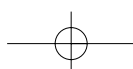
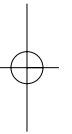
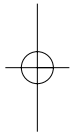
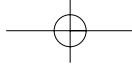


# Prediction of Spontaneous Preterm Birth

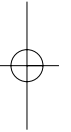
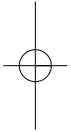
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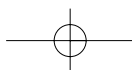
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# Prediction of Spontaneous Preterm Birth

## Voorspelling van Spontane Vroeggeboorte

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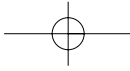
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op gezag van de Rector Magnificus, Prof. Dr W.H. Gispen,  
ingevolge het besluit van het College voor Promoties  
in het openbaar te verdedigen  
op dinsdag 28 mei 2002 des middags te 4.15 uur

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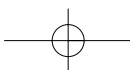
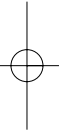
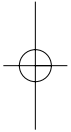
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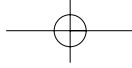
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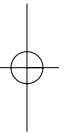
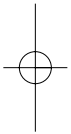
**Promotores:**

Prof. dr. G.H.A. Visser  
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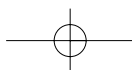




*If I am not for myself, who will I be?  
If I am only for myself, what am I?  
If not now, when?  
(Hillel)*



*Voor Paul en  
voor mijn ouders*



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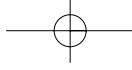
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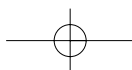
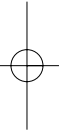
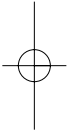


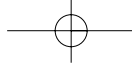




# 1

## Introduction



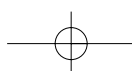


## Introduction

Preterm birth, defined as a delivery before the completion of 37 weeks of gestation, is a leading cause of neonatal morbidity and the second leading cause of neonatal mortality.<sup>1,2</sup> Preterm birth includes preterm labor with intact membranes (PTL;  $\pm$  40%), preterm premature rupture of membranes (PPROM;  $\pm$  40%), and indicated delivery because of deteriorating maternal or fetal health ( $\pm$  20%).<sup>3</sup> Preterm delivery occurs in approximately 7 to 11% of all births in western countries.<sup>4,5</sup> Its incidence has increased during the last decade. Main reasons are (1) a higher incidence of multiple births due to fertility-enhancing drugs and procedures; (2) a tendency toward early (including preterm) induction or Cesarean section for pathological pregnancies; (3) an increase in registration of births near the borderline of viability; and (4) a more accurate estimated gestational age by the increasing use of early ultrasound.<sup>6</sup> Neonatal intensive care has improved the survival rate for babies, including those born at the very threshold of viability, but the proportion of survivors with disabilities is still high.<sup>6</sup>

In this thesis we will focus on spontaneous preterm birth (SPB), which includes PTL and PPROM. The strategies to prevent or reduce SPB have not been effective until now. SPB is a syndrome produced by a wide variety of disease conditions operating through different pathogenic pathways and mechanisms.<sup>7</sup> With the recent advances in understanding the pathogenesis of SPB, a number of techniques have been proposed to predict SPB.

It is of clinical relevance to be able to predict SPB, if an intervention is available that is likely to improve outcome. Such an intervention should preferably prevent preterm birth at all. Unfortunately this can presently not yet been achieved in most cases. However, there are interventions improving outcome. The use of tocolytic agents reduces uterine contractions, which prolongs pregnancy with an average of several days. In this time period corticosteroids can be administered to improve the fetal lung maturity.<sup>8-10</sup> The opportunity to administer corticosteroids to the mother is an important intervention recommended by the National Institute of Health as it strongly reduces neonatal morbidity and mortality.<sup>9,10</sup> Since tocolytic and steroid therapy may result in maternal and/or fetal side effects, use of these therapies should be limited to women with true preterm labor at high risk for SPB. Another reason to identify women at risk for a preterm birth is to allow appropriate maternal transport to a tertiary care center. Optimal care can be



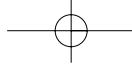
provided for the newborn from birth onwards in a neonatal intensive care center for neonates born before 32 gestational weeks. It is also important to identify the women at low risk for SPB, to prevent the use of unnecessary interventions.

Past (and current) approaches to predict those women who will deliver preterm, have relied on (1) demographic information (such as ethnicity, age, marital status,<sup>2</sup> (2) previous pregnancy history (e.g. prior spontaneous or induced abortion, preterm birth in prior pregnancies<sup>11</sup> and (3) clinical indicators in the current pregnancy such as cervical change, increasing uterine contraction frequency and vaginal bleeding.<sup>12</sup> Multiple gestations also have a high risk of preterm birth, 50% of all twin pregnancies and practically all of the higher-order multiple pregnancies are born preterm.<sup>13</sup> (4) Other risk factors associated with spontaneous SPB are occupational,<sup>14</sup> environmental,<sup>15</sup> psychosocial,<sup>2,16-18</sup> behavioral, and nutritional factors.<sup>19</sup> Previous SPB, African-American race, and second-or third trimester bleeding have been associated most consistently with SPB. Among women with singleton pregnancies, a previous preterm birth is the strongest historic predictor, with relative risks reported in the range of 2 to 6.<sup>20-22</sup> Moreover, until now preterm birth risk scoring systems based on arbitrarily selected or weighted epidemiological, historical, and clinical risk factors have insufficient predictive value.<sup>20,21,23,24</sup>

One of the main reasons that treatment to reduce preterm birth is so ineffective is that the individual cause is rarely determined during prenatal care. It will remain difficult to reduce preterm births if we cannot act on their causes. The failure of traditional approaches to predict SPB is likely to be an inadequate understanding of the underlying heterogeneous pathogenesis of SPB. It is important to get more insight in the pathophysiology in order to be able to discover new predictive/diagnostic tests and new therapeutic modalities in the future. The understanding of the pathogenesis has substantially improved recently and different pathways have been described in the literature.<sup>7</sup> New biochemical fluid markers (cytokines, hormones and enzymes) might be relevant in the etiological model of SPB.

### **Aims of the thesis**

The obstetric problem SPB is the basis for the studies described in the present thesis. As outlined above it is of clinical relevance to discover early etiologic markers. This would allow us to identify subgroups of patients at high risk of preterm birth to improve the efficacy of our management. Therefore it is our goal to present the



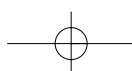
latest ideas regarding the pathogenesis and to describe the efficacy of (new) biochemical and biophysical markers for predicting preterm birth based on a review of the literature. We will focus on a variety of hormones, cytokines and enzymes and will describe whether these markers can be useful in routine obstetrical practice.

**Aim 1: to provide a systemic review of the literature regarding the pathogenesis and methods to predict spontaneous preterm birth**

Secondly, we would like to discover novel early etiologic markers. From the literature we know that matrix metalloproteinase-1 and -9 (MMP-1 and MMP-9) are important in the maintenance and breakdown of the extracellular matrix of the amniochorion and cervix.<sup>25</sup> They play an important role during cervical dilatation in human parturition. The presence of the biochemical marker MMP-1 has been studied in human cervical tissue,<sup>26</sup> the placenta,<sup>27</sup> amniotic fluid<sup>28</sup> and serum.<sup>29-32</sup> The involvement of MMP-9 in parturition has been demonstrated in the amnion of rat<sup>33</sup> and humans,<sup>34</sup> in amniotic fluid,<sup>35,36</sup> urine<sup>37</sup> and plasma.<sup>38</sup> The purpose of our study is to evaluate whether MMP-1 and -9 are detectable in a new medium, cervicovaginal secretions. This will be studied in women during pregnancy and in preterm and term labor. If cervicovaginal MMP-1 and/or MMP-9 are detectable, we aim to evaluate the usefulness of these markers in the prediction of SPB.

**Aim 2: to assess the usefulness of matrix metalloproteinase-1 and -9 in predicting spontaneous preterm birth**

To date, the cervical length as measured by transvaginal ultrasonography (TVS) and fetal fibronectin (FFN) levels in cervical or vaginal secretions have been most strongly and consistently associated with subsequent SPB.<sup>7,20,21</sup> A decade ago, TVS was introduced as a non-invasive technique for the assessment of cervical length. Currently, it is widely used in clinical obstetric care. However considerable variability in cervical length measurements have been described in the literature. Therefore the two studies regarding cervical length presented in this thesis aim to assess the methodological and sociodemographic influences on the test, which have not been addressed yet. Purposes of the studies are to further characterize



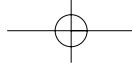
how cervical length varies between various racial groups and other sociodemographic factors by gestational age intervals. Besides we aim to establish basic population norms of central length (nomograms) over time and clarify their relationship both at term and preterm birth.

**Aim 3: to assess normal cervical length across gestation and the influence of sociodemographic factors on cervical length at term and preterm birth**

One of the causes of SPB is cervical incompetence. Cervical incompetence is usually treated by bed rest and/or transvaginal cervical cerclage.<sup>39</sup> A cerclage can be inserted prophylactically, prior to pregnancy or in the first trimester, or therapeutically after detection of cervical changes during pregnancy. TVS is used to identify cervical changes such as funneling and shortening. Recent studies have shown that a cerclage results in measurable cervical lengthening. It is not known whether this relative restoration of cervical anatomy after prophylactic or urgent cerclage predicts pregnancy outcome.<sup>40</sup> Our purpose is to determine whether the degree of cervical lengthening after cerclage predicts term delivery. The second aim is to evaluate the usefulness of serial cervical length measurements after cerclage to predict pregnancy outcome.

**Aim 4: to determine the usefulness of cervical length measurements after cerclage and their predictive value of spontaneous preterm birth**

Aims 2, 3 and 4 of the thesis are covered by means of patient studies performed in New York. The last aim is completed in the Netherlands and includes the health-care providers. It is our purpose to evaluate the usefulness of the above-mentioned methods to predict SPB in the 'unique' Dutch obstetric care system.<sup>41,42</sup> The first line obstetrical care providers (midwives and general practitioners practicing obstetrics) have to make a reliable assessment to refer a patient with symptoms of threatened preterm delivery to the gynecologist. The Obstetric Indication List (= 'Verloskundige Indicatie Lijst' (VIL))<sup>43</sup> is a good resource for risk selection in the Dutch obstetric care. However, the guidelines in the VIL regarding preterm birth are only briefly described. The impression exists that there are different

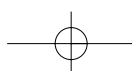
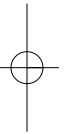
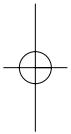


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*Chapter 1*

views regarding diagnosing and treating threatened preterm birth among and within the three professional groups active in the Dutch obstetric care. A questionnaire was conducted to get insight in the consultation between the first and second line regarding SPB, to be able to create new guidelines in the future. The objective of our study is to describe the management and views regarding threatened preterm birth, views about mutual cooperation and the acceptance of the VIL among midwives, general practitioners and gynecologists. The second aim is to provide insight in the use of (new) predictors of SPB and treatment modalities by the Dutch gynecologists.

**Aim 5: to study the management and views regarding spontaneous preterm birth in Dutch obstetric care**



## Reader's companion

This thesis consists of two parts. In the first part the pathogenesis and (new) methods for prediction of spontaneous preterm birth are described. An overview will be given of the possible mechanisms resulting in uterine contractions, cervical change, rupture of the membranes and finally to spontaneous preterm birth. A review is provided of the most important biophysical and biochemical markers to predict SPB (chapter 2). Furthermore a new etiologic marker for SPB will be assessed. In a case-control study we sought to determine whether matrix metalloproteinase-1 and -9 levels in cervicovaginal fluid differ in women during pregnancy compared to women at term or in preterm labor (chapter 3).

Chapters 4-6 focus on the assessment of the length of the cervix by TVS. This is a diagnostic method already used often in clinical practice, but where standardization is lacking. In chapter 4 we aim to create nomograms with an observational cohort study of sonographically determined cervical length measured at 3 to 4-week intervals. This will be studied in 125 women with uncomplicated, singleton pregnancies that resulted in term deliveries. The association of sociodemographic factors with changes in the length of the cervix across gestation will be described. In chapter 5 nomograms will be provided for 4 different race-groups in 777 women with uncomplicated, singleton pregnancies that resulted in term deliveries and 79 women who delivered preterm. The racial variation in cervical length and its relation with preterm delivery will be described. In chapter 6 the results of cervical length measurements after cerclage are described to determine whether this relative restoration of cervical anatomy after cerclage predicts pregnancy outcome. Fifty women with a prophylactic cerclage and 30 with an urgent cerclage had sonographic examinations before and after cerclage and thereafter three measurements until 32 weeks gestation.

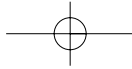
The second part outline the views and management regarding the diagnosis and treatment of preterm birth in the obstetrical care in the Netherlands. In chapter 7 the views on risk selection, management and mutual cooperation regarding SPB under Dutch first line obstetrical care providers (midwives and general practitioners) and obstetrician/gynecologists are evaluated. In chapter 8 the use of (new) diagnostic tests and treatment modalities for SPB under 85 Dutch obstetrician/gynecologists are presented. Chapter 9 contains the summary and discussion. Clinical guidelines will be provided for the general population and for women at risk for SPB or with symptoms of threatened SPB.

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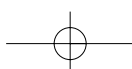
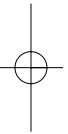
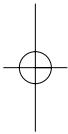
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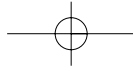


*Chapter 1*

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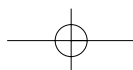
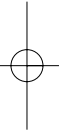
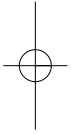
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# 2

## Pathogenesis and methods for the prediction of spontaneous preterm birth



## Introduction

In the last decade a lot of theories have been described regarding the cause of spontaneous preterm birth (SPB). In this chapter we will describe a model of the pathogenesis of SPB. Furthermore a systematic review will be provided regarding various methods to predict SPB.

## Method

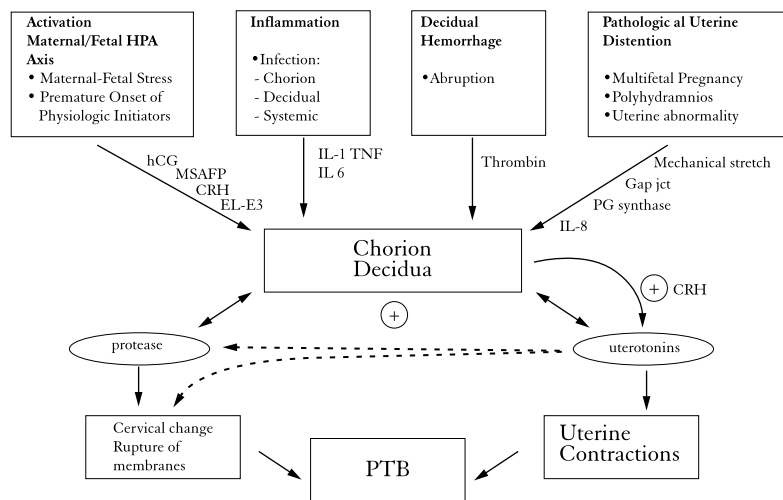
The Pubmed (formerly Medline) database and the Cochrane library were used to conduct a literature search to locate relevant articles regarding various methods to predict SPB, published between January 1995 and January 2002. The search was restricted to articles published in the English language. The words we used to search were: 'preterm birth' or 'premature labor' and 'CRH', 'estrogen/estriol', 'MSAFP', 'HCG', 'doppler', 'relaxin', 'Interleukine-1/6/8', 'G-CSF', 'bacterial vaginosis', 'thrombin/TAT', 'fetal fibronectin', 'cervical length', 'MMP-1/9', 'fetal breathing movement'. Articles reporting results of original research and meta-analyses were primarily consulted. Studies were reviewed and evaluated for quality per predictor. The selection was based on methodological qualities and applicability. The following study designs were included in our review: randomized controlled trials, well designed controlled trials without randomization, cohort or case-control analytic studies, multiple time series with or without the intervention. Review articles, opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees were also employed for this overview of biophysical and biochemical predictors of SPB. Studies with other designs, or small sample sizes were excluded. Guidelines published by institutions such as the National Institute of Health (NIH) and the American College of Obstetricians and Gynecologists (ACOG) were also reviewed. Additional studies were located by reviewing bibliographies of identified articles.

## Pathogenesis of spontaneous preterm birth

Since the last decade there is growing clinical and experimental evidence that most cases of SPB result from four primary pathogenic processes that may occur either in isolation or in combination.<sup>1</sup> While each process follows a unique biochemical cascade, they share a common final biological pathway, involving the release of prostaglandins which generate uterine contractions and an increased

expression of genital tract proteases which promote cervical change and rupture of membranes (Figure 1). To ascertain patients at risk, given these heterogeneous biochemical and biophysical pathways, a combination of pathogenic-specific markers will be needed.

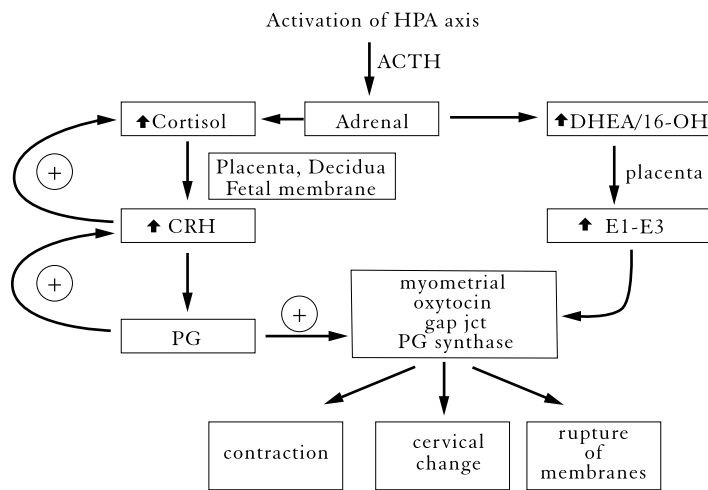
**Figure 1** Pathways of Preterm Birth (PTB) due to preterm Premature Rupture of the Membranes (PPROM) and/or Preterm Labor (PTL) (reprinted with permission from: Lockwood and Kuczynski, markers of risk for preterm delivery; J.Perinat. Med 1999; 27, 5-20)



### A. Activation of the maternal and/or fetal hypothalamic pituitary adrenal (HPA) axis

There is evidence that premature activation of the maternal and/or fetal HPA axis due to maternal or fetal stress plays an important role in the genesis of SPB. Hormonal mediators of HPA activation as well as markers of abnormal placentation are indicators of the risk of SPB. Maternal and fetal stress lead to increased expression of placental and amniochorion-decidual corticotropin-releasing hormone (CRH) (Figure 2).<sup>1</sup> Both maturation and activation of the fetal HPA axis lead to rising fetal cortisol and dehydroepiandrosterone sulfate (DHEAS) levels. Rising fetal cortisol levels stimulate production of CRH in placenta, membranes and decidua, which in turn, stimulates prostaglandin produc-

**Figure 2.** The role of estrogens and CRH resulting from activation of the fetal HPA axis, leading to uterine contractions, cervical changes, and/or rupture of the fetal membranes. (reprinted with permission from: Lockwood and Kuczynski, markers of risk for preterm delivery; J.Perinat. Med 1999; 27, 5-20).



tion in the decidua and fetal membranes. CRH directly and indirectly, augments androgen expression (DHEAS), through pituitary adrenocorticotropin (ACTH) release.

These androgens are converted in the placenta to estrogens (E1-3) which enhance the myometrial oxytocin receptors and facilitate contractions. Elevated maternal serum alpha-fetoprotein (MSAFP) and human chorionic gonadotropin (hCG) are markers of vascular abnormalities and IUGR and among patients delivering preterm without infections or pre-eclampsia it can also be predictive of SPB.<sup>2,3</sup>

The epidemiological profile of risk for these conditions is mainly in nulliparous patients, unmarried and poor mothers, patients reporting stress and anxiety.

### B. Decidual-amniochorionic and systemic inflammation

Today, between 30% and 40% of SPB are thought to be attributable to maternal infections and are considered preventable<sup>4,5</sup> Ascending genital tract infections or systemic bacterial and viral infections may lead to activation of systemic and/or

local cytokine network, which appears to be the principal mechanism for SPB in such patients.<sup>6</sup> This generates interleukin-1 beta (**IL-1 $\beta$** ) and tumor necrosis factor-alpha (TNF- $\alpha$ ), which stimulate uterotonin (prostaglandins, endothelins, leukotrienes) and **proteases** (collagenases, plasmin) production by the myometrial and cervical cells and also by decidua and membranes. These pro-parturition effects are amplified by IL-1/TNF-mediated induction of: a) **IL-6** and CRH expression which further enhance prostaglandin production; and b) **IL-8**, a granulocyte chemotactant and activator, which causes the release of elastases and collagenases. Granulocyte stimulating factor (**G-CSF**) is another cytokine that plays a role modulating an inflammatory response. Particular striking is the association between bacterial vaginosis (**BV**) and SPB.<sup>4</sup> Systemic infections are also associated with PTL and/or SPB<sup>1</sup> and despite controversial results from studies regarding asymptomatic bacteriuria, Romero et al. showed in a meta-analysis that untreated asymptomatic bacteriuria during pregnancy significantly increased rate of low birth weight and preterm birth.<sup>7</sup> These findings suggest that an infection even remote from the uterus can activate an inflammatory process that triggers an uteroplacental response, leading to SPB.

