

## A Critical Assessment of Preterm Labor Prevention Strategies

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Preterm birth is second only to congenital diseases in causing morbidity and mortality in infants. To prevent preterm labor and delivery, a number of strategies have been developed. When choosing a strategy to prevent preterm birth, however, physicians must remember that preterm delivery arises from three separate conditions: iatrogenic preterm labor, premature rupture of membranes, and idiopathic preterm labor. Many of the programs that have been developed focus on patients who are at high risk for iatrogenic preterm birth and premature rupture of membranes, but do not include patients

who are likely to experience idiopathic preterm labor. Since idiopathic preterm labor is the most common cause of preterm birth and is the most amenable to early intervention with tocolytic agents, more preterm labor education efforts should be included in prenatal care programs. In addition, further research is needed to delineate which features of preterm birth prevention programs are responsible for the beneficial effects that have been observed.

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*There is a great temptation to take the simple path, uncritically follow the precepts of leaders in the field, or succumb to the seduction of the uncontrolled studies.<sup>1</sup>*

Perhaps no other field of medicine is as susceptible to "bandwagon medicine," that is, the widespread adoption of practices with scant proof of efficacy, as obstetrics. The reason for this tendency is that in obstetrics two human lives are involved. Any deviation from perfection is viewed critically, and if a promising technique or technology has not been used and a less than perfect outcome occurs, the physician is held accountable.

The physician's desire to ensure that every reasonable action has been taken leading to the safe delivery of a healthy infant has led to the widespread use of technologies with little evidence that pregnancy outcomes are actually improved by these interventions. An example of this tendency is universal continuous electronic fetal monitoring. This intervention was originally introduced as a tool to improve outcomes in high-risk pregnancies, and was of questionable value even in that patient population,<sup>2-4</sup> but its use has been expanded to include all pregnancies. Only now, after continuous fetal monitor-

ing has become the standard of care, are researchers questioning its efficacy.<sup>5-9</sup> As one expert lamented, "It is unfortunate that randomized, controlled trials were not carried out before this form of technology became universally applied."<sup>10</sup>

As controversy over continuous electronic fetal monitoring grows, physicians are now faced with other technologies that have shown initial promise. These technologies address the prevention of preterm birth. The need for such programs is clear. Preterm births occur in about 10% of all pregnancies, and prematurity is second only to congenital defects in causing neonatal morbidity and mortality.<sup>11</sup> Furthermore, the costs of caring for low-birthweight infants are astronomical: the estimated average total charges in 1985 for a very premature infant was \$22,678 as compared with \$484 for a term infant.<sup>12</sup> Estimates of the cost per surviving low-birthweight infant are much higher.<sup>13</sup> The total costs of neonatal intensive care alone for premature infants approached \$5 billion in 1985.<sup>14</sup> Thus, prevention of preterm birth will have significant morbidity, mortality, and economic benefits.

A critical review of preterm prevention strategies is therefore warranted. This article examines preterm prevention strategies, reviewing both randomized and non-randomized studies of various interventions. This article does not address the utility or comparative properties of various tocolytic agents, but instead focuses on the behavioral, technical, and prophylactic pharmaceutical in-

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Table 1. Subtypes of Preterm Labor

Subtype	Characteristics of Risk Groups	% of Preterm Births
Iatrogenic preterm labor	Young age, lower socioeconomic class, twins, maternal illness	25
Premature membrane rupture	Young age, lower socioeconomic class, maternal cervical infection or vaginal colonization, uterine or placental abnormality	25
Idiopathic preterm labor	Higher socioeconomic class, illicit drug use, obesity	50

interventions that have been introduced and evaluated in the past 10 years. Readers interested in efficacy trials of tocolytic agents are referred to several other reviews on that topic.<sup>15,16</sup>

### The Nature of Preterm Birth: Three Problems Masquerading as One

Like many troubling problems in medicine, preterm birth cannot be explained by a single cause. Rather, preterm labor and birth occurs in patients with a variety of risk factors and widely diverse socioeconomic backgrounds and medical histories.<sup>17</sup> Preterm birth arises from three distinct sources: iatrogenic preterm labor, premature rupture of membranes, and idiopathic preterm labor (Table 1). While it is convenient to discuss preterm labor and preterm birth as if the problem arises from a single cause, only when the heterogeneous nature of the problem is understood can the successes and failures observed in preterm birth prevention programs be placed in a proper perspective.

