PROTOCOL 42

Preterm Labor

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Clinical significance

Preterm labor precedes approximately 50% of preterm births. Preterm birth is the foremost problem in obstetrics and accounts for most perinatal death. Preterm birth occurs in 11.5% (2012 data) of the approximately 4 million births in the United States. As such, there are over 500,000 preterm births in the United States each year. Over 75% of perinatal deaths related to preterm birth occur in babies born between 22 and 31 weeks of gestation. The rate of perinatal morbidity is also indirectly proportional to gestational age at birth (Table 42.1).

Pathophysiology

The pathophysiology of preterm labor is not well understood. At least four main mechanisms have been described: inflammation/infection, abruption (decidual bleeding), maternal and/or fetal stress, and excessive mechanical stretching of the uterus. Although arising from different pathways, and often more than just one, all spontaneous preterm births utilize a final common biochemical conduit that usually includes increased genital tract prostaglandin and protease production coupled with functional progesterone withdrawal related to progesterone receptor function. Disparities in preterm birth rates between racial groups may reflect both environmental stressors and differing genetic predispositions.

Diagnosis

Unfortunately, there are many differing definitions of preterm labor. The classic definition involves “uterine contractions (greater than 6/60 minute)
Table 42.1  Survival and major morbidities by gestational age at birth in 2008

<table>
<thead>
<tr>
<th>GA (weeks)</th>
<th>Survival (%)</th>
<th>Chronic lung disease (%)</th>
<th>Severe IVH (%)</th>
<th>Necrotizing enterocolitis (%)</th>
<th>Severe ROP (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 22</td>
<td>3.3</td>
<td>33.3</td>
<td>33.3</td>
<td>33.3</td>
<td>66.7</td>
</tr>
<tr>
<td>22</td>
<td>6.0</td>
<td>77.8</td>
<td>52.0</td>
<td>11.1</td>
<td>57.9</td>
</tr>
<tr>
<td>23</td>
<td>34.3</td>
<td>79.2</td>
<td>33.8</td>
<td>15.9</td>
<td>46.9</td>
</tr>
<tr>
<td>24</td>
<td>59.2</td>
<td>74.7</td>
<td>29.5</td>
<td>12.4</td>
<td>34.7</td>
</tr>
<tr>
<td>25</td>
<td>75.3</td>
<td>65.9</td>
<td>20.1</td>
<td>11.6</td>
<td>26.2</td>
</tr>
<tr>
<td>26</td>
<td>80.0</td>
<td>51.7</td>
<td>17.2</td>
<td>10.2</td>
<td>14.2</td>
</tr>
<tr>
<td>27</td>
<td>89.4</td>
<td>35.9</td>
<td>9.7</td>
<td>6.8</td>
<td>7.0</td>
</tr>
<tr>
<td>28</td>
<td>91.2</td>
<td>25.8</td>
<td>6.3</td>
<td>7.2</td>
<td>3.0</td>
</tr>
<tr>
<td>29</td>
<td>94.3</td>
<td>16.2</td>
<td>4.3</td>
<td>4.9</td>
<td>1.0</td>
</tr>
<tr>
<td>30</td>
<td>96.8</td>
<td>11.0</td>
<td>1.9</td>
<td>3.4</td>
<td>0.7</td>
</tr>
<tr>
<td>31</td>
<td>96.7</td>
<td>7.3</td>
<td>1.9</td>
<td>2.4</td>
<td>0.6</td>
</tr>
<tr>
<td>32</td>
<td>97.5</td>
<td>4.1</td>
<td>1.3</td>
<td>1.7</td>
<td>0.2</td>
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<tr>
<td>33</td>
<td>98.1</td>
<td>3.1</td>
<td>1.4</td>
<td>1.0</td>
<td>0.9</td>
</tr>
<tr>
<td>34</td>
<td>98.4</td>
<td>4.4</td>
<td>1.5</td>
<td>0.9</td>
<td>0.0</td>
</tr>
</tbody>
</table>