The epidemiological profile of risk for infections are women at risk for acquiring sexually transmitted diseases (e.g. young, poor, minority, unmarried, inner city women) harboring vaginal pathogens including bacterial vaginosis.

### C. Decidual hemorrhage

Recurrent decidual hemorrhage presenting as vaginal bleeding occurring in the first and subsequent trimesters is associated with a 3-fold increase in adjusted relative risk for SPB due to preterm contractions.<sup>8</sup> This pathway of decidual hemorrhage causes SPB in about 20%. Harger et al. observed that vaginal bleeding in more than one trimester carried the highest identifiable risk of preterm premature rupture of membranes (PPROM), with an odds ratio of 7.4.<sup>9</sup> Ekwo et al. found a high positive predictive value for recurrent vaginal bleeding and SPB when their previous pregnancy had been complicated by PPROM. Less than a quarter of patients delivering preterm have recurrent vaginal bleeding.<sup>10</sup> Hemorrhage leads to local thrombin generation, which binds to cellular receptors in the decidua to enhance protease production. Thrombin is a component of the coagulation cascade and is a potent uterotonic agent. In vitro studies demonstrated a mechanistic explanation for increased myometrial activity, observed with clinically apparent

intrauterine bleeding, such as placental abruption.<sup>11,12</sup> An indicator of thrombin activation would need to be used for minimal or occult intrauterine bleeding. One such test, thrombin-antithrombin III (TAT) complex levels, measures the amount of activated thrombin bound to antithrombin III, an endogenous thrombin antagonist. Several investigators observed that TAT levels progressively rise throughout gestation, increase further with labor, and reach a peak with the delivery of the placenta.<sup>11</sup>

The epidemiologic profile of risk for decidual hemorrhage-associated SPB includes older, parous, married, college-educated women,<sup>13</sup> distinct from the profile for both infection - and stress - associated SPB.

#### **D. Pathological uterine distension.**

Conditions associated with pathologic uterine “stretch” include those which promote an abnormal increase in intrauterine volume (multifetal gestations, polyhydramnios), or conditions limiting uterine expansile capacity, such as a T-shaped uterus due to *in utero* DES exposure or to Müllerian duct anomalies. Both clinical settings are strongly associated with the occurrence of preterm labor and/or PPROM (20% of all SPB causes). The mechanism accounting for this association appears to involve the transduction of a signal initiated by mechanical stretch of uterine myometrial (via increases in gap junctions), cervical, and fetal membrane cells through the cellular cytoskeleton to activate cellular protein kinases.<sup>14</sup>

The epidemiologic profile of risk for this condition is women with multifetal gestations, polyhydramnios and uterine anomalies. The only available diagnostic method playing a role in this cascade is sonographic detection of the above-mentioned conditions.

Regarding the pathogenesis we conclude that each of these biochemical processes share a final common pathway characterized by increased uterotonins (e.g., oxytocin, endothelin, and leukotriene) and proteases (e.g., matrix metalloproteinases or collagenases, plasminogen activators, plasmin, and elastase) expression causing uterine contractions, cervical change and fetal membrane rupture. Mediators of these diverse biochemical pathways (e.g., CRH, estriol, IL-6, thrombin) and by-products of fetal membrane extra cellular matrix (ECM) degradation (e.g., FFN) present unique biochemical signatures predicting the occurrence of a subsequent



preterm labor with intact membranes and/or premature rupture of the fetal membranes. Cervical incompetence is not mentioned in the model, but is considered as an early manifestation of the usual preterm birth processes (i.e., hemorrhage, infection, or overdistention but not stress). In this case the stimuli (thrombin, cytokines and mechanical stretch) occur at a point when the uterus has no gap junctions, oxytocin receptors or myosin light chain kinase and so there are no contractions. However, proteases and IL-8 promote cervical change and thus incompetence.

### **Methods for the prediction of spontaneous preterm birth (review)**

#### *Epidemiologic factors*

Past and current approaches to predict those women who will deliver preterm, have relied on demographic information, previous pregnancy history and current pregnancy findings as cervical change, increasing uterine contraction frequency and vaginal bleeding. Other variables associated with SPB are occupational, environmental, psychosocial, behavioral and nutritional factors. These above-mentioned factors are also described in chapter 1. Previous preterm birth, black race, and second- or third trimester bleeding have been associated most consistently with SPB.

#### *Uterine monitoring*

At least 13 randomized controlled trials have examined the efficacy of home uterine activity monitoring (HUAM) for the prevention of SPB. These studies have varied in design, inclusion criteria, and measurements of outcomes. Results have also varied, with some trials reporting no difference and some reporting a difference in pregnancy outcome in monitored and unmonitored women. The largest study involved 2422 women at risk and showed no improvement in outcome.<sup>15</sup> Although HUAM is approved by the U.S. Food and Drug Administration (FDA) for women with a prior SPB, data are insufficient to support a benefit from HUAM for the prevention of SPB.<sup>16-18</sup> Therefore this system of care can not be recommended.

## Pathway specific biochemical markers for the prediction of SPB

The following section reviews the pathway-specific and common-pathway biochemical markers to predict the spontaneous onset of labor or rupture of the fetal membranes prior to 37 weeks' gestation.

### *Corticotropin-Releasing Hormone (CRH)*

CRH is a 41-amino acid peptide first identified in 1980, and initially localized to the hypothalamus where its release into the portal circulation stimulates pituitary adrenocorticotrophic hormone (ACTH) production which, in turn, enhances adrenal cortisol secretion.<sup>19</sup> Moreover, CRH mediates the autonomic, immunological and behavioral responses of mammals to stress.<sup>19,20</sup> CRH is also synthesized in the placenta, fetal membranes and decidua.<sup>21-23</sup> Several studies have demonstrated that increased levels of CRH indicate a higher risk for preterm delivery.<sup>24,25</sup> McLean et al. showed that among patients who delivered preterm, a rise in CRH occurred six weeks earlier in the second trimester.<sup>26,27</sup> This suggests that in some patients, the timing of parturition is determined early in gestation. So it was hoped that this marker might allow the identification early in pregnancy of patients at risk for SPB. Maternal serum CRH concentrations are elevated as early as 18 weeks gestation in women with subsequent SPB.<sup>24,25,28-32</sup> In a large prospective study about 1047 low-risk women recruited at 15-20 weeks of gestation, mid-trimester maternal CRH was significantly associated with preterm birth before 34 weeks.<sup>28</sup> However, the authors concluded that when used alone the measurement has a low predictive power because of the very low risk of the studied population (positive predictive value of 3.6% with a SPB prevalence of 1.1%). Plasma CRH levels rise during the second half of pregnancy, peak during labor, and rapidly decline postpartum.<sup>26,29,32</sup> The pre-parturition increase in CRH is accompanied by a fall in CRH binding protein, leading to a rapid increase in circulating bioactive CRH at term.<sup>26</sup>

The poor predictive efficacy of CRH elevations may be related to limitation of its role to SPB due to maternal or fetal stress. Since this 'stress' pathway only account for one-third of all SPBs, CRH elevation can only predict 30% of all patients delivering prematurely.<sup>30,33</sup> Furthermore, the significant variability of CRH between different weeks of gestation and among different patients makes interpretation of serum levels difficult.<sup>28</sup> Other assessments in large prospective studies

are required before this marker can be introduced in to clinical practice. Thus far there is no commercial diagnostic test available for CRH.

### *Estrogen*

Estriol begins to appear in maternal blood during the 9th week gestation and its plasma concentration continues to increase throughout pregnancy.<sup>34</sup> Circulating maternal estriol is derived from fetal adrenal precursors. Premature and/or stress-induced activation of the fetal hypothalamic-pituitary-adrenal (HPA) axis enhances fetal adrenal dehydroepiandrosterone sulfate (DHEAS) production. Upon transfer to the placenta DHEAS is converted to estradiol (E2) and estrone (E1). In addition, DHEAS can be 16-hydroxylated in the fetal liver. In the placenta this is converted to estriol (E3).<sup>35</sup> For many years, the measurement of estriol, urinary or plasma, was used as a marker of fetal-placental well-being. This diagnostic test has disappeared with the development of fetal heart rate monitoring devices. The increase in estrogens directly affects myometrial contractility.<sup>36</sup>

Initial studies employing longitudinal sampling have demonstrate a rise in both plasma and salivary E3 two to five weeks before the onset of labor whether occurring at term deliveries or preterm. This increase in E3 may be a used to diagnose threatened preterm labor in women at high-risk for SPB.<sup>36,37</sup> Germain et al. observed a 20% surge in maternal E2 nine days before the onset of both preterm and term labor.<sup>38</sup> McGregor et al. conducted a multi-site, triple blinded prospective study in which they measured salivary estriol every week from 22 weeks onward in 241 pregnant women.<sup>36</sup> The advantages of salivary determinations are the ease and non-invasiveness of its collection, the stability of the concentration during transport, and a reliable and reproducible assay technique. A salivary E3 level greater than or equal to 2.3 ng/ml was found to have a sensitivity of 71%, a specificity of 77% (Likelihood ratio 3.1).<sup>36</sup> The test has reduced effectiveness in women who were treated with glucocorticoid therapy. Furthermore its utility is not known in patients with placental abruption, premature rupture of membranes, incompetent cervix, intrauterine fetal growth restriction and twin pregnancy, because these patients were excluded from the study. The test has a negative predictive value of 98%, but has poor specificity, and a very poor positive predictive value (9%).<sup>36,39</sup> An additional concern is the test's greatly reduced effectiveness at identifying patients at risk for SPB prior to 30 weeks gestation, precisely the group at highest risk for perinatal morbidity and mortality.

Estrogens can be measured in saliva, serum, and cervicovaginal secretions. Although the U.S. Food and Drug Administration (FDA) has recently approved a commercially available salivary E3 test (Salest<sup>TM</sup>) which can target a select population at risk for premature labor, its utility is limited to generally low-risk patients with a gestational age greater than 30 weeks who were not treated with glucocorticoid therapy. The tests low positive predictive value is likely to lead to unnecessary interventions. Based on above-mentioned concerns and the limited evidence available, the test cannot be recommended at this time for screening patients for PTL. Before any conclusion can be reached, other studies are needed. Currently, this marker should be used only as part of a research protocol.

### *Relaxin*

Relaxin is a protein produced by the corpus luteum and secreted into the peripheral circulation. Levels of relaxin during pregnancy are increased in the first trimester, slightly decrease thereafter, but remain elevated in the second and third trimester above that found in the non-pregnant state. Relaxin is thought to synergize with progesterone to suppress myometrial contractions but more importantly it may be one of the major components involved in cervical ripening. Both the cervix and the human fetal membranes have relaxin receptors and relaxin stimulates collagenase in the cervix and the human fetal membrane.<sup>40</sup> In two small studies it was observed that relaxin was increased at 30 weeks in most patients who experienced subsequent preterm labor.<sup>41,42</sup> The demonstration of increased relaxin mRNA in the decidua of patients in preterm labor, even in the absence of infection, is a strong indication of the role relaxin plays in preterm labor.<sup>43</sup> Vogel et al. reported that serum relaxin collected at 18 gestational weeks was an independent predictor for SPB < 34 weeks (odds ratio, 11.3; 95% CI 2.1-59.1).<sup>44</sup>

Relaxin can be measured in the maternal serum and may serve as a major contributor of cervical ripening. Relaxin levels correlate with cervical change. Some small studies reported that an increase of relaxin was associated with subsequent preterm labor. Further studies are required to determine the specific role of relaxin as a useful covariate to identify women at risk for SPB. The test is not available for clinical use, yet.

*Maternal serum  $\alpha$ -fetoprotein (MSAFP) and human chorionic gonadotropin (hCG)*

Studies have repeatedly found that women with a single, anomaly-free fetus, and high MSAFP levels in their second trimester, are at increased risk of delivering preterm.<sup>3,45,46</sup> However, the reason for this association is presently unknown. Unexplained high levels of MSAFP have been associated with both ultrasonographic placental abnormalities and vascular and inflammatory placental lesions observed at delivery.<sup>47</sup> Weiner et al. measured MSAFP and umbilical artery Doppler waveforms in 144 consecutive women referred for amniocentesis, and observed a 50% preterm birth rate in women in the high MSAFP group.<sup>48</sup> They also observed that Doppler indices tended to be more often abnormal (indicating increased downstream resistance) in women referred for an elevated MSAFP. Employing a stepwise multiple linear regression, they noted that gestational age at delivery could be predicted during the mid-second trimester using a combination of the umbilical artery Doppler velocimetry and MSAFP.

Gonen and colleagues observed that women with human chorionic gonadotropin (hCG) levels greater than 4 MOM had an increased risk of SPB (odds ratio 3.3; 95% CI 1.3-8.2).<sup>49</sup> Van Rijn et al. showed an increased risk of SPB (relative risk 7.8; 95% CI 3.2-19.0) when MSAFP  $\geq$  2.5 MOM and hCG  $\geq$  2.5 MOM.<sup>3</sup> Given that elevated MSAFP and hCG values are also linked to uteroplacental vascular abnormalities and fetal growth restriction, these findings provide further support for the association between fetal stress and SPB.<sup>1</sup>

Both MSAFP and hCG are measured in maternal serum. In the absence of fetal malformations or multiple gestations, MSAFP and/or maternal serum hCG elevations in the second trimester are associated with an increased risk of SPB. The positive predictive value of 41% may justify intensified obstetric surveillance in women with unexplained elevated (or very low) MSAFP and/or maternal serum hCG values for an increased risk of PTL and/or fetal IUGR. Commercial diagnostic tests are available. However, because of low sensitivity, negative and positive predictive values, MSAFP and hCG testing are not recommended for clinical use as predictors of SPB. The negative predictive value of maternal serum screening is too low for it to be useful as a screening instrument for adverse pregnancy outcome.

*Interleukine (IL)-1 $\beta$ , 6, 8*

The inflammatory cytokines IL-1 $\beta$  and TNF $\alpha$  are indirect uterotonins since they increase local prostanoid production.<sup>33</sup> IL-6 is secreted by decidual and chorionic cells in response to IL-1 $\beta$  and TNF $\alpha$  stimulation. The quantity of IL-6 that is produced exceeds that of IL-1 $\beta$  by approximately 1000-fold.<sup>33,50</sup> Furthermore, elevated amniotic IL-6 levels as early as 16 weeks' gestation and increased placental IL-6 expression have been associated with SPB, particularly in the presence of intra-amniotic infections (IAIs).<sup>51-54</sup> A cohort study from Lockwood et al. evaluated the role of cervical IL-6 elevation in the prediction of SPB of 161 asymptomatic women.<sup>55</sup> Levels of IL-6 were measured by immunoassay. A receiver-operator characteristics (ROC) curve analysis indicated that a single cervical IL-6 value > 250 pg/ml, present between 24 and 36 weeks gestation, optimally identified patients with a subsequent preterm delivery. There was a 4.2-fold increase in maximal cervical IL-6 concentrations among patients with preterm versus term deliveries (sensitivity 50.0%, specificity 85.0%, positive predictive value (PPV) 47.2% and negative predictive value (NPV) 86.4%). Goepfert et al. confirmed the above-mentioned findings that cervical IL-6 at 24 weeks is higher in women who subsequently had a SPB at < 35 weeks than in women who delivered at term. However, elevated cervical IL-6 concentrations were not independently associated with SPB. A positive fetal fibronectin (FFN) test result was strongly associated with elevated cervical interleukin 6, but bacterial vaginosis (BV) was not.<sup>56</sup> Elevated cervical and serum IL-6, and amniotic fluid IL-8 levels are strongly associated with the presence of intra-amniotic infections.<sup>57-59</sup> IL-8 recruits and activates granulocytes, which release an extremely potent extracellular matrix (ECM)-degrading elastase.<sup>60</sup> Cervical granulocyte elastase activity is also associated with cervical change and SPB.<sup>61</sup>

The cytokines IL-1 $\beta$ , -6, -8 can be measured in maternal serum and cervical secretions. They play a role in inflammation-based SPB. Lower genital tract IL-6 and IL-8 concentrations appear to be related to subsequent SPB. However, presently there are no consistent results regarding the usefulness in predicting spontaneous preterm birth. IL-1 $\beta$ , IL-6, IL-8 are not commercially available for clinical use.

### *Granulocyte colony-stimulating factor (G-CSF)*

Granulocyte colony-stimulating factor (G-CSF) is a cytokine produced by monocytes, which, among other characteristics, attracts circulating leukocytes into tissue. G-CSF has been found in placental macrophages and in decidual cells. Goldenberg et al. showed that elevated plasma G-CSF levels collected at 24 and 28 weeks' gestation in low risk pregnant women, were associated with subsequent early (<32 weeks) SPB, especially within the next 4 weeks, but not with late SPB. Elevated plasma G-CSF levels at 24 weeks have been associated with SPB at 24 to 28 weeks' gestation (sensitivity 54%; specificity 79%; PPV 2% and NPV 99%).<sup>62</sup> At 28 weeks' gestation an elevated plasma G-CSF value is associated with SPB at 28 to 31 weeks' gestation (sensitivity 37%; specificity 95%; PPV 7% and NPV 99%). The adjusted odds ratios are ranging from 6 to 25 measured in plasma at 24 to 28 weeks' gestation. Early SPB seems to be associated with an inflammatory process that is identifiable by the presence of a cytokine in maternal plasma several weeks before the early SPB. However, later SPB does not seem to be associated with such a process.

G-CSF is present in plasma and amniotic fluid and concentrations can be measured with enzyme-linked immunosorbent assay (ELISA). G-CSF is a marker for inflammation and appears to be a powerful predictor of early preterm birth. The test is not available yet for clinical use. Whether the test itself will be useful in predicting SPBs will depend on a number of factors, including sensitivity and positive predictive values in various populations.

### *Bacterial Vaginosis*

The syndrome bacterial vaginosis (BV) was defined by Gardner and Dukes in 1955 as a nonspecific vaginitis caused by haemophilus vaginalis.<sup>63</sup> Since 1977, studies have shown the importance of anaerobes in this clinical syndrome. To date, BV is seen as a common condition in which the normal vaginal microflora, lactobacilli and a small numbers of anaerobes, are replaced by a polymicrobial overgrowth of anaerobes, gardnerella vaginalis and mycoplasma hominis. BV is fairly common, with a prevalence ranging from 10% to 25% in a general obstetric population to 64% of patients in clinics for sexually transmitted diseases.<sup>63-65</sup> Fifty percent of women with BV are asymptomatic.<sup>66</sup> The condition is found more frequently in African-American (22%) than in Caucasian (8%) women.<sup>67</sup> The pres-

ence of BV has been associated with SPB independent of other known risk factors and is suggested as a potentially treatable risk factor for SPB.<sup>63,68</sup>

Bacterial vaginosis is associated with an increased risk of preterm rupture of membranes (odds ratio: 7.3),<sup>68</sup> low birthweight<sup>69</sup> and SPB (odds ratios ranging from 1.8 to 2.8).<sup>63,70</sup> BV is probably a marker for a subclinical infection of the upper genital tract, which may lead to SPB. Trials on screening and treating BV in pregnant women to reduce the incidence of SPB have been conducted in mixed pregnant populations with varying results. In some small randomized controlled trials treatment with oral antibiotics (metronidazole with or without erythromycin) in women with BV who are at risk for SPB (history of previous preterm delivery or low prepregnancy weight) has resulted in a reduction of the SPB rate.<sup>71</sup> However, other studies have not confirmed a reduction of the SPB rate after BV treatment.<sup>72,73</sup> A recent meta-analysis reviewed five trials involving 1504 women.<sup>74</sup> Analysis of women with low risk for SPB included trials with the following treatments, amoxicillin, clindamycin and metronidazole (with or without erythromycin). Although investigators found antibiotic therapy was effective at eradicating BV, no difference in the rate of SPB between the two groups was observed. However, analyzing the subgroup of women with a previous preterm birth, the difference in SPB was significant, with an odds ratio of 0.37 (95 % confidence interval, 0.23-0.60). This meta-analysis did not include results from the most recent and largest double-blinded, randomized controlled trial. Carey et al. found no difference in the rates of SPB between the treatment and placebo group in a trial of 1953 women who had asymptomatic BV in a general obstetrical population. While Brocklehurst et al. showed a reduction in SPB after BV treatment in women with SPB in history, Carey et al. did not demonstrate a significant difference in preterm birth rates in the subgroup with a history of SPB.<sup>73,74</sup> A recent review from Berg et al. reported that there are insufficient data to suggest that screening and treating women in either low or high risk will reduce the overall rate of preterm birth.<sup>75</sup> Prophylactic treatment of low-risk women or in high-risk women without BV is not indicated, because it may change the normal vaginal flora to an intermediate type or to BV which may increase the risk of SPB.<sup>76</sup> Future studies must include data on the neonatal and postpartum sequelae to understand the risks of antibiotic treatment.