Iatrogenic preterm labor accounts for 25% of all preterm deliveries. The majority of preterm births in this category are secondary to complications of pregnancy such as uncontrollable maternal preeclampsia, deteriorating maternal medical condition, and worsening intrauterine growth retardation. This type of preterm delivery is sometimes referred to as "medically indicated" preterm delivery. Medically indicated preterm birth is seen primarily in high-risk, young, indigent mothers who are most prone to the medical and obstetrical complications that necessitate an earlier-than-optimal delivery.<sup>17,18</sup> A second cause of iatrogenic preterm birth is poorly timed elective induction or cesarean section. Thus, preterm birth prevention for iatrogenic causes must emphasize controlling maternal medical problems and improving the nutritional status of patients as well as ensuring proper pregnancy dating, particularly when elective induction or cesarean section are anticipated.

Premature rupture of membranes accounts for an additional 25% of preterm births. In most cases, patients experience rupture of membranes without prior uterine contractions, which makes early intervention particularly difficult. Women at higher risk for spontaneous premature rupture of membranes include poorer, younger patients who are at higher risk for sexually transmitted diseases such as *Chlamydia trachomatis* or who have bacterial vaginosis<sup>19,20</sup>; African-American women<sup>19</sup>; and women who have previously had premature rupture of membranes.<sup>21</sup> Since patients with premature rupture of membranes respond poorly to tocolytic therapy,<sup>22</sup> strategies to prevent premature membrane rupture would be extremely valuable. Unfortunately, the cause of premature rupture of membranes is poorly understood. There is some evidence that premature rupture of membranes is associated with vaginal and cervical infections, and some current prevention strategies that are discussed below focus on this observation. Additional research that explores the cause of premature rupture of membranes may enable the development of other strategies to combat this problem.

The final type of preterm birth is idiopathic. Idiopathic preterm birth accounts for about 50% of all preterm births. Idiopathic preterm labor refers to the spontaneous onset of contractions with progressive cervical dilatation and effacement for no apparent reason. Because idiopathic preterm labor generally responds fairly well to early aggressive tocolytic therapy, preterm-birth prevention programs have placed their emphasis on reducing the incidence of idiopathic preterm birth. Programs in preterm-birth prevention emphasize education, identifying patients who are experiencing contractions, and using prophylactic medications to prevent spontaneous contractions. Although most patients who experience idiopathic preterm labor are considered low risk in that they do not fit any of the high-risk categories for preterm labor, risk factors for idiopathic preterm labor do exist. These include maternal obesity<sup>23</sup> and recent illicit drug use, particularly cocaine.<sup>24</sup> Identification and treatment of patients who abuse drugs during pregnancy may reduce the incidence of spontaneous preterm labor in this group. Risk factors that have not been clearly linked to an increase in idiopathic preterm labor include maternal anemia<sup>25</sup> and maternal occupational activities.<sup>26-28</sup>

### Preterm Birth Prevention Strategies: What Are We Doing Now?

This discussion focuses individually on three aspects of preterm birth prevention: (1) behavioral techniques, (2) uterine monitoring, and (3) the use of prophylactic medications. The literature on these topics was reviewed, and

studies that used either random allocation or historical comparisons were selected, based on a MEDLINE search and review of bibliographies of articles generated by this search. Uncontrolled studies and case reports were not reviewed. Attention was paid to three particular features of each study: (1) the methodology employed in the prevention program; (2) study design, either randomized control or historical control; and (3) the population that was used for the study, either selected high-risk women or relatively unselected women, which included those at low risk.

