestation at least to the point of fetal lung maturity. Tocolytic therapy should be initiated unless there are contraindications, such as advanced labor, fetal distress, anomalies incompatible with life, eclampsia, severe hemorrhage, or severe cardiovascular, respiratory, or renal disease.

Several drugs have been tested or used as tocolytic agents, including β-adrenergic receptor agonists, magnesium sulfate, antiprostaglandins, calcium channel blocking agents, narcotics, and sedatives. Currently the drugs used most commonly to arrest labor are β-adrenergic agonists and magnesium sulfate.[16] Both of these tocolytic drugs probably inhibit myometrial activity by reducing the amount of available intracellular calcium.

β-*Agonists*

Of several β-adrenergic agonists that have been used to inhibit preterm labor — isoxsuprine, ritodrine, salbutamol, terbutaline, and fenoterol — only ritodrine is specifically indicated for this use in the United States.[17] Terbutaline, however, is also commonly used for preterm labor in many parts of this country.

β-adrenergic agonists have been widely used because of their reported effectiveness in arresting labor[18,19] and prolonging gestation[20-22]; however, their impact on perinatal outcomes is less clear. A randomized trial of 106 women in preterm labor from 24 to 33 weeks' gestation failed to show that tocolytic therapy improved perinatal outcomes.[23] Similarly, a meta-analysis of 16 controlled trials of β-adrenergic agonists by King, et al.[24] found that, although these agents were effective in delaying delivery and decreasing the frequency of preterm births and low birth weight, there were no benefits on perinatal mortality or severe respiratory disorders.[24] It is possible that the absence of significant perinatal findings in these studies could have been partially due to inadequate sample sizes. As demonstrated by Caritas, et al.,[25] to realize a reduction in perinatal mortality from 10 to 5 percent, 1200 patients would need to be randomized between a treat-

ment and placebo group if the limit for a type I error is set at 0.05 and a type II error at 0.10. Further, these studies could have demonstrated perinatal benefits from tocolytic therapy if they had selected only women in the early stages of labor. Studies that have researched the effectiveness of tocolytic therapy in women whose preterm labor was diagnosed at earlier stages through preterm birth prevention programs generally demonstrated improved obstetric outcomes.[1] It seems, then, that if adequate sample sizes were observed and labor was diagnosed at an early stage, the resulting gestational gains would produce advantages for the neonate.

When β-adrenergic agonist therapy is given, side effects that may occur include maternal tachycardia, hypotension, apprehension, depression, pulmonary edema, hyperglycemia, hyperinsulinemia, hypokalemia, lactic acidosis and ketoacidosis, emesis, headaches, tremulousness, fever, hallucinations, and neonatal hypoglycemia. Less common maternal side effects include transaminase elevation, paralytic ileus, cerebral vasospasm, and respiratory arrest caused by increased muscle weakness in association with myasthenia gravis.[26] The risk of certain side effects can be reduced by using concentrated intravenous solutions[27] or moderating the dosing schedule.[28] Alternative delivery systems, such as the subcutaneous pump, can also be useful in lowering side effects while increasing efficacy.[29] When different β-adrenergic agonists are compared, there do not appear to be great differences in either maternal side effects or neonatal morbidity and mortality.[30] Ritodrine, however, might have more initial treatment failures than terbutaline,[31] and it also has the disadvantage of being more expensive.[26]

Magnesium Sulfate

Magnesium sulfate has been used both as a first-line tocolytic medication and as an alternative agent when β-adrenergic agonists are contraindicated, as with patients having hyperthyroidism or chronic β-blockade therapy. Compared with β-adrenergic agonists, magnesium sulfate has similar efficacy but fewer side effects.[32] Side effects that can occur, however, include cardiovascular or renal problems, vomiting and diarrhea, and depression of the respiratory and central nervous systems.[17,33] Magnesium can also adversely affect the biophysical profile, increasing the occurrence of nonreactive nonstress test results and diminishing fetal breathing movements.[34]

Certain patients with preterm labor who are refractory to single-drug treatment can be successfully managed with a combination of magnesium and a β-adrenergic agonist. Although this combination often results in more cardiovascular side effects initially,[26] side effects can be reduced by discontinuing the combined regimen for a brief period, and then restarting both drugs, advancing doses more gradually, if necessary. When this procedure was used in 95 women whose preterm labor could not be controlled with a single drug, the initial complication rate of 64 percent dropped to 21 percent when the two tocolytic medications were restarted, and the proportion of near-term deliveries increased significantly, from 19.5 percent to 50 percent.[35]

Other Tocolytic Agents

In addition to β-adrenergic agonists and magnesium sulfate, other drugs that have been recently tested for their tocolytic activity include indomethacin and nifedipine. Although indomethacin has been found to be an effective tocolytic drug with relatively few maternal side effects,[36] it can have adverse neonatal effects, such as transient ductal constriction and primary pulmonary hypertension.[26,37] In addition, nonsteroidal anti-inflammatory agents can decrease amniotic fluid volume.[38] Nifedipine is also reported to be an effective tocolytic agent and, compared with ritodrine, produces fewer side effects for both the mother and infant.[39,40] Additional studies, however, are needed before this drug is widely recommended for tocolysis.