The diagnosis of BV requires a wet-mount or gram stain of vaginal secretions obtained from the posterior vaginal fornix using a sterile cotton swab. Amsel's cri-



teria for BV are characterized by the presence of typical discharge, clue-cells, increased pH, a positive amine test and lack of lactobacilli.<sup>77</sup> Another method to diagnose bacterial vaginosis is described by Nugent.<sup>78</sup>

Thus, although some trials have shown an association with the presence of BV and preterm birth, most large trials have failed to demonstrate that treatment of BV can prevent SPB. The presence of anaerobic flora in the upper genital tract may be the link between BV and SPB. BV may not be the cause of SPB but a downstream marker of some other underlying pathology. There remains discussion whether treatment of BV in women with a history of SPB lowers the risk of SPB. Until larger, better-randomized studies of antibiotic treatment for BV during pregnancy become available, we conclude that BV treatment is indicated only in patients with a history of SPB. There is no indication for screening to identify or prevent preterm birth in a general population.<sup>79</sup>

#### *Lactoferrin*

Lactoferrin is an iron-binding glycoprotein originally described as present in milk and to a lesser extent in exocrine fluids, such as bile and tears. Lactoferrin may be important in iron uptake by the intestinal mucosa and probably acts as a bacteriostatic agent by rendering iron unavailable as a nutrient to bacteria. Its presence in neutrophils and its release during inflammation indicate that lactoferrin may also be involved in the immune response to infection.<sup>80</sup> Lactoferrin is present in low concentrations in amniotic fluid during early pregnancy, with levels increasing as pregnancy progresses. One study has shown that lactoferrin levels in amniotic fluid were higher in women in preterm labor with an amniotic fluid infection than in women in preterm labor without infection. Cervical lactoferrin correlated well with other markers (e.g. IL-6, sialidase activity and BV) of lower genital tract infection. Only very high levels in the cervix are associated with SPB but with low sensitivity. Currently, lactoferrin testing does not seem to be helpful in the prediction of SPB and it is not available for clinical use.

#### *Thrombin, thrombin-antithrombin (TAT)-complexes*

Thrombin subserves a number of hemostatic functions, such as generation of fibrin and activation of the clotting co-factors (factor V and VIII) and platelet activation.<sup>1</sup> In addition to its pro-coagulant properties, thrombin also enhances expres-

sion of tissue-type and urokinase-type plasminogen activator (PA). The PA's generate plasmin from plasminogen, which can directly degrade the crucial components of the extracellular matrix (ECM) laminin, fibronectin, collagen III. Plasmin activates the matrix metalloproteinases (MMP)<sup>1,11,12</sup> Thrombin also triggers the release of MMPs from the decidua. Finally, thrombin binds to myometrial receptors to trigger contractions.<sup>81</sup> Decidual hemorrhage and consequent thrombin generation, thus leads to a proteolytic cascade of damaging the ECM of the fetal membranes, promoting premature rupture of the membranes and cervical change and stimulating contractions. Thrombin-antithrombin (TAT) complex levels are elevated in patients with preterm labor who are destined to deliver before term and in patients destined to rupture their fetal membranes.<sup>11,81</sup> This suggests that preterm labor resulting in preterm birth is associated with the activation of thrombin.<sup>11</sup> Further and larger studies are required to determine the role of TAT-complexes in the prediction of SPB. The test is not available yet in clinical practice.

### **Final common pathway biochemical and biophysical predictors of preterm birth**

Although each of the pathogenic mechanisms described above has a distinct biochemical and epidemiological profile, each converges on a common pathway involving increased genital tract uterotonin (e.g. prostaglandin) and protease expression. These proteolytic processes at the decidua and membranes lead to a breakdown of the ECM of the fetal membranes and cervix. Approaches to the detection of these pathological processes are the identification of fetal fibronectin (FFN) in cervico-vaginal secretions, the transvaginal sonographic determination of cervical length, the previously described uterine contraction monitoring, and the identification of MMP in various media.

#### *Fetal Fibronectin (FFN)*

Fibronectins are large-molecular-weight glycoproteins found in extracellular matrix (ECM) and plasma.<sup>82</sup> FFN is produced during fetal life by amniocytes and cytotrophoblasts of the chorion and placenta.<sup>83</sup> In the latter site it is localized in the extravillous cytotrophoblast of the anchoring villi and cytotrophoblastic shell. In the fetal membranes, FFN is concentrated at the junction of the decidua and chorion. Its presence in the cervicovaginal secretions is normal prior to the 20th

week.<sup>82</sup> By 22 weeks, the amnion, chorion and decidua basalis fuse with the decidua parietalis and FFN is not normally released in vaginal mucus.

Numerous trials have shown both an association between the presence of cervico-vaginal FFN and SPB.<sup>82,84</sup> They show a decrease in the risk of SPB in the absence of cervicovaginal FFN. The mechanisms responsible for the presence of FFN in cervicovaginal secretions in cases of threatened SPB are unknown, however, separation of the chorion from the deciduous membrane of the lower uterine segment may allow its release. FFN secretion in the cervical canal may also occur in response to a chorionic inflammation (with accompanying proteolysis).<sup>82</sup> The cell attachment properties of fibronectin disrupt preceding PPRM and preterm labor, allowing fibronectin to leak into cervicovaginal secretions. In initial studies, the presence of cervicovaginal FFN after 21 weeks was found to be predictive of SPB. It is difficult to compare the results because of differences in study populations, protocols, and methodological quality. Recent meta-analyses among 29 and 27 relevant studies regarding FFN have confirmed this association in populations at both low and high risk for SPB.<sup>85-87</sup> The inclusion period was generally 24 to 34 weeks; a quantitative test was used, with 50 ng/ml the cut-off for a positive determination. Two principal types of populations have been studied: the asymptomatic general population and populations at risk for SPB.

Table 1 reports the prevalence of SPB in symptomatic women and provides the predictive efficiency of FFN. The review of published studies confirms a clear association between FFN and SPB, with excellent sensitivity, specificity and negative predictive values. The likelihood ratios are also high, but rarely greater than 5.

**Table 1.** Cervico vaginal FFN and the prediction of SPB in symptomatic patients

Authors	FFN Site	n	Sensit. (%)	Spec. (%)	PPV (%)	NPV (%)
Lockwood <sup>82</sup>	Cervix/vag.	117	82	82	83	81
Bittar <sup>90</sup>	Cervix	102	79	86	77	87
Iams <sup>88</sup>	Vagina	192	44	76	60	76
Peaceman <sup>91</sup>	Vagina	763	41	86	45	85
Rozenberg <sup>92</sup>	Vagina	76	70	70	45	87
Bartnicki <sup>93</sup>	Vagina	112	68	90	79	83

A negative FFN was associated with a greater than 95% likelihood of not delivering within 14 days of a negative test result.<sup>88,91</sup>

The use of the FFN test in women with suspected preterm labor appears to have significant utility in reducing unnecessary interventions and admission. In a before-and-after study (1800 women in each period), Joffe et al. reported the effect of using FFN for women with threatened preterm birth. Knowledge of the FFN test result reduced the number and duration of admissions for preterm labor as well as the number of tocolytic prescriptions without a negative impact on neonatal outcome.<sup>89</sup> There was a 50% cost-reduction (\$ 486,000/year) based on a reduction in admissions and charges per admission in women with threatened SPB.

Fetal fibronectin is also predictive of SPB in asymptomatic patients (Table 2). Lockwood et al. showed that among asymptomatic patients and patients at moderate risk for SPB, FFN appeared equally predictive of SPB. Its presence in cervicovaginal secretions preceded SPB by > 3 weeks.<sup>84</sup> Goldenberg et al. found that a positive FFN at 24 weeks was associated with a > 60-fold increased risk of SPB.<sup>97</sup> Thus, the presence of FFN in vaginal or cervical secretions before 35 weeks is a moderately good predictor of SPB but appears to be most useful as an indicator of women at low risk for preterm birth.

The predictive power of FFN is stronger at earlier gestational age (24-28 weeks) than later in pregnancy and is stronger for short-term prediction (7-14 days) than for SPB overall.<sup>97</sup> Nonetheless, reviewing all of these studies, Khan et al. showed that only 26% of the authors' conclusions about the diagnostic value of FFN met

**Table 2.** Cervical-vaginal FFN and the prediction of SPB in asymptomatic patients.

Authors	FFN Site	N	Sampling weeks	Sensit. (%)	Spec. (%)	PPV (%)	NPV (%)
Lockwood <sup>84</sup>	Vagina	326	24-36	68	80	30	95
Hellemans <sup>95</sup>	Cervix	133	26-36	60	85	25	96
Greenhagen <sup>96</sup>	Cervix	108	24-34	62	84	24	97
Goldenberg <sup>97</sup>	Cervix	2929	22-30	63	98	15	100

<sup>1</sup>SPBs < 28 weeks

the 'golden standard' and that 66% of the authors overestimated the diagnostic values of their test.<sup>98</sup> In view of the lack of an effective management to offer after a positive test, it does not seem reasonable to recommend this test for all pregnant women at this time, without a further assessment of such strategy except as marker of women not in need of intervention.

FFN determinations are conducted on specimens collected from the vaginal pool or cervical mucus at the external os using a speculum examination. The sampling should be performed between 24 weeks and 35 weeks of gestation.<sup>91</sup> To prevent false-positives, the following criteria should be met for the use of FFN-testing: intact amniotic membranes, minimal cervical dilatation (< 3 cm); no cerclage; no vaginal bleeding; no intercourse within 24 hours; no digital examination within past 24 hours; no use of vaginal lubricants or disinfectants.<sup>83</sup> The U.S. Food and Drug Administration (FDA) approved the FFN test in 1995. The current test is a rapid immunoassay with results available within 30 minutes.<sup>99</sup>

Thus, the presence of FFN in cervical and vaginal fluid is an important marker for impending SPB<sup>83</sup> in both high-risk asymptomatic and symptomatic women with both single and multiple test strategies. Fetal fibronectin testing is available for clinical use to identify patient subgroups. Those testing positive need additional observation and/or intervention. Patients with a negative test and nonspecific clinical signs and symptoms may safely be observed in the outpatient setting for at least 14 days. The test should not be routinely used to screen low-risk, asymptomatic women, because the incidence of SPB in this population is low.<sup>87</sup>

#### *Cervical length shortening measured by transvaginal sonography (TVS)*

The human cervix has been shown to be a dynamic organ throughout gestation, varying markedly in both shape and length.<sup>100</sup> As delivery approaches, the cervix begins to shorten in association with effacement and dilatation. If a change in the cervix were to be used for the prediction of SPB, a standardized method of cervical evaluation is needed. During the past 20 years, ultrasound assessment of the cervix has moved from a research tool to a standard part of obstetric diagnostic imaging. A number of investigators have observed that shortened cervical lengths determined by TVS are predictive of SPB in both symptomatic and asymptomatic patients with singleton gestations (Table 3). Iams et al. evaluated the cervical length of 2915 pregnant women at 24 and 28 weeks with singleton gestations. The

**Table 3.** Cervical length and the prediction of SPB in singleton gestations.

Authors	Gestational age (weeks)	Cervical length cut off (cm)	Study Population.	n	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)
Gomez <sup>106</sup>	29	< 1.9	Sympt.	59	73	78	67	83
Crane <sup>107</sup>	24	< 3	Sympt.	136	81	65	46	90
Hassan <sup>102</sup>	14-24	≤ 2.5 ≤ 1.5	Sympt.	6877	15 8	98 99	31 47	96 96
Iams <sup>101</sup>	24 28	< 3 < 3	Asympt.	2915 2531	54 70	76 68	9 7	97 98

study confirmed that there is an inverse relationship between the transvaginal cervical length and the frequency of SPB.<sup>101</sup> The mean cervical length at 24 weeks gestation was  $34.0 \pm 7.8$  mm for nulliparous women and  $36.1 \pm 8.4$  mm in parous women, the mean cervical length at 28 weeks was 1.5 mm shorter. Iams concluded that a cervical length less than 25 mm at 24 weeks gestation or the presence of a funnel that accounts for 50% of the cervical length predict an increased risk for SPB. Hassan et al. reported that nearly 50% of patients with a cervical length  $\leq 15$  mm on a second-trimester sonogram had an early SPB.<sup>102</sup> Cook et al. reported in a small study that 95% of women ‘at risk’ for SPB with closed endocervical canal with a length of  $< 21$  mm before 20 weeks were associated with delivery  $< 34$  weeks.<sup>103</sup> As is the case for FFN, it seems more valuable to use the NPV of the test. In a patient with preterm contractions, the absence of a funnel at the internal cervical os and a cervical length of 30 mm or greater indicates that the patient is not at increased-risk for SPB. These observations could prevent unnecessary tocolysis and intervention.<sup>101</sup>

There have only been a few studies on cervical length as a predictor of outcome in twin gestations. The role of the cervical length is less clear than in the singleton population. Crane et al. noted that a cervical length of  $< 3$  cm was a poorer predictor of SPB in symptomatic patients with twin gestations, achieving a sensitivity of 75%, specificity of 30%, and positive and negative predictive values of 63% and 43%, respectively.<sup>107</sup> Imseis et al. found that cervical length measurement of  $> 3.5$

cm between 24-26 weeks' gestation was a marker for twin gestations at low risk for delivery at < 34 weeks' gestation.<sup>108</sup> Goldenberg et al. found that a cervical length of < 2.5 cm at 24 weeks' gestation and Guzman et al. that a cervical length < 2.0 cm between 15-28 weeks' gestation were good predictors of SPB in twin gestations.<sup>104</sup> The primary finding in triplets is that the average cervical length compared with gestational age-matched controls was shorter.<sup>105</sup> The mean cervical length in triplets was  $25.0 \pm 8.0$  mm at 24 weeks gestation, compared with  $35.2 \pm 8.3$  mm in singletons.<sup>110</sup>

The length of the cervix is the distance between the internal os and external os measured by TVS.<sup>101</sup> Measurements can be affected by numerous confounding factors such as different operators and techniques (e.g., placing the electronic calipers or recording the best image), variable machine quality, differing cut-off values or varying degrees of bladder filling. Thus, standardization of measurements is important. In summary, many studies agree on an inverse relationship between the transvaginal cervical length and the frequency of SPB. The high negative predictive value of a cervical length of greater than 30mm could prevent unnecessary tocolysis and intervention.<sup>101</sup> Transvaginal ultrasonography is available for use in daily clinical practice.

#### *Combining cervical ultrasound and fetal fibronectin*

In a multicenter trial, Iams et al found a short cervix (defined as < 25 mm), particularly if associated with a positive FFN test result, to be a strong predictor of SPB.<sup>111</sup> Rozenberg et al. studied a population of women hospitalized with symptoms of preterm labor.<sup>92</sup> Although the two tests had similar diagnostic values, they did not identify all of the same patients who subsequently delivered prematurely. The authors concluded that neither test was to be preferred over the other. Rizzo et al. have conducted a comparable study, in which they concluded that FFN was superior to ultrasound. In fact, the difference was moderate: for FFN and ultrasound, respectively, the sensitivity was 80.9 and 70.2 %, and the specificity 83.6 and 80.3%.<sup>112</sup> A more recent trial by the National Institute of Child Health and Human Development Maternal Fetal Medicine Network examined the sequential use of both methods to try to stratify risk groups as well as determine etiologies of SPB.<sup>109</sup> The presence of either a cervix less than 25 mm in length at less than 35 weeks of gestation or a positive FFN test was strongly associated with SPB, especially in women with a history of SPB. These data are particularly use-

ful in decreasing the assessed risk of SPB in women with classic risk factors and negative results of one or both tests. The tests do not identify precisely the same cases, which suggests that the etiology may be different. Further studies are needed to explain these mechanisms and to be able to propose management that is appropriate and efficacious for each of the groups that one or the other marker may identify. The success of interventions once a short cervix is identified or positive FFN test result is obtained remains uncertain.

#### *Proteases / Matrix metalloproteinases (MMP-1 -2 and -9)*

The MMPs are a family zinc-dependent ECM degrading enzymes. Interstitial collagenase (MMP-1) cleaves collagen types I, II and III<sup>113</sup> while the gelatinases (MMP-2 and -9) further degrade denatured collagen fragments generated by interstitial collagenase. The MMPs and their natural inhibitors, the Tissue Inhibitors of Metalloproteinases (TIMPs) are produced by amnion, chorion, and decidua and are important in the maintenance and breakdown of the ECM of the amniochorion and cervix.<sup>113</sup> Rajabi et al. observed an 8-fold increase in serum MMP-1 activity in patients with SPB compared with patients having uncomplicated pregnancies delivering at term.<sup>1,114</sup> Interpolation of these raw data suggest a sensitivity of 94%, a specificity of 92%, positive predictive value of 89% and negative predictive value of 96%. Furthermore increased MMP-9 expression has also been associated with the onset of term labor. It results in the degradation of the ECM of the fetal membranes and facilitates their rupture under both physiological and pathological conditions. It remains to be seen whether similar elevations are present in SPB. Large increases in MMP-2 have also been described in preterm prematurely ruptured membranes.<sup>115</sup> It has been suggested that MMP-2 is the activator of proMMP-9 and cleaves it into active forms.<sup>116</sup>

The presence of MMP-1 has been studied in human cervical tissue<sup>114</sup>, the placenta<sup>117</sup>, amniotic fluid<sup>118</sup> and serum.<sup>119-122</sup> Those studies provide evidence that MMP-1 plays an important role during cervical dilatation in human parturition. The involvement of MMP-9 in parturition has been demonstrated in rat amnion,<sup>116</sup> human amniochorion,<sup>123</sup> amniotic fluid,<sup>124,125</sup> fetal membranes, urine<sup>126</sup> and plasma.<sup>127</sup> Increased expression of MMP-9 protein and activity has been demonstrated as a marker for preterm as well as term labor in fetal membranes, as well as amniotic fluid.<sup>118</sup> These tests are not yet available for clinical use.



### *Nitrite and nitrate concentration*

Nitrite and nitrate concentration are active metabolites of nitric oxide and are elevated in patients with chorioamnionitis.<sup>128</sup> Elevation of nitrite and nitrate concentration in vaginal secretions is accompanied by premature rupture of membranes and precedes premature delivery.<sup>129</sup> Because nitric oxide has been known to activate MMPs and induce apoptotic cell death in various cells, overproduction of nitric oxide may not only be a predictive marker but may also be involved in cervical ripening, fragility of membranes and subsequent premature delivery. Suppressors of nitric oxide synthesis may be candidate therapeutic agents. There is no clinical test available.

### *Fetal breathing movements (FBM)*

Breathing movements occur for the first time at about ten weeks of gestation. The incidence of FBM increases till 30 weeks of gestation, when breathing movements are present for about 30% of the time. Breathing may occur in short or longer lasting spells, with regular or irregular breathing. The breath-to-breath intervals decrease till about 30 weeks and increase thereafter.<sup>130</sup> Fetal breathing movements are affected by many variables, such as maternal glucose intake (increase) and diurnal variations. FBM are reduced in active labor, presumably due to a rise in prostaglandins, which has a direct inhibiting effect on the fetal respiratory center.<sup>131</sup> The incidence of fetal breathing movements is reduced about three days before the onset of spontaneous labor at term and during the latent phases of labor.<sup>132</sup> In patients with induced labor, breathing movements remain essentially unchanged until the active phase of labor and then diminish significantly, such that only few episodes of short duration of fetal breathing are seen up to delivery.<sup>133</sup> Cessation of FBM appears to be a normal physiologic event during labor at term and during elective oxytocin induction of labor that results in delivery.<sup>134</sup> Investigators have documented this phenomenon during preterm labor,<sup>135,136</sup> while others have been unsuccessful in replicating this observation.<sup>137-139</sup> Women with preterm labor, intact membranes and presence of FBM have a very high chance of not being delivered within a week (sensitivity 92%; PPV 93%).<sup>135,136</sup> This does not hold for situation with ruptured membranes.

Real-time ultrasound observation of FBM is considered to be present when it is sustained for 30 seconds or more and is considered to be absent when no sus-

tained breathing movements can be detected in 45 minutes.<sup>140</sup> It is unclear how much time exactly is required to diagnose the absence or presence of fetal breathing movements, because long periods of apnea are a normal phenomena, so a long examination period can be necessary to come to a diagnosis. This makes the method less appealing for use in clinical practice. When a fetus of a woman with preterm labor without rupture of the membranes shows fetal breathing movements, it is likely that the pregnancy will last. In all other cases of pregnancy complications the absence or presence of FBM has no clinical relevance. This method would be available for use in clinical practice, however to date it is seldomly used.

*Summary review predictors of SPB*

Recent clinical and experimental evidence supports the concept that most SPBs result from one of four distinct but frequently overlapping primary pathogenic mechanisms: activation of the maternal or fetal HPA axis due to stress; inflammation to pre-existing or ascending genital tract infections; decidual hemorrhage or placental abruption; and pathologic distention of the uterus due to multiple ges-

**Table 4.** Preferable site and gestational age (weeks) of sampling of SPB Markers.

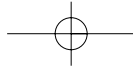
Predictor	Site sampled	Gestational age (weeks)	Diagnostic test available
HUAM	Abdomen	25-34	+
CRH	Serum, plasma	17,22,25,28	
E2/E3	Serum,saliva,CVS	17,22,25,28	+
MSAFP	Serum	22	
HCG	Serum, CVS	17	
Uterine Art.Doppler	Uterus (Ultrasound)	20,23	
Relaxin	CVS	22	
IL-6, IL-8	Serum,cervix, AF	18,30	
G-CSF	Serum, AF	22,25,28	
BV	Plasma, AF	24,28	
TAT	Vagina	12,20,28	+
FFN	Serum	22,25,28,31	
Cx Length	CVS	22,25,28,31	+
MMP-1	Vagina (TVS)	22,25,28,31	+
MMP-9	Serum,	22,25,28	
FBM	Serum, CVS,Urine	22,25,28	
	Uterus (Ultrasound)	28,32	+

tations or polyhydramnios. In the final biochemical pathway various uterotonins and enhanced genital tract protease activity promote myometrial contractions, rupture of membranes and cervical change. Given the fact that most patients with maternal stress, uteroplacental vascular abnormalities, bacterial vaginosis, and vaginal bleeding do not deliver preterm, variations in host susceptibility can play a role in the occurrence of prematurity. Thus, SPB is a multifactorial process occurring when the sum of the stimuli for labor exceed the ability of the maternal host to resist that stimuli. Various risk factors (including obstetrical history and socio-economic and epidemiological risk factors) and biochemical markers from the model have been evaluated as potential predictors of SPB. In Table 4 the location and gestational age of sampling for all the potential predicting variables of SPB are summarized. All these factors have some relationship to SPB.

