

# Premature Labor, Part I: Risk Assessment, Etiologic Factors, And Diagnosis

Dwenda K. Gjerdingen, M.D.

**Abstract: Background:** This paper, the first of a two-part series on premature labor, reviews the recent literature on the causes of and risk factors for preterm labor and methods of diagnosis.

**Methods:** A review of the literature on risk determination and diagnosis of preterm labor was conducted by searching MEDLINE files from 1983 to the present, using the key terms "preterm labor," "premature labor," "preterm labor and infection," and "uterine monitoring." Additional references were accessed by cross-referencing the bibliographies of the articles obtained through this search.

**Results and Conclusions:** Risk factors for preterm labor, which include items related to the pregnant woman's demographic characteristics, history, daily habits, and current pregnancy, have been combined into scoring systems commonly used by clinicians and researchers to single out women at risk for preterm delivery. When such systems are tested in obstetric populations, results show variable success in predicting preterm labor or birth. These inconsistent results could be due, in part, to important factors that have often been omitted from scoring systems, such as chemical abuse, poor nutrition, little social support, demanding work, multiple sexual partners, past or current sexually transmitted diseases, and other gynecologic infections. Women who are considered high risk for preterm labor can benefit from participating in preterm birth prevention programs that incorporate home monitoring, patient education regarding the signs and symptoms of preterm labor, frequent contacts with health professionals, and cervical examinations. (J Am Board Fam Pract 1992; 5:495-509.)

It has been said that spontaneous preterm delivery is the most important problem facing providers of obstetric care in the early 1990s.<sup>1</sup> Despite recent advances in perinatal medicine, the incidence of preterm births, usually defined as births occurring before 37 weeks' gestation, has climbed from 8.9 percent in 1980 to 10 percent in 1986.<sup>2</sup> This 10 percent sample of births contributes more than 60 percent of perinatal morbidity and mortality.<sup>3</sup> The cost of this problem is enormous; in fact, neonatal intensive care is said to be the most expensive service in our health care delivery system today.<sup>2</sup> Added to the immediate intensive care costs are the long-term custodial costs that are required for many premature children who have neurodevelopmental handicaps. Even more overwhelming than the financial costs are the unmeasured per-

sonal costs that premature birth can bring to affected children and their families.

That our problems with preterm labor are increasing in spite of sophisticated technology is worrisome, and this increase can be attributed to some key issues. First of all, our understanding of preterm labor itself is incomplete; at a very basic level we are unable to agree on a standard definition for preterm labor. Consequently, many definitions have been offered that vary in terms of gestational age, frequency of contractions, and presence or degree of cervical changes.<sup>4-7</sup> Universal criteria for the diagnosis of preterm labor have been recommended, however, and include the following:<sup>8</sup>

- Gestation 20 to 37 weeks
- Documented uterine contractions (four in 20 minutes or eight in 60 minutes)
- Either ruptured membranes or intact membranes with one of the following: (1) documented cervical change by a single examiner, (2) cervical effacement greater than 75 percent, or (3) cervical dilatation greater than 2 cm.

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

Although this definition provides a useful framework for our discussion about preterm labor, it is limited in that it can miss the early stages of labor in some patients.

A second key problem that impedes our progress with preterm births is our limited knowledge of the etiology and pathophysiology of preterm labor. Because of these limitations, our efforts with preterm births have focused more on cure rather than prevention. Though we are gaining some understanding of causative factors, often these factors represent major societal problems that are difficult for the clinician to manage. For example, we are beginning to appreciate the growing role of recreational drugs and infectious diseases — including sexually transmitted diseases — in preterm labor. The recognition of such problems, complicated as they can be, is key to improving our preterm birth rate.

The purpose of this paper is to review reports published in the recent medical literature on preterm labor focusing on the recognition of factors that can predispose women to preterm birth, the importance of early diagnosis of preterm labor, and techniques for achieving early diagnosis.

## Methods

A review of the literature on risk determination and diagnosis of preterm labor was conducted by searching MEDLINE files from 1983 to the present, using the key terms "preterm labor," "premature labor," "preterm labor and infection," and "uterine monitoring." Additional references were accessed by cross-referencing the bibliographies of the articles obtained through this search.

## Etiology and Risk for Preterm Birth

Critical to the proper diagnosis and management of preterm labor is an understanding of the etiology of this problem. In a 1982 study of 355 premature infants, the cause of preterm birth was attributed to maternal or fetal complications in 35 percent of cases. These complications included multiple gestation, hypertension, abruptio placentae, congenital malformations, placenta previa, incompetent cervix, and other miscellaneous conditions. The remainder of preterm births were due to prematurely ruptured membranes (35 percent) and idiopathic preterm labor (30 percent).<sup>9</sup>

Several of the known causes of preterm birth, together with other demographic, socio-

economic, and medical factors that are either directly or indirectly related to preterm births, have been mathematically evaluated to determine their relative contribution to a woman's risk for premature labor. As a result, risk-scoring systems have been developed to aid clinicians in prospectively distinguishing women who are more prone to give birth to premature infants. Perhaps the most widely used risk-scoring system in this country is that developed by Creasy and colleagues,<sup>10</sup> which is a modification of the Papiernik-Berkhauer system. Specific variables used in the Creasy, et al. system include age; height; weight; marital, socioeconomic, and employment statuses; number of children; heavy work; a long and tiring trip; smoking; short interpregnancy interval; complications of the current pregnancy; cervical dilatation or effacement; uterine irritability; and a history of abortions, pyelonephritis, uterine anomalies, diethylstilbesterol exposure, and premature delivery. When this system was tested on 966 pregnant patients registered at a New Zealand hospital, 9 to 13 percent of the population fell into the high-risk group, which predicted 64 percent of all preterm births.<sup>10</sup>