Oral Tocolysis

Once preterm labor has been suppressed with parenteral tocolytic medications, oral tocolysis can be accomplished with either β-adrenergic agonists or magnesium tablets. In a recent study of 50 women whose preterm labor was arrested with parenteral tocolysis, 23 women were randomized to receive oral magnesium (200 mg every 3 to 4 hours), and 27 to receive oral terbutaline (2.5 to 5 mg every 3 to 4 hours). Although the number of patients who had deliveries before 36 weeks' gestation was similar between groups, a smaller proportion of the group taking

magnesium experienced side effects — 47.8 versus 81.5 percent.[33] Further, the cost of oral magnesium treatment was found to be about one-third that of terbutaline treatment.

Another prospective trial of oral magnesium randomized into three groups 75 women in preterm labor who were between 24 and 34 weeks' gestation and who had been successfully treated with intravenous magnesium: those taking oral magnesium (SLOW MAG, 534 mg every 4 hours), those taking oral ritodrine (20 mg every 4 hours), and those having no treatment. Both the oral ritodrine and magnesium treatment groups showed an insignificant increase in the proportion of women who were delivered at more than 36 weeks' gestation (56 percent, 56 percent, and 48 percent). Here, too, fewer women receiving magnesium therapy than those receiving ritodrine therapy experienced side effects (20 versus 48 percent).[41] Oral magnesium has also been used prophylactically in women at high risk for preterm labor, and in one small study examining this application, oral magnesium was not more effective than placebo.[42]

To summarize, the small studies currently available on the use of oral tocolytic agents following intravenous therapy for preterm labor have reported questionable benefit over placebo. When oral agents are compared, magnesium appears safer than β-adrenergic agonists, yet similar in efficacy. Larger studies are needed to evaluate whether oral tocolytic drugs are indeed beneficial and under which circumstances they should be used.

Gestational Age Limits for Tocolytic Therapy

The gestational age boundaries for tocolytic therapy have been set by some investigators at 20 to 36 weeks; however, these boundaries are controversial.[43] Some physicians do not give, or at least initiate, tocolytic therapy beyond 33 or 34 weeks' gestation because of the decreasing cost-benefit ratio[44] and the relatively low infant mortality beyond this stage.[45,46] In a retrospective study conducted more than a decade ago by Korenbrot, et al.,[44] costs were analyzed for 365 mother-infant pairs: 229 of the women had received tocolytic treatment for preterm labor, and 136 had not. The investigators concluded that treatment provided between 26 and 33 weeks' gestation was clearly cost effective, with savings of $11,240 per birth, but treatment given beyond 33 weeks' gestation produced no savings. One cannot generalize these findings, however, because of the retrospective, nonrandom design of this study. In addition, the number of women who were more than 33 weeks' gestation who received tocolytics was relatively small, including only 30 women at 34 to 35 weeks and 13 women at 36 to 37 weeks.

Another study investigated the cost of neonatal care for 137 infants born at 24 to 34 weeks' gestation and found that the average cost (in 1977 dollars) per surviving infant decreased from $68,000 at 25 weeks' gestation to $9000 at 34 weeks' gestation.[47] While this study does provide some idea of cost comparisons for preterm births of various gestational ages, it did not look at how tocolytic therapy affects the cost of perinatal care or whether savings might be gained by delaying births beyond 34 weeks' gestation. Therefore, it is not fair to conclude on the basis of this little evidence that tocolytic therapy beyond 33 to 34 weeks' gestation is not cost effective.

Other investigators believe that tocolytic therapy after 33 weeks is useful. Gonik and Creasy[48] have advocated initiating tocolytic agents up to 36 weeks' gestation and continuing treatment until 37 or 38 weeks, claiming that such delays in birth decrease the rate of several neonatal morbidity factors, including respiratory distress, patent ductus arteriosus, the need for intensive care, and the overall number of hospital days. Recent cost analyses performed on home-monitoring programs found a financial advantage of monitoring and treating high-risk women up to 36 to 37 weeks' gestation; however, costs were not determined separately for different gestational age groups.[49-51] Objective evidence either supporting or refuting the treatment of preterm labor in intermediate gestations is meager. So, before clinicians conclude that the treatment of preterm labor beyond a given gestational age is not justified, prospective studies with random designs should be conducted that look at both perinatal morbidity and mortality outcomes and that select women in the early stages of labor. In addition, cost analyses should be performed for less intensive forms of management — for example, oral outpatient tocolysis, limited activity, and intermittent monitoring — for women with intermediate gestations of 34 to 37 weeks.