### Conclusion

Only transvaginal cervical ultrasonography, FFN, salivary estriol, HUAM, FBM and BV are used in clinical practice. To date, the best predictor of early preterm birth is FFN, with consistently high odds ratios reported. For example, in the overall population study, at 24 weeks' gestation a positive FFN test result has an odds ratio of 40 for predicting a SPB at < 32 weeks' gestation.<sup>97</sup> The next most effective predictor is a short cervix determined by ultrasound with an odds ratio of approximately 8.<sup>101</sup> At present, ultrasonography to determine cervical length, FFN testing, or a combination of both are likely to be useful in determining women at high risk for preterm labor. However, their primary clinical usefulness may rests with their negative predictive value given the lack of proven treatment options to prevent SPB. FFN testing may be useful in women with symptoms of preterm labor to identify those with negative values and, thus, a reduced risk of SPB, thereby avoiding unnecessary intervention. We must, however, keep in mind that no therapy has yet been proven to be efficacious, especially in a general population.

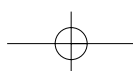
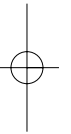
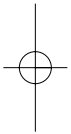
Based on consistent scientific evidence there are no current data to support the use of salivary estriol or HUAM. Granulocyte colony-stimulating factor (G-CSF) in plasma at 24 and 28 weeks' gestation has adjusted odd ratios ranging from 6 to 25 for early SPB.<sup>62</sup> However larger studies are needed for G-CSF and other biochemical markers (e.g. CRH, Il-6, relaxin, MMP-1, -9, MSAFP, hCG). Bacterial vaginosis has an odds ratio of approximately 2.3 for SPB at < 32 weeks' gestation,



*Chapter 2*

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and most other predictors, if significant at all, has odds ratios of  $\leq 2$ .<sup>68</sup> There is still controversial data regarding the role of BV screening and treatment as strategy to identify and reduce SPB. Screening for risk of SPB by means other than historic risk factors has not been shown to be efficacious in the general obstetric population.



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# 3

## Matrix metalloproteinase-1 and -9 in cervicovaginal fluid from women during pregnancy and in labor

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## Abstract

**Objective.** We sought to determine whether cervicovaginal fluid matrix metalloproteinase-1 and -9 (MMP-1 and MMP-9) levels differed during pregnancy compared with those at term or in preterm labor.

**Study design.** We used sensitive immunoassays to measure MMP-1 and -9 levels in cervicovaginal secretions. Cases (n=32) included women who delivered preterm, and were sampled more than 3 week prior to delivery (n=19), within 1 week of delivery (n=7) and during spontaneous labor (n=6). Controls consisted of 80 women matched for race, age and gestational age, delivering at term and who were sampled at 20-32 weeks (n=47), within one week of delivery (n=14) and during term labor (n=19).

**Results.** Among cases and controls, cervicovaginal MMP-1 levels were low and unaffected by labor. Among non-laboring control patients the median and range of MMP-9 concentrations were also low (0; 0-0.04 ng/ml), and these remained unchanged with advancing gestational age. However, MMP-9 levels increased significantly within 1 week of term labor (0.8; 0-22.8 ng/ml;  $p=0.001$ ), and during term labor (6.6; 0-30.6 ng/ml;  $p=0.04$ ) with the highest values observed among laboring patients with ruptured membranes (24.8; 19.2-30.6 ng/ml;  $p=0.002$ ). Among cases, MMP-9 concentrations were unaltered prior to preterm labor, but increased among patients in preterm labor (0.3; 0-30 ng/ml;  $p=0.02$ ).

**Conclusion.** Cervicovaginal MMP-1 levels were low and unchanged during either preterm or term labor. In contrast, MMP-9 levels increased during term and preterm labor but did not predict preterm delivery in asymptomatic patients.



## Introduction

The delivery of infants prior to 37 weeks of gestation complicates 10 % of births in the USA<sup>1</sup> and is a leading cause of neonatal morbidity and mortality.<sup>2</sup> Traditional methods of predicting women at risk that rely on obstetrical history, demographic factors or premonitory symptoms are inaccurate.<sup>3</sup> Biochemical and biophysical techniques that have been employed for prediction of preterm delivery include intermittent antenatal uterine contraction monitoring,<sup>4</sup> transvaginal sonographic measurement of cervical length,<sup>5-8</sup> assays of biochemical markers such as salivary estriol,<sup>9,10</sup> corticotrophinreleasing hormone,<sup>11-13</sup> cytokines and fetal fibronectin in cervicovaginal secretions.<sup>14,15</sup> With the exception of fetal fibronectin, none of these endpoints alone, has proved sufficiently sensitive and specific to justify its incorporation into routine antenatal care at low or even high risk.

We postulated that the release of chorionic fetal fibronectin and structural changes in the cervix preceding labor reflect proteolytic degradation. The human cervix is predominantly a fibrous organ with less than 15 % smooth muscle. It has a highly organized arrangement of collagen fiber bundles in a proteoglycan matrix, which gives it the structural rigidity it needs to retain the conceptus until term.<sup>16</sup> Matrix metalloproteinases (MMPs) are a family of zinc-dependent extracellular matrix-degrading enzymes. Interstitial collagenase (MMP-1) cleaves collagen types I, II and III.<sup>17</sup> The gelatinases (MMP-2 and -9) further degrade denatured collagen fragments generated by interstitial collagenase. MMPs and their natural inhibitors are produced by the amnion, chorion and decidua and are important in the maintenance and breakdown of the extracellular matrix of the amniochorion and cervix.<sup>17</sup> The presence of MMP-1 has been studied in human cervical tissue,<sup>18</sup> the placenta,<sup>19</sup> amniotic fluid,<sup>20</sup> and serum.<sup>21-24</sup> Those studies provide evidence that MMP-1 plays an important role during cervical dilatation in human parturition. The involvement of MMP-9 in parturition has been demonstrated in the rat amnion,<sup>25</sup> human amniochorion,<sup>26</sup> amniotic fluid,<sup>27,28</sup> urine<sup>29</sup> and plasma.<sup>30</sup> The purpose of our study was to evaluate whether MMP-1 and -9 are detectable in the cervicovaginal secretions of women during pregnancy and in preterm and term labor, and, if so, whether cervicovaginal MMP-1 and/or -9 may be useful markers of preterm birth.

We hypothesized that, since the MMP's act to regulate the fetal membrane and extracellular matrix of the cervix, there should be a measurable elevation in their

concentrations in cervicovaginal fluid during the process of breakdown of fetal membrane structure and the process of cervical ripening. Further, increased concentrations should be apparent whether these processes are occurring at term or preterm.

## Materials and Methods

Data reported in this study were acquired as part of an ongoing prospective cohort study to evaluate sociodemographic, biochemical and clinical factors that may be used for the prediction of preterm delivery. Study sites included the Women's Health Clinic at Bellevue Hospital Center, New York, USA and the Department of Obstetrics and Gynecology of the University Medical Center Utrecht, the Netherlands. The local institutional review boards approved the study and we obtained informed consent from all patients. Term delivery was defined as delivery at or after 37 completed week's gestation. All patients had an estimated date of confinement determined by the date of last menstrual period (LMP) and confirmed by serial ultrasounds.

Cases (n=32) included women who delivered preterm, and where sampled more than 3 weeks prior to delivery (n=19), within 1 week of delivery (n=7) and during spontaneous labor (n=6). Controls consisted of 80 women matched for race, age and gestational age, delivering at term and who were sampled at 20-32 weeks (n=47), within 1 week of delivery (n=14) and during labor (n=19). All participants screened negatively for bacterial vaginosis and sexually transmitted diseases.

The collection of cervicovaginal secretions during pregnancy was performed sequentially at 3-4 week intervals between 20 and 32 weeks' gestation. For this cross-sectional study, only one specimen for each gestational age (20-24, 25-28, 29-32 weeks) was used for analysis. All comparison groups contained one sample only for each woman. In the event that we had more than one sample available for analysis, we selected the sample from the earliest gestational age period. Spontaneous preterm and term labor were defined as active labor resulting in delivery with cervix dilatation. Vaginal and cervical samples were collected separately from the posterior fornix of the vagina and from the endocervical canal during a speculum exam using a Dacron swab. Since we detected no difference between MMP-1 or MMP-9 concentrations collected from the vagina or the cervix, we report values for vaginal specimens only, since these were collected

more frequently. The swab was placed in an antiprotease solution, containing an anti-protease buffer consisting of 750  $\mu\text{L}$  of 1% bovine serum albumin in Tris buffer (BSA-TBS) with 5 mmol/l EDTA, 5 mmol/l phenolmethylsulfonylfloride (PMSF) and 0.5 trypsin inhibitory units of aprotinin. This buffer does not effect the MMP-1 or MMP-9 immunoreactivity in the respective enzyme-linked immunosorbent assays (ELISAs). The specimens were refrigerated after collection and centrifuged for 10 minutes at 2500 rpm at a temperature of 4° C. Following centrifugation, 0.25 ml of the supernatant was aliquotted into microfuge tubes and stored frozen at - 80° C until assayed.

Commercially available ELISAs for MMP-1 and -9 (Oncogene, Cambridge, MA, USA) were used to measure the MMP-1 and-9 in the cervicovaginal secretion supernatants. The intra-assay coefficient of variability (CV) was 6%, and the interassay CV was 12% CV for both biochemical endpoints. The lower limit of detection of MMP-1 and -9 was 0.055 ng/ml with values below this designated as undetectable. For analysis, we used the value of 0 ng/ml for the undetectable samples. There was no significant difference between samples collected in the Netherlands and in New York. For statistical analysis the  $\chi^2$  test was used for evaluation of rates and proportions. Continuous variables were compared by the Wilcoxon signed-rank sum tests, with two-tailed  $\alpha < 0.05$  considered significant.

## Results

Table 1 illustrates the demographic and obstetric characteristics of the 32 women who delivered preterm and in the study population 80 age, race and gestational age matched controls that delivered at term. In the study population the total cervicovaginal samples available for the assays were MMP-1 (n=190) and MMP-9 (n=107). Only 26% of all specimens had detectable levels of MMP-1. Among cases and controls, cervicovaginal MMP-1 levels were unaffected by labor. Table 2 demonstrates that, among non-laboring control (term) patients (> 3 weeks prior to delivery), MMP-9 concentrations were low. However, MMP-9 levels increased significantly within 1 week of term labor and during term labor. The highest MMP-9 values were observed among laboring patients with ruptured membranes.

Table 3 demonstrates that, among cases, MMP-9 levels were unaltered prior to preterm labor, but increased among patients in preterm labor. Figure 1 shows that the median MMP-9 levels were barely detectable during pregnancy, were

**Table 1.** Sociodemographic characteristics of the study population for matrix metalloproteinase (MMP)-1 and MMP-9.

Characteristic	Preterm (n=32)			Term (n=80)		
	>3 weeks prior to delivery (n=19)	<1 week prior to delivery (n=7)	In labor (n=6)	>3 weeks prior to delivery (n=47)	<1 week prior to delivery (n=14)	In labor (n=19)
<b>Race</b>						
Black	4	0	0	4	0	1
Asian	5	0	0	10	0	4
Hispanic	9	1	2	21	7	7
White	1	6	4	12	7	7
<b>Parity</b>						
Nulliparous	5	5	3	23	6	7
Multiparous	14	2	3	24	8	12
<b>Maternal age</b>						
< 20 yr.	2	0	1	2	2	3
20 < 35 yr.	14	5	4	39	9	12
≥ 35 yr.	3	2	1	6	3	4
<b>Number of patients assayed for MMP-1</b>						
	18	6	5	42	4	9
<b>Number of patients assayed for MMP-9</b>						
	3	6	6	14	14	18

increased in preterm and term labor and displayed a more than ten-fold increase in the presence of ruptured membranes. The significant correlation between MMP-9 levels and cervical dilatation is shown in Figure 2 ( $r = 0.48$ ;  $p < 0.02$ ).

**Table 2.** Median and range of matrix metalloproteinase (MMP)-9 values (ng/ml) in detectable cervicovaginal secretions collected more than 3 weeks and less than 1 week prior to delivery, and in term labor, with or without rupture of the membranes (ROM).

	>3 weeks prior to delivery (n=28)	<1 week prior to delivery (n=14)	In labor (n=28)	No ROM (n=20)	ROM (n=8)
<b>MMP-9</b>	0 (0-0.04)	0.8 (0-22.8)	6.6 (0-30.6) *	1.3 (0-14.4)	26.5(15.5-30.6)†

\*p<.001 by the Kruskal-Wallis multiple group rank sum test for the comparison of the three time period groups;

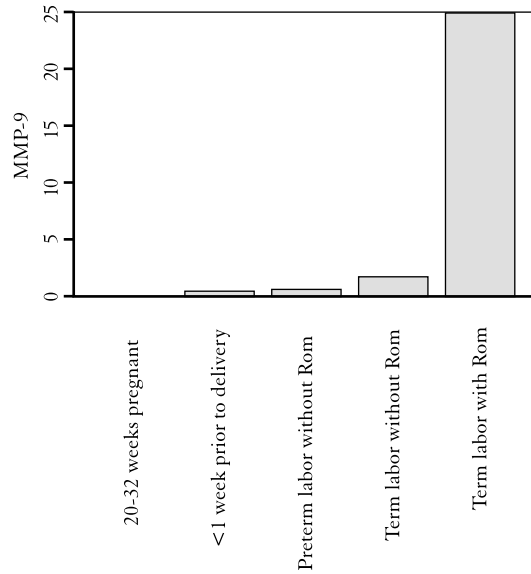
† p<.001 by the Wilcoxon rank sum test for the comparison of the term ROM vs. no ROM groups.

**Table 3.** Median and range of matrix metalloproteinase (MMP)-9 values (ng/ml) in detectable vaginal secretions collected during pregnancy (non-labor) and in preterm labor.

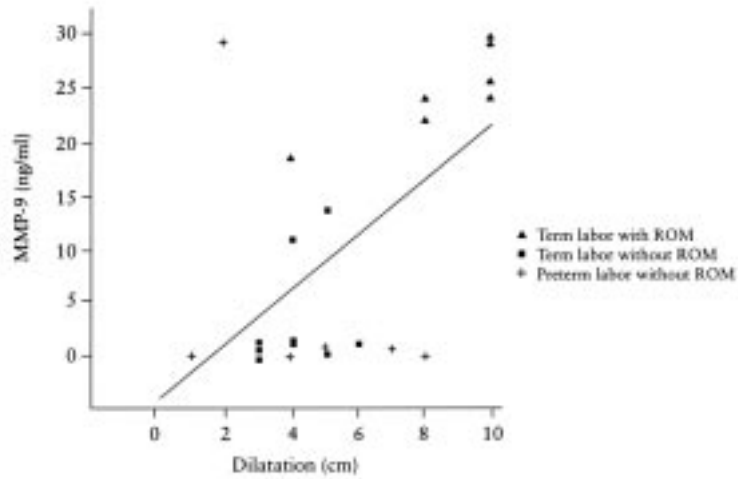
	Preterm non-labor (n=9)	Preterm labor (n=5)	p-value*
<b>MMP-9</b>	0 (0-0.14)	0.3 (0-30)	0.02

\* By the Wilcoxon rank sum test

**Figure 1.** Association of median matrix metalloproteinase (MMP)-9 during pregnancy, prior to delivery and in preterm and term labor with or without rupture of membranes.



**Figure 2.** Correlation between matrix metalloproteinase (MMP)-9 concentration and cervical dilatation in term labor with and without rupture of membranes (ROM) and in preterm labor without ROM.



## Comments

Rajabi and colleagues<sup>18</sup> found that MMP-1 levels were increased 13-fold in the human lower uterine segment and cervix at parturition. In human placentas a significant increase of total collagenase activity has been shown after the onset of labor.<sup>19</sup> After inactivation of tissue inhibitor of MMP-1, a 12- to 17-fold increase in collagenase activity was found. Vadillo-Ortega and co-workers<sup>20</sup> found increased levels of MMP-9 in amniotic fluid of patients with normal term labor and preterm rupture of membranes.

Elevated levels of collagenolytic activity, measured in cervical biopsies from pregnant women who delivered at term,<sup>18</sup> indicate that collagenase may play an active role in the cervical ripening process. As collagenase acts extracellularly in the matrix, it might diffuse into the serum and provide a signal of incipient labor. Rajabi and associates<sup>23</sup> showed no change in serum MMP-1 activity throughout pregnancy until the onset of term labor and an eight-fold increase during preterm labor. They suggested that serum MMP-1 might be a valuable marker for detecting preterm labor. Granström and colleagues<sup>21</sup> reported that serum collagenase at term was higher than in the non-pregnant state. MMP-1 levels were higher in women with a ripe cervix than in those described as having stiff and inelastic cervixes. Contrary to these reports, Morrison and co-workers<sup>22</sup> found no elevation in serum collagenase at term labor. These inconsistent findings may be due to the use of different assay methods.

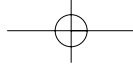
Immediately prior to and during labor, we expected increases in the cervicovaginal secretion of MMP-1. However, we now report that cervicovaginal MMP-1 was not associated with the onset of preterm or term labor. It is possible that MMP-1 activity is restricted to the tissue and not released into cervicovaginal secretions. Prior to accepting this conclusion, however, our cross-sectional sampling methodology should be compared with a longitudinal study, in which a group of women have their MMP levels measured over time, through labor and delivery. An additional caveat relates to the nature of the ELISA assay. Whereas total immunological levels of MMP generally correlate well with biological activity, it is possible that tissue inhibitors of metalloproteinase activity could have influenced our results. For example, MMP activity might be increased in the absence of elevated concentrations if inhibitor levels are reduced. Given our findings, the ELISA assay of vaginal MMP-1 does not seem useful for prediction of preterm delivery.

In our study, among controls, cervicovaginal MMP-9 values were low more than 3 weeks prior to the onset of term labor, increased within 1 week of labor, reached relatively high concentrations in labor and peaked with membrane rupture. In contrast, among cases, MMP-9 levels remained unchanged until the onset of spontaneous preterm labor.

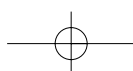
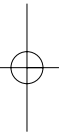
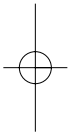
The presence of MMP-9 has been studied in rat amnion,<sup>25</sup> human amniochorion,<sup>26</sup> amniotic fluid,<sup>27,28</sup> urine<sup>29</sup> and plasma.<sup>30</sup> Vellido-Ortega and colleagues<sup>26</sup> demonstrated with Western blot analyses that MMP-9 protein increased in the human amniochorion with labor. MMP-9 is expressed by amnion epithelium, macrophages, chorion laeve trophoblast and decidual cells. The increased expression of MMP-9 will result in degradation of the extracellular matrix of the fetal membranes and facilitate their rupture under both physiological and pathological conditions. Athayde and co-workers<sup>27</sup> showed that women with preterm premature rupture of membranes had higher MMP-9 concentrations in amniotic fluid than women in spontaneous preterm labor with intact membranes. Women with an intra-amniotic infection had higher concentrations of MMP-9 than women without infection.<sup>27</sup> Locksmith and associates<sup>28</sup> found MMP-9 levels in the amniotic fluid to be reliable for diagnosing intra-amniotic infection. Recently, a simple non-invasive assay was used to quantitate urinary MMP-9 activity among a small group of patients (n=15) with threatened premature labor.<sup>29</sup> This study showed that both positive and negative predictive values for a risk of premature delivery were 80%. Tu and co-workers<sup>30</sup> reported that plasma MMP-9 concentrations, assayed with an ELISA, remained unchanged throughout pregnancy, but increased in women who presented with spontaneous labor.

The timing of MMP-9 expression in the cervicovaginal secretions in our study is comparable with the findings of Tu and colleagues<sup>30</sup> in plasma. We also showed an association of cervicovaginal MMP-9 expression with rupture of the membranes, as was previously described in plasma and amniotic fluid.<sup>26,30</sup> We anticipated that preterm labor would be preceded by a prolonged period of cervical remodelling and ripening, causing earlier release of MMP-9 into cervicovaginal secretions than was found preceding term labor. However, our results indicate that term labor was preceded by earlier release of MMP-9. We did find a significant correlation between MMP-9 expression and cervical dilatation.