## Behavioral and Educational Approaches

Behavioral approaches to preterm birth prevention emphasize early detection of the signs and symptoms of preterm labor so that preterm labor can be recognized and tocolysis initiated early in the course of labor. The foundation of behavioral prevention strategies is education. Patients and providers are informed of the signs and symptoms of preterm labor. Patients are seen on a weekly basis, and the symptoms of preterm labor are reviewed frequently. Patients are told that if they experience these symptoms, they should seek immediate care. Likewise, providers are instructed to carefully observe patients who present with premature contractions and to employ early tocolysis for any cervical change. Some programs also include weekly cervical examinations to note any progressive changes in cervical dilatation or effacement. All health care providers involved in the care of the patient participate in the program.

An important aspect of the behavioral techniques of preterm labor prevention relies on the patient identifying the symptoms that can predict preterm labor. Several studies have addressed whether specific signs and symptoms are useful for predicting preterm labor. Case-control studies have noted that patients who were diagnosed as having preterm labor had a greater frequency of uterine contractions, menstrual-like cramps, backache, and increased vaginal discharge preceding preterm labor.<sup>29,30</sup> One study also noted an increased sensation of pelvic pressure in patients who experienced preterm labor,<sup>29</sup> while another study noted an increase in urinary frequency in preterm labor patients.<sup>30</sup> Both of these studies suffer from recall bias, however: patients in the preterm labor group were likely to have been in a heightened state of anxiety and more likely to respond positively to queries about their recent symptoms than patients who were questioned as part of a routine clinic visit. Results from a prospective study that examined common symptoms in a group of patients in a preterm labor high-risk program did not confirm any of these findings.<sup>31</sup> All of the afore-

Table 2. Literature Review of Behavioral Preterm Birth Prevention Programs

Study	Population*	Result
Randomized, controlled studies		
Main (1989) <sup>32</sup>	High risk	No effect
Goldenberg (1990) <sup>33</sup>	High risk	No effect
Heins (1990) <sup>34</sup>	High risk	No effect
Historical, controlled studies		
Herron (1982) <sup>35</sup>	High risk	Reduction
Konte (1988) <sup>36</sup>	High risk	No effect
Mueller-Heubach (1989) <sup>37†</sup>	High risk	Reduction
Meis (1987) <sup>38</sup>	All patients	Reduction
Yawn (1989) <sup>39</sup>	All patients	Reduction

\*Population refers to studies that prescreened patients and offered preterm birth prevention only to high-risk patients, or studies that offered preterm birth prevention to all patients in the patient population.

†Study began as a randomized controlled trial, but investigators discovered that patients in the control group were also being instructed in the signs and symptoms of preterm labor; results were then pooled for both arms of the study and compared with historical rates of preterm birth.

mentioned symptoms increased as the gestation of pregnancy increased, but none was associated with preterm delivery. In the present study it was found that vaginal discharge and diarrhea were the only symptoms associated with preterm labor. Thus, while patients who experience preterm labor may report an increase in several symptoms in the days preceding their labor, these symptoms do not appear to be useful in predicting preterm labor or delivery.

*Effectiveness of the strategy.* Several studies have evaluated behavioral prevention programs (Table 2). Using a scoring system developed by Creasy and co-workers,<sup>35,40</sup> many trials have focused on high-risk women and have generally shown little benefit from behavioral prevention strategies.<sup>32-37</sup> However, as pointed out by others,<sup>41,42</sup> the high-risk scoring system tends to identify patients who are at high risk for medically indicated iatrogenic preterm delivery or preterm premature rupture of membranes; the scoring system has a poor sensitivity and positive predictive value when used in lower risk populations.<sup>43</sup>

In less selected populations, as shown by the two studies that did not limit their population to high-risk women,<sup>38,39</sup> behavioral and educational methods were effective at reducing preterm birth rates. This is consistent with observations that idiopathic preterm labor is most prevalent in lower-risk individuals.