Tests of the Creasy, et al. risk-scoring system by other investigators have not had the same results. In a study of 380 inner-city California women by Main, et al.,<sup>11</sup> less than one-half of the preterm deliveries (30 of 62) came from the high-risk group. The Creasy, et al. system used with a black inner-city population failed to distinguish at-risk patients, even after adjusting the score cutoff and reweighting factors with discriminate analysis.<sup>12</sup> Disappointing results were also seen in two large indigent populations that were part of the March of Dimes Multicenter Preterm Birth Prevention project. Here, risk scores based on modifications of the Creasy, et al. system showed that positive predictive values were only 16 percent and 18 percent.<sup>13,14</sup>

Other risk-scoring systems have been developed since that of Creasy, et al. Holbrook, et al. tested their modification of the Creasy, et al. system on 7329 women from a university clinic in San Francisco, and 18 risk factors yielded a high-risk group of 14 percent, with a sensitivity of 41 percent.<sup>15</sup>

Ross and colleagues<sup>16</sup> more recently developed a risk-scoring system for prematurity using linear logistic regression; 22 risk factors were selected,

18 of which individually would qualify a woman as high risk for preterm birth, and the remaining 4 of which, when used as pairs, would place her at high risk. When this system was used on 8240 patients from a primarily Hispanic population, it had a 55.6 percent sensitivity and a 68.4 percent specificity for picking out women who would give birth to a premature infant. The following items were included in the Ross, et al. system but not in that of Creasy, et al: a history of neonatal death, classic Cesarean section or myomectomy, chronic hypertension, renal disease, marijuana or narcotic abuse, psychiatric hospitalization, and with the current pregnancy, size-date discrepancy, severe anemia, and preeclampsia.

Higher sensitivity rates have been reported for a risk-scoring system developed in Finland. Hakala and Ylikorkala<sup>17</sup> constructed a scale of 13 factors that predicted 22 percent of women to be high risk; 65 percent of preterm deliveries came from this group. Although most of these 13 factors were similar to those seen in the Creasy, et al. system, four were unique: primiparity, late admission to antenatal care, abnormal growth of the fetus or uterus, and previous fetal or neonatal loss.

An advantage of the Ross, et al. system over the systems developed by Creasy, et al. and Hakala and Ylikorkala is its inclusion of marijuana and narcotic abuse. The observation by Ross, et al. that chemical use was significantly associated with prematurity is not surprising and has been noted by other investigators as well. In a recent study comparing 137 drug-using women with 123 controls (women selected from a general obstetric population registry, matched for demographic variables, tobacco use, and medical complications), drug-using women had a higher rate of preterm deliveries (23 percent versus 7 percent), and their infants had lower birth weights (2910 g versus 3309 g).<sup>18</sup> Another investigation found higher rates of positive results on urine screening for toxic substances in 141 patients in preterm labor than in 108 patients experiencing uncomplicated labor at term: 17.0 percent versus 2.8 percent.<sup>19</sup>

Unfortunately, the problem of chemical abuse by pregnant women appears to be increasing rapidly. A Minnesota hospital trade group reported that the number of addicted newborns in the group rose from 79 in 1987 to 198 in the following year, representing an increase of 150 percent

in 1 year.<sup>20</sup> Recognizing the increasing rate of drug use among pregnant women and that chemical use is related to preterm birth, it seems likely that prenatal chemical use is one reason for the increasing rate of prematurity. While the growing crisis of chemical abuse during pregnancy needs to be addressed by society at large, clinicians could reduce the impact of this problem by recognizing expectant mothers' use of drugs, increasing prenatal surveillance of drug users, and encouraging participation in chemical dependency and preterm birth prevention programs.

Information about the probability of preterm birth associated with various risk factors has been compiled from several investigations,<sup>2,14,16,17,21,22</sup> and is displayed in Table 1. It is important to recognize that when two or more factors are combined, the risk for preterm birth can increase substantially. For example, Roberts, et al.<sup>22</sup> reported that the women who are smokers and pregnant with twins have nearly twice the rate of preterm delivery as nonsmokers with twins: 63 percent versus 32 percent.

Although Table 1 lists several important risks not included in the earliest risk-scoring systems, not all pertinent variables are addressed. Potentially important missing items include number of sexual partners, diagnosis of a sexually transmitted disease, nutrition, social support, and a job that demands long hours or prolonged periods of standing. Such missing factors could be one reason that approximately one-half of preterm births occur in women who are not thought to be at risk. Certainly more work is needed to develop and refine systems that select for women who are susceptible to preterm delivery. Future investigation of risk-scoring systems should pay particular attention to various obstetric and gynecologic infections, as there is mounting evidence that infection could be responsible for a significant proportion of preterm labors.<sup>23,24</sup>

### ***The Role of Infection in Preterm Labor***

The importance of infection in preterm labor is substantiated by recent biochemical and clinical research. Takahashi and colleagues<sup>25,26</sup> demonstrated that bacterial products, including endotoxin, stimulate endogenous phospholipase A<sub>2</sub> by a receptor-mediated mechanism, resulting in liberation of arachidonic acid and prostaglandin formation. The prostaglandins in turn initiate and



Table 1. Risk Factors for Preterm Birth.