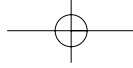
While, there might be an important role for MMP-9 in the mechanisms of labor and membrane rupture, MMP-9 levels prior to preterm delivery are not significantly increased in comparison to MMP-9 throughout pregnancy. MMP-9 therefore does not appear to be useful as a predictor of preterm birth. However, since we measured MMP-9 in the same manner as MMP-1, i.e. with an ELISA, the limitation discussed above applies to MMP-9 as well. Interestingly, MMP-9 might be useful to confirm a suspicion of premature rupture of membranes if amniotic fluid cannot be collected for a confirmatory fern or pH test. Future research is necessary to study the usefulness of such a confirmatory test.



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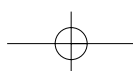
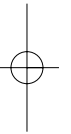
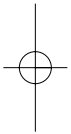
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*Chapter 3*

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# 4

## Cervical length in uncomplicated pregnancy: A study of sociodemographic predictors of cervical changes across gestation

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## Abstract

**Objective.** We conducted this study to evaluate sociodemographic factors to be associated with changes in the length of the cervix across gestation in pregnancies that resulted in term deliveries.

**Study design.** This study was an observational cohort design. In 125 women with a singleton pregnancy cervical length was determined and measured at 3 to 4-week intervals between 20 and 32 weeks gestation. We developed a structured questionnaire to collect psychosocial and sociodemographic characteristics. Bivariate analysis, analysis of variance, and regression analysis were used to study variation in cervical length.

**Results.** Overall, cervical length decreased minimally as gestational age progressed. However, among African-American patients cervical length decreased significantly with increasing gestational age ( $p = .006$ ). In addition, high psychosocial stress was associated with significantly shorter cervixes later in gestation, independent of race ( $p = .003$ ). Finally, women whose occupations involved skilled manual labor had shorter cervixes ( $p = .02$ ).

**Conclusions.** Women who are black, under stress, or working as skilled manual laborers demonstrate significant shortening of the cervix during gestation. Given that a shorter cervix predisposes to preterm delivery, our findings provide new insights into the well-described association of these psychosocial and sociodemographic factors with an increased risk of preterm delivery.

## Introduction

The human cervix has been shown to be a dynamic organ throughout gestation, varying markedly in both shape and length.<sup>1</sup> As term approaches, the cervix begins to shorten, in association with effacement and dilatation. Recently, reduction in cervical length determined sonographically during the second and third trimesters has been correlated with increased risk of preterm delivery.<sup>2-4</sup>

Among women with uncomplicated pregnancies, there are minimal data on the correlations of psychosocial and sociodemographic variables with cervical length across gestation. Moreover, published studies aimed at developing reference ranges for cervical length throughout uncomplicated pregnancy contain conflicting information.<sup>2-7</sup> We believe it is important to ascertain whether this observed variability in cervical length reflects methodological differences in cervical length measurements (ie, interobserver variation; different methods of reporting cervical length, such as using mean versus minimal values, and variation in degree of bladder distention) or biological variability that may be associated with differential exposure to risk factors.

Therefore, we undertook this study to test the hypothesis that, in uncomplicated pregnancies that resulted in term deliveries, there is significant variability among women in the length of the cervix, and that this variability correlates with psychosocial and sociodemographic factors.

## Material and methods

Data reported in this study were acquired as part of an ongoing prospective cohort study to evaluate psychosocial, sociodemographic and clinical factors that may be used for the prediction of preterm delivery. From July 1996 to June 1997 we serially evaluated cervical length using vaginal ultrasonography in 125 patients with singleton pregnancies that progressed to term in the Women's Health Clinic at Bellevue Hospital Center. We obtained prior approval for the study from the institutional review board, and we obtained informed consent from all patients as part of the enrollment process. We defined term delivery as delivery at or after 37 completed weeks' gestation. All patients were < 23 weeks' gestation at enrollment, and all had a well-confirmed estimated date of confinement by date of last menstrual period and ultrasound. Patients who had a first prenatal visit after 23 weeks

of gestation, who had documented ruptured membranes, or who had chromosomal or congenital anatomic abnormalities of the fetus were ineligible to participate. The study population consisted predominantly of publicly insured or uninsured patients. Key sociodemographic characteristics are listed in Table 1.

**Table 1.** Sociodemographic characteristics of the study population (n = 125).

Characteristic	No	%
<b>Race</b>		
Black	29	23
Asian	24	19
Hispanic	52	42
White	20	16
<b>Parity</b>		
Nulliparous	57	46
Multiparous	68	54
<b>Marital status</b>		
Single (unsupported)	45	36
Married	61	49
Living together	19	15
<b>Maternal age</b>		
< 20 y	12	10
20 < 35 y	102	81
≥ 35 y	11	9
<b>Education</b>		
< 9 y	20	16
9 - 12 y	16	13
High school degree	69	55
College or graduate degree	20	16
<b>Income</b>		
< \$10,000/ y	55	44
\$10,000 < \$20,000/ y	57	36
> \$20,000/ y	10	8
Not reported	3	2



A single ultrasonographic operator performed all cervical length measurements to eliminate the possibility for interobserver variability in measurement technique. The intraobserver variability was 3.0 mm, on the basis of a sample of 24 repeat measurements. Cervical length was evaluated serially at 3- to 4- week intervals that coincided with routine prenatal care visits. The range of gestational ages at which we measured cervical length was 20-32 weeks. We attempted to obtain at least 1 cervical length measurement at each of 3 gestational age periods of 20-24 weeks, 25-28 weeks and 29-32 weeks. When only 2 of these periods were represented ( $n=31$ ), that period's measurement was treated as missing data for the analysis. In those instances in which we collected 2 measurements in a given gestational age interval ( $n=22$ ), we averaged the measures in subsequent analyses.

Ultrasonographic scans were performed with a Siemens Sonoline Prima ultrasound unit. After the patient emptied the bladder, she was placed in the lithotomy position. A 6.5-MHz transvaginal transducer was covered with a sterile condom. The endocervical canal was visualized in the sagittal plane, and the calipers were placed at the furthest points between the internal and external os. When funneling was present, we measured the distance over which the endocervical walls were juxtaposed. Because pressure against the cervix generated by insertion of the transducer can influence the length of the endocervical canal, it was measured 3 times at each session. When different values were obtained, the minimum value was used, consistent with previously described methods.<sup>3,4</sup>

Information regarding obstetrical history, complications during the current pregnancy, sociodemographic factors, and other clinical characteristics of the patient were obtained from the medical record and by a self-administered questionnaire. The questionnaire was distributed and explained during the first study visit, between 20 and 24 weeks of gestation. The women completed the questionnaire at home, and the responses were reviewed with the patient during the next study visit. The questionnaire represents a significant modification of previously developed instruments<sup>8,9</sup> and was tailored to the specific objectives of this study. We pretested and then revised it on the basis of initial responses of volunteers who did not participate in the study.

Stress was evaluated according to a weighted scale of 35 life events (Table 2) to measure the level of psychosocial stress that occurred during the pregnancy and in the year before conception. On the basis of relative stress scoring systems,<sup>9</sup> each

life event on the inventory was assigned a numeric score. Life events that occurred in the year before the pregnancy were weighted by a factor of two thirds compared with those that occurred during pregnancy, on the basis of subjective pretest assessments of the relative difference in perceived stress during these times. The sum of the weighted scores represents the overall psychosocial stress score.

**Table 2.** Listing of major life events contributing to stress scale.

**Life events used for stress-scale:**

- Trouble with your boss / co-workers
- Family troubles
- Major arguments with husband / partner
- Sexual difficulties
- You experienced a major illness or injury
- A loved one experienced a major illness or injury
- Serious financial problems
- Death of spouse / close family member
- Addition of a new 'family' member
- Major change in behavior of family member
- You moved to another neighborhood
- You experienced a change in your self-esteem
- You moved to another state
- You moved to another country
- Death of close friend
- You or your husband / partner were arrested
- You were married
- You were divorced
- You were separated from your husband /partner
- You achieved special successes
- You were physically hurt by someone close to you.
- You were laid off or fired from work
- Your husband / partner was laid off or fired from work
- You took on a new loan or mortgage
- You experienced foreclosure on a mortgage or loan
- You have become homeless
- You were denied a Green Card
- You or your partner are unable to find work
- You are fearful that someone at home will hurt you
- You started or graduated from school
- A child has left home (on bad terms)
- You were a victim of rape
- A child was expelled from school

Four categories of income and education (Table 1) were created from the responses. These were based on the standard US Bureau of the Census classification.<sup>10</sup> Similarly, occupation was stratified into 4 groups, according to the census classification as follows: (1) unskilled (no usual employment, homemaker) and partly skilled (protective service, private household, other service); (2) skilled (transportation, construction trade, handlers, skilled crafts, repair, operators, fabricators, and laborers); (3) intermediate (technical, administrative support and sales); and (4) professional (managerial and professional specialty).<sup>10</sup> To measure overall socioeconomic status, we divided the sum of individual scores derived for maternal and paternal education, occupation, and family income into 4 quartiles, lowest, low, moderate, and high socio-economic status.

We developed an exercise score (0-12), computed by adding points assigned for varying amounts of the following weekly activities: flights of stairs climbed; hours of light, moderate, or heavy physical exercise; and hours of housework per week. Questions regarding the women's attitude toward the pregnancy included the degree to which the respondents had planned the pregnancy and the degree of anxiety associated with confirmation of the pregnancy. The women were also queried concerning the convenience of the timing of the pregnancy and the reaction of the husband or partner and children to the pregnancy. A single weighted score (0-20) was used to categorize the woman's attitude toward the pregnancy. Body mass index was calculated with the formula (weight [kg] / height<sup>2</sup> [m]). The weight used in this calculation was the reported prepregnancy weight recorded during the woman's first prenatal visit.

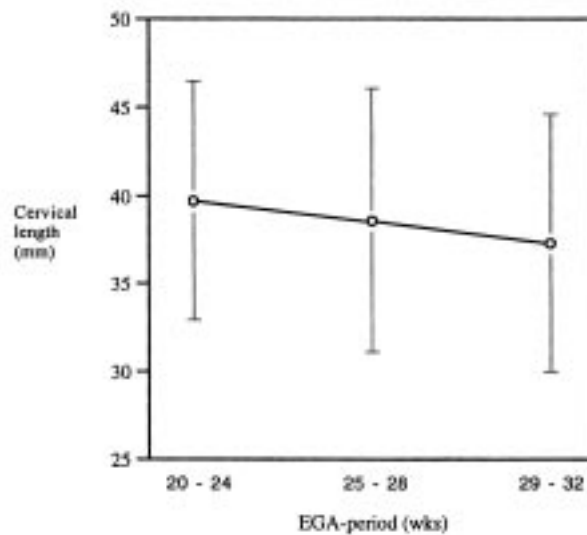
Data analysis was performed with the aid of the JMP statistical analysis software, version 3.1.5 (SAS Institute Inc, Cary, North Carolina). Required sample sizes were computed at the beginning of the study using a power analysis of the expected difference in mean cervical length for participants who possessed one of the preselected sociodemographic characteristics of interest (e.g. marital status). We enrolled sufficient participants for an  $\alpha$  value of .05 and a  $\beta$  value of .20. For this study, we considered it important to detect mean differences in cervical length of  $\geq 4.0$  mm. Probability values  $< .05$  were considered to indicate a statistically significant difference in this study. Analysis techniques included the  $\chi^2$  test for binomially distributed outcomes, student t-tests and analysis of variance for continuous, normally distributed variables, and the Wilcoxon rank-sum test for non-normally distributed data. Multiple stepwise regression analysis was used to evaluate

the association of cervical length with psychosocial and sociodemographic factors. Finally, change in cervical length over time was evaluated by repeated-measures analysis of variance.

### Results

Demographic characteristics of the study population are shown in Table 1. Cervical length data on the study population appear in Table 3. When the group of women as a whole is considered, as gestation proceeded, cervical length did not change significantly (Figure 1). The overall mean cervical length was 39.7 mm ( $\pm 6.8$  mm) at 20-24 weeks, 38.6 mm ( $\pm 7.5$  mm) at 25-28 weeks, and 37.3 mm ( $\pm 7.3$  mm) at 29-32 weeks (Table 3). However, among African-American patients, cervical length shortened significantly as gestation proceeded (Figure 2). Moreover, this difference was statistically significant when compared with other ethnic groups ( $p=.006$ , Table 3). Level of stress and length of the cervix were inversely associated (Figure 3). Patients in the highest category of psychosocial stress had a shorter cervix in the gestational period from 25-28 weeks ( $p=.004$ ) and from 29-32 weeks ( $p=.003$ ), compared with patients with lower psychosocial stress scores (Table 3).

**Figure 1.** Overall mean cervical length change in 3 different gestational age groups ( $p$  not significant). Open circles, mean cervical length.



**Table 3.** Cervical length (in millimeters) in 3 gestational age periods, grouped by various sociodemographic and psychosocial characteristics.

Characteristic	%	20-24 wk	25-28 wk	29-32 wk	mean
<b>Overall mean cervical length</b>	100	39.7 ± 6.8	38.6 ± 7.5	37.3 ± 7.3	
<b>Race</b>					
Black	23	39.3 ± 7.7	36.9 ± 8.9	33.0 ± 5.5 *	36.5 ± 6.2
Asian	19	39.8 ± 6.5	39.5 ± 7.3	40.1 ± 7.3	39.7 ± 6.0
Hispanic	42	40.2 ± 6.4	39.7 ± 6.7	38.0 ± 6.7	39.3 ± 5.6
White	16	39.1 ± 7.1	37.3 ± 7.0	37.9 ± 8.8	37.7 ± 6.7
<b>Stress score</b>					
Lowest	56	40.0 ± 6.0	39.2 ± 7.8	38.5 ± 7.1	39.3 ± 6.1
Low	17	39.7 ± 8.1	39.5 ± 5.2	36.5 ± 7.2	39.4 ± 5.0
Moderate	16	41.5 ± 6.6	40.4 ± 5.7	38.7 ± 7.0	40.3 ± 5.7
Severe	11	36.1 ± 7.9	30.6 ± 7.5 †	30.5 ± 5.9 ‡	30.8 ± 5.2
<b>Maternal occupation</b>					
Partly skilled	64	40.0 ± 6.7	39.3 ± 7.1	37.8 ± 7.6	39.0 ± 6.0
skilled	5	33.1 ± 5.5	26.0 ± 7.7 *	26.7 ± 4.7 §	30.0 ± 4.3
intermediate	30	39.9 ± 7.0	38.8 ± 7.3	37.2 ± 6.3	38.1 ± 5.9
professional	1	45.9 ± 0.8	37.6 ± 1.3	41.3 ± 2.1	41.6 ± 1.4

Analysis of variance was used to evaluate the data. For all values without symbols, differences were not statistically significant.

\* p= .006

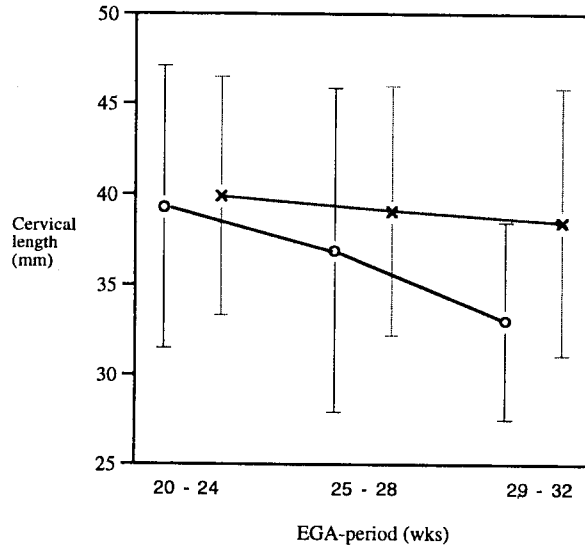
† p= .004

‡ p= .003

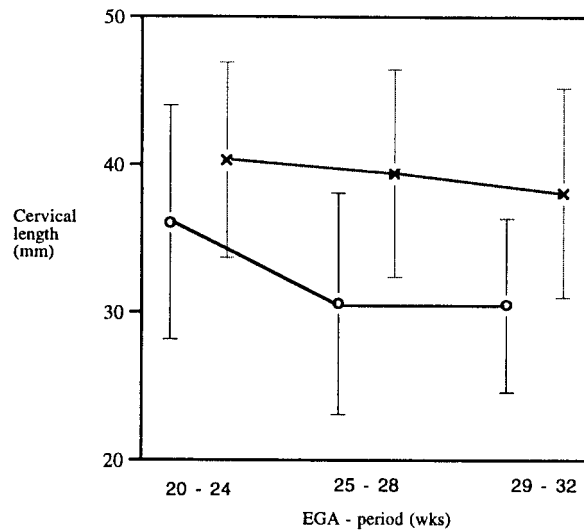
§ p= .02

Parity, age, and a composite measure of socio-economic status (ie, paternal education, maternal education, paternal occupation, maternal occupation, and family income) showed no significant association with cervical length. When maternal occupation was evaluated separately, women who worked as skilled manual laborers demonstrated a significant shortening of cervical length at 25-28 weeks (p=.006) and 29-32 weeks of gestation (p=.02, Table 3). Furthermore, in our sample population, length of the cervix was not associated with certain other sociodemographic factors such as marital status, education, height, prepregnancy

**Figure 2.** Mean cervical length in African-American versus non-African-American women. The trend is significant by analysis of variance ( $p = .006$ ). *Open circles*, African-American women; *x*, non-African-American women.



**Figure 3.** Mean cervical length in women with severe stress compared with women with lower stress levels. The trend is significant by analysis of variance (25-28 weeks,  $p = .004$ ; 29-32 weeks,  $p = .003$ ). *Open circles*, severe stress; *x*, lowest to moderate stress.



body mass index, attitude toward pregnancy, exercise level, religion, and working during pregnancy. Because short cervical length has been associated with an increased risk of preterm birth, we also evaluated other reported risk factors for preterm delivery in our sample, even though all of the women delivered at term. Thus, no association was found between cervical length and prior preterm delivery, prior cervical surgery, and clinical factors such as oral contraceptive use, presence of a urinary tract infection, bacterial vaginosis, yeast infection, or anemia. Similarly, we found no significant association between cervical length and current smoking behavior, history of drug use, or current alcohol use. Multiple stepwise regression analysis revealed no added predictive value of these traditional preterm delivery risk factors on cervical length. These risk factors were rarely present in our study population, however, so that we can make no definitive statement concerning a possible association with cervical length at this time.

### Comment

Data on cervical length during uncomplicated pregnancies have been inconsistent.<sup>2,3,5</sup> Values for mean cervical length described in the literature vary significantly from 32 mm to 48 mm. Suggested cut off values for the prediction of preterm delivery vary from 18 to 40 mm.<sup>2,3,7</sup> In addition, there is controversy over when cervical shortening occurs in uncomplicated pregnancies. Reported values vary from 16 to 31 weeks.<sup>2,3,5,6</sup> These studies were conducted among different populations, which may account for some of the reported variation. Our data show that mean cervical length does not decrease significantly across gestation in our general study population (Figure 1).

At the initiation of this study, we hypothesized that the discrepant results regarding cervical length reported in the literature can be attributed to differences in psychosocial and sociodemographic factors among the various study populations. Papiernik et al.<sup>11</sup> proposed that preterm delivery could be predicted by the identification of multiple risk factors that either predated or accompanied pregnancy. Historic and demographic factors that were found to be associated with preterm delivery by univariate analysis included prior preterm delivery (12.5% increased risk over baseline), maternal stature < 1.52 m (7.4% increased risk), maternal age < 21 years or > 36 years (6.5% increased risk), and the lowest socio-economic classification (13.3% increased risk).<sup>8,11</sup> We found no association of cervical length with these sociodemographic factors in our study population of women who

delivered at term. Previous research indicates racial differences in risk for premature birth. African-American women are at a higher risk of preterm delivery, with risks ranging from 10.8 % to 18.8%.<sup>12,13</sup> Kleinman and Kessel<sup>14</sup> found an overall black/white ratio of 3.0 for very low birth weight infants (92 % of these infants were born preterm), and among women at low risk the black/white ratio was even higher, at 3.4.

Our data show that shorter cervixes develop in black women with increasing gestational age when compared with other groups. Although all of the women in our study delivered at term, there are nonetheless differences between African-American women and other women in the duration of gestation. Papiernik et al.<sup>15</sup> reported that among French women the most common gestational week of delivery at term was 39 weeks for African-American patients, but 40 weeks for white patients. Goldenberg et al.<sup>16</sup> also report that African-American infants are born earlier than white infants. In studies published to date, different theories have been offered to explain these data, such as lower socio-economic status among African-Americans; a higher prevalence of known risk factors such as hypertension, diabetes, and anemia; higher risk of maternal infection; differences in psychosocial factors; and genetic predisposition. Goldenberg et al.<sup>16</sup> suggest that powerful yet unknown risk factors are more prevalent among black women are responsible for their shorter gestations. Thus, African-American women may possess a characteristic, or be differentially exposed to a risk factor (e.g., ascending infection leading to chorioamnionitis and subsequent preterm rupture of the membranes)<sup>17</sup> that predisposes them to shorter gestations. We suggest that black women might react differently to an exposure based on a genetic component of yet-unspecified origin. Our finding of a significant shortening of the cervix during gestation among blacks may reflect this reaction.