In practice, most clinicians in this country probably favor longer, rather than shorter dura-

tions of tocolytic therapy. In a recent national survey of 690 obstetricians by Taslimi, et al.,[2] more than 70 percent stated that they usually discontinued tocolytic medications between 36 and 37 weeks' gestation. Continuing tocolytic therapy up to this point, provided that side effects are being monitored, also makes good sense for many family physicians who might not have complete, on-site support for resuscitating premature infants.

Corticosteroids

Glucocorticoids have been widely prescribed to women in preterm labor to decrease the risk of neonatal respiratory distress; however, this practice is not universal.[17] Reasons given for not using antenatal steroids have included the following: they can intensify diabetic and hypertensive problems, increase the risk of infection, delay wound healing, cause pulmonary edema (especially if combined with a tocolytic agent), and increase the risk of neonatal sepsis.[17] Nevertheless, reports by several recent investigators have made a strong case for the continued use of steroids in preterm labor.

Two studies researched antenatal corticosteroid treatment for premature infants who weighed less than 1000 g at birth. Doyle and colleagues[52] observed 170 infants with birth weights between 500 and 999 g: 67 infants had had antenatal betamethasone exposure and 103 had not. A higher rate of steroid-exposed infants, compared with controls, survived their primary hospitalization (68.7 versus 41.7 percent). In a similar study by Papageorgiou and colleagues,[53] 33 infants with birth weights between 600 and 1000 g had had a complete 24-hour course of antenatal steroids, and 53 infants had either had an incomplete course of steroids (n = 20) or no steroids at all (n = 33). Here, too, the full-treatment group showed the advantage, with a higher rate of survival (90.1 versus 56.6 percent), a lower rate of respiratory distress syndrome (27.2 percent versus 73.6 percent), and less need for intermittent positive pressure ventilation (42.4 versus 81.1 percent). In this study no differences between groups were seen for maternal, fetal, or neonatal infections.[53]

Kwong and Eagan[54] conducted a study with women from 24 to 28 weeks' gestation who had been excluded from a surfactant study. When the 36 women who had received at least 24 hours of betamethasone and ritodrine therapy were compared with 37 whose labor was too advanced to receive steroids or tocolytic agents, infants from the treatment group had a significantly lower rate of hyaline membrane disease (28 versus 68 percent). Although not significant, the treatment group also showed a trend toward a lower mortality rate (25 versus 32 percent) and a higher incidence of neonatal sepsis (15 versus 6 percent). It is noteworthy that each of these three studies of very low birth weight infants included some women with prematurely ruptured membranes.

A recent study by Gamsu and colleagues[55] looked at infants with higher gestational ages — up to 34 weeks — and found similar positive results with steroid treatment. This study had several advantages over the previously described studies in that it was a prospective, randomized, double-blind, multicenter trial that observed a relatively large number of women (n = 251) in preterm labor. For infants of women who received at least 24 hours of treatment, respiratory distress syndrome was less frequent (2.9 versus 9.6 percent). The greatest advantage of therapy was seen for the subgroup of infants born before 34 weeks' gestation and within 8 days of trial entry, whose mothers had been treated for at least 24 hours. In this group, none of 27 infants treated with antenatal steroids and 7 of 32 of control infants developed respiratory distress syndrome. Further, the neonatal mortality rate was 7.4 percent for the treatment group and 40.6 percent for the control group. The steroid group showed no increase in maternal or neonatal sepsis even though, here too, some women with premature rupture of membranes were included.

An earlier study by Taeusch and colleagues[56] also included women with longer gestations (up to 33 weeks or more) and similarly found a significant reduction in severe respiratory distress syndrome in the group of infants with antenatal steroid treatment (3 versus 17 percent). The neonatal death rate in the two groups was comparable, however — 15 percent for steroid-treated infants and 14 percent for the control infants. While the steroid group had no deaths secondary to respiratory distress, four of the eight deaths were attributed to infections. Conversely, four out of 10 deaths in the control group were due to respiratory distress syndrome, and only one death was related to infection. The infectious complications

noted in the steroid group could have been a result of the high rate of prolonged ruptured membranes in this study: more than one-half of the women had had ruptured membranes for more than 24 hours.

When results of individual studies are analyzed or reviewed together, findings also favor corticosteroid treatment. In Kwong and Egan's review[54] of 20 studies on steroid preterm labor — including the national collaborative study — all but one of the studies showed positive results with corticosteroid treatment. Crowley and colleagues[57] combined data from 12 controlled trials involving more than 3000 participants to show that corticosteroids not only reduce the occurrence of respiratory distress syndrome overall, but also reduce the risk of intraventricular hemorrhage, necrotizing enterocolitis, and neonatal death. There was no strong evidence suggesting adverse effects from corticosteroids.

