

# Prevention of Preterm Birth in Modern Obstetrics



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## KEYWORDS

• Preterm birth • Preterm birth prevention • Progestins • Cerclage • Pessary

## KEY POINTS

- Tocolytic therapy may be useful for delaying delivery long enough to permit administration of antenatal corticosteroids and/or maternal transport to a tertiary care center, but long-term use does not result in clinically significant pregnancy prolongation.
- Activity restriction has no proven benefit in the prevention of preterm birth and may result in substantial maternal morbidity.
- Cervical pessary usage is a potentially promising intervention, but further research is needed to determine the effectiveness of this device.
- Progestin prophylaxis and, in certain situations, cerclage placement are the most effective interventions in prevention of recurrent spontaneous preterm birth.
- Although there has been progress in recent decades, obstetricians and researchers still have a long way toward preventing preterm birth.

Preterm birth (PTB) continues to be the leading cause of neonatal death, causing more than 1 million deaths worldwide each year. In the United States, 11.72% of all babies were born before 37 weeks of gestation in 2011, representing the lowest PTB rate in more than a decade.<sup>1</sup> Despite this reassuring trend, the United States continues to have the highest PTB rate of any industrialized country. Despite the dedication of billions of dollars and untold hours of work, the solution to the problem of PTB remains elusive worldwide. This article focuses specifically on prevention of spontaneous preterm delivery, processes that account for 70% to 80% of all early births. The

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interventions that have been attempted to prevent spontaneous PTB are reviewed, some of which have been successful in some populations, whereas others have ultimately fallen out of favor because of lack of effectiveness.

## **INEFFECTIVE INTERVENTIONS**

### ***Home Tocometry***

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Home uterine activity monitoring has been proposed as a method of identifying women in early preterm labor, potentially allowing intervention to prevent delivery. This type of monitoring may be performed via subjective patient report or, more commonly, via use of home tocometry. Despite being initially heralded as a useful tool, tocometry has since fallen out of favor.

Numerous randomized controlled trials have evaluated the use of home monitors such that an exhaustive review of all of the available literature is beyond the scope of this article. For example, a recent Cochrane Review included 15 randomized controlled trials.<sup>2</sup> This meta-analysis showed no reduction in delivery before 37 weeks of gestation with home uterine monitoring.<sup>2</sup> When low-quality studies were excluded from the analysis, there were also no significant reductions in PTB before 34 weeks of gestation or neonatal intensive care unit admissions.<sup>2</sup>

If there is any benefit to home uterine activity monitoring, it may simply be the increased exposure of high-risk patients to specialized nurses and/or physicians. At present, the American College of Obstetricians and Gynecologists does not recommend use of home tocometry to screen for or prevent spontaneous PTB.<sup>3</sup>

### ***Tocolytics***

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Several tocolytic agents have been used over the last several decades. These agents vary in mechanisms of action, dosing regimens, and side effects but they all have one thing in common: their lack of efficacy in preventing PTB. As shown in **Table 1**, these agents may be beneficial in the short term, thereby allowing administration of antenatal corticosteroids and/or maternal transport to a level 3 center, but long-term effectiveness has not been shown. These agents are almost destined to fail because they are not initiated until it is too late.<sup>16</sup> By the time a woman presents with symptomatic preterm labor or preterm premature rupture of membranes, the underlying process has been ongoing for weeks if not months.<sup>16</sup> Tocolytic agents thus address the symptoms of preterm labor without affecting the cause of the process.<sup>16</sup>

### ***Activity Restriction***

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Many women diagnosed with advanced cervical dilatation, advanced cervical effacement, or threatened preterm labor are asked to adhere to activity restrictions. Activity restriction is probably the most commonly prescribed intervention to prevent PTB. These restrictions range from light restriction (1 hour or less of continuous rest during waking hours) to moderate restriction (1–8 hours of continuous rest) or even strict bed rest.