Maternal stress has been associated with preterm delivery. The link between maternal stress and preterm delivery is suggested by the increased preterm delivery rate among (1) unmarried and poor mothers,<sup>18</sup> (2) patients who experience major stressful events,<sup>8,19-21</sup> and (3) those with objective and subjective evidence of anxiety.<sup>8,20,21</sup> In addition, our data show that women who experience severe stress have a significantly shorter cervix between 25 and 32 weeks when compared with women in lower psychosocial stress categories.



The shorter cervical length in women with severe stress might be explained by the fact that chronic stress leads to an increase in maternal plasma cortisol. As a result, placental corticotropin-releasing hormone production will increase.<sup>22,23</sup> This might disturb the biochemical balance between corticotropin-releasing hormone and corticotropin-releasing hormone-binding protein as gestation progresses, leading to a premature excess of unbound bioactive corticotropin-releasing hormone in the maternal circulation. Bioactive corticotropin-releasing hormone has been reported to stimulate oxytocin action and increase prostaglandin release, thereby stimulating uterine smooth muscle contractions and proteolytic degradation of the cervical connective tissue,<sup>24</sup> which would be reflected in shortening of the cervix.

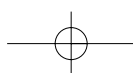
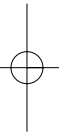
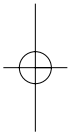
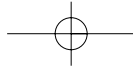
Mamelle et al.<sup>25</sup> reported in a large French survey among pregnant women that 38.4 % of skilled workers experienced intense occupational fatigue during pregnancy. In addition, a weekly working time of more than 40 hours and shift work were found to be risk factors. They also found that mental stress (doing routine work and work requiring little attention) and environmental factors (noise, cold temperature, very wet atmosphere and manipulation of chemical substances) significantly increase the risk of preterm delivery to as high as 10.3%, compared with 5.8% among all working women. Albeit in only a small sample of women (n=5), we found a significant association of skilled manual labor with shortened cervical length. A larger sample size and more detailed data on the work environment would be required, however, to support a conclusion that this type of work impacts cervical length through its generation chronic physical and mental stress.

In conclusion, we have shown that 3 psychosocial and sociodemographic factors (African-American race, stress and skilled manual labor) are associated with a shorter cervical length with increasing gestational age in uncomplicated pregnancy. These results suggest potential application in the management of patients who are at risk for preterm delivery. The physiologic shortening of the cervix with increasing gestational age in African-American women, patients under severe stress, or skilled manual laborers may prove important when evaluating cervical length. It is possible that the observed cervical shortening that occurs in women who are African-American, stressed, or skilled laborers may either reflect or promote pathological processes. As has been shown in several studies,<sup>2-4,7</sup> cervical shortening before development of preterm labor has been associated with a significant risk of preterm delivery. Therefore, our findings suggest areas for additional research concerning the biologic mechanisms that promote preterm delivery in these 3 separate subgroups.

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## Racial variation in cervical length and preterm delivery

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Preliminary results

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## Abstract

**Objective.** To assess variation in cervical length among African-American, Hispanic, Asian, and Caucasian women by transvaginal sonography and to study if associations between preterm birth and cervical length are related to ethnic origin.

**Methods.** A prospective cohort was undertaken of women seeking prenatal care between 1996 and 2001. They were recruited to undergo serial transvaginal cervical sonography at 20-24, 25-28 and 29-32 weeks. Maternal race was determined by patient's self-report. Data from previous pregnancies and outcome of the index pregnancy were abstracted from the medical record. Preterm delivery was defined as delivery <37 weeks gestation. Data were analyzed by chi-square tests, t-tests, analysis of variance (ANOVA) and by multiple linear regression. Nomograms and percentiles of cervical length were generated for each ethnic group.

**Results.** A total of 856 pregnancies were included in the study, 65.5% Hispanic, 11.6% Asian, 9.5% Caucasian, and 13.4% African-American. Preterm rates did not significantly differ by race or ethnicity, but African-Americans delivered on average earlier (38.4 weeks) than the other groups (ANOVA,  $P < 0.05$ ). Between 20 and 33 weeks all women displayed progressive cervical shortening except Asians. African-American women had shorter cervixes across all 3 gestational age intervals than the other ethnic groups (ANOVA,  $p < 0.001$ ). Between 20 and 24 weeks, significant differences in cervical length between women who delivered preterm compared with those delivering at term were observed only amongst African-Americans (31.4 mm vs. 37.7mm, t-test,  $p = 0.006$ ). Significant differences in cervical length between patients delivering preterm compared with those delivering at term were noted amongst both African-Americans and Hispanics at 25-28 weeks and amongst all groups in the 29-32 week interval.

**Conclusions.** This data suggests that the predictive value of cervical length varies with gestational age among different racial and ethnic groups.

## Introduction

During the past decade, transvaginal ultrasonographic measurements of the cervix have been described as a reliable predictor of preterm labor and delivery. Iams et al. reported a mean cervical length at 24 weeks of 35.2mm in his predominantly (63%) African-American population of singleton gestations.<sup>1</sup> They found that women with transvaginal cervical lengths of less than 26mm (<10<sup>th</sup> percentile at 24 weeks gestation) had a relative risk of 9.5 for preterm delivery, but the positive predictive value for preterm delivery was only 17.8%. Several authors described cervical shortening throughout normal pregnancy and in relation to spontaneous preterm birth (SPB) although the reported timing of these changes was not consistent.<sup>2-5</sup>

In our previous study we ascertained whether this observed variability in cervical length reflected methodological or sociodemographic factors.<sup>6</sup> We found that shorter cervical lengths were independently associated with African-American race, psychological stress, and skilled manual labor in women who delivered at term.<sup>6</sup> Several reports which concluded that short cervical lengths between 19 and 24 weeks gestation were associated with an increased risk of preterm delivery were conducted in populations predominantly composed of African-Americans.<sup>1,7-9</sup> Thus, we questioned whether the ethnic origin of a patient plays a role in the predictive value of cervical length measurements for spontaneous preterm birth. Given the variations in cervical length measurements at various gestational age time points and in various ethnic groups, we sought to establish basic population norms over time. We aim to assess if association between preterm birth and cervical length are related to ethnic origin.

## Material and Methods

Women seeking prenatal care at Bellevue Hospital between July 1996 and November 2001 were recruited to participate in an ongoing prospective cohort study to evaluate psychosocial, demographic, and clinical risk factors that may predispose to preterm labor and delivery. Preterm delivery was defined as a delivery, greater than 25 weeks and less than 37 weeks gestation. In our inner-city population, the overall incidence of preterm delivery was about 10%. The Institutional Review Board approved this study and all women with singleton pregnancies signed informed consent at the time of enrollment. All women were less than 23 weeks gestation at enrollment and had an estimated date of delivery established by

last menstrual period and/or ultrasound. Patients who had a first prenatal visit after 23 weeks of gestation, who had chromosomal or congenital anatomic abnormalities of the fetus or had a medically indicated 'elective' preterm delivery, were ineligible to participate. Information regarding obstetric history, complications during the current pregnancy, sociodemographic factors, other clinical characteristics of the patient, pregnancy outcome and neonatal data was obtained from the (prenatal) medical record, patient's self-report and by a self-administered questionnaire. The questionnaire was distributed and explained during the first study visit, between 20 and 24 weeks and the responses were reviewed with the patient during the next study visit. The questionnaire represented a significant modification of previously developed instruments and was previously validated to measure stress, four categories of income and education, socio-economic status, occupation, exercise during pregnancy and the women's attitude toward the pregnancy.<sup>6</sup>

Transvaginal sonographic cervical length measurements were obtained during the three gestational age intervals (20-24, 25-28 and 29-32 completed weeks). The ultrasound exams were performed with a Siemens Sonoline Prima ultrasound unit using a 6.5-MHz transvaginal probe in the manner as described previously by us.<sup>6</sup> Cervical length measurements were followed longitudinally over time. The primary health care providers for the patients were blinded to all ultrasound findings performed as a part of this research protocol in order to assess the natural history of any potential cervical changes.

Data analysis was performed with the aid of the JMP statistical analysis software (Version 4.0.3, Copyright 1989-2000, SAS Institute Inc.) and SPSS for Windows (Version 6.1.4, Copyright 1989-1995, SPSS Inc.). Analysis techniques included the chi-square test for binomially distributed outcomes, student t-test and analysis of variance (ANOVA) for continuous, normally distributed variables. Multiple linear regression analysis was used to determine the relationship of demographic characteristics (age, marital status, socio-economic status, ethnicity), past obstetric history (parity, prior preterm birth, prior spontaneous abortion < 20 weeks), body mass index, stress, exercise, smoking, attitude towards pregnancy, and cervical length at the three gestational age intervals with gestational age of delivery. Separate regression analysis was done to explore an independent association of the above-mentioned factors and cervical length at 20-24, 25-28 and 29-32 weeks. Nomograms for the 5<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, and 95<sup>th</sup> percentiles were generated longitudinally over time for the 4 racial/ethnic groups.



## Results

During the study period, 910 women with singleton pregnancies underwent 2<sup>nd</sup> trimester cervical ultrasound examinations at three predetermined gestational age intervals. Fifty-four women contained exclusion criteria, which made them ineligible for participation in the study. The final study population consisted of 856 women. African-American women were older, had higher rates of prior preterm birth and were more often multiparous (Table 1). Although African-American women had on average a shorter gestational age at delivery, there was no statistically significant difference in preterm birth rate (< 37 weeks) amongst the four groups of women. However early preterm birth < 35 weeks gestation occurred more often in the African-American population.

Cervical length was normally distributed with mean values of 39.2 mm between 20-24 weeks; 37.6 mm between 25-28 weeks; and 36.3 mm between 29-32 weeks'

**Table 1** .Data regarding demographics, obstetrical history and pregnancy outcome by ethnic group. PTB = preterm birth, SD= standard deviation.

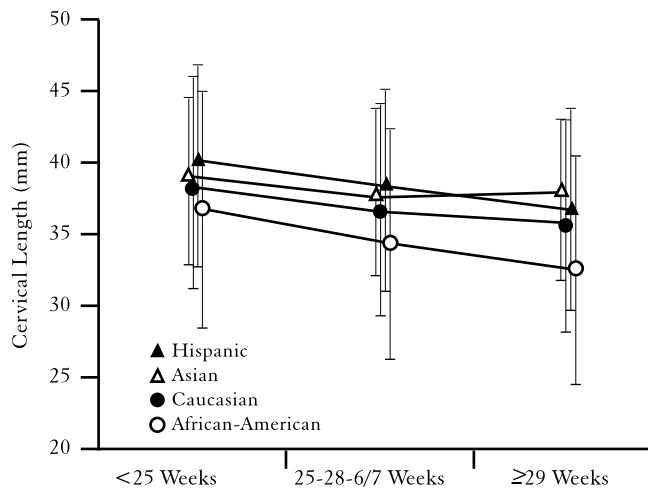
	Hispanic	Asian	Caucasian	African-American
<b>Number (%)</b>	561 (65.5)	99 (11.6)	81 (9.5)	115 (13.4)
<b>Age in years (SD)</b>	26.1 (5.5) *	27.5 (5.0)	27.4 (5.3)	28.6 (5.6) *
<b>Parity (mean (SD))</b>	1.0 (1.2)	0.9 (1.1)	0.5 (0.8)	1.4 (1.7) *
<b>Prior preterm birth (%)</b>	49 (8.4)	6 (6.1)	4 (4.9)	18 (15.7) *
<b>Weeks at delivery (SD)</b>	39.2 (1.9)	38.9 (2.6)	39.3 (1.5)	38.4 (3.1) *
<b>% preterm birth &lt; 37 weeks</b>	8.0	13.3	7.6	14.4
<b>% preterm birth &lt; 35 weeks</b>	2.9	7.1	0	9.9*
<b>Cervical Length in mm (SD)</b>	38.3 (6.1)	38.4 (5.5)	37.0 (6.8)	34.7 (7.2) *

\* P<0.05 by ANOVA

gestation. All patients had progressive cervical shortening across the observation period except Asians (Figure 1). The mean cervical length of African-American women was shorter across all three gestational age intervals compared to the other ethnic groups (ANOVA,  $p < 0.001$ ), also after controlling for possible confounding factors (preterm birth, obstetrical history, sociodemographic factors). The 5<sup>th</sup>, 25<sup>th</sup>, 50<sup>th</sup>, 75<sup>th</sup>, and 95<sup>th</sup> percentiles for cervical lengths of the Hispanics (as largest group of our study population) and the African-Americans are shown in Figure 2. The 5<sup>th</sup> percentile of the African-Americans decreased from 20 weeks to 33 weeks from 20 mm to 16 mm and the 5<sup>th</sup> percentile of the Hispanics from 26 to 25 mm.

African-American women who delivered preterm had shorter cervixes at 20-24 weeks than African-American women delivering at term (31.4 mm vs. 37.7 mm,  $t$ -test,  $p = 0.006$ ; Table 2). This difference was not found for the other ethnic groups. At 25-28 weeks only African-American and Hispanic women showed a significant difference of mean cervical length between women who delivered preterm and those who delivered at term. At 29-32 weeks significant differences in cervical length were noted between women delivering preterm compared to those delivering at term in all four racial/ethnic groups.

**Figure 1.** Cervical Length Changes Across Gestational Age by Race (Mean  $\pm$  SD).



ANOVA,  $p < 0.001$  for African-Americans at all time intervals

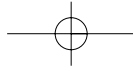
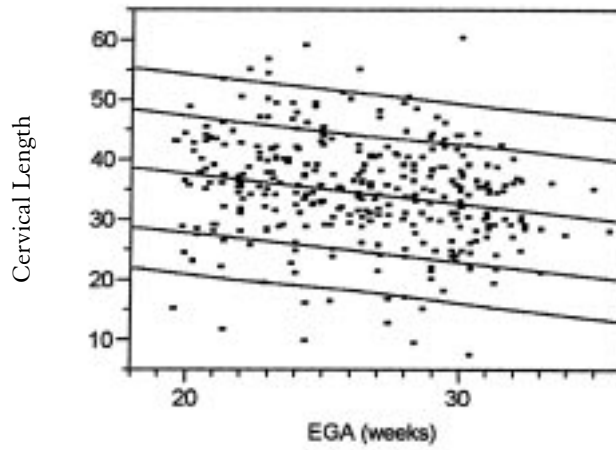


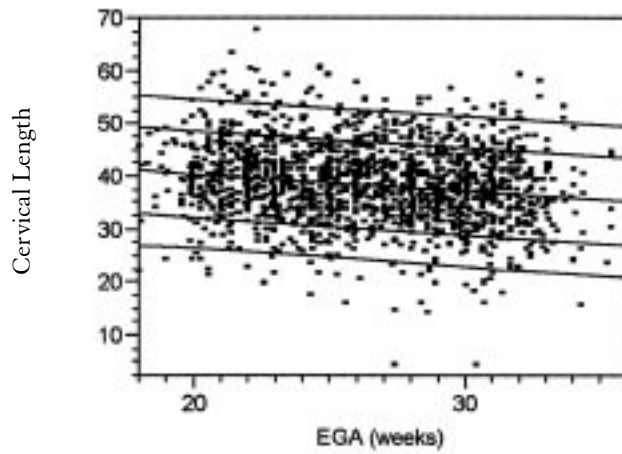
Figure 2. Nomograms for Cervical Length Measurements by EGA in Hispanics and African-Americans.

African-Americans

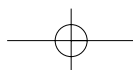


— 25<sup>th</sup> and 75<sup>th</sup> Percentiles  
- - - 5<sup>th</sup> and 95<sup>th</sup> Percentiles

Hispanics



— 25<sup>th</sup> and 75<sup>th</sup> Percentiles  
- - - 5<sup>th</sup> and 95<sup>th</sup> Percentiles



**Table 2.** Comparison of mean cervical length at three gestational age groups within four ethnic groups between women who delivered at term and women who delivered preterm (PTB) (< 37 and < 35 weeks).

Mean (SD) cervical length	Hispanic (n=523)		Asian (n=98)		Caucasian (n=74)		African-American (n=115)	
	n		n		n		n	
<b>20-24 6/7 week</b>								
Term	469	39.9 (7.3)	443	38.3 (6.2)	75	37.1 (6.9)	67	35.7 (7.7)
PTB < 37 weeks	40	39.8 (6.9)	40	37.0 (3.3)	12	35.3 (17.1)	6	31.4 (9.9)*
PTB < 35 weeks	14	38.1 (6.1)	14	37.5 (3.2)	7	-	-	29.0 (10.2)*
<b>25-28 6/7 weeks</b>								
Term	443	38.6 (6.9)	443	38.3 (6.2)	75	37.1 (6.9)	67	35.7 (7.7)
PTB < 37 weeks	40	35.1 (6.9)*	40	34.6 (6.7)	8	31.9 (11.7)	5	25.2 (6.9)*
PTB < 35 weeks	16	34.3 (8.4)*	16	32.3 (7.7)*	5	-	-	23.8 (9.1)*
<b>29-32 6/7 weeks</b>								
Term	463	37.1 (7.2)	463	39.0 (7.3)	68	36.4 (7.1)	66	33.3 (7.3)
PTB < 37 weeks	32	34.5 (7.0)*	32	31.5 (6.6)*	12	30.5 (10)	6	27.8 (10.9)*
PTB < 35 weeks	9	30.1 (8.2)*	9	28.6 (6.1)*	6	-	-	28.0 (9.7)*

\* P < 0.05 by t-test of comparison of mean cervical length per ethnic group 'term' with 'PTB < 37 weeks' and 'term' with 'PTB < 35 weeks'.

When preterm birth was defined as a delivery before 35 weeks our findings were similar, except for the Caucasians, who did not deliver before 35 weeks in our study population. At 20-24 weeks gestation only the African-Americans showed a significant difference in cervical length between women who delivered < 35 weeks compared to those who delivered thereafter. Cervical length measured at 25-28 and 29-32 weeks were significantly different between the women who delivered < 35 weeks compared to those delivering thereafter in all racial/ethnic groups.

Multiple linear regression analysis of the total study population demonstrated significant independent associations between gestational age at delivery and racial/ethnic origin, prior preterm birth, and mean cervical length at 25-28 and 29-32 weeks. Regression analysis was also utilized to show any independent associations with cervical length. Mean cervical length per gestational age interval was also associated with racial/ethnic origin and with cervical length measurements at the other gestational ages. When analyzed for each racial/ethnic group we observed that mean cervical length at 20-24 weeks was associated with 'maternal age' among Hispanics, with 'parity' among Asians and with 'stress' among African-Americans. The mean cervical length at 25-28 weeks in Asian women was related to 'socio-economic status' and in African-Americans cervical length at 29-32 weeks was associated with 'prior preterm birth'.

## Discussion

This study - in an ethnically diverse New York City population - demonstrated progressive cervical shortening between 20 and 33 weeks gestation among African-American, Caucasian and Hispanic but not Asian women. African-American women had significantly shorter cervixes across all 3 gestational age intervals compared with the other groups. African-American women who delivered preterm had shorter cervixes at 20-24 weeks gestation than African-American women who delivered at term. This difference was not found among the other racial/ethnic groups until 25-28 weeks among Hispanics and 29-32 weeks for Caucasians and Asians. Thus, the earliest and strongest association between a shortened cervical length and preterm birth was found among African-American women, an ethnic group which consistently displays a shorter mean cervical length across the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters. One of the limitations of our study design is that the size of ethnic groups was different. It gives low numbers in the group of

Asians and Caucasians who delivered preterm. Furthermore we did not find relevant confounding factors in the total study population, but we can not preclude that there are none. It might be that we could not detect it with our study design.

