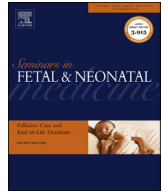




Contents lists available at ScienceDirect

## Seminars in Fetal &amp; Neonatal Medicine

journal homepage: [www.elsevier.com/locate/siny](http://www.elsevier.com/locate/siny)

## Review

## Multiple gestations and preterm birth

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## S U M M A R Y

**Keywords:**  
 Preterm birth  
 Short cervix  
 Progesterone  
 Cerclage  
 Pessary  
 Fetal fibronectin

Preterm birth is a major concern in modern obstetrics, and an important source of morbidity and mortality in newborns. Among twin pregnancies, especially, preterm birth is highly prevalent, and it accounts for almost 50% of the complications observed in this obstetrical population. In this article, we review the existing literature regarding the prediction and prevention of preterm birth in both symptomatic and asymptomatic twin pregnancies. In asymptomatic twin pregnancies, the best two predictive tests were cervical length (CL) measurement and cervicovaginal fetal fibronectin (fFN) testing. A single measurement of transvaginal CL at 20–24 weeks of gestation <20 mm or <25 mm is a good predictor of spontaneous preterm birth at <28, <32, and <34 weeks of gestation. A CL beyond 25 mm is associated with a 2% risk for birth before 28 weeks and with a 65% chance for a term pregnancy. Cervicovaginal fFN may be slightly less accurate than CL; however, it has a high negative predictive value in women presenting with threatened preterm labor, as <2% of these women will deliver within one week if the fFN is negative. In symptomatic twin pregnancies, no tests have proven accurate in predicting the risk of preterm birth. For the prevention of preterm birth in asymptomatic twins, regardless of CL, no treatment including bed rest, limitation of home activities, prophylactic tocolysis, progesterone, or cerclage has been shown to reduce the rate of preterm birth. Cervical pessaries might be of interest in cases where there is a short cervix (<25 mm and <38 mm, respectively) but these results need to be confirmed in future trials.

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## 1. Preterm birth in twins: epidemiology

Prematurity is one of the leading causes of perinatal morbidity, mortality, and long-term neurodevelopmental impairment. According to a recent national, prospective, population-based French cohort study (EPIPAGE-2), a child born at 25 weeks has a 40% risk for death before discharge from hospital, and about 45% of the survivors are expected to have moderate-to-severe handicap as infants [1]. Both survival and neurological prognosis improve with advancing gestational age. Children born at 32 weeks have a 98.2% survival rate according to EPIPAGE-2 [1], with only 4.4% risk for cerebral palsy at the age of 2 years [2] and 8% risk for neurodevelopmental delay [3] according to the original French cohort study EPIPAGE-1, conducted in 1997.

The risk of prematurity is much higher in twins than in singletons. In the USA in 2013, the twin birth rate reached a new high with 33.7 per 1000 total births. National Vital Statistics also revealed that the rate of preterm birth (PTB) was 56.6% in twins vs 9.7% for singletons, a risk more than 12 times higher [odds ratio (OR): 12.8; 95% confidence interval (CI): 12.6–12.9]. The prematurity rate before 32 weeks was 11.3% for twins and 1.5% for singletons, with an odds ratio of 8.2 (95% CI: 8.0–8.3) [4]. Among twins, in a prospective study of 800 dichorionic and 200 monochorionic twin pregnancies, 29% of dichorionic pregnancies developed a maternal or fetal condition, leading to birth before 36 weeks, whereas 34% of the monochorionic twins were born before 34 weeks [5]. In a recent meta-analysis, the pooled rates of birth before 37, 34 and 32 weeks for twins, independent of chorionicity, were 41%, 13% and 7%, respectively [6].

The discrepancies observed are probably due to a different pathophysiology of PTB among multiple pregnancies, which includes intrauterine infection or inflammation, cervical insufficiency, uterine overdistension, hormonal disorders, uterine ischemia, abnormal allograft reaction, or allergy [7]. It is therefore

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important to search for specific predictive factors for PTB among asymptomatic twin pregnancies and among twin pregnancies with symptoms of labor.

## 2. Prediction of preterm birth in asymptomatic twin pregnancies

### 2.1. Chorionicity

Chorionicity is one of the most important factors that contribute to the development of PTB in twins. Monochorionic diamniotic (MCDA) twins are at higher risk compared with dichorionic (DCDA) twins for PTB and prenatal complications. In a historical cohort of 1407 twin pregnancies, the rate of birth before 28 weeks was 11% for MCDA compared with 7% for DCDA twins, and the rates for birth before 32 weeks were 26% compared with 18%, respectively [8]. Monochorionic diamniotic twins were also at increased risk for fetal death (even at term), necrotizing enterocolitis, and neurological morbidity. A significant contributor of prematurity and morbidity in MCDA twins is twin-to-twin transfusion syndrome (TTTS). In a recent multicenter study of about 10,000 twin pregnancies, the rate of birth before 34 weeks was 24% in the MCDA group compared with 16% in the DCDA twin group [9]. The rates of preterm premature rupture of membranes (PPROM) and pregnancy-induced hypertension, however, were similar between the two types of twins, and most of the difference in the rates of prematurity could be attributed to TTTS in MCDA twins, which was 7.3% before 37 weeks. Other MCDA-specific complications affecting prematurity rates include selective intrauterine growth restriction (sIUGR) [10] and twin anemia–polycythemia sequence (TAPS) [11].