Despite its common use, literature supporting the efficacy of bed rest for prevention of spontaneous PTB is lacking, with randomized controlled trials showing no benefit.<sup>17,18</sup> Furthermore, although the recommendation for bed rest is primarily based on a no-harm-no-foul principle, emerging data indicate that there are potential negative effects to activity restriction. Pregnant women in general are at an increased risk for venous thromboembolic disease, a risk that is only increased in the setting of bed rest. Activity restriction is also associated with a significant decrease in muscle strength and coordination, and there are psychological and socioeconomic impacts that must be considered. Not only can activity restriction result in financial difficulties

**Table 1**  
Effectiveness of tocolytic agents

Class of Tocolytic	Examples	Short-term Benefits	Long-term Effects	Comments
Beta-adrenergic receptor agonists	Terbutaline sulfate Ritodrine hydrochloride	PTB rates reduced within 48 h of administration (RR, 0.68; 95% CI, 0.53–0.88) <sup>4</sup> May postpone delivery long enough to permit antenatal corticosteroid administration	No reduction in either total PTB rates or perinatal mortality <sup>4</sup> Prolonged use not associated with differences in gestational ages at delivery or PTB rates <sup>5,6</sup>	FDA warning against the use of terbutaline for >48–72 h (lack of efficacy and concerns about serious maternal heart problems) <sup>7</sup>
Calcium channel blockers	Nifedipine	PTB rates reduced within 7 d (RR, 0.82; 95% CI, 0.7–0.97) <sup>8</sup> Decreased PTB rates before 34 wk of gestation (RR, 0.77; 95% CI, 0.66–0.91) <sup>8</sup> Reduction in neonatal respiratory distress syndrome (RR, 0.63; 95% CI, 0.46–0.86) <sup>8</sup>	One randomized controlled trial comparing nifedipine with placebo (APOSTEL-II): no difference in adverse perinatal outcomes, gestational age at delivery, or pregnancy prolongation <sup>9</sup>	May be beneficial in the short term or for symptomatic contractions
Cyclooxygenase inhibitors	Indocin	Reduced PTB rates within 48 h of administration <sup>10</sup>	No difference in neonatal outcomes <sup>11</sup>	Use limited by fetal side effects, including premature closure of the ductus arteriosus and oligohydramnios Short courses (48 h) reasonable before 32 wk of gestation
Magnesium sulfate	Not applicable	None identified	No differences in PTB rates or neonatal respiratory distress <sup>12</sup>	Administration recommended for fetal neuroprotection (prevention of cerebral palsy specifically) <sup>13</sup>
Selective oxytocin-vasopressin receptor antagonists	Atosiban	Trend toward increased delivery within 48 h <sup>14</sup>	Trend toward increased risks of PTB at <28 wk and <37 wk of gestation <sup>14</sup>	Not available in the United States
Nitric oxide donors	Transdermal nitroglycerin	None identified	No clear benefit identified <sup>15</sup>	Further research needed

*Abbreviations:* APOSTEL, assessment of perinatal outcome with sustained tocolysis in early labor; CI, confidence interval; FDA, US Food and Drug Administration; RR, relative risk.

caused by lack of work, this intervention is clearly associated with disruption of family life and increased anxiety and depression.

In the setting of potential harm with no proven benefit, the use of activity restriction should be minimized for the prevention of spontaneous PTB. Per the American College of Obstetricians and Gynecologists, “these measures have not been shown to be effective for the prevention of PTB and should not be routinely recommended.”<sup>19</sup>

## INTERVENTIONS OF QUESTIONABLE EFFICACY

### *Treatment of Urogenital Tract Infections*

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Given the suspected link between PTB and inflammation, it seems logical that eradication of urogenital tract bacteria might reduce the risk of early delivery. Numerous studies have therefore addressed the relationship between PTB and such microbes as *Trichomonas vaginalis*, bacterial vaginosis, *Candida*, *Chlamydia trachomatis*, gonorrhea, and group B *Streptococcus*. More importantly, as shown in [Table 2](#), researchers have sought to determine whether treatment of such infections can reduce this risk.