Risk Factors	Odds Ratio	Percent Who Have Preterm Delivery
<b>Demographic</b>		
Age (more than 35 years)	1.4 <sup>17</sup>	
Lower class	1.2 <sup>17</sup>	
Single parent	1.4 <sup>17</sup>	9 <sup>14</sup>
Black		10 <sup>14</sup>
<b>History</b>		
Previous preterm delivery	2.5 <sup>16</sup> -3.6 <sup>17,21</sup>	23 <sup>14</sup> -30 <sup>22</sup>
Two or more previous preterm deliveries		32 <sup>22</sup> -> 70 <sup>2</sup>
Previous preterm delivery with premature rupture of membranes		29 <sup>14</sup>
Previous induced abortion	1.3 <sup>16</sup>	
Two or more abortions	1.4 <sup>17</sup>	
Three or more abortions	2.9 <sup>21</sup>	
Second trimester abortions		14 <sup>14</sup>
Habitual abortions	2.2 <sup>16</sup>	
Previous pregnancy loss	1.3 <sup>16</sup> -1.6 <sup>17</sup>	
Classic Cesarean section	1.6 <sup>16</sup>	
Previous myomectomy	22.8 <sup>16</sup>	
Chronic hypertension	1.8 <sup>16</sup>	
Urinary tract infection	1.1 <sup>16</sup>	
Renal disease	2.1 <sup>16</sup>	
Psychiatric hospitalization	1.4 <sup>16</sup>	
<b>Daily Habits</b>		
Smoking	1.3 <sup>17</sup> -1.4 <sup>16</sup>	
Marijuana abuse	2.1 <sup>16</sup>	
Narcotic abuse	1.9 <sup>16</sup>	
<b>Current Pregnancy</b>		
Primiparity	1.3 <sup>17</sup>	
Preterm contractions, uterine irritability	3.5 <sup>17</sup>	25 <sup>2</sup> -35 <sup>14</sup>
Preterm labor after tocolysis		70 <sup>2</sup>
Twin gestation		36 <sup>22</sup> -50 <sup>2</sup>
Bleeding after 20 weeks	5.3 <sup>16</sup>	
Threatened abortion	4.1 <sup>16</sup>	
Late admission to prenatal care	2.0 <sup>17</sup>	
Size-date discrepancy	1.4 <sup>16</sup> -1.7 <sup>17</sup>	
Large uterine myoma, hydramnios		15-25 <sup>2</sup>
Uterine septae, DES with lesion		20-30 <sup>2</sup>
Incompetent cervix	12.5 <sup>16</sup>	17 <sup>22</sup> -25 <sup>2</sup>
Cervical length less than 1 cm (before 28 weeks' gestation)		50 <sup>14</sup>
Cervical dilatation without labor (more than 1 cm)		20 <sup>2</sup>
Gravida 5-8		12 <sup>14</sup>
Gravida 9 or more		32 <sup>14</sup>
Severe anemia	2.2 <sup>16</sup>	
Surgery requiring hospitalization	1.9 <sup>16</sup>	
Preeclampsia, mild	1.7 <sup>16</sup>	
Prenatal treatment or urinary tract infection	2.0 <sup>21</sup>	
Prenatal treatment of nonyeast vaginitis	1.8 <sup>21</sup>	

Note: results are presented either as an odds ratio or as percentage of women who will develop preterm labor, depending on the statistics provided in the individual references.

DES = diethylstilbestrol.

maintain labor. Evidence supporting the role of prostaglandins in infection-induced preterm labor is also found in a recent study by van der Elst and colleagues,<sup>27</sup> in which increased prostaglandin products were found in the membranes and placentas of patients with chorioamnionitis who had been delivered of their infants preterm. It is also hypothesized that neutrophils and their constituent enzymes, together with bacteria and their proteases, can weaken the amniochorion, thereby predisposing to premature rupture of membranes.<sup>28</sup>

The prevalence of positive amniotic fluid cultures in women in labor with intact membranes ranges from 3 percent to 48 percent.<sup>29-36</sup> This wide range of frequency could be due to differences in sample characteristics or methods. For example, most studies of preterm labor include only patients with cervical changes; however, in Weible and Randall's study<sup>29</sup> showing a positive amniotic fluid culture rate of only 3 percent, one-fifth of the women had no documentation of cervical dilatation or effacement. Similarly, the inclusion criteria for Duff and Kopelman's study,<sup>30</sup> which reported a 4 percent positive culture rate, did not require participants to show cervical changes, so it is questionable whether all of these women were truly in labor.

Women with positive amniotic fluid cultures constitute only a subset of those whose pregnancy is affected by infections. When other markers for infection are considered, the relation between preterm labor and infection appears even stronger. Cammu, et al.<sup>37</sup> studied the prevalence of infection in spontaneous preterm labor by conducting histological examinations of placentas from 66 women with uncomplicated preterm labor and 66 women with uncomplicated labor at term. The rate of infection was significantly higher for the preterm labor group — 62 percent, compared with 12 percent. Cammu, et al. also looked at C-reactive protein as a marker for infection, and although it was found to be positive in 92 percent of women who had preterm deliveries and histological evidence of infection, its low sensitivity in this study — 57 percent — suggests that this marker may have limited clinical usefulness for diagnosing intrauterine infections. Gas-liquid chromatography of amniotic fluid samples has also been used to discover infections in women in preterm labor whose traditional microbiologic amniotic cultures were negative.<sup>38</sup> These findings

might be explained by extra-amniotic infections whose bacterial byproducts invade the amniotic fluid.