The success of these two studies also brings into question the usefulness of routine cervical examinations, since they either were not performed at all<sup>38</sup> or were performed only in high-risk individuals.<sup>39</sup> Weekly cervical examination was originally found to be a predictor of subsequent preterm labor in high-risk patients,<sup>44-48</sup> but in low-risk populations, the vast majority of patients who

later experience preterm labor have no antecedent change in their cervical examination.<sup>47</sup> Even in high-risk populations, where adding weekly cervical examination to other high-risk factors improves the predictability of preterm labor, it does so only marginally.<sup>48</sup> Progressive cervical changes on weekly examinations between 25 and 28 weeks, combined with other high-risk factors, have a sensitivity of only 63% in predicting preterm labor as compared with 55% using high-risk factors alone. Later in pregnancy, the observation of increasing cervical dilatation or effacement is even less helpful. Thus, weekly cervical examination designed primarily to identify patients at higher risk of preterm labor by noting progressive opening of the internal os adds little to the educational and supportive measures offered to patients at risk for preterm labor.

**Conclusions.** Behavioral and educational preterm prevention programs have been shown to be effective among unselected patients but are not successful when limited to high-risk populations. Since the cost of these educational efforts is negligible and there is no potential harm to the patient, all patients should be instructed in the symptoms of labor in the late second or early third trimester. Providers should be diligent in the evaluation of suspected preterm labor and should employ early tocolysis. Cervical examinations have not been demonstrated to be an effective adjunct in preventing preterm birth.

The standard schedule of patient visits, which has the patient return at monthly intervals until 32 or 34 weeks, was originally designed to detect and treat preeclampsia<sup>49</sup> and is inadequate for appropriate preterm labor education and prevention. Patients should be seen on a weekly or biweekly schedule throughout the third trimester.

Additional prospective randomized trials would be helpful in identifying those components of a preterm birth prevention strategy that are most effective.

## Periodic Uterine Monitoring

The development of home uterine contraction monitoring was initially based on observations that periodic contractions are an important warning sign for patients who are at higher risk of spontaneous preterm labor,<sup>50</sup> but many patients do not detect contractions reliably.<sup>51,52</sup> Thus, the educational efforts expended in behavioral programs discussed above will be ineffective if patients cannot detect early contractions.

This strategy combines patient education on preterm delivery with home uterine contraction monitoring using a portable tocodynamometer, which can transmit data over telephone lines to obstetric centers for interpretation.<sup>53</sup> Patients generally monitor their uterine activity for a prescribed period several times each day. The

Table 3. Studies of the Usefulness of Home Uterine Monitoring

Study	Population*	Result
Katz (1986) <sup>57</sup>	High risk	Reduction
Morrison (1987) <sup>58</sup>	High risk	Reduction
Iams (1987) <sup>59</sup>	High risk	No effect
Iams (1988) <sup>60</sup>	High risk	No effect
Hill (1990) <sup>61</sup>	High risk	No effect†
Knipple (1990) <sup>62</sup>	Twin gestation	No effect
Mou (1991) <sup>63</sup>	High risk‡	Reduction

\*Population refers to studies that prescreened patients and offered preterm birth prevention only to high-risk patients, or studies that offered preterm birth prevention to all patients in the patient population.