In addition to treatment aimed at specific infections, antibiotic therapy in general has been proposed as an intervention to prevent PTB or at least prolong gestation. This strategy seems valid in the setting of preterm premature rupture of membranes, but such therapy does not seem to be effective in women with intact amniotic membranes. For example, in the ORACLE II trial, women in spontaneous preterm labor were randomized to receive erythromycin alone, amoxicillin and clavulanate potassium alone, erythromycin and amoxicillin and clavulanate potassium, or placebo.<sup>40</sup> No differences were shown in PTB rates or composite neonatal outcomes.<sup>40</sup> A similar study by Romero and colleagues<sup>41</sup> also failed to show a benefit to empiric antibiotic therapy. However, critics of such studies argue that perhaps the wrong antibiotic was used or the antibiotic was started too late in the process of parturition to make a difference. Regardless, the current literature does not support the use of empiric antibiotic therapy for prevention of PTB or prolongation of gestation.

In addition, the presence of infection and/or inflammation distant from the urogenital tract is also associated with increased PTB rates. Moderate to severe periodontitis is associated with an approximately 2-fold increased risk of PTB.<sup>42,43</sup> Despite this association, treatment of periodontal disease does not reduce the risk of a woman delivering prematurely and should currently be recommended only as part of routine health maintenance.<sup>44–46</sup>

### *Pessary*

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Use of the cervical pessary has been touted as a noninvasive cerclage. The Arabin pessary, a flexible ringlike silicone device, has been most effective in published trials. The smaller inner diameter of this device should fit around the cervix snugly, thereby minimizing exposure of fetal membranes to the vaginal flora.<sup>47</sup> The inclination of the cervical canal is also changed, directing it posteriorly so that the weight of the pregnancy centers on the anterior lower segment.<sup>47</sup>

Since its first use, multiple studies have been published investigating the efficacy of this intervention, with varying pessary types, research designs, and patient populations reported. The PECEP (Pesario Cervical Para Evitar Prematuridad) trial, the largest trial to date, was a randomized controlled trial that enrolled women with cervical shortening (cervical length  $\leq 25$  mm). Of women assigned to the pessary arm, 6% delivered before 34 weeks' gestation; an 82% reduction compared with the 27% of women who delivered prematurely in the expectant management arm.<sup>48</sup> This trial has been criticized because of a higher-than-expected rate of PTB in the control arm, questionable ability to generalize, and lack of administration of progestin therapy.

**Table 2****The link between urogenital infections and PTB**

<b>Infection</b>	<b>PTB Association</b>	<b>Treatment Effect</b>	<b>Recommendation</b>
<i>T vaginalis</i>	Increased risk of PTB with infection	Treatment of asymptomatic infection may increase the risk of PTB <sup>20</sup>	Routine screening and treatment in asymptomatic women not recommended
Bacterial vaginosis	Strong predictor of PTB (up to a 7.6-fold increased risk) <sup>21</sup>	No benefit seen in several RCTs using clindamycin or metronidazole <sup>22–25</sup>	Routine screening and treatment in asymptomatic women not recommended
Vaginal candidiasis	No clear association <sup>26</sup>	One RCT showed a reduction in PTB rates (RR, 0.34; 95% CI, 0.15–0.79) in asymptomatic women screened and treated in the second trimester <sup>27</sup>	More research needed
<i>C trachomatis</i>	Inconsistent literature	Retrospective cohort study showing an RR of 0.54 (95% CI, 0.37–0.8) for delivery at 32–36 wk gestation in patients treated at <20 wk <sup>28</sup> RCT showed no reduction in PTB rates with treatment between 23 and 29 wk of gestation <sup>29</sup>	Treatment indicated to prevent neonatal morbidity
<i>Neisseria gonorrhoea</i>	Two retrospective studies showing an association <sup>30,31</sup>	No studies evaluating treatment effect	Definitive research cannot be performed because of public health issues
Group B <i>Streptococcus</i> colonization	Meta-analysis of cohort studies showed no relationship Meta-analysis of cross-sectional and case-control studies showed an association <sup>32</sup>	No benefit in prevention of PTB <sup>33</sup>	Treatment should follow CDC guidelines to prevent neonatal morbidity and mortality <sup>34</sup>
Asymptomatic bacteriuria	Inconsistent literature <sup>35</sup>	Cochrane Review showed no reduction in PTB rates with treatment <sup>36</sup>	Treatment recommended for reduction of maternal morbidity and mortality
Cystitis	Three retrospective studies showing an increased risk of PTB (RR, 1.03–1.38) <sup>37,38</sup>	No studies showing a reduction in PTB rates after treatment	Treatment recommended for reduction of maternal morbidity and mortality
Pyelonephritis	Associated with an increased risk of PTB (OR, 1.3; 95% CI, 1.2–1.5) <sup>39</sup>	No studies to date showing a reduction in PTB rates with treatment	Treatment recommended for reduction of maternal morbidity and mortality