### 2.2. History of previous preterm birth

Facco et al. retrospectively compared between 1995 and 2005 the gestational age at delivery for pregnant patients carrying twins and having a history of PTB ( $n = 23$ ) or not ( $n = 270$ ) in a previous singleton pregnancy. Women with a history of PTB had an increased risk of PTB in both univariate [73.9% vs 44.4%; odds ratio (OR): 3.5; 95% CI: 1.4–9.37] and multivariate analyses (OR: 3.3; 95% CI: 1.3–8.7) [12]. Another retrospective study based on an American birth registry between 1995 and 2000 found similar results [13]. The risk of PTB before 35 weeks for nulliparous women ( $n = 635$ ), multiparous women without a history of PTB ( $n = 418$ ) or with a history of PTB ( $n = 215$ ) was 32.9%, 23.0% and 37.7% ( $P < 0.001$ ), respectively [13].

### 2.3. Cervix digital examination

In a randomized study of 5602 singleton pregnancies, Buekens et al. demonstrated that systematic cervix digital examination at each prenatal visit did not reduce the rate of premature births in comparison with symptom-indicated cervix examination [6.7% vs 6.4%; relative risk (RR): 1.05; 95% CI: 0.85–1.29] [14]. Unfortunately, such studies have not been performed in a population of twin pregnancies. Nevertheless, a French multicenter prospective cohort study showed that among 153 twin pregnancies at 27 weeks of gestation, transvaginal cervical length measurement was a better predictor of PTB before 34 weeks than cervical examination [15].

### 2.4. Uterine activity evaluation

Many authors have hypothesized that abnormally high uterine activity recorded by tocography or by the patient herself could

identify patients at risk for PTB. However, the literature does not support this point of view. In 1996, a study of 778 patients enrolled in a premature birth prevention program (633 singletons and 145 twins) showed that patients correctly identified only 17.2% of contractions recorded through tocography by abdominal palpation [16]. Further, this correlation was significantly lower for the pregnant patients carrying twins compared to those with a singleton pregnancy.

In 1995, a meta-analysis of six randomized trials involving a total of 260 twin pregnancies did not find any difference between a group of “daily home tocography” versus “abdominal palpation,” with regards to the incidence of premature births (RR: 1.01; 95% CI: 0.79–1.30;  $P = 0.95$ ) [17]. Finally, an observational prospective double-blind study in 2006 demonstrated similar results. Frequency of uterine contractions was significantly increased in twins compared to singletons ( $P = 0.002$ ), but it was not different among patients who gave birth prematurely or at term [18].

### 2.5. Cervical length measurement in asymptomatic women

Sixteen studies have found a significant association between a shortening of cervical length during pregnancy and the risk of PTB. From this association stems the idea to measure the cervical length by transvaginal ultrasound in order to determine whether an asymptomatic population of pregnant women with twins is at risk of PTB. A recent meta-analysis summarized data from all the 16 studies ( $n = 3213$ ) on asymptomatic twin pregnancies with cervical length measurements at 20–24 weeks [6]. Usually, convincing predictive accuracy of a test is defined as a positive likelihood ratio  $>10$  and/or negative likelihood ratio  $<0.1$ . This study found that the most accurate cut-off for the prediction of birth before 28 weeks was cervical length at  $\leq 25$  mm [area under the curve (AUC) 0.86, sensitivity (Se) 64%, specificity (Sp) 93%, positive likelihood ratio (PLR) of 9.6, negative likelihood ratio (NLR) of 0.40], whereas a cervical length of  $\leq 20$  mm was the most accurate predictor for birth before 32 weeks (AUC 0.80, Se 39%, Sp 96%, PLR 10.1, NPV 0.64), and before 34 weeks (AUC 0.77, Se 29%, Sp 97%, PLR 9, NLR 0.74). Therefore, in asymptomatic women, a cervical length of  $\leq 20$  mm at 20–24 weeks was associated with 42.4% risk of birth before 32 weeks and 62% risk of birth before 34 weeks. A cervical length of  $\leq 25$  mm was associated with 26% risk of birth before 28 weeks; in contrast, a longer cervix was associated with only 1.4% risk of birth before 28 weeks and 63.2% chance of birth after 37 weeks [6]. One further systematic review published after this meta-analysis confirmed its findings in asymptomatic women [19]. In summary, a single measurement of transvaginal sonographic cervical length at 20–24 weeks of gestation is a good predictor of spontaneous PTB at  $<28$ ,  $<32$ , and  $<34$  weeks of gestation in asymptomatic women with twin gestations.

On the contrary, when studying the change in cervical length over time, a recent systematic review found that this change had a low to moderate predictive accuracy for PTB at  $<34$ ,  $<32$ ,  $<30$ , and  $<28$  weeks of gestation in women with twin gestations [20].

However, so far there have been no studies showing that the identification of a group at risk of PTB by measuring transvaginal cervical length in twin is helpful in providing appropriately timed antenatal corticosteroids. Consequently, no studies have shown benefits in the systematic measure of cervical length by transvaginal ultrasound in terms of improvement of maternal and neonatal health. Some could then argue that such systematic measurement of cervical length may even cause harm by administering inadequately timed antenatal corticosteroids and unnecessary hospitalization.

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