Thus, most studies, including the larger collaborative and multicenter trials, have shown that steroid treatment is advantageous for infants of women in preterm labor at 34 weeks' gestation or less and generally results in fewer neonatal deaths and less respiratory disease. This advantage was greatest for infants who received at least 24 hours of antenatal treatment and for whom treatment was given within 1 week before birth.

Antibiotics

Recognizing that infection plays a major role in preterm labor, it is important to look at the role of antibiotics in managing preterm labor. In this section, discussion is centered on the role of antibiotic treatment and its relation to maternal and neonatal outcomes in three situations that relate either directly or indirectly to preterm labor: prenatal infection or colonization with known pathogens, idiopathic preterm labor, and preterm premature rupture of membranes.

Prenatal Colonization with Known Pathogens

Practitioners have long recognized the importance of treating certain prenatal gynecologic infections, such as syphilis or gonorrhea, that might otherwise produce neonatal problems. There has been perhaps less consistency in screening for and treating other pathogens. Part I discussed the risks associated with several other maternal infections and concluded that chlamydial cervicitis, bacterial vaginosis, urinary tract infections, and severe respiratory tract infections all appear to contribute to preterm labor, whereas group B streptococcus and *Chlamydia* could produce adverse neonatal outcomes.[1] It seems reasonable, then, that women with any of these prenatal infections should be treated. Recent studies have been conducted to determine the neonatal impact of treating antenatal *Chlamydia*, mycoplasmas, and group B streptococcus infections.

Schachter, et al.[58] offered erythromycin treatment to 184 pregnant women with cervical chlamydial infections; 60 women and 59 of their infants made up the treatment group, while the 32 women who refused treatment together with 24 of their infants served as the control group. *Chlamydia* infection developed in only 7 percent of infants from the treatment group compared with 50 percent of infants from the control group ($P < 0.001$). Recognizing these benefits of treatment and the risks of transmission without treatment, the Centers for Disease Control now recommends treatment of all prenatal *Chlamydia* infections.[59]

Treating prenatal *Mycoplasma* infections can also have a positive impact on the neonate. When a 6-week course of erythromycin, clindamycin, or placebo was given to 1071 pregnant women whose vaginal cultures were positive for *Ureaplasma urealyticum* or *Mycoplasma hominis*, women whose treatment with erythromycin was begun in the third trimester gave birth to infants who weighed more than infants born to placebo-treated women — 3331 g compared with 3187 g.[60] Earlier erythromycin treatment and treatment with clindamycin had no effect. Although this study did not evaluate gestational age differences between groups, the observation that the erythromycin group had fewer low-birthweight infants than the placebo group (2 versus 10 infants weighing 2500 g or less) suggests a gestational age effect. The overall weight difference between groups represented only a 5 percent gain, however, and additional studies should be performed before antibiotic treatment of prenatal mycoplasma infections is routinely advised.

The treatment of women with group B streptococcus has been discussed by several investigators. In a study of 199 parturients heavily colonized with group B streptococcus who were randomized to receive either penicillin or no antibiotic,

infants of the treated group had a lower incidence of early onset group B streptococcal disease (1.1 versus 9.0 percent).[61] Similarly, in Boyer and Gotoff's study[62] of 160 women with positive prenatal streptococcal cultures who were considered high risk because of either preterm labor or prolonged ruptured membranes (> 12 hours), a higher rate of neonatal sepsis occurred in infants whose mothers received no antibiotics compared with those whose mothers received intrapartum ampicillin: 6 versus 0 percent.[62] Therefore, the treatment of prenatal streptococcal infections appears to produce small, though important, advantages for the neonate. Further studies are needed to determine whether all pregnant women colonized with group B streptococcus should be treated or only those with preterm labor or preterm premature rupture of membranes.

Idiopathic Preterm Labor

Knowing that infections probably play a substantial role in preterm labor, one might question the place of antibiotics in idiopathic preterm labor. Surprisingly, only a few small investigations have prospectively studied the impact of antibiotic treatment on the course of spontaneous preterm labor. Of the five studies outlined in Table 1,[63-67] three showed that the use of antibiotics in idiopathic preterm labor was associated with increased gestational age.[63,64,67] Both of the antibiotics tested in these studies — erythromycin and ampicillin — appeared to be beneficial. The absence of significant findings in two studies by Newton, et al.[65,66] could have been due to such factors as a lower rate of certain pathogens in these populations, delays before the administration of antibiotics, and β error. It should be noted that the more recent of these two studies demon-

Table 1. Studies on the Use of Antibiotics in Idiopathic Preterm Labor.