Abbreviations: CDC, US Centers for Disease Control and Prevention; OR, odds ratio; RCT, randomized controlled trial.

The ProTWIN trial then evaluated the prophylactic use of Arabin pessaries in multiple-gestation pregnancies, showing no differences in PTB rates or a composite of poor perinatal outcomes in women randomized to receive a pessary compared with controls.<sup>49</sup> These findings prompted the investigators to conclude that, “in unselected women with a multiple pregnancy, prophylactic use of a cervical pessary does not reduce poor perinatal outcome.”<sup>49</sup>

Despite these critiques, pessaries have several advantages compared with surgical cerclage. As a nonsurgical alternative, pessary use can be expected to result in decreased hospital costs and anesthesia exposure. Complications such as bleeding, infection, and rupture of membranes are also likely to be less common with pessary than cerclage. In addition, few complications and/or side effects have been reported with the use of cervical pessaries, with patients primarily complaining of increased vaginal discharge and discomfort with placement and removal of the device.<sup>48</sup>

Pessary use is currently a promising but unproven therapy for prevention of preterm labor. Multiple trials are currently in process to better define the populations that may benefit from this device.

## SUCCESSFUL THERAPY

### *Lifestyle Modifications*

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Women should be counseled about simple and cost-effective interventions that may reduce their risk of early delivery. For example, smoking is a known risk factor for PTB. Although there are no randomized controlled trials that show a reduction in PTB rates with smoking cessation, all pregnant women who admit to tobacco use should be encouraged to quit and provided with resources to assist with cessation. In addition, because PTB is most common in women with an interpregnancy interval of less than 6 months, women should be counseled about safe pregnancy spacing.

However, the expected treatment effect is not seen for all interventions. For example, although poor prenatal care is linked to PTB, enhanced prenatal care with more frequent visits and improved education does not necessarily improve outcomes. For example, the March of Dimes Multicenter Prematurity Prevention Trial showed no difference in PTB rates in women assigned to a program of enhanced care involving frequent visits and increased education; a finding that was confirmed by a later Cochrane Review.<sup>50,51</sup> Likewise, interventions designed to enhance social support do not seem to effectively prolong gestational length.<sup>52,53</sup> Regardless, prenatal care and social support are recommended because of other benefits on maternal and fetal health.

### *Progestational Agents*

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Current evidence supports the use of progestin prophylaxis in certain populations for prevention of PTB. One group that seems to benefit from this therapy is women with a history of a prior spontaneous PTB. In 2003, Meis and colleagues<sup>54</sup> showed that 17-alpha-hydroxyprogesterone caproate (17OHP) significantly reduced the risk of recurrent preterm delivery before 37 weeks' gestation with a relative risk (RR) of 0.66 (confidence interval [CI], 0.54–0.81). A trial by da Fonseca and colleagues<sup>55</sup> then showed a reduction in recurrent PTB rates using progesterone administered via a vaginal suppository: 13.8% of women in the progesterone group delivered before 37 weeks of gestation compared with 28.5% in the placebo group ( $P = .03$ ), with incidences of delivery before 34 weeks of gestation of 2.8% versus 18.6% respectively ( $P = .002$ ).<sup>55</sup> However, a trial by O'Brien and colleagues<sup>56</sup> failed to show a reduction in recurrent PTB rates using a progesterone gel, but a Cochran Review including 36 randomized controlled trials subsequently showed statistically significant reduction in

risks of such important outcomes as PTB at less than 34 weeks (RR, 0.31; 95% CI, 0.14–0.69), PTB at less than 37 weeks (RR, 0.55; 95% CI, 0.42–0.74), and perinatal mortality (RR, 0.50; 95% CI, 0.33–0.75).<sup>57</sup>