### **The Relation of Specific Infections to Preterm Labor**

Several specific infections of the cervix and vagina have been associated with preterm labor, including bacterial vaginosis,<sup>21,31,39-43</sup> *Bacteroides* species,<sup>44,45</sup> *Candida albicans*,<sup>31,32,46</sup> *Chlamydia trachomatis*,<sup>39,43,47-49</sup> *Fusobacterium* species,<sup>35</sup> group B streptococci,<sup>39,50,51</sup> *Mobiluncus* species,<sup>21</sup> *Mycoplasma hominis*,<sup>21,35,52</sup> *Neisseria gonorrhoeae*,<sup>39,53,54</sup> *Staphylococcus aureus*,<sup>21</sup> *Trichomonas vaginalis*,<sup>39</sup> and *Ureaplasma urealyticum*.<sup>35,39,44,52</sup>

Clinicians and researchers do not completely agree about which microbial agents are definitely associated with preterm labor. Two smaller studies, for example, showed no association between preterm labor and infections with group B streptococcus, *Gardnerella vaginalis*, or *Mycoplasma hominis*.<sup>31,44</sup> The absence of such associations could have been due to the relatively small number of preterm labor patients in these studies (n = 35,54). Recent debate about the importance of individual pathogens in preterm labor has centered on a few organisms: *Chlamydia*, group B streptococcus, and mycoplasmas (including *Ureaplasma urealyticum*).

### **Chlamydia**

The reported significance of *Chlamydia* in preterm labor varies among studies. In a prospective investigation of 268 women examined before 19 weeks' gestation by Martin, et al.<sup>47</sup> 18 (6.7 percent) women had cervical cultures positive for *Chlamydia trachomatis*. Infected women had a greater frequency of preterm births (28 percent versus 6 percent) and higher stillbirth or neonatal death rates (33 percent versus 3.4 percent).

Although some conflicting information is found with larger studies, the weight of evidence points to an association between chlamydial infections and preterm births. Heggie, et al.<sup>55</sup> prospectively studied 215 women who had endocervical cultures positive for *Chlamydia* during their pregnancies. When these women were compared with matched controls, no differences were found in the frequencies of premature birth, premature rupture of membranes, or neonatal death. In a study by Sweet, et al.<sup>56</sup> of 270 pregnant

women with endocervical cultures positive for *Chlamydia trachomatis* compared with 270 matched controls, no significant differences were noted between groups for premature rupture of the membranes, preterm delivery, amnionitis, intrapartum fever, small-for-gestational-age infants, postpartum endometritis, or neonatal sepsis. For the subset of women with recent or invasive chlamydial infection, as indicated by the presence of IgM antibodies, however, the rate of preterm delivery was higher than for controls: 19 percent versus 8 percent. Similarly, Harrison, et al.<sup>57</sup> found that IgM-seropositive *C. trachomatis*-infected women had more low-birth-weight infants and more premature rupture of membranes than either IgM-negative or culture-negative women. Gravett, et al.<sup>43</sup> examined the effects of *Chlamydia* and bacterial vaginosis on obstetric and neonatal outcomes in 534 gravid women and found that *Chlamydia* infections were independently associated with preterm labor, preterm premature rupture of membranes, and low birth weight.

A sixth study considered the importance of women's variable responses to treatment by comparing three groups of women: 244 who were successfully treated for *Chlamydia*, 79 who failed to respond to treatment, and 244 *Chlamydia*-free control women who were not treated, but were at high risk for chlamydial infection. The successfully treated women, compared with those who failed treatment, showed improvements in the rate of premature delivery, premature rupture of membranes, and small-for-gestational-age infants. The successfully treated women also had significantly fewer preterm deliveries than the controls.<sup>48</sup>

Thus, it appears that prenatal chlamydial infections can contribute to preterm deliveries. Further, antepartum chlamydial infections are important because of their potential adverse effects on the newborn. For infants born through *Chlamydia*-infected birth canals, the risk of developing inclusion conjunctivitis ranges from 18 to 50 percent, the risk of nasopharyngeal infection from 15 to 20 percent, and the risk of pneumonia from 11 to 18 percent.<sup>56</sup> Continued antenatal screening and treatment of chlamydial infections is therefore advised.

### **Group B Streptococcus**

A review of seven studies of genital colonization with group B streptococcus by Romero, et al.<sup>58</sup> did not show strong evidence of an association

between prematurity and group B streptococcal colonization. Four of these studies,<sup>39,44,52,59</sup> however, were of questionable value because of their small size, only 23 to 32 women with positive cultures. Of the three larger studies, two looked at more than 400 women with positive group B streptococcal cultures and found no differences in rates of prematurity between women with positive group B streptococcus cultures and those with negative cultures.<sup>56,60</sup> The largest of the studies reviewed was a prospective cross-sectional study of 6706 women whose cultures for group B streptococcus were done shortly after their admission to the hospital for delivery. Compared with women with negative cultures, the women with positive cultures had a higher frequency of prematurely ruptured membranes (15.3 percent versus 8.1 percent) and preterm delivery (5.4 percent versus 1.8 percent).<sup>50</sup>