†Report of this study incorrectly concludes that monitoring caused a reduction, but only a minority of subjects were included in analysis.<sup>64</sup>

‡Analysis on outcomes excluded all patients delivered for medical reasons and twin gestations.

data are reviewed by nurses at the perinatal center, who contact the patient to give further directions. Intervention is based on the observation that before the onset of preterm labor, patients experience an increase in the frequency of uterine contractions<sup>50,54,55</sup> and that by targeting these women for closer attention, preterm labor can be diagnosed at an earlier stage of cervical dilatation and effacement, thus permitting more effective tocolytic therapy to be instituted.<sup>56</sup>

**Effectiveness of the strategy.** Several studies of this approach have documented success with home uterine activity monitoring in high-risk populations (Table 3). The validity of at least one of these studies<sup>61</sup> is suspect, however,<sup>64</sup> and most other studies have included only small numbers of patients.<sup>57,58,63</sup>

Results from other trials suggest that the monitoring is not as important as the frequent nurse contact and support that patients in the monitored group receive by virtue of their conversations with the nurses who review their uterine activity data.<sup>59</sup> Studies have also documented differences in the level of anxiety in patients who wear monitors as compared with controls<sup>65,66</sup>; this may influence the likelihood that they will experience contractions.

One final limitation to studies of the use of home uterine monitoring to date is that they have been limited to high-risk patients. As noted earlier, the sensitivity and positive predictive value of the risk-scoring scale is very low for idiopathic preterm labor. If home uterine monitoring is restricted to high-risk patients only, the majority of idiopathic preterm birth will not be prevented. Attempts have been made, however, to identify patients in low-risk populations who are likely to experience preterm labor.<sup>67</sup> Using the results of 1 hour of uterine monitoring between 28 and 32 weeks of gestation obtained while low-risk patients waited for their clinic appointment, Main et al<sup>67</sup> were able to predict an increased

risk of subsequent preterm labor in a group of lower risk, indigent, black clinic patients. Uterine activity of over six contractions in 1 hour identified 75% of the patients who were subsequently admitted with preterm labor. This low-cost screening test may be a useful tool in screening low-risk patients and identifying those patients who should be recategorized as higher risk. Further evaluation of this technique may make home uterine monitoring a more effective tool for lower-risk patients.

*Conclusions.* Home uterine contraction monitoring has been shown to be successful in reducing preterm birth in high-risk populations, but is limited in that this technology has not been evaluated for low-risk women who account for the majority of idiopathic preterm births.

Current studies do not adequately assess the effects of the monitor itself as distinguished from the effects of increased attention paid to patients in the monitored group (the Hawthorne effect). Thus, further research is necessary before home uterine contraction monitoring can be recommended.

Further research to identify which low-risk women are at greatest risk for preterm labor may make home uterine monitoring a more effective strategy for preventing idiopathic preterm birth.

## Prophylactic or Adjunctive Medications

### *Tocolytic Agents*

The use of prophylactic tocolytic agents is an attractive strategy for patients who are at high-risk for preterm labor. Since most tocolytics are believed to exert their effect through smooth-muscle uterine relaxation, early or prophylactic use of these medications may be effective at preventing the initiation of labor.

*Effectiveness of the strategy.* The use of tocolytic agents prophylactically in patients at high risk for preterm labor has not been demonstrated to reduce the incidence of preterm labor or delivery.<sup>68,69</sup> In some subgroups, the use of prophylactic tocolytic agents actually increased the rate of preterm labor delivery.<sup>69</sup>

*Conclusions.* Prophylactic use of tocolytic agents in high-risk patients is not advised.

Furthermore, cervical change on weekly examinations is not an indication for tocolysis. The lack of evidence that prophylactic tocolytic agents prevent preterm birth presents a dilemma for the physician who performs a routine cervical examination and discovers that a patient's cervix has changed from the preceding week. Often, the physician may use tocolytic agents. Use of tocolytic agents, especially beta-mimetic agents, in this manner may actually diminish the subsequent effective-

ness of the tocolytic agent because of rapid down-regulation of uterine receptors.

### *Calcium Supplementation*

A recent report<sup>70</sup> has shown encouraging results in reducing preterm delivery and preterm labor in a group of primarily black pregnant teenagers whose diet was supplemented with calcium carbonate during the last half of pregnancy. Hypothesizing that calcium reduces uterine muscle tone, Villar and Repke<sup>70</sup> started patients in their adolescent pregnancy clinic on four Os-Cal-500 pills per day and compared these patients with a double-blinded control group.