Author	No.	Methods	Results
McGregor, et al.[63] (1986)	17	Women < 34 weeks' gestation who were prescribed tocolytic therapy for preterm labor were randomized to a group treated with enteric coated erythromycin and a group treated with placebo for 7 days	Of women who had a cervical dilatation of ≥ 1 cm (8 treated women and 9 controls), the average time from treatment to delivery was greater for the control group (32.5 versus 22.4 days)
Morales, et al. [64] (1988)	150	Women from 21–34 weeks' gestation who were prescribed tocolytic therapy for spontaneous preterm labor (cervical dilatation of 1–5 cm) were randomized into 3 groups: 50 were prescribed erythromycin, 53 ampicillin, and 47 served as controls. Treatment was prescribed for 10 days orally	The 2 treatment groups showed important delays from treatment to delivery (29 days for erythromycin, 32 days for ampicillin, and 17 days for controls)
Newton, et al.[65] (1989)	95	Women prescribed tocolytic therapy for idiopathic preterm labor between 24 – 34 weeks' gestation, with a cervical dilatation of 1 cm or greater, were randomized into 2 groups: 48 women were prescribed intravenous ampicillin for 3 days plus oral erythromycin for 7 days, and 47 were prescribed placebos	There were no important differences between groups in gestational age, infant birth weight, or prolongation of gestation
Newton, et al.[66] (1991)	86	This double-blind study randomized women who were in preterm labor (cervical dilatation of ≥ 2 cm) and prescribed intravenous tocolytic therapy to 2 groups: intravenous ampicillin-sulbactam and oral indomethacin, or placebo. Antibiotic treatment was given every 6 hours for 12 doses	No important differences were seen between groups in obstetric or neonatal outcomes. However, the antibiotic-treatment group showed a trend toward longer gestations (34.5 versus 33.5 weeks), more deliveries occurring after 36 weeks' gestation (46 versus 37 percent), and fewer low-birth-weight infants (55 versus 69 percent)
Winkler, et al.[67] (1988)	19	Women who were prescribed tocolytic therapy for preterm labor, with intact membranes and a cervical dilatation of 1–3 cm, were randomized to an erythromycin treatment group (n = 9) or a placebo group (n = 10)	The erythromycin treatment group had longer gestations than the control group (43 versus 20 days)

strated favorable (though statistically insignificant) trends for the group treated with ampicillin-sulbactam and indomethacin; on the average, these women had a greater mean gestational age at delivery (34.5 versus 33.5 weeks), a higher frequency of deliveries at 36 weeks' gestation or more (46 versus 37 percent), and fewer low-birth-weight infants (55 versus 69 percent).

These studies as a whole suggest that antibiotic treatment of women with idiopathic preterm labor could prove useful in delaying delivery; however, additional larger studies are needed to confirm these benefits and to determine which antibiotics would be most useful.

Preterm Premature Rupture of Membranes

The management of women whose preterm labor is preceded by premature rupture of membranes presents unique challenges and should be considered apart from women with idiopathic preterm labor. Here, the risk of infection is even greater because of the possibility of both preexisting infections that could have triggered the rupture of membranes and subsequent infections that could develop when the natural barrier to infection — the amniotic sac — is no longer intact. This increased risk raises questions about aspects of management that could alter the progression of infection: should the timing of delivery be managed actively or expectantly, should prophylactic antibiotics be used, and are corticosteroids helpful?

Although some authors have advocated early intervention in managing pregnancies complicated by preterm premature rupture of membranes with timed delivery at 28 to 32 weeks' gestation, such intervention could result in more neonatal mortality from respiratory distress syndrome than would have occurred from infection.[68] Consequently, many clinicians have managed this problem with passive expectant strategies, including bed rest, observation, and avoidance of pelvic examinations.[69] Outcomes with expectant management, however, are not always ideal either, as seen in Major and Kitzmiller's study[70] of 70 women who had premature rupture of membranes at a mean gestation of 23.7 weeks. Here, treatment consisted of hospitalization, bed rest, antibiotics for patients with clinical evidence of amnionitis, and tocolytic agents for women who developed regular contractions. Outcomes of this management included a mean latency period of 12 days, perinatal survival of 63 percent, respiratory distress syndrome in 52 percent, and amnionitis in 43 percent.

Recognizing the risk of infectious morbidity and mortality in infants born to women with preterm premature rupture of membranes, several investigators have sought to determine whether more active management with prophylactic antibiotics would improve outcomes. A 1963 investigation of nearly 2000 women with premature rupture of membranes (including both preterm and term gestations) randomized participants to receive either oral demethylchlortetracycline or placebo from the time of diagnosis to the 3rd postpartum day. Although the treatment group showed no reduction in perinatal mortality, the mothers in this group had a decreased rate of endometritis, parametritis, and postpartum pyelonephritis. This benefit was noted despite the relatively low dose of oral tetracycline — 150 mg twice a day prescribed to women in the treatment group.[71]