Two more recent intermediate-sized studies not included in the review by Romero, et al. also showed conflicting results. In a study of 1050 pregnant women by Motorras, et al.,<sup>61</sup> 121 were colonized with group B streptococcus at some time between the 17th and 42nd weeks of gestation. Positive cultures were associated with a higher rate of premature rupture of membranes but not with preterm delivery. The characteristics of this patient population, however, were atypical and could have blurred some distinctions between culture-positive and culture-negative groups: 69 percent were admitted to the hospital because "they represented some type of pathology."<sup>61</sup> In a prospective study of 692 consecutive pregnant women by McDonald, et al.,<sup>51</sup> the 91 (13.2 percent) women who were colonized with group B streptococcus at 24 weeks' gestation had a higher rate of both preterm labor (18.7 percent versus 5.5 percent) and premature rupture of membranes (9.9 percent versus 2.7 percent). Unlike previous investigations, this study documented most factors known to place women at risk for preterm labor or premature ruptured membranes and found that, even if women with these risk factors were excluded, the significant findings persisted. Although the studies on group B streptococcus and preterm labor have reported conflicting results, the significant outcomes seen in two of the studies — one with a very large population, and the second with controls for other risk factors — suggest that group B streptococcus

might have a significant though modest effect on preterm labor. Additional well-designed studies are needed to substantiate this finding.

Regardless of the role of group B streptococcus in preterm labor, this pathogen, like *Chlamydia*, is important because of its potential effects on the premature infant. Group B streptococcus is seen in up to 30 percent of expectant mothers, and 50 to 70 percent of affected women will give birth to infants who will be colonized.<sup>62</sup> Although only 1 percent of colonized infants become septic overall, the attack rate is much higher for preterm infants. This risk is compounded by the presence of premature or prolonged ruptured membranes: group B streptococcal sepsis occurs 7.2 times more often in infants born more than 18 hours after ruptured membranes than in those born less than 6 hours after ruptured membranes.<sup>63</sup> The increased rate of sepsis seen in these infants is reflected in their higher mortality rates, which approach up to 90 percent for preterm infected infants.<sup>62</sup>

#### *Mycoplasmas*

Support for the role of mycoplasmas in preterm labor comes from the Romero, et al.<sup>35</sup> study of 24 women with positive amniotic fluid cultures in preterm labor, in which two of the three most frequently isolated organisms were *Mycoplasma* species: *Ureaplasma urealyticum* (n = 6) and *Mycoplasma hominis* (n = 4). These two organisms were also linked with preterm labor in the Lamont, et al.<sup>52</sup> study comparing 72 women who had spontaneous preterm labor with 26 controls who had elective Cesarean sections at the same gestational age. Here, the respective frequencies of positive cultures in the study and control groups were 24 percent and 8 percent for *M. hominis*, and 80 percent and 46 percent for *U. urealyticum*. McGregor, et al.<sup>21</sup> also found a higher rate of *M. hominis* colonization in women with preterm (38 percent) versus term (9 percent) deliveries; however, the numbers in this study were small — only 9 women had preterm births.

Larger studies do not find the mycoplasmas to be important in preterm labor or delivery. Naessens and colleagues<sup>64</sup> examined placentas from 511 consecutive women who gave birth to infants of at least 26 weeks' gestation, and in the 153 patients whose placentas were culture-positive for mycoplasma, no adverse effects were



seen on gestational age or maternal and infant health. Similarly, in a recent study of nearly 5000 women, in which 65.9 percent of women were found to be colonized with *U. urealyticum* in mid-pregnancy, the presence of this organism did not appear to be associated with preterm labor or delivery.<sup>65</sup> Finally, in a recent analysis of nine cohort studies (none of which was previously discussed in this section), Romero, et al.<sup>66</sup> examined the association between genital mycoplasma infections and prematurity; they concluded that the weight of evidence did not support an association between genital colonization with *Mycoplasma* species and prematurity or low birth weight.

### *Bacterial Vaginosis*

While the controversy over the role of group B streptococcus and mycoplasmas in preterm labor continues, investigators generally agree on the relation of bacterial vaginosis to preterm labor. Bacterial vaginosis is one of the most frequent vaginal infections seen in sexually active women, and its prevalence in pregnant women approaches 15 percent to 20 percent.<sup>40</sup> Although this infection is not generally considered to be a serious problem for most women, it can produce complications for those who are pregnant. In Martius and Eschenbach's recent review of bacterial vaginosis and prematurity,<sup>40</sup> bacterial vaginosis was consistently associated with prematurity, and this relation was independent of other selected genital flora. Gravett, et al.<sup>31</sup> found that bacterial vaginosis, as identified by gas-liquid chromatography, occurred in 43 percent of women with "spontaneous" preterm labor, compared with 14 percent of women with term labor. These findings concur with other reports of an association between bacterial vaginosis and preterm labor,<sup>21,39,41-43</sup> and point to the need for antenatal screening and treatment of this disorder.

### *Preterm Premature Rupture of Membranes*

Infection also plays an important role in preterm labor that is secondary to premature rupture of membranes, as seen by the relatively high rates of positive amniotic fluid cultures — 15 to 43 percent — in women with preterm premature rupture of membranes.<sup>67</sup> When histological examination of the placenta has been used to identify intrauterine infection, the rate of infection in women with preterm premature rupture of mem-

branes is at the upper end of this range.<sup>68</sup> A third indicator of the relatively high rate of infection in women with preterm premature rupture of membranes is the frequency of clinically diagnosed chorioamnionitis. In a retrospective study of 70 women with premature rupture of membranes before 26 weeks' gestation who were managed expectantly, amnionitis developed in 43 percent of the women.<sup>69</sup> These high rates of infection can occur as a result of two processes. First, pre-existing infection can weaken the amnion, thus predisposing to premature rupture of membranes; and second, once the membranes are ruptured, infection can ascend from the vagina to the intrauterine space.