*Effectiveness of strategy.* Preterm delivery in the calcium supplementation group was 6.4% as compared with 17.9% in the control group. Furthermore, those patients who gave birth prematurely in the experimental group were all delivered for medical reasons (iatrogenic preterm delivery) or had premature rupture of membranes. The idiopathic preterm delivery rate in the calcium group was zero compared with 6.3% in the control group. The use of calcium also reduced the incidence of preeclampsia in the supplementation group and decreased the iatrogenic preterm delivery rate.

*Conclusions.* While these data are promising, it is too early to advocate routine use of calcium supplementation. Since calcium appears to affect both iatrogenic and idiopathic preterm labor, it would be an ideal drug for use in all pregnancies. Demonstration of a reduction in idiopathic preterm labor in more affluent populations, ie, those who are at greater risk for idiopathic preterm labor, is needed before greater use of prophylactic calcium can be advocated.

### *Antibiotics and Preterm Labor*

Several studies have linked vaginal colonization with idiopathic preterm labor and with premature rupture of membranes.<sup>19,20</sup> In addition, an elevated amniotic white blood count has been correlated with later preterm delivery.<sup>71</sup> Based on these findings, it has been suggested that antibiotics be employed as an adjunct in patients who present with preterm rupture of membranes or preterm labor.<sup>72</sup> Since both bacterial vaginosis and *Chlamydia trachomatis* have been consistently linked to preterm birth, strategies have been aimed at these two conditions.

*Effectiveness of strategy.* Table 4 contains a list of several prospective randomized trials of a variety of antibiotics used either prophylactically or in conjunction with tocolytic therapy for patients who presented with premature rupture of membranes or idiopathic preterm labor.

Only one study has examined the use of prophylactic

Table 4. Studies of Adjunctive Antibiotics in Preterm Birth Prevention\*

Study (Primary Author)	Population†	Antibiotic	Results
McCormack (1987) <sup>73</sup>	Patients with <i>Ureaplasma</i>	Erythromycin	Prolonged gestation
McGregor (1986) <sup>74</sup>	Idiopathic preterm labor	Erythromycin	Prolonged gestation
Newton (1989) <sup>75</sup>	Idiopathic preterm labor	Erythromycin plus ampicillin	No benefit
Morales (1988) <sup>76</sup>	Idiopathic preterm labor	Erythromycin or ampicillin	Prolonged gestation‡
Winkler (1988) <sup>77</sup>	PROM, high CRP	Erythromycin	Prolonged gestation
Amon (1988) <sup>78</sup>	PROM	Ampicillin	Prolonged gestation
McGregor (1991) <sup>79</sup>	All preterm labor	Clindamycin	Prolonged gestation‡
Thomsen (1987) <sup>80</sup>	Group B streptococcal urine colonization	Penicillin	Decreased PROM and preterm labor

\*All trials were prospective, randomized trials.

†Population refers to studies that prescreened patients and offered preterm birth prevention only to high risk patients, or studies that offered preterm birth prevention to all patients in the patient population.

‡See text for limitations of findings.

PROM denotes premature rupture of membranes; CRP, C-reactive protein.

antibiotics during prenatal care.<sup>73</sup> McCormack and co-workers evaluated the use of erythromycin in patients who were found to be colonized with *Ureaplasma* and found prolonged gestation in those patients who were treated. Subsequent cultures showed, however, that there was no difference in *Ureaplasma* colonization between patients receiving treatment and control patients. It is unlikely that the results of this study are due to eradication of *Ureaplasma*; unfortunately, cultures for other organisms such as group B streptococcus and *Mycoplasma*, both of which are sensitive to erythromycin, were not performed.