Progestin prophylaxis is not effective in women with multiple gestations,<sup>58–62</sup> but another group that may benefit from therapy is women with cervical shortening. Fonseca and colleagues<sup>63</sup> in 2007 showed a reduction in preterm delivery before 34 weeks of gestation (RR, 0.56; 95% CI, 0.36–0.86) using progesterone suppositories in asymptomatic women with cervical shortening. A subsequent study by Hassan and colleagues<sup>64</sup> showed a similar reduction in PTB before 33 weeks of gestation (RR, 0.55; 95% CI, 0.33–0.92) using progesterone gel in this population. Grobman and colleagues<sup>65</sup> failed to show a reduction in preterm delivery rates in women with cervical shortening who were exposed to 17OHPC, but a meta-analysis by Romero and colleagues<sup>66</sup> showed that vaginal progesterone supplementation reduced the risk of PTB (RR, 0.69 with 95% CI, 0.55–0.88 for delivery <35 weeks; RR, 0.50 with 95% CI 0.30–0.81 for delivery <28 weeks) and associated morbidity in asymptomatic, otherwise low-risk women with cervical shortening.

Progestin prophylaxis therefore seems to be an important tool in the armamentarium to prevent PTB. As shown in **Fig. 1**, this therapy should be considered in women with prior preterm deliveries and those with cervical shortening less than 20 mm, but current research does not support its use in other clinical situations.<sup>67</sup>

### **Cerclage**

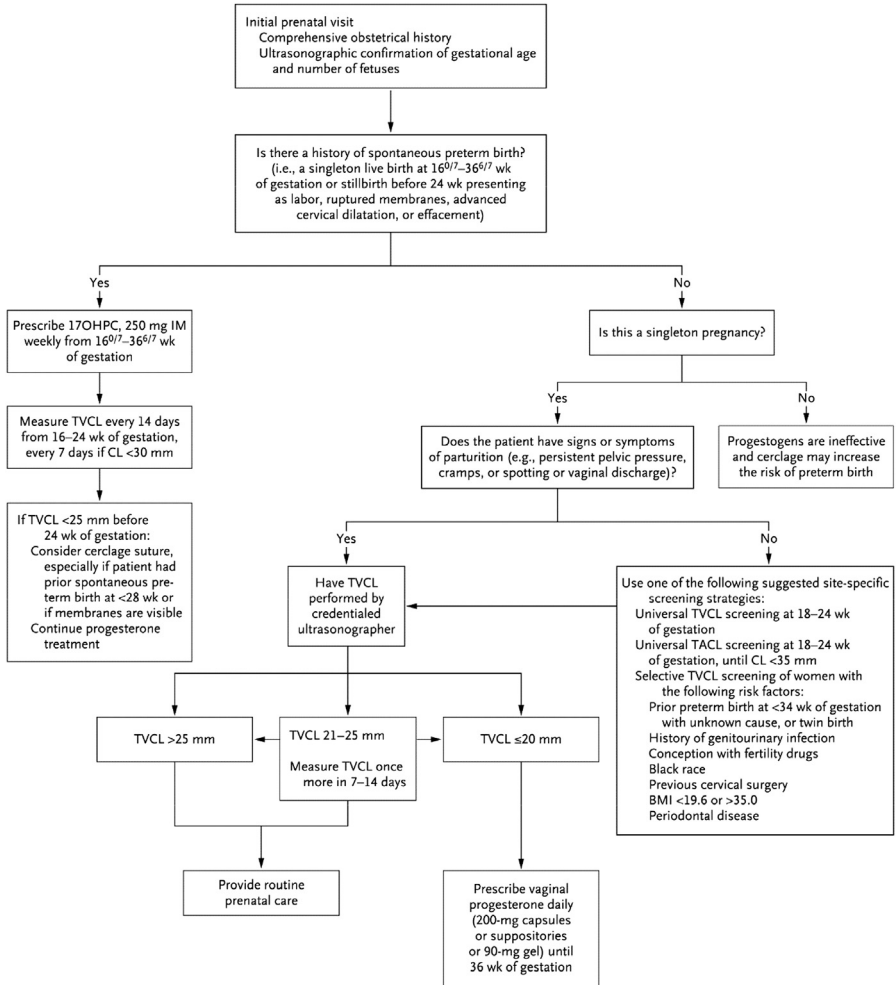
The indications for cerclage placement have changed over the decades, with current practices more concerned with placement of indicated cerclages in women with cervical shortening despite progestin prophylaxis rather than placement of cerclages in the early second trimester based solely on a history of PTB.