### *Nongynecological Infections*

Nongynecological infections, such as those of the urinary or respiratory systems, can also provoke preterm labor. A meta-analysis by Romero, et al.<sup>70</sup> of four cohort studies on bacteriuria and preterm delivery showed that untreated asymptomatic bacteriuria during pregnancy increased the rates of preterm delivery. In this analysis nonbacteriuric patients had about one-half the risk of preterm delivery of those with untreated asymptomatic bacteriuria. Further, antibiotic treatment greatly reduced the chances of having a low-birth-weight infant.

Severe maternal respiratory tract infections pose an even greater threat. In a study of 25 pregnant patients admitted to a Los Angeles hospital in the mid-1980s with a diagnosis of pneumonia, 44 percent of the women developed preterm labor and 36 percent had preterm deliveries. Other complications seen in these pregnancies included one maternal death, one stillbirth, and two neonatal deaths.<sup>71</sup>

In conclusion, infection appears to play an important role in preterm labor and delivery. Specifically, there is evidence that preterm labor is at least related to and likely stimulated by the following maternal infections: *Chlamydia* cervicitis, bacterial vaginosis, urinary tract infections, and severe respiratory infections. Investigations about the role of group B streptococcus and mycoplasmas in preterm labor show conflicting results; however, both group B streptococcus and *Chlamydia*, when left untreated prenatally, can produce mild to serious infections in the newborn.

## **Early Diagnosis of Preterm Labor Birth Prevention Programs**

The early diagnosis of preterm labor is key to its successful management. A growing awareness in the medical community of the importance of early diagnosis prompted the development of preterm birth prevention programs in the 1980s. The first preterm birth prevention programs typically included the following components: risk assessment, frequent prenatal office visits with cervical examinations, patient education about self-detection of contractions, and techniques for preventing preterm births. When such a program was tested on 1150 patients from the University of California, the preterm delivery rate fell from 6.75 percent to 2.43 percent.<sup>72</sup> A similar result was found when a basic preterm birth prevention program was used in a rural practice: the preterm birth rate decreased from 3.2 percent to 1.3 percent.<sup>5</sup> No significant gains in gestational age were seen, however, when such preterm birth prevention strategies were used with approximately 1000 high-risk women from a predominantly black, indigent population.<sup>73</sup> The effectiveness of such programs might be related to the appropriateness of the educational effort to a given population. For example, when a prenatal education videotape in both English and Spanish translations was tested on 615 high-risk patients in the Bronx, women who viewed the videotape demonstrated a significant improvement in knowledge about preterm birth.<sup>74</sup>

### **Home Monitoring**

A recent adjunct to many preterm birth prevention programs is electronic home monitoring. The effectiveness of home-monitoring systems has been tested in several studies<sup>75-83</sup> as outlined in Table 2. Eight of the nine investigations found home uterine monitoring to be associated with fewer preterm births or longer gestations.<sup>75,76,78-83</sup>

While two of the studies showed positive outcomes with monitoring for general high-risk populations,<sup>78,81</sup> several studies showed improvements for unique groups, such as women with twin gestations,<sup>75,80</sup> women who developed preterm labor,<sup>75,76,80,82</sup> and women who were monitored after they had been successfully treated for preterm labor with tocolytics.<sup>79,83</sup> It is noteworthy that three of the studies<sup>76,77,83</sup> were at

least partially funded by Tokos Medical Corporation, a manufacturer of home-monitoring devices, and four of the studies were associated with one group of collaborators,<sup>76,80,81,83</sup> while two were affiliated with another.<sup>78,79</sup>

These studies described similar methods, sampling women at high-risk for preterm delivery who were assigned (usually randomly) to control and experimental groups. Women in the experimental groups were given portable uterine monitors and instructed to record and transmit monitor information for 1 hour or more each day, usually beginning at some point in the second trimester. Both groups were usually instructed in the signs and symptoms of preterm labor and self-palpation of contractions.

Although electronic monitoring has been shown to be superior to self-palpation in the detection of early labor,<sup>84,85</sup> its role in preventing preterm deliveries continues to be debated.<sup>86-89</sup> Part of this debate focuses on methodologic deficiencies of available studies, including inadequate randomization, mishandling of withdrawals, or selecting for analysis only women who actually experience preterm labor.<sup>89</sup> The recent study by Mou and colleagues<sup>82</sup> avoided some of these problems by using a more carefully designed randomization process than most; however, they selected for analysis only those women who eventually developed preterm labor. The 2-week gain in gestational age for the monitored group would have appeared more impressive if it had occurred in the entire population of high-risk women, rather than in the select group of women who experienced preterm labor (statistics for the entire population are not reported). Nevertheless, the gestational and neonatal gains seen in this subgroup should not be overlooked, and the recognition of labor at earlier stages in women who were monitored is an important finding.

Another important question raised in the debate about home monitoring is whether the favorable outcomes often seen with monitored women are due to monitoring as such, or to the frequent nurse contacts that often accompany electronic monitoring. In most of the studies, the monitored women communicated daily with a nurse about the monitor tracings and any symptoms of preterm labor, whereas non-monitored women had contact with health professionals only during routine prenatal visits or



Table 2. Studies That Investigate the Effect of Home Uterine Monitoring on Preterm Births in High-Risk Populations.