GA, gestational age.
Chronic lung disease is defined as need for oxygen therapy at 36 weeks of postmenstrual age.
Severe IVH: grades III and IV.
Necrotizing enterocolitis includes medical and surgical.
Severe ROP (retinopathy of prematurity) is defined as greater than grade 2.
Source: Data from Vermont Oxford Network 2007. Courtesy of Kevin Dysart, MD.

and documented cervical change by manual examination with intact membranes at 20–36 6/7 weeks of gestation.” Most women with this diagnosis of preterm labor deliver at term (37 weeks or beyond) even without intervention. Transvaginal ultrasound (TVU) cervical length (CL) and fetal fibronectin (FFN) are currently the two tests with the best data for good prediction of preterm birth in women with preterm labor. Therefore, we like to add other criteria to the definition above: “in the presence of TVU CL less than 20 mm, or TVU 20–30 mm and positive FFN.” The vast majority of women with these characteristics will deliver preterm. In contrast, women with preterm uterine contractions and manual cervical change but a TVU CL 30 mm or greater have a less than 2% chance of delivering within 1 week and less than 10% chance of delivering prior to 35 weeks of gestation.

Treatment

Preterm labor is better prevented than treated. The most important issues regarding management of a woman with true preterm labor are:
Figure 42.1  A proposed algorithm for combined cervical length (TVU CL) and fetal fibronectin (FFN) screening for women with symptoms of threatened preterm labor. TVU, transvaginal ultrasound; CL, cervical length; FFN, fetal fibronectin. Source: Ness et al., 2007. Reproduced with permission of Elsevier.

- Treat only the women with true preterm labor and a real risk of preterm birth. A randomized trial by Ness et al. has shown benefit (reduction in preterm birth and quicker triage time) when women with threatened preterm labor are managed according to the algorithm shown in Fig. 42.1.
- Optimize fetal status:
  - *Transfer:* Assess for transfer to appropriate level hospital, usually with level III nursery.
  - *Corticosteroids for fetal maturity:* A course of antenatal corticosteroids (ACS) should be given to all women with true preterm labor, or at high risk for preterm birth within the next 7 days when between 23 and 34 weeks 6 days of gestation. All pregnant women between 23 0/7 and 33 6/7 weeks of gestation at high risk of preterm birth within
7 days should be offered treatment with a single course of ACS. This single course of ACS consists of two doses of 12 mg betamethasone given intramuscularly 24 hours apart; or four doses of 6 mg dexamethasone given intramuscularly 12 hours apart. A single course of ACS administered to women at increased risk of preterm birth between 23 and 33 6/7 weeks of gestation reduces morbidity (RDS, IVH, NEC, NICU admission, etc.) and mortality in infants. Regarding the effects of betamethasone compared with dexamethasone, a meta-analysis shows a lower incidence of IVH with betamethasone. The current benefit and risk data support use of one rescue courses of ACS in women with history of preterm labor who have a new risk for preterm birth (e.g., PPROM), are two weeks or more after first steroid course, and are still less than 34 weeks of gestation.

- **Tocolysis:**
  - The goal of tocolysis is to prevent imminent preterm birth, in order to have sufficient time to administer corticosteroids and, if necessary, allow for maternal in utero transfer to a hospital with appropriate neonatal care.
  - Given their safety profiles and effectiveness at delaying delivery for both 48 hours and 7 days, nifedipine (e.g., 20 mg po every 6 hours) or indomethacin (e.g., 100 mg po/pr loading, then 50 mg po/pr every 6 hours; for 48 hours or less, and always before 32 weeks of gestation) are the primary tocolytics we use clinically.
  - There is no evidence to support the use of maintenance tocolysis after successful arrest of preterm labor. There is not sufficient evidence to administer tocolysis once ACS have been administered.