In a 1988 study of women with preterm premature rupture of membranes by Amon, et al.,[72] 82 participants were managed expectantly and randomly assigned either to receive ampicillin prophylaxis or not to receive antibiotics. For women who received ampicillin, the risk of delivery and the rate of neonatal infection were lower. A similar study of 165 women with preterm premature rupture of membranes found that ampicillin prophylaxis decreased the rate of chorioamnionitis and neonatal sepsis; however, this reduction in maternal and neonatal infections was limited to those patients who were colonized with group B streptococci.[73]

Another broad-spectrum penicillin — mezlocillin — was tested in a recent prospective randomized double-blind study of 85 women with premature rupture of membranes having an average gestational age of 29 weeks. Forty women received intravenous mezlocillin for 48 hours followed by oral ampicillin until delivery, and 45 women received intravenous and oral placebo. Results showed that the treatment group had an increased latency period (time from ruptured membranes to delivery) of 8.25 days compared with 3.82 days, a reduced frequency of chorioamnionitis (8 versus 36 percent) and endometritis-myometritis (12 versus 33 percent), and improved neonatal outcomes, including reduced

sepsis, respiratory distress syndrome, intraventricular hemorrhage, mortality, and prolonged hospitalization.[74]

Third-generation cephalosporins also have been used for the management of preterm premature rupture of membranes. Fortunato and colleagues[75] studied ceftizoxime, which, although perhaps less effective against group B streptococcus, has the advantages of a broad spectrum of activity and the capability of achieving high concentrations in fetal blood and amniotic fluid. Based on these characteristics, they tested ceftizoxime along with three other antibiotics — cefoxitin, cefazolin, and ampicillin — in a group of 112 women with prematurely ruptured membranes and a mean gestational age of 31 to 33 weeks. When the 55 women in the treatment group were compared with 57 control women, the treatment group showed a longer mean latent phase (7.34 days versus 1.86 days). There was also a trend toward a lower rate of neonatal infections in the treatment group. Although there were no differences in the length of latent phase between the small groups of patients treated with different antibiotics, postpartum ceftizoxime appeared to be more effective than the other antibiotics in preventing postnatal infections.[69]

Based on their experience, Fortunato, et al.[75] proposed a protocol for managing preterm premature ruptured membranes that consisted of obtaining cervical cultures, monitoring the mother and infant carefully for evidence of infection and fetal well-being, and administering prophylactic antibiotics (they used ceftizoxime) to all women and tocolytics to women with evidence of labor. In this protocol, on-going evaluation of the fetus called for twice-weekly assessment of amniotic fluid volume by ultrasound: if fluid was absent, delivery or termination of the pregnancy was discussed.[69] Other investigators also have emphasized the importance of residual amniotic fluid in pregnancies complicated by premature rupture of membranes.[76]

The management of women with preterm premature rupture of membranes and concomitant group B streptococcal infections is of particular interest. As noted earlier, group B streptococcal infections pose a greater risk to infants born prematurely or whose mothers have a history of premature rupture of membranes.[62] Yet the time required to determine group B streptococcal status in women who are admitted with preterm labor or premature rupture of membranes can impair effective treatment. For many, culture results are not known until after delivery. Newton and Clark[77] reviewed 140 cases of preterm delivery complicated by premature rupture of membranes and found that, of 16 women with positive group B streptococcal cultures, only 4 remained asymptomatic and had latent periods long enough for the results of cultures obtained on admission to be available. They concluded that group B streptococcus greatly complicates the conservative management of preterm premature rupture of membranes and that the effectiveness of intrapartum prophylactic ampicillin could be compromised by waiting for culture results.

Techniques to avoid treatment delays in women with group B streptococcal infections have been suggested by other investigators. Boyer and Gotoff[62] obtained group B streptococcal cultures prenatally and subsequently treated culture-positive women who were admitted to the hospital with preterm labor or prolonged rupture of membranes. As described earlier, this treatment resulted in lower rates of neonatal bacteremia, but it is likely that, with the transient nature of this organism, some culture-negative women were treated and others who became colonized after being cultured remained untreated.

Minkoff and Mead[78] have suggested a less costly strategy based on current culture status. They advise that cultures for group B streptococcus should be obtained for all patients admitted in preterm labor or with preterm premature rupture of membranes. If labor is suppressed with tocolytics, antibiotic therapy could be delayed until culture results are known; if labor cannot be inhibited, antibiotics should be given until a negative culture result is seen. Patients whose cultures are positive should receive 2 g of ampicillin every 6 hours for 24 hours, then 500 mg orally every 6 hours for 2 weeks or through the time of delivery if this occurs before 2 weeks. Other investigators have broadened this recommendation to include prophylactic antibiotic treatment for all women with either premature labor or premature rupture of membranes (with or without labor) until culture results are known[79] or regardless of culture results.[69]

Given the high rate of infection in women with preterm premature rupture of membranes and

the positive outcome found in preliminary studies testing early treatment with antibiotics, it appears that prophylactic antibiotics can be useful in delaying delivery and improving neonatal outcomes in women with preterm premature rupture of membranes. Larger studies should be conducted, however, to confirm these findings and to determine which antibiotics should be used.