Author	Methods	Education	Contact with Health Workers	Results
Dyson, et al. <sup>75</sup> (1991)	247 women were randomized to a home monitor group and an education-palpation group, and 143 were assigned to a standard care group. Of these, 189 were twin gestations and 201 were singleton gestations	The two experimental groups received initial education in the signs and symptoms of labor and were taught self-palpation	Women from the 2 experimental groups were contacted $\geq 5$ d/wk by a nurse	For patients with preterm labor, both experimental groups showed significantly longer gestational ages for singletons and twins at delivery. When the monitored and education groups were compared, monitoring produced better outcomes with twin gestations, but not with singletons
Hill, et al. <sup>76</sup> (1990)	299 women from 4 tertiary care centers were randomly assigned to control and home monitor groups. Analyses were performed on the 98 women who developed preterm labor (55 monitored women and 43 controls)	Both groups received initial education about signs and symptoms of preterm labor and self-palpation. This information was reinforced for controls at each prenatal visit	All patients had prenatal visits every 2 weeks. In addition, home monitor patients had daily nurse contacts	Of women who developed preterm labor, monitored patients experienced a significant increase in early detection of preterm labor, successful tocolysis, and prolongation of pregnancy to term — 58% versus 35% term deliveries
Iams, et al. <sup>77</sup> (1988)	266 women were randomized to an electronic monitor group (n = 184) and an education-palpation group (n = 82), where contractions were palpated and recorded for 1 hour twice daily	Women in the education-palpation group received an initial education session about the signs and symptoms of preterm labor and the self-palpation of contractions	Women in the education-palpation group had nurse contact 5 d/wk, and those in the monitored group had daily nurse contact	There were no significant differences between groups in gestational age or birth weight
Katz, et al. <sup>78</sup> (1986)	The sample consisted of 76 women at risk for preterm labor who received electronic uterine monitoring 3–4 times a day, and 76 controls, who were matched for age, parity, and risk indicators	Instruction about the signs and symptoms of preterm labor and self-monitoring was given to 87% of the monitored group and 82% of controls	Both groups were seen for routine prenatal visits at intervals of 1–4 weeks. In addition, monitored women who developed contractions were contacted	Women in the monitored group had a lower frequency of failed tocolysis (5% versus 25%) and preterm births (59% versus 88%)
Katz, et al. <sup>79</sup> (1986)	Of 120 women who completed an inpatient course of parenteral tocolytic medications for preterm labor, 60 were placed on daily home monitoring, and 60 who served as controls were matched for age, parity, and risk factors. All patients were asked to limit their activity	All patients received instructions about the signs and symptoms of recurrent preterm labor and self-palpation	Verbal feedback about monitor tracings was given to women in the home monitor group	The monitored group had a lower frequency of failed tocolysis and consequently a lower incidence of preterm births (15% versus 34%)

Table 2. continued.

Author	Methods	Education	Contact With Health Workers	Result
Knuppel, et al. <sup>80</sup> (1990)	45 women with twin gestations from 4 centers were randomly assigned to either daily home monitoring and perinatal nursing support (n = 19) or an education group (n = 26). Analyses were conducted on the 30 women who developed preterm labor (14 monitored, 16 controls)	Members of the education group received instruction about the signs and symptoms of preterm labor and about self-palpation	Both groups had scheduled prenatal visits at least every 2 weeks. In addition, women in the monitored group had daily telephone contact with a nurse	The monitored group showed an earlier detection of preterm labor (cervical dilatation at diagnosis = 1.6 versus 2.9 cm), and a lower rate of preterm delivery secondary to failed tocolysis (7% versus 44%)
Morrison, et al. <sup>81</sup> (1987)	Participants were randomly assigned to 2 groups: a uterine activity monitor group (n = 34) and a control group (n = 33)	Both groups were instructed in the signs and symptoms of preterm labor and in self-monitoring techniques	Controls were contacted by telephone at least twice a week, while monitored patients had daily telephone contact with a nurse	A higher proportion of monitored patients had term deliveries (85% versus 55%)
Mou, et al. <sup>82</sup> (1991)	377 women at risk for preterm labor from 3 centers were prospectively and randomly assigned to a high-risk prenatal care group or a prenatal care plus twice-daily monitoring group. Comparisons were made between the 43 monitored women and 39 controls who developed preterm labor	All women received education about the signs and symptoms of preterm labor and about uterine self-palpation	Nursing care, routine visits, and nonroutine visits were similar in both groups. The monitored group did not receive increased nursing support	For the 82 women who developed preterm labor, those in the monitored group had longer gestations (36.6 versus 34.9 wk), less cervical dilatation at diagnosis (1.4 versus 2.5 cm), and infants with greater birth weight, fewer days in intensive care, and fewer requirements for mechanical ventilation
Watson, et al. <sup>83</sup> (1990)	Women who had been successfully treated for preterm labor were randomly assigned to daily home uterine monitoring and nursing support (n = 33) or to a standard-care group (n = 34)	Patients in both groups received initial education on the signs and symptoms of recurrent preterm labor and on self-palpation	Women in the monitored group were contacted daily by a nurse, while controls were asked to contact their physician if they experienced symptoms of preterm labor	The rate of preterm birth was lower in the monitored group (47% versus 84%)

if problems developed. Nurse contact was therefore generally more frequent for the experimental groups, and this effect could have influenced positive outcomes. Only in studies by Iams, et al.<sup>77</sup> and Mou, et al.<sup>82</sup> were nurse contacts between groups similar; while results of Mou, et al. showed significant gains from monitoring, those of Iams, et al. did not.