Racial differences in rates of preterm births and low birth weight infants have been the topic of longstanding research and debate.<sup>10</sup> Epidemiological studies of ethnically diverse groups have shown that African-American women were more likely to experience preterm birth, followed by Hispanic, Asian and Caucasian women.<sup>11-13</sup> It has been suggested that the increased rates of preterm birth in African-American women in the United States have been attributed to differences in socio-economic factors. Such as poor health care, poor nutrition, short pregnancy interval, increased exposure to infectious agents, and increased stress during pregnancy. There is also data to suggest that shortened gestation and lower birth weights infants persist in African-American women after controlling for these risk factors.<sup>12-15</sup>

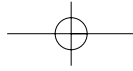
While not specifically addressed in prior studies, this racial/ethnic group variation in cervical length and its preterm birth predictive value is supported by prior studies. Iams et al. described cervical shortening with increasing gestational age after 20 weeks' gestation, with median values falling from 35-40 mm at 24-28 weeks to 30-35 mm after 32 weeks.<sup>1</sup> The likelihood of spontaneous preterm birth increased as cervical length at 24-28 weeks decreased. This applied specifically to the subjects whose cervixes shortened by 6 mm or more, between 24 and 28 weeks. Interestingly, the population studied by Iams and colleagues consisted of more than 60% of African-Americans.<sup>1</sup> Also studies by Hassan et al., Heath et al. and Hibbard et al. linking shortened cervixes to prematurity evaluated predominantly African-American populations.<sup>7-9</sup> The population studied by Heath and associates contained 50% African-Americans. They observed that the mean cervical length of African-American women was significantly shorter than that of Caucasians at 23 weeks gestation.<sup>8</sup> They concluded that short cervical length at 23-24 weeks gestation was associated with increased risk of preterm delivery. Hassan et al. evaluated a population containing 81% African-Americans and noted that women with a cervical length of  $\leq 15$  mm at 20-24 weeks had a 48% risk of early preterm birth.<sup>7</sup> In contrast, Kushnir et al. studied a population composed of only 2% African Americans and reported that shortening of cervical length started from about 30 weeks.<sup>4</sup>

Dijkstra et al. previously evaluated only women who delivered at term and observed that African-American women had shorter cervixes than women of other ethnic groups.<sup>6</sup> The current study evaluates a larger population including preterm deliveries and confirms our previous findings at term.<sup>6</sup> We now provide strong evidence that cervical length measurements predict preterm birth at 20-24 weeks only among African-American women, who have shorter cervixes at that age than other racial/ethnic groups. For the other groups, shortening of the cervix starts later and has a substantial relation to preterm birth when measured after 25 weeks in Hispanics and after 29 weeks in Caucasians and Asians. A short cervix may provide a less effective barrier to ascending genital tract infections. This observation may contribute to the far higher risk for infection-associated preterm membrane rupture and preterm labor with intact membranes among African-American women. In our study Hispanics for instance seem to have more reserve capacity, because they start off with a longer cervix that shortens across gestation at a slower rate. The Caucasian and Asian women in our study have the longest cervixes and the least gestational-age related shortening. This might give them a lower risk of infection-associated prematurity. The reasons why African-American women may have shorter cervixes are unknown but could reflect biological (e.g., higher endogenous estradiol, polymorphisms in cytokine receptor genes) or environmental factors. The latter may include increased stress, exposure to environmental toxins, poor nutrition, and increased exposure to infectious agents. From a practical perspective, our study suggests that the value of cervical length measurements may be limited prior to 25 weeks in racial/ethnic groups other than African-Americans and before 29 weeks among Caucasians and Asians. When measuring cervical length by transvaginal sonography in order to assess risk for preterm birth, consideration should be given to ethnic background when interpreting results.

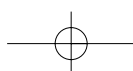
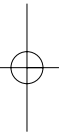
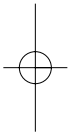
## References

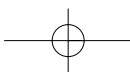
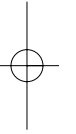
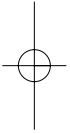
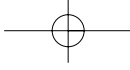
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# 6

## Change in cervical length after cerclage as a predictor of preterm delivery

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## Abstract

**Objective.** To determine whether the degree of cervical lengthening after cerclage and whether serial follow-up measurements of cervical length after cerclage are predictive of pregnancy outcome.

**Methods.** Eighty women whose primary physician determined that a prophylactic ( $n = 50$ ) or urgent cerclage ( $n = 30$ ) was indicated had transvaginal ultrasonographic evaluation before and after cerclage. Thereafter, most women had three additional transvaginal ultrasound examinations until 32 weeks' gestation. At each examination, the mean of three measurements was calculated. Statistical analyses were done by t-test, analysis of variance, and logistic regression, with significance set at  $p < .05$ .

**Results.** The mean  $\pm$  standard deviation precerclage cervical length was 27.2 (10.3 mm and after cerclage was  $34.1 \pm 9.9$  mm ( $n = 80$ ,  $p < .001$ , paired t test). No significant association was found ( $r = -0.26$ ) between the difference in cervical length (postcerclage - precerclage lengths) and pregnancy outcome. Patients with a prophylactic cerclage had a mean cervical length that was consistently longer in patients delivering at term compared with those who delivered preterm at 20 to 32 weeks' gestation. In the urgent cerclage group a significant difference in cervical length between those who delivered at term compared with preterm was evident only at 28 to 32 weeks.

**Conclusion.** The increase in cervical length after cerclage is not predictive of term delivery. Serial cervical length measurements in the late second or early third trimester predict preterm birth but could provide earlier warning in patients with a prophylactic cerclage than in patients with urgent cerclage.

## Introduction

The measurement of cervical length by transvaginal ultrasonography has been used to assess the risk of preterm delivery in women with poor obstetric histories, potential preterm labor, cervical incompetence and multiple pregnancies. There appears to be an inverse relationship between cervical length and risk of preterm delivery.<sup>1-3</sup> Women who have a cervical cerclage for suspected cervical incompetence remain at increased risk for preterm labor and delivery. Historically, these women were followed up after cerclage using digital or speculum examinations, although some clinicians avoid vaginal examination.<sup>4</sup>

At present, the result of a cerclage procedure on cervical length can be viewed by transvaginal ultrasonography. Studies of postelective cerclage have shown some correlation with eventual pregnancy outcome.<sup>4,5</sup> Andersen et al<sup>4</sup> reported that a short upper cervical segment before 30 weeks' gestation was associated with a significantly higher risk of preterm delivery before 36 weeks. Rana et al<sup>5</sup> also reported the importance of ultrasonographic follow up after cerclage. When early signs of cerclage failure or funneling were detected, immediate intervention with hospitalization and tocolysis was undertaken which improved the final outcome of the pregnancy.

Recent studies showed that prophylactic, urgent, and emergency cerclage procedures resulted in measurable cervical lengthening.<sup>6-8</sup> It is not known whether this relative restoration of cervical anatomy after prophylactic or urgent cerclage predicts pregnancy outcome. Our purpose was to determine whether the degree of cervical lengthening after cerclage predicts term delivery. The second aim of the study was to evaluate the usefulness of serial measurements of cervical length after cerclage, until 32 weeks' gestation, to predict pregnancy outcome.

## Materials and Methods

A prospective observational study was conducted using a protocol approved by our institutional review board. All women treated with either a prophylactic or urgent cerclage between January 1997 and July 1999 at the New York University Medical Center, who had transvaginal ultrasonographic evaluation of the cervix 48 hours before cerclage and within 72 hours after cerclage were included in the study (n = 80). Women who had an emergency cerclage were excluded. After cer-

clage, most women had three additional transvaginal ultrasound examinations until 32 weeks' gestation. Sonography was done at the New York University Medical Center or Bellevue Hospital Perinatal Diagnostic Units. To minimize interobserver variability, only one sonographer participated in the study at each site, and each woman had cervical measurement at one site only. A maternal-fetal medicine specialist reviewed all measurements.

Prophylactic cerclage ( $n = 50$ ) was placed at  $14.3 \pm 2.8$  weeks. The indication was a history of cervical incompetence (based on one or more of the following conditions: history of second-trimester pregnancy loss, history of diethylstilbestrol (DES) exposure in utero, cervical conization, and uterine anomaly) or a history of preterm birth with early cervical dilation without uterine contractions. An urgent cerclage ( $n = 30$ ) was placed at  $19.7 \pm 3.1$  weeks in women with a cervical length shorter than 25 mm confirmed by transvaginal ultrasound before 24 weeks' gestation.

Cervical length, defined as the length of the closed endocervical canal, was measured by transvaginal sonography using a 7.0 MHz probe (Acuson EV7, Acuson Corp., Mountain View, CA). In cases of cervical funneling, the apex of the funnel was considered the beginning of the closed endocervical canal and the external os was considered the distal end of the endocervical canal. In each case, after the woman emptied her bladder, the probe was inserted into the vagina until it met resistance. The probe was then withdrawn slightly to reduce compression, and three measurements were taken. The mean of the three measurements was used for analysis. None of the patients had contractions, bleeding, or discharge. None received prophylactic tocolysis, but some received prophylactic antibiotics at the discretion of the operator. In 65 patients, a modified Shirodkar procedure as described by Frieden et al.<sup>9,10</sup> was done. In 15 patients a McDonald cerclage<sup>11</sup> was placed, where the choice of suture material was left to the operator. Seventy subjects were needed to achieve 80% power to detect a 30% difference in the rate of preterm delivery, with  $\alpha = .05$ . Cervical length measurements before and after cerclage between 20-32 weeks were compared using paired t-test, analysis of variance, and logistic regression using JMP statistical software (SAS Institute, Cary, NC).

## Results

Sociodemographic characteristics and obstetric histories of the study population are shown in Table 1. No significant difference in baseline characteristics and in precerclage and postcerclage measurements was noted between patients who had Shirodkar compared with McDonald sutures. Mean gestational age at delivery was 36 weeks and 4 days (95% confidence interval [CI], 35.4, 37.4), and mean birth weight was 2760 g (95% CI, 2567, 2952 g). In total, 32 women (40%) had a

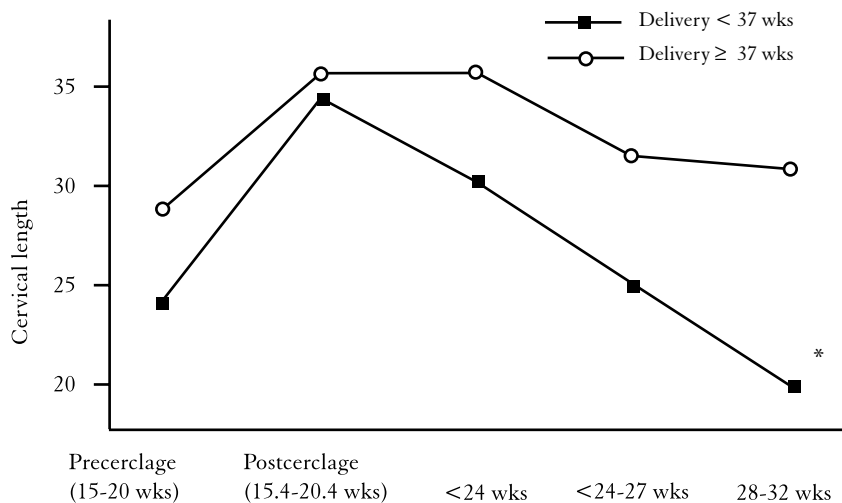
**Table 1.** Sociodemographic factors and obstetrical history of study population (n = 80).

Characteristic	n	%
<b>Race</b>		
Black	8	10
Asian	2	3
White	61	76
Hispanic	9	11
<b>Parity</b>		
Nulliparous	48	60
Primiparous	17	21
Multiparous	15	19
<b>History of cervical incompetence based on one or more of following conditions: (n = 50)</b>		
Diethylstilbestrol exposure utero	6	8
Uterine anomaly	1	1
Cervical conization	2	3
Previous cerclage	11	14
Second trimester loss	47	59
Previous preterm birth	24	30
<b>Type of pregnancy</b>		
Singleton	64	80
Twin	12	15
Triplet	4	5
<b>Maternal age (year)</b>		
median	34	
(range)	(22-46)	

preterm birth (less than 37 completed weeks' gestation), distributed in the same proportion in women with a prophylactic and urgent cerclage. The reasons for preterm birth were spontaneous preterm labor (ten women, 30%), preterm premature rupture of membranes (seven, 24%), induction for suspicion of intra amniotic infection (three, 10%), indicated preterm birth (four, 12%), planned cesarean after determination of fetal lung maturity (four, 12%), and second-trimester loss (four, 12%).

The mean precerclage cervical length was  $27.2 \pm 10.3$  mm, and the mean postcerclage length was  $34.1 \pm 9.9$  mm ( $n = 80$ ,  $p < .001$ , paired t-test). There was no significant association ( $r = -0.26$ ) between the difference in cervical length (postcerclage - precerclage length) and pregnancy outcome. A significant relationship could be shown between gestational age at delivery and length of the cervix between 28 and 32 weeks ( $r = 1.4$ ,  $p = .002$ ). Figure 1 shows a decrease in

**Figure 1.** Comparison of the mean cervical length (in mm) before and after cerclage, using 5 gestational age categories, in women who delivered preterm or at term. Prophylactic and urgent cerclage groups were combined. Precerclage was measured between 15-20 weeks' gestation; postcerclage was measured between 14 4/7 and 20 4/7; < 24 weeks was measured between the postcerclage measurement and 24 weeks; 24-27 weeks; and 28-32 weeks.



\*  $p = .002$



**Table 2.** Comparison of cervical length measurements between prophylactic and urgent cerclage (by *t*-test).

	Prophylactic cerclage ( <i>n</i> = 50)	Urgent cerclage ( <i>n</i> = 30)
Preoperative cervical length	31.4 (± 9.8)	20.1 (± 6.9) †
Postoperative cervical length	37.4 (± 9.5)	28.6 (± 8.3) ‡
Cervical difference (post-pre)	6.0 (± 7.5)	8.5 (± 5.9)
Mean cervical length (20 - 23 wk)	34.3 (± 9.1) ( <i>n</i> = 37)	29.6 (± 8.3) ( <i>n</i> = 18)
Mean cervical length (24 - 27 wk)	31.4 (± 11) ( <i>n</i> = 28)	26.2 (± 6.9) ( <i>n</i> = 25)
Mean cervical length (28 - 32 wk)	30.4 (± 10.9) ( <i>n</i> = 22)	25.2 (± 7.4) ( <i>n</i> = 24)
Mean cervical length (> 32 wk)	33.5 (± 11.4) ( <i>n</i> = 12)	24.0 (± 3.9) * ( <i>n</i> = 11)

Values are reported as mean and standard deviation in millimeters.

† *p* = .001

‡ *p* = .001

\* *p* = .01

cervical length over time in women who delivered before 37 weeks' gestation. The mean cervical length, measured between 28 and 32 weeks, was significantly different in women who delivered preterm compared with those who delivered at term ( $21.0 \pm 5.7$  compared with  $30.3 \pm 9.5$  mm, respectively;  $P = .002$ ). The mean standard deviation of all measurements shown in Figure 1 is  $\pm 8.9$  mm.

Table 2 shows the mean cervical length and standard deviation before and after prophylactic and urgent cerclage. The association between cervical length before and after cerclage with pregnancy outcome in the prophylactic cerclage group is shown in Table 3. Cervical length before and after urgent cerclage related to preg-

**Table 3.** Comparison of cervical length measurements with pregnancy outcome in women after a prophylactic cerclage (by t-test).

	Preterm < 37 wk (n = 19)	Term ≥ 37 wk (n = 31)
Preoperative cervical length	28.6 (± 9.9)	33.1 (± 9.9)
Postoperative cervical length	36.3 (± 9.0)	38.1 (± 9.9)
Cervical difference (post-pre)	7.6 (± 6.9)	5.0 (± 7.8)
Mean cervical length, (20 - 23 wk)	28.8 (± 5.8) <sup>§</sup> (n = 13)	37.3 (± 9.2) <sup>†</sup> (n = 24)
Mean cervical length, (24 - 27 wk)	23.3 (± 7.7) (n = 8)	34.7 (± 10.8) <sup>‡</sup> (n = 20)
Mean cervical length, (28 - 32 wk)	20.5 (± 5.6) (n = 4)	32.6 (± 10.7) <sup>§</sup> (n = 18)

Values are reported as mean and standard deviation in millimeters.

<sup>†</sup>  $p = .005$

<sup>‡</sup>  $p = .01$

<sup>§</sup>  $p = .04$

nancy outcome is shown in Table 4. In the prophylactic cerclage group, the mean cervical length was consistently longer in women who delivered at term compared with those who delivered preterm at 20-23, 24-27, and 28-32 weeks' gestation (Table 3). However, in the urgent cerclage group a statistically significant difference in cervical length between those who delivered at term comparing to those who delivered preterm was evident only at 28-32 weeks (Table 4).

**Table 4.** Comparison of cervical length measurements with pregnancy outcome in women after an urgent cerclage (by t test).

	<b>Preterm &lt; 37 wk (n = 19)</b>	<b>Term ≥ 37 wk (n = 31)</b>
<b>Preoperative cervical length</b>	19.2 (± 6.1)	20.8 (± 7.6)
<b>Postoperative cervical length</b>	29.3 (± 7.4)	28.0 (± 9.1)
<b>Cervical difference (post-pre)</b>	10.1 (± 4.7)	7.2 (± 6.6)
<b>Mean cervical length, (20 - 23 wk)</b>	31.6 (± 6.8) (n = 8)	28.0 (± 9.3) (n = 10)
<b>Mean cervical length, (24 - 27 wk)</b>	27.0 (± 6.1) (n = 10)	25.7 (± 10.8) (n = 15)
<b>Mean cervical length, (28 &gt; 32 wk)</b>	21.2 (± 6.1) (n = 9)	27.5 (± 7.3) * (n = 15)

Values are reported as mean and standard deviation in millimeters.

\*  $p = .04$

## Discussion

Both prophylactic and urgent cerclage resulted in a statistically significant increase in cervical length. Contrary to our expectations, the degree of cervical lengthening after cerclage did not contribute to the success of the procedure. Serial postoperative examinations showed that progressive shortening of the cervix between 24 to 32 weeks resulted in an increased risk of premature birth compared with subjects whose cervix remained a relatively constant length during the course of the pregnancy. Nevertheless, our cohort of patients delivered on average near term, when neonatal morbidity would be expected to be low.

The effects of cerclage in women believed to have incompetent cervices have been difficult to prove because many studies were limited because subjects were used as their own controls.<sup>6,12</sup> It is likely that the historical difficulty in diagnosis of the incompetent cervix makes it difficult to identify patients who might benefit from cerclage. Retrospective studies of cervical cerclage showed that cerclage increased obstetric intervention, as judged by admission to hospital, use of oral beta-mimetic agents, induction of labor, and cesarean delivery.<sup>13</sup> A cerclage has an important beneficial effect in a minority of pregnant women.<sup>13,14</sup> One randomized controlled trial has shown modest benefit in one in 25 operations, with a large 95% CI (one in 12 to one in 300 procedures).<sup>12</sup> That study, likely the largest to date, used clinical uncertainty about placing a cerclage as the major eligibility criterion, reflecting the lack of standardized diagnosis.

Others have reported increased cervical length after cerclage. Funai et al,<sup>6</sup> Althuisius et al,<sup>7</sup> and Guzman et al<sup>8</sup> agreed that a perioperative change in cervical length was a result of cerclage application. All described a significant cervical lengthening varying from 27 to 36 mm in 31 patients after prophylactic cerclage,<sup>6</sup> from 21 to 34 mm in 34 patients after urgent cerclage,<sup>7</sup> and from 2 to 27 mm in 29 patients after emergency cerclage.<sup>8</sup>

The differences in the various studies are mostly based on operative technique, method of ultrasonographic surveillance, indication for cerclage, and gestational age at cerclage placement. In our study, a difference was noted between the mean gestational age at placement of a prophylactic cerclage and an urgent cerclage ( $14.3 \pm 2.8$  weeks compared with  $19.7 \pm 3.1$  weeks). Andersen et al<sup>4</sup> commented that perioperative cervical length measurements can be affected by the exact place-

ment of the suture and can be increased falsely by a cerclage placed near the external os. Because of those results, we chose to measure only the length of the endocervical canal.

We studied the effect of cervical lengthening after the 72-hour postoperative period to predict birth outcome, as did Guzman et al.<sup>8</sup> They showed that all patients continued to have progressive shortening of the upper cervix on serial postoperative examinations, with this measurement being less than 10 mm before 28 weeks' gestation in all patients. In our study, serial postoperative examination results were similar, albeit only through measurements of the endocervical canal. The patients with continued cervical shortening after cerclage had an increased risk of premature birth compared with patients in whom the cervical length remained relatively constant during pregnancy.

Although it is not known whether the cervix is shorter in women with a multiple compared with a singleton pregnancy, we realize that women with multiple gestations have an increased risk of premature birth in comparison with singleton pregnancies. The 12 patients with a twin pregnancy and four with triplet gestation did not have cerclage placement because of multiple gestation. The indication was based on a history of cervical incompetence or was predicated on cervical shortening starting with a relatively short preoperative cervical length. However, when those patients were excluded from analysis, the results were not significantly different.

In both prophylactic and urgent cerclage groups there was a steady decrease in cervical length in patients who delivered at term and in those who delivered preterm. However, patients who delivered at term retained the postoperative increase in cervical length longer. They showed a more modest decrease in length over time compared with patients who delivered preterm. Further, in the prophylactic cerclage group, there was a statistically significant difference across gestational age (20-32 weeks) in mean cervical length in patients who delivered at term compared with those delivered preterm. However, in the urgent cerclage group no statistically significant difference was noted until 28 to 32 weeks. Although serial assessment of cervical length is a valuable tool in assessing the risk of premature delivery, it might not be as useful a marker in patients who have urgent cerclage until much later in gestation.

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*Chapter 6*

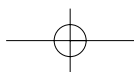
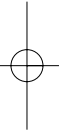
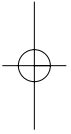
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It is not known whether patients with significant shortening of the cervix have other risk factors that influence the length of the cervix. Dijkstra et al<sup>15</sup> showed that black women, women with severe stress and women who are skilled manual laborers had significant shortening of the cervix in the same period of gestation, between 24 and 32 weeks. Unfortunately, the sample of African-American patients with sufficient cervical length measurements was too small to draw any conclusions. Information about stress and profession was not known in the present cohort of patients.