- **Magnesium for neuroprotection**
  - Magnesium sulfate has been shown in five trials enrolling over 6000 women to significantly decrease cerebral palsy from 5.3% in placebo controls to 4.1%. The American College of Obstetricians and Gynecologists and the Society for Maternal Fetal Medicine have stated that “physicians electing to use magnesium sulfate for fetal neuroprotection should develop specific guidelines regarding inclusion criteria, treatment regimens (e.g., 4 mg loading dose, then 1 gram/hour), concurrent tocolysis, and monitoring in accordance with one of the larger trials.”

- **Other interventions**
  - There are insufficient data to recommend hydration, bed rest or decreased activity, progesterone or antibiotic therapy for prevention of preterm birth in women with preterm labor. Therefore, these interventions should be avoided, or reserved for clinical trials.
Complications

Preterm birth is associated with severe complications for the neonate. These include both short-term and long-term complications for the baby born too soon. Short-term, at times devastating, complications are listed in Table 42.1. Long-term complications include, among others, cerebral palsy, cognitive defects (e.g., low IQ), school difficulties, behavioral problems, and diminished long-term survival and reproduction.

Follow up

An episode of preterm labor usually does not give rise to a preterm birth. After administering ACS in the hospital, the woman can usually be discharged home. There are no interventions that are proven to prevent preterm birth between discharge and eventual delivery. Bed rest, frequent visits, and education on contractions have either been insufficiently studied or not proven beneficial so far. If the woman does have a preterm birth, postpartum counseling regarding how to prevent a recurrent preterm birth is extremely important.

Prevention

Prevention is of most importance. Several preventive interventions have been shown to be successful in reducing the risk of preterm birth (Table 42.2). These should be widely implemented, both at the local level (doctor–patient), and at the national level (government incentives and policies to assure implementation).

Conclusions

The incidence of preterm birth in the United States had increased more than 30% in the 20 years up to 2006. This was mostly due to increases in use of assisted reproduction (and consequent multiple gestations), and indicated preterm birth. Among other causes, coding of births at 22–24 weeks of gestation as preterm instead of miscarriages has undoubtedly increased the incidence in the United States. From its peak of 12.8% in 2006, the incidence of spontaneous preterm birth has decreased over 10% to about 11.5% in 2012. Implementation of preventive strategies
Table 42.2 Suggested prevention strategies to avoid preterm births

| Preconception | Avoid extremes of age  
|               | Aim for desirable interpregnancy interval (highest risk of PTB with interval less than 6 months)  
|               | Avoid multiple gestations, with an emphasis on responsible ART  
|               | Folate supplementation  
|               | Vaccinations (especially varicella, rubella, hepatitis B)  
|               | Balanced diet  
|               | Exercise  
|               | Avoid less than 120 lb maternal weight or BMI less than 19 kg/m²  
|               | Avoid illicit drug use and alcohol use  
|               | Avoid sexually transmitted infections  
|               | Optimize any medical disease (e.g., diabetes, hypertension, hypothyroidism, hyperthyroidism, asthma, lupus, HIV)  
|               | Stop or substitute with safer medications any teratogenic drug  
| Prenatal care  | Early ultrasound  
|               | Screen for and treat asymptomatic bacteriuria  
|               | Balanced diet  
|               | Proper weight gain (at least 15 kg over 40 weeks for nonobese women)  
|               | Avoid smoking, illicit drug use and alcohol  
|               | Avoid prolonged standing more than 3 hours/day  
|               | Avoid long work hours more than 39 hours/week  
|               | Avoid shift work  
|               | Avoid vaginal douching  
|               | Screen for domestic violence and provide resources  
|               | Screen for and treat sexually transmitted infections |

PTB, preterm birth; ART, assisted reproductive technologies; BMI, body mass index.

(as shown in Table 42.2) will help continue to decrease this incidence, which is still one of the highest in the world.

**Suggested reading**