Three additional investigations<sup>76,90,91</sup> (two of which report from the same database<sup>76,91</sup>) shed some light on the relative importance of monitor-

ing and nurse contacts — as well as office examinations — in preterm birth prevention programs. In these studies women who were at risk for preterm labor were enrolled in preterm birth prevention programs that included patient education about the signs and symptoms of preterm birth, daily home monitoring, daily symptom reporting to nurses, and routine prenatal office visits. The relative contribution of the last three of these procedures toward the diagnosis of preterm labor was found to be 24 to 31 percent for home

**Table 3. Percentage of Identification of Preterm Labor by Various Methods.**

Author	No.	Home Monitor Alone	Symptom Report Alone	Home Monitor Plus Symptom Report	Office Examination*
Hill, et al. <sup>76</sup> (1990) and Martin, et al. <sup>91</sup> (1990)	42	31	24	26	19
Iams, et al. <sup>90</sup> (1990)	51	24	24	43	9

\*In the Hill, et al. and Martin, et al. studies, the office examination included routine office visits, scheduled nonstress tests, and evaluations for decreased fetal movement. In the Iams, et al. study, the office examination referred to a cervical check.

monitor alone, 24 percent for symptom report alone, 26 to 43 percent for home monitor and symptom report together, and 9 to 19 percent for the office examination (Table 3). These findings have suggested that both home monitoring and symptom reporting to nurses are important — and nearly equally so — in making an early diagnosis of preterm labor. Cervical examinations and nonstress tests performed during routine prenatal visits also appear to contribute, though to a lesser degree.

Perhaps the benefit of cervical examinations did not appear as great as that of monitoring and nurse contacts because they occurred less frequently: office visits were scheduled every 2 weeks in the studies of Hill, et al. and Martin, et al., and at an unspecified frequency in the study by Iams, et al. Other investigators also have acknowledged the value of early cervical changes in predicting preterm delivery,<sup>92,93</sup> so it is likely that regular cervical examinations would contribute to the diagnosis of preterm labor. Further, it is reassuring that the practice of performing regular cervical examinations does not appear to increase morbidity related to infections or premature rupture of membranes.<sup>94</sup>

Both cervical examinations and telephone contacts with high-risk patients are low-risk, low-cost procedures when compared with other sophisticated obstetric procedures. In contrast, it would seem that ambulatory monitoring for all patients at risk for preterm labor would be an expensive undertaking. A recent study conducted by a major insurance carrier on 79 women at risk for preterm labor, however, reported a net savings of approximately \$11,500 per patient when ambulatory monitoring was used between 24 and 36 weeks' gestation.<sup>95</sup> Morrison and colleagues<sup>96</sup> compared the cost of pregnancy for 33 self-palpation patients and 34 monitored patients, and found that savings for the monitored group was \$5900 per patient ( $P = 0.06$ ). A second study by Morrison, et al.<sup>97</sup> showed that

savings can be much greater when ambulatory monitoring is used in high-risk Medicaid populations: the savings in this study of 130 women were \$23,573 per patient. Thus, it appears from these early studies that ambulatory uterine monitoring for high-risk women is cost effective.

Although preterm birth prevention programs have helped to improve early detection of preterm labor in high-risk women, they miss a great number of women who are initially labeled as low risk but will nonetheless develop preterm labor. In response to this concern, Main and colleagues<sup>98</sup> have suggested that intermittent weekly monitoring of uterine contractions for 1 hour during routine office visits might provide an effective screening tool for all pregnant women. In their sample of 139 black inner-city women who were monitored at least three times for 1 hour between 28 and 32 weeks' gestation, a contraction frequency of more than 6 per hour on at least one occasion predicted subsequent preterm labor with a sensitivity of 75 percent and a specificity of 79 percent. Katz, et al.<sup>99</sup> also reported that preterm labor can be predicted by an increased frequency of contractions up to several weeks before the onset of labor. Thus, intermittent monitoring of so-called low-risk patients could prove useful in further distinguishing women who are prone to develop preterm labor, but additional studies are needed.

#### **Biochemical Markers**

Other methods for diagnosing preterm labor have been investigated, though less vigorously than home monitors. In particular, potential biochemical markers — for example, plasma estradiol-17 $\beta$ , progesterone, and C-reactive protein — have been studied, but they have not been found to be adequate diagnostic tools.<sup>100</sup> The results of a recent multicenter study of fetal fibronectin appear quite promising, however. Fetal fibronectin, a protein found in amniotic



fluid and placenta tissue, was detected at high levels in the cervical or vaginal secretions of 94 percent of women with preterm rupture of membranes and in 50 percent of women with preterm labor and intact membranes. Further, its presence singled out women who later had preterm deliveries, with a sensitivity and specificity of more than 80 percent.<sup>100</sup> If subsequent tests confirm these results, fetal fibronectin could serve as an important marker for women at risk for preterm delivery.

### Summary

The early detection of preterm labor is critical to its effective management, and measures that appear to improve early diagnosis in high-risk women include electronic uterine monitoring, self-palpation for contractions, frequent nurse contact, and cervical examinations. Using these measures in high-risk populations could facilitate an earlier diagnosis of preterm labor, thus setting the stage for more effective treatment, which is discussed in Part II of this series.

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