Although none of the individual randomized controlled trials show an improvement in PTB rates with cerclage placement, a meta-analysis by Berghella and colleagues<sup>68,69</sup> found that cerclage placement was associated with an RR of 0.70 (95% CI, 0.55–0.89) for recurrent PTB before 35 weeks' gestation.<sup>70–73</sup> Cerclage placement was also associated with a decreased risk for recurrent PTB before 37 weeks' gestation (RR, 0.7 with 95% CI, 0.58–0.83), 32 weeks' gestation (RR, 0.66 with 95% CI, 0.48–0.91), 28 weeks' gestation (RR, 0.66 with 95% CI, 0.43–0.96), and 24 weeks' gestation (95% CI, 0.48 with 95% CI, 0.26–0.9), as well as a reduction in composite mortality and morbidity (RR, 0.64 with 95% CI, 0.45–0.91).<sup>69</sup>

Women enrolled in the trials discussed earlier were not concurrently treated with supplemental progesterone. No randomized controlled trial has been performed to date evaluating the efficacy of cerclage placement in women also treated with progestins. Rafael and colleagues<sup>74</sup> retrospectively examined this issue, showing no difference in the rate of recurrent PTB before 35 weeks' gestation with concurrent therapy (odds ratio, 1.72 with 95% CI, 0.5–5.89), suggesting that there may not be a cumulative effect with these two treatment modalities. Again, further research is needed to better define the utility of combined therapy.

### **Interventions to Limit Nonindicated Deliveries Before 39 Weeks of Gestation**

One of the most successful quality improvement campaigns in obstetrics recently has involved a push toward elimination of elective deliveries before 39 weeks of gestation. This change reflects the growing understanding of the morbidity and mortality associated with late preterm and early term births, including increased risks of such complications as hypothermia, respiratory distress, hypoglycemia, infection, apnea of the newborn, hyperbilirubinemia, and feeding difficulties.<sup>75</sup> There also seems to be



**Fig. 1.** Clinical use of progestin prophylaxis. BMI, body mass index; CL, cervical length; TACL, transabdominal cervical length; TVCL, transvaginal cervical length. (From Iams JD. Prevention of preterm parturition. *N Engl J Med* 2014;370:1861; with permission.)

long-term morbidity, particularly neurodevelopmental issues, associated with these births before 39 weeks.<sup>75</sup>

Such initiatives primarily focus on the timing of either elective deliveries or those in the setting of obstetric complications (ie, preeclampsia, intrauterine growth restriction, oligohydramnios, diabetes mellitus).<sup>76</sup> Deliveries related to spontaneous preterm labor or preterm premature rupture of membranes are less likely to be affected by these quality improvement programs, but they still represent an important milestone in the quest to reduce PTB rates overall.

## SUMMARY

Preterm labor is a complex disease characterized by the interplay of multiple different pathways. As such, prevention of preterm labor and delivery is complicated as well,



and it is highly likely that no single intervention will be effective for every woman. In addition to this complexity, one of the major obstacles to prevention is the early identification of women at risk, who do not usually present with symptoms until weeks or even months after the underlying process first started. Successful therapy therefore needs to be initiated far in advance of symptoms, examination findings, or even ultrasonography findings. To be effective worldwide, such therapy also needs to be inexpensive and easily obtainable. Researchers and clinicians must collaborate to achieve all of these essential qualifications if a cure for PTB is to be found.

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