Newton,<sup>75</sup> Morales,<sup>76</sup> McGregor,<sup>74</sup> and their co-workers evaluated the adjunctive use of erythromycin in patients who presented with idiopathic preterm labor. Based on evidence that maternal intravenous ampicillin administration reduces neonatal group B streptococcal meningitis and sepsis, all the patients in the trial of Newton et al<sup>75</sup> were treated with ampicillin; experimental patients were given erythromycin as well. Morales et al,<sup>76</sup> on the other hand, treated patients with either ampicillin or erythromycin vs placebo. Morales et al demonstrated prolonged gestation in patients, but subsequent microbiologic studies showed that only patients who were colonized with group B streptococcus benefited from antibiotic treatment; ampicillin and erythromycin were equally effective. In the study by Newton and colleagues, the addition of erythromycin to ampicillin showed no benefit compared with ampicillin alone. The results of McGregor and co-workers<sup>74</sup> were consistent with those of the other two groups.

Other studies<sup>77,78</sup> have evaluated both erythromycin and ampicillin in patients with premature rupture of membranes. Amon and co-workers<sup>78</sup> tested ampicillin vs placebo in all patients who presented with premature rupture of membranes and found a substantial reduction in subsequent chorioamnionitis and preterm delivery in the treated

group. Winkler et al<sup>77</sup> limited their study to patients who had premature rupture of membranes and an elevated C-reactive protein level, which has been linked to *Ureaplasma* infection. In this group, erythromycin-treated patients gave birth to babies who weighed an average of 300 g more and arrived 9 days later than those of the control subjects. Of interest, however, is that beneficial results were limited to patients who were found to be *Ureaplasma*-positive on subsequent culture. Patients who were *Ureaplasma*-negative and were treated with erythromycin actually gave birth 9 days earlier than patients receiving placebo, and their infants weighed an average of 350 g less.

Based on findings that bacterial vaginosis predisposes patients to premature rupture of membranes, McGregor and co-workers<sup>79</sup> evaluated the usefulness of clindamycin in patients who present with preterm labor. Results showed an overall improvement in gestational age and birthweight in patients treated with clindamycin, but the benefit was most pronounced in patients with a diagnosis of bacterial vaginosis. The benefits of clindamycin were limited, however, to women who presented before 33 weeks of gestation.

Finally, the importance of treating urinary tract infections during pregnancy was underscored by results from Thomsen and co-workers.<sup>80</sup> Routine urinary cultures from patients in the early trimester revealed a small number (<2%) who were colonized with group B streptococcus. Treatment of these women with penicillin resulted in a fivefold reduction in subsequent preterm rupture of membranes and a sixfold reduction in preterm labor compared with placebo-treated controls.

**Conclusions.** Administration of antibiotics to patients who present in idiopathic preterm labor or with premature rupture of membranes may prolong gestation. Both intravenous ampicillin and erythromycin have been shown to be effective. In addition, the treatment of

bacterial vaginosis may also be warranted, particularly in patients who present before 33 weeks of gestation.

To date there is little evidence to show that prophylactic antibiotics influence future preterm labor. Studies suggest that several microbiologic agents may play a role in preterm labor and in rupture of membranes. Additional studies that evaluate the effectiveness of prophylactic antibiotics may be helpful in determining which patients, if any, benefit from routine use of these agents to prevent idiopathic preterm labor or premature rupture of membranes.

## Recommendations

Based on the promising early work in preterm birth prevention, many enthusiastically embarked on preterm birth prevention programs that featured weekly patient visits, frequent cervical examinations, and home uterine monitoring. But how appropriate are these programs? As pointed out by others,<sup>43,49</sup> no strategy has been successful at reliably predicting which patients will experience preterm labor. More research into this problem will assist in determining if a single successful preterm prevention strategy can be defined. Nevertheless, several strategies show promise and have been associated with prolonged gestation at little risk to patients and little cost to the health care system. These findings warrant several recommendations that may guide physician behavior until further research is performed.