Women with preterm premature rupture of membranes also probably benefit from the use of corticosteroids. Data from seven trials consisting of 901 women with preterm premature rupture of membranes showed that corticosteroids reduced the risk of respiratory distress syndrome by a degree similar to that observed among infants of all corticosteroid-treated mothers without greatly increasing the rate of neonatal infection. Nevertheless, the authors cautioned that corticosteroid administration was more likely to increase the occurrence of neonatal infection than decrease it.[57]

Not included in the analysis by Crawley, et al.[57] were the results from a recent prospective study by Morales, et al.,[73] which also showed a positive effect of antenatal steroid treatment in women with premature rupture of membranes. In this study, 165 women at less than 34 weeks' gestation with premature rupture of membranes were randomized to one of four groups: no treatment, steroids only, ampicillin only, and steroids plus ampicillin. Infants born to mothers who had received antenatal steroids showed a reduction in the rate of respiratory distress syndrome (26 versus 53 percent), bronchopulmonary dysplasia (9 versus 23 percent), severe grades of intracranial hemorrhage (3 versus 15 percent), and patent ductus arteriosus (6 versus 18 percent). Survival was highest in the group that received both steroids and antibiotics.

Thus, the advantage of antenatal steroid treatment given to infants born prematurely appears to hold even in the face of prematurely ruptured membranes. Although there may be a trend toward increased maternal and neonatal infections with steroid therapy, this disadvantage is outweighed by improved respiratory tract outcomes, as seen by the persistent gains in perinatal survival. Furthermore, antenatal steroid therapy has not produced delayed problems in surviving children; i.e., physical, motor, or developmental deficiencies within the first 3 years of life.[80]

A Preterm Birth Prevention and Management Protocol

This two-part review on preterm labor presented here and in the preceding article[1] has synthesized important information about causative factors, effective diagnostic techniques, and the pharmacological management of preterm labor. To implement the conclusions drawn throughout this review, a management protocol is proposed in Figure 1. The first step in this protocol is to assess the presence of risk factors for preterm labor: it is recommended that all pregnant women be scored for their risk of preterm labor at the first prenatal visit and that measures be taken to reduce risks whenever possible. The initial assessment should also include screening for syphilis, gonorrhea, *Chlamydia*, bacterial vaginosis, and bacteriuria; diagnosed infections should then be appropriately treated. Early screening and treatment of group B streptococcal infections could also be beneficial, although further studies are needed to assess the benefit of screening all pregnant women for this pathogen. In addition, all expectant mothers should be educated about the signs and symptoms of preterm labor — for example, back or abdominal pains, pelvic pressure, or palpable contractions — and should be instructed to report such symptoms immediately. Subsequent prenatal visits should include a review of any symptoms potentially related to preterm labor as well as a cervical examination.

Women who are at high risk for preterm labor should be enrolled in a preterm birth prevention program that includes daily home uterine monitoring with nurse contacts and more frequent prenatal visits, beginning at 24 weeks' gestation or earlier, if necessary. Attempts should again be made to reduce risk factors, such as those related to work, infections, nutrition, smoking, or drug use.

When preterm labor is suspected or diagnosed, the patient should be hospitalized, prescribed bed rest, and monitored for uterine activity and fetal well-being. In addition, tests again should be conducted for gonorrhea, *Chlamydia*, bacterial vaginosis, urine infection, group B streptococcus, and if indicated, recent drug use. Preterm labor, as documented by regular uterine contractions and cervical changes, should be treated with parenteral tocolytic agents and possibly antibiotics. If labor is suppressed, the patient can be switched to

oral tocolytic medications and, if stable, discharged to her home with limited activity, daily home monitoring, and advice to avoid sexual stimulation.

If labor is not suppressed with tocolytic therapy, antibiotics should be administered to cover potential group B streptococcus and other infections, at least until culture results are known. In addition, women who are 34 weeks' gestation or less should receive corticosteroids to reduce the risk of neonatal respiratory distress, and their infants should be delivered in a facility that provides high-risk neonatal services. One investigator has reported that predelivery transfers of such women to perinatal centers is associated with a 30 percent reduction in fetal mortality.[14]

Women with preterm premature rupture of membranes, which often results in preterm labor, should also have cervical specimens cultured for infections. Compared with women who experience idiopathic preterm labor, women with preterm premature rupture of membranes can derive even greater benefit from prophylactic antibiotics, and early studies have suggested both maternal and neonatal benefits from routine administration of antibiotics. These pregnancies also likely benefit from tocolytic and corticosteroid therapy. It is important that health care workers do not iatrogenically increase the risk of infection for patients with premature rupture of membranes. Therefore, it is recommended that the initial assessment include a sterile speculum examination and that digital examinations be postponed until labor begins.