*Recommendation 1: All patients should receive education regarding the signs and symptoms of preterm labor during the early third or late second trimester of pregnancy.*

Because of problems in reliably predicting which patients will require preventive services, obstetric providers should make preterm birth prevention education a high priority for all patients, not just for high-risk women. High-risk scoring systems can identify women who are more likely to experience premature rupture of membranes or iatrogenic preterm delivery due to complications of pregnancy, but these systems are inadequate at identifying most low-risk women who are likely to experience idiopathic preterm labor. Reliance on high-risk scoring systems in preterm labor prevention programs is an error. Every patient is at high risk for preterm labor and should be treated as such. Preterm labor education is cheap and harmless and should be part of routine prenatal care.

*Recommendation 2: Home uterine monitoring has not been shown to be consistently effective even in high-risk women and should not be routinely used. Additional research is needed to better define the usefulness of this new technology*

*and to delineate which aspects of home uterine-monitoring programs may be responsible for the observed successes.*

Every preterm prevention technology runs the risk of causing the Hawthorne effect, that is, any additional service or attention to patients is more likely to result in a favorable outcome. While it may be difficult to differentiate between the effects of monitoring and the effects of increased attention, this task is necessary to avoid the overuse of this new technology. Evidence supporting the use of home uterine monitoring is limited to three studies, none of which included more than 45 patients in the treatment arm of the study. Larger studies have failed to replicate the promise shown in these smaller trials. Further research will be needed to define the utility of home uterine monitoring before it can be recommended for routine use.

*Recommendation 3: Prophylactic tocolytic agents should not be routinely used to prevent preterm labor; prophylactic calcium requires further research before it can be recommended for routine use.*

Evidence shows that tocolytic agents are not helpful in preventing subsequent preterm labor. Use of these agents may also interfere with future response to tocolytics. Therefore, patients should not be placed on tocolytic agents unless preterm labor is clearly documented.

Although calcium administration has been linked to a reduction in preterm labor, further study, including replication of these early findings, is warranted before calcium is routinely given to pregnant patients. Questions concerning which patients may benefit from calcium use should be addressed before calcium supplementation is added to prenatal care.

*Recommendation 4: All patients who present with idiopathic preterm labor or premature rupture of membranes who are colonized with group B streptococcus should receive antibiotic therapy with ampicillin or erythromycin as an adjunct to tocolysis.*

This recommendation is based on two lines of evidence. First, convincing evidence suggests that ampicillin therapy during preterm labor or after prolonged rupture of membranes reduces neonatal group B streptococcal infection.<sup>81</sup> Withholding antibiotic administration until culture results are known is ineffective at preventing chorioamnionitis and neonatal infection.<sup>82</sup> Recent advances in rapid detection of group B streptococcus may help in identifying those patients who should receive antibiotics; however, in the absence of those results, ampicillin, or erythromycin in the penicillin-allergic patient, should be administered until the patient is stable and labor has stopped.<sup>83</sup> Evidence that this intervention may also prolong gestation makes the argument for routine antibiotic use even more compelling. However, the

efficacy of antibiotic use by pregnant women who are also colonized with group B streptococcus has not been proven and is therefore not recommended.

*Recommendation 5: Treatment should be provided for patients with urinary tract infection or colonization in the third trimester or with bacterial vaginosis.*

While evidence supporting treatment of urinary tract infection is clear, there is less evidence that early treatment of bacterial vaginosis causes a reduction in preterm labor or rupture of membranes. Since bacterial vaginosis has been correlated with these two adverse outcomes, treatment appears justified; however, additional prospective studies examining the efficacy of this approach would be useful.

## Summary

Preterm birth prevention is an important role for the obstetric provider. Initial trials using a variety of educational, technical, and pharmaceutical approaches show promise. While some of these advances can be incorporated into the delivery of obstetric care now, further research is needed to more accurately predict which patients will experience preterm labor and to define which populations may benefit from these interventions.

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