Although this review provides important information about effective management strategies for preterm labor, additional research is needed to clarify several issues. First, a better understanding of the etiology of preterm labor is needed, so that treatments can focus more directly on causes rather than cures. Once etiologic factors are more fully understood, risk-scoring systems should be adapted to include

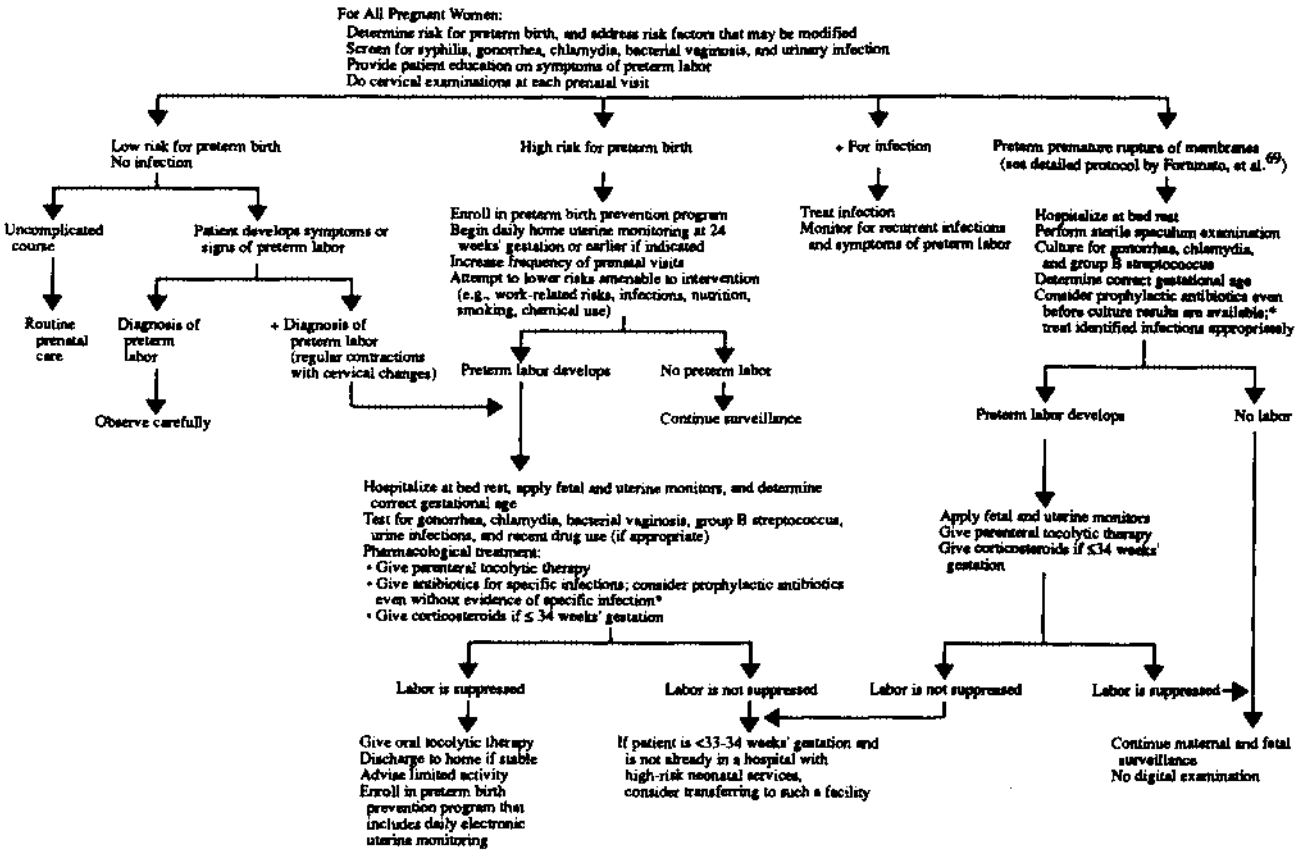

Figure 1. Preterm birth prevention and management protocol.
***Controversial management strategies that require further study.**

these factors. Sensitive risk-scoring systems would enable clinicians to select more accurately those women who are truly at risk for preterm labor. Additional research is also needed on risk reduction; for example, which smoking cessation or drug treatment programs are most effective for pregnant women? How should work characteristics be modified to reduce the risk of preterm birth to pregnant workers? Which nutritional substances are most important in preventing preterm births? Finally, more information is needed on the pharmacologic treatment of preterm labor. Larger studies are needed that address the role of antibiotics in both idiopathic preterm labor and preterm labor secondary to premature rupture of membranes. Other studies should address the optimal duration of tocolytic therapy.

Preterm births are a major problem for the health care profession, for the economy, and for families and individuals in this country. It is important that researchers, educators, clinicians, and society as a whole work together to address comprehensively the problems associated with preterm labor and delivery.

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