The relative risk of premature delivery increases as cervical length becomes shorter, so it is reasonable to hypothesize that prophylactic cerclage might reduce risk by restoring cervical anatomy, and this could be a greater barrier to ascending infection. In the present study, it was clear that the response of the cervix to cerclage, as defined by change in the length of the endocervical canal, did not predict pregnancy outcome. After cerclage, serial cervical length measurements with transvaginal sonography might be indicated to predict preterm birth if a progressive shortening of cervical length is noted in the late second or early third trimester. This shortening could alert the clinician to consider increased surveillance for signs and symptoms of preterm labor, utilization of fetal fibronectin testing, and limitation of physical activity. Also, one might consider corticosteroids to hasten fetal lung maturation. Although an increase in cervical length after cerclage was not predictive of outcome, progressive cervical shortening after cerclage was predictive of preterm delivery. It is not known why progressive cervical shortening occurs earlier in patients who have a prophylactic cerclage than in patients who have urgent cerclage.

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# 7

## Threatened preterm birth; views and management of midwives, general practitioners and gynecologists in the Netherlands

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## Abstract

**Objective.** To study the management and views regarding threatened preterm birth among the three professions providing obstetrical care in the Netherlands.

**Method.** A questionnaire was sent to a random sample of 30% of midwives, general practitioners and representatives of all Dutch obstetrical gynecological practices addressing management and views on threatened preterm birth, mutual co-operation and the Obstetric Indication List ('Verloskundige Indicatie Lijst' (VIL))

**Results.** The response of the midwives was: 72% (100/139), general practitioners 56% (89/159) and obstetrician/gynecologists 73% (86/118). In general, there seemed to be consensus on the management of preterm birth among the three groups. There was less agreement regarding the management of women with 'contractions' at 25/30 weeks, 'suspicion of cervical incompetence' at 25/30 and 35 gestational weeks and a prior conization in history. Seventy-five percent of both the obstetrician/gynecologists and midwives agreed that obstetrical care of a current pregnancy by a obstetrician gynecologist was indicated, when a prior preterm birth had taken place < 34 weeks of gestation, while general practitioners defined the borderline at < 35 weeks. The three professional groups were positive regarding mutual co-operation and the 'VIL'.

**Conclusion.** There seems to be agreement in the Netherlands regarding the risk selection of preterm birth among the three professional groups active in obstetrical care. The problem of preterm birth moved from < 37 to < 35 weeks. At this moment the 'VIL' is better accepted than 10 years ago.

## Introduction

Preterm birth is a leading cause of neonatal morbidity and mortality. It is one of the most important threats of the developing child.<sup>1-4</sup> Preterm birth, defined as a delivery before 37 completed weeks of gestation, complicates 7% of all births in the Netherlands.<sup>5</sup> Internationally the preterm birth rate increases, and also in the Netherlands the percentage of preterm newborns admitted on a neonatal intensive care unit increased slightly.<sup>4,6</sup> The ability to predict whether a woman is at risk of preterm delivery has only value, if an intervention is available that is likely to improve the outcome. It has been shown, that beta-mimetics prolong pregnancy, for an average of several days, allowing the administration of corticosteroids.<sup>7</sup> The opportunity to administer corticosteroids to the mother is an important intervention associated with decreased neonatal morbidity and mortality. Another reason to identify women at risk for early preterm birth (before 32 weeks of gestation) is to allow appropriate maternal transport to a tertiary perinatal care center for the women being managed at general hospitals without appropriate neonatal care. It is also important to identify women at low risk for PTB in order to prevent the use of unnecessary interventions.

The Dutch obstetrical care system is unique in comparison with other western countries.<sup>8,9</sup> Low risk pregnant women (80%) receive obstetrical care provided by midwives (80%) and general practitioners (20%).<sup>9-11</sup> Thirty percent of all pregnant women still deliver at home.<sup>5,9,10</sup> First line obstetrical care providers have to make a reliable assessment to transpose the delivery to the hospital under their own care, or refer to the obstetrician/gynecologists (further mentioned as 'gynecologists'), if medical or obstetrical problems (before, during or after the delivery) take place (40%). The Obstetric Indication List ('Verloskundige Indicatie Lijst' (VIL) contains guidelines which mark the border between the first and second line. It is a good source for risk selection in the Dutch obstetrical care. The guidelines in the VIL regarding preterm birth are only briefly described.<sup>12</sup>

The impression exists that there are different strategies and views regarding diagnosing and treating threatened preterm birth among and between the three professional groups respectively, active in the Dutch obstetrical care.<sup>13,14</sup> This study aimed to answer the following questions. (1) What are the management and views regarding threatened preterm birth among the three professions providing obstetrical care in the Netherlands. (2) What are the views about mutual co-oper-

ation and the acceptance of the VIL among midwives, general practitioners (providing obstetrical care) and gynecologists, on behalf of future guidelines for consultation between the first and second line

## Methods

*Design.* An observational study was performed.

*Study population.* A random sample of (a) 30% of independent resided midwives practices, (b) 30% of general practitioners practices active in obstetrical care and (c) all representatives of the 118 Dutch gynecologists practices.

*Data collection.* A questionnaire was sent by mail addressing the following variables:

1. Characteristics of the various obstetrical care providers (age, sex, type of practice, type of hospital, obstetric experience, frequency of regional obstetric meetings and urbanization grade).
2. Management of threatened preterm birth was measured with six written cases (vignettes)<sup>15</sup> concerning symptoms of spontaneous preterm birth (SPB) at different gestational age periods (25, 30 en 35 weeks); (answer categories: 1a. no consequences management in first line; 1b. consequences management within first line; 2. consultation gynecologist; 3. referral gynecologist).
3. Views concerning the division of responsibilities between the first and second line obstetrical care providers (6 items); (answer/categories: 1. first line obstetrical care providers; 2. combination of first line obstetrical care provider and gynecologist; 3. gynecologist). Besides, we asked for the boundaries of gestational age of a prior SPB, after which the prenatal care in the next pregnancy can be provided by the first line caregivers, or has to be provided by the gynecologist (answer categories 1: 33 wk to 5: 37 wk).
4. The views of the Obstetric Indication List guidelines ('Verloskundige Indicatie Lijst' (VIL)) regarding threatened preterm birth, the acceptance of the VIL in general (5 items) and the satisfaction regarding mutual co-operation (3 items); (answer categories on a five-point Likert-type scale ranging from 1. entirely disagree to 5. entirely agree).

*Data entry.* This was performed with an 'optical reading' system (Teleform) and the statistical analyses were performed with SPSS. Control of data entry took place with unlogical codes and missing data.

*Analyses.* First, frequencies and means of the characteristics of the three professional groups were calculated ( $\bar{x}$ ; sd). The management and views were handled

as rank order scales. Correlation between the personal characteristics of the professionals and their views and management were analyzed with Spearman rank correlation coefficient ( $r_s$ ). Correlations  $\geq .25$  were considered relevant (analogue of the Pearson  $r$ : expected variance  $\geq 5\%$ ). The ratings on the Likert type answer categories were described with means  $\pm$  standard deviation ( $\bar{x}$ ;  $sd$ ). Differences between the means were analyzed with ANOVA, and  $p < .05$  was considered significant.

## Results

*Response.* From the sample of 139 midwives practices a total of 100 completed questionnaires were returned (response rate 72%); 89 completed questionnaires were sent back from the sample of 159 general practitioners practices active in obstetrical care (56%), and from the 118 gynecologists practices 86 (73%) questionnaires were returned.

The most striking differences within the three professional groups were the 'amount of deliveries per care', the 'frequency of participating in obstetric meetings' and the 'degree of urbanization' (Table 1). A strong association was found between the answers at 25 and 30 gestational weeks ( $r_s$  varied from .76 en .93; not in table). In further analyses, the answers of 30 weeks were used as an indicator for both gestational ages (Table 2). Seventy to ninety percent of the three professional groups stated that 'unspecific abdominal complaints' at 25/30 en 35 weeks and 'contractions' at 35 weeks gestation belong in the first line. The three professional groups did not agree on the management for 'contractions' at 25/30 weeks, 'a patient with fear because of a prior preterm birth' and 'a suspicion of cervical incompetence' at 25/30 and 35 gestational weeks. The midwives wanted to keep more patients under their own care, in comparison to general practitioners and more than the gynecologists expect. Seventy to ninety percent of the three professional groups stated that women with 'vaginal bleeding' and 'rupture of membranes' unrelated to gestational age need to get their obstetrical care from the gynecologist. There was no association between the (personal) characteristics of the three professional groups and their management.

The majority of all three professional groups agreed that 'DES-daughters without anomalies' belong in the first line and 'DES-daughters with anomalies' in the second line. Regarding 'conization in history' there was no alignment within the

**Table 1.** Characteristics of midwives, (mw; n=100), general practitioners (gp; n=89\*) and gynecologists (gyn; n=86) in %.

	mw	gp	gyn	
<b>Practice</b>			<b>Hospital</b>	
Solo	28	54	Gen. (without residency)	59
Duo	21	34	Gen. (with residency)	33
Group	51	12	University	8
<b>Sex</b>				
Male	3	84		74
Female	97	16		26
<b>Age/years (<math>\bar{x}</math>; sd)</b>	40 (10.9)	47 (5.8)		48 (7.6)
<b>Deliveries/year</b>			<b>Self/direct</b>	<b>Indirect</b>
0-29	-	77	38	17
30-49	2	18	8	12
50-100	24	5	14	14
>100	74	-	40	57
<b>Grade of urbanization</b>				
Municipal area	41	4		75
Urban area	29	5		17
Rural area	30	91		8
<b>Participation in district obstetrical meetings</b>				
≥ 1x/6week	92	34		71
1x/6month	8	18		26
≤ 1x/year/never	-	48		3

\*) With 'gp' in text and tables we mean a general practitioner practicing obstetrics.

three professional groups (Table 3). Seventy-five percent of the gynecologists and midwives agreed that obstetrical care of a current pregnancy by a gynecologist was indicated, when a prior preterm birth had taken place < 34 weeks of gestation, and general practitioners defined the borderline at < 35 weeks (Figure 1).

Seventy-eight percent of the first line care providers and 74% of the gynecologist stated that they accept the 'VIL' in total. However, 30% of the midwives and the gynecologists did not agree upon the guidelines for threatened preterm birth in

**Table 2.** Frequencies (%) of management of the three professional groups practicing obstetrics regarding 6 complaints/symptoms of threatened preterm birth presented in the first line with a gestational age of 25/30 and 35 weeks. The gynecologist was asked to respond which management from the first line will be appropriate; midwives(mw), n=100; general practitioners (gp), n=89; gynecologists (gyn), n=86.

	25 and 30 weeks			35 weeks		
	First line	Consultation of gyn	Referral to gyn	First line	Consultation of gyn	Referral to gyn
<b>Unspecific abdominal gp pain</b>						
	mw	4	1	96	3	1
	gp	7	2	94	4	2
	gyn	20	10	86	10	4
<b>Contractions</b> (2 days, several times per hour painful (Braxton Hick's) contractions)						
	mw	16	8	88	8	4
	gp	31	29	75	14	11
	gyn	29	31	72	16	12
<b>A patient with fear because of a prior preterm birth</b>						
	mw	30	14	68	23	9
	gp	34	29	57	20	23
	gyn	29	43	65	17	18
<b>Suspicion cervical incompetence</b> (heavy feeling lower abdomen)						
	mw	37	23	39	40	21
	gp	33	18	50	34	16
	gyn	28	35	38	29	33
<b>Vaginal bleeding</b> (sudden, painless, bright red)						
	mw	28	66	6	31	63
	gp	13	72	16	18	66
	gyn	7	93	2	10	88
<b>Rupture of membranes</b> (positive ferning)						
	mw	8	92	-	10	90
	gp	11	89	6	22	72
	gyn	4	96	3	11	86

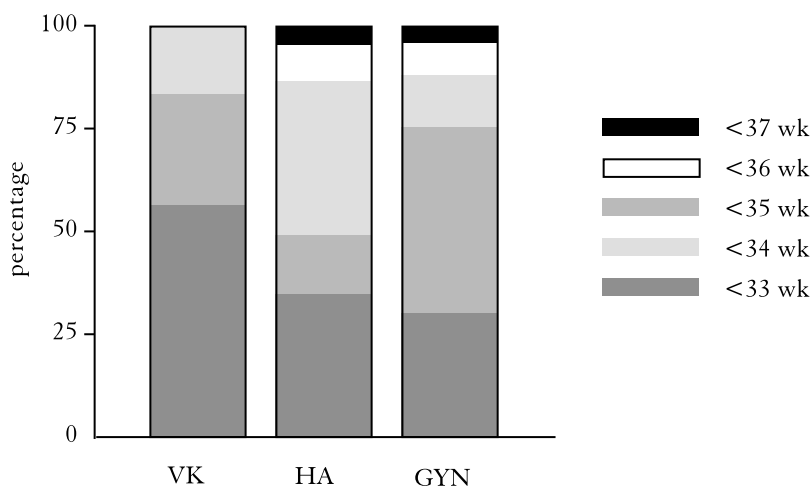
**Table 3.** Frequencies (in %) of the views of first line care providers (midwives and general practitioners) and second line (gynecologist) regarding the division of responsibilities between the first and second line. Who is responsible for the prenatal/obstetric controls of the following pregnancy of a woman with a complicated obstetrical or gynecological history? (mw, n=100; gp, n=89; gyn, n=86).

		First line	Co-operation first and second line	Second line
<b>DES-daughter without uterus-abnormalities</b>	mw	80	16	4
	gp	66	28	6
	gyn	75	18	7
<b>Conization in history (because of abnormal cervix cytology)</b>	mw	34	37	29
	gp	36	43	21
	gyn	26	38	36
<b>Preterm birth in history (with ruptured membranes at 28 weeks gestation)</b>	mw	30	30	40
	gp	19	62	19
	gyn	10	30	60
<b>DES-daughter with uterus-abnormalities</b>	mw	4	28	68
	gp	3	35	62
	gyn	2	28	70

the ‘VIL. The first line care providers - the general practitioners more than the midwives - were in general satisfied with the mutual co-operation with the gynecologists ( $\bar{x}^{(sd)}$ : 4.1<sup>(.9)</sup>, respectively 3,7<sup>(1.0)</sup>;  $p = .03$ ) and vice versa: satisfaction of gynecologists of co-operation with general practitioners practicing obstetrics and with midwives (3.6<sup>(.8)</sup>, respectively 3,9<sup>(.8)</sup>;  $p = .03$ ). The general practitioners practicing obstetrics were more satisfied with the co-operation of midwives, than the other way around (3.5<sup>(1.1)</sup> and 2,8<sup>(1.3)</sup> respectively;  $p = .02$ ).



**Figure 1.** Endorsement of the three professional groups with the statement that obstetrical care of a current pregnancy by a gynecologist was indicated, when a prior preterm birth had taken place from < 33 weeks till < 37 weeks (percentages) (vk=midwife, n=70; ha=general practitioner, n=75; gyn, n=75).



### Conclusion

In general, there seemed to be consensus about the management of preterm birth among the three professional groups. With symptoms of threatened preterm birth at 35 weeks there are less referrals to the gynecologist than earlier in the pregnancy. The three professional groups agree that the problem of preterm birth is not longer at a gestational age of < 37 weeks but has moved to < 35 weeks. Furthermore, the view of the three professional groups regarding the 'VII' was positive.

The response of midwives and gynecologists to the questionnaire is satisfying. The response of the general practitioners was moderate. The respondents did not differ from the professional groups relating to age, sex and urbanization grade.<sup>16-19</sup> The group of solo working midwives and general practitioners responded slightly more often compared to their colleagues in group practices. The response of the gynecologists from the residency hospitals was higher than from the total group of general hospitals without residency programs. Until now, the management and

views regarding threatened preterm birth has not been researched before in the Netherlands. Since it was the purpose of our study to describe strategies and possible dilemmas in this field, the vignettes method was appropriate. Although this method does not present the actual behavior of the respondents accurately, it does show differences among and between the three professional groups. Further research on process and outcome of management of the three professional groups requests prognostic data collection.

Early preterm birth at 25 and 30 weeks can have serious consequences. In general, there seemed to be consensus among the three professional groups that at these gestational ages women with symptoms of 'contractions', 'vaginal bleeding' and 'rupture of membranes' need to be under care of the gynecologist. Symptoms of 'vaginal bleeding' and 'rupture of membranes' at 35 weeks also belonged in the second line. Late preterm birth that occur above 35 weeks of gestation, is not likely to have major effect on perinatal outcome and treatment as tocolytics does not take place anymore. There is a discussion within and between the three professional groups, which have to be responsible for the care of women with 'preterm contractions', symptoms with 'a suspicion of cervical incompetence' and women with 'fear because of a prior preterm birth' at 25/30 gestational weeks. This is probably caused by the sometimes unclear and less specific symptoms of threatened preterm birth. Kragt et al. described the prognostic value of symptoms relating to SPB of all pregnant women, who consulted the gynecologist with symptoms of threatened preterm birth. Uncertainty of diagnosis occurred in 40% of the cases of threatened preterm birth.<sup>14</sup> Hopefully new predictive tests, as fetal fibronectin, in cervico-vaginal secretions,<sup>20-22</sup> bacterial vaginosis<sup>23</sup> and ultrasonographic assessment of the length of the cervix<sup>24</sup> will have added value in predicting and diagnosing preterm birth.<sup>25</sup>

About 75% of responding gynecologists and midwives agreed that obstetrical care of a current pregnancy was indicated by a gynecologist, when a prior preterm birth had taken place < 34 weeks of gestation, and for the general practitioners it was < 35 weeks. Several authors studied the recurrent risk of preterm delivery.<sup>26-28</sup> Especially for the early (20-31 weeks) prior preterm birth there is a higher risk of a singleton preterm delivery in the following pregnancy. For women who delivered their first newborns at 32 to 36 weeks, the crude rate of recurrent preterm delivery declined moderately.<sup>28</sup>

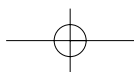
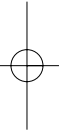
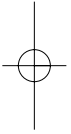
In general, there seems to be agreement about the management among the three professional groups. However, there are some differences between the first line care providers. The general practitioners consult and refer to the gynecologist more often than the midwives. In general the professional groups are satisfied with the mutual co-operation. The co-operation between the general practitioners and midwives seems less satisfying, which might be a result of the different positions of these professional groups and may be because of an insurance problem, 'de primaatkwestie'. We expect the mutual co-operation will improve in the future, since, the biggest differences in views between the midwives and general practitioners are behind us and the 'primaatkwestie' is abandoned since July 2001. At this moment co-operations between midwives and general practitioners are established to stand together to maintain the possibility of home delivery in the Netherlands. Hopefully this will also lead to regular attendance of the general practitioners at the district obstetrical meetings. At this moment the 'VIL' is better accepted than 10 years ago, especially by the gynecologists (74% in comparison with 37% in 1991).<sup>19</sup> The three professional groups do not fully agree with the less specified guidelines regarding threatened preterm birth in the 'VIL'.

This study was conducted in a time period that there are still doubts about the best diagnostics and treatment regarding threatened preterm birth. Guidelines based on evidence are hardly available yet, but this is an ongoing process. In our study there is agreement regarding the risk selection of women with symptoms of threatened preterm birth. Our findings can hopefully be used for new guidelines regarding threatened preterm birth in the Netherlands.<sup>25</sup> The Dutch system of obstetrical care is based on the continuous assessment of risk. Appropriate risk-selection is important to maintain our unique system with the possibilities of home deliveries, which is under pressure at the moment. The midwives already got governmental aid of the ministry of Health ('VWS'). Hopefully, the general practitioners working in the rural areas will also be able to maintain this part of their job in the future. This is also dependent on the investments in education and logistics for the general practitioners that wants to practice obstetrics.

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# 8

## Are diagnostic tests and treatment modalities in threatened preterm birth standardized? A questionnaire among Dutch gynecologists

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## Abstract

**Objective.** To describe how Dutch gynecologists implement 'modern' diagnostic tests and treatments in cases of threatened preterm birth.

**Method.** A questionnaire was sent by mail to representatives from all Dutch gynecological practices addressing diagnosis and treatment management of threatened preterm birth. Correlation between personal characteristics of the gynecologists their management, and their views were analyzed with the Spearman rang correlationcoefficient ( $r_s$ ).

**Results.** The response rate was 72% (85/118), and showed variation in management style; cervical length measurements as well as testing for bacterial vaginosis were frequently done (50-80% of the gynecologists reported to do so) and treated BV in cases of a positive result. Fetal fibronectin testing, however, was hardly used. Tocolytics and corticosteroids were frequently given to women with preterm membrane ruptures without labor, while antibiotics were rarely prescribed. There was a correlation between working in hospitals with and without residency programs and different management approaches. Gynecologists working in hospitals without residency programs administered tocolytics and repeated corticosteroid treatment more frequently and prescribed less antibiotics to women with preterm membrane ruptures than those working in hospitals with residency programs.

**Conclusion.** Standardized use of 'modern' diagnostic tests and treatment modalities for threatened preterm birth is lacking among Dutch gynecologists.



## Introduction

Preterm birth is a leading cause of neonatal morbidity and mortality, and one of the most important health threats to the developing child.<sup>1-4</sup> Preterm birth, defined as delivery before 37 completed weeks of gestation, complicates 10% of all hospital births in the Netherlands.<sup>5-7</sup> Internationally the preterm birth rate increases, and also in the Netherlands the percentage of preterm newborns admitted to a neonatal intensive care unit increased.<sup>1,5</sup>

Until now it is unclear which diagnostic and treatment methods for threatened preterm birth are appropriate.<sup>1,8,9</sup> This is probably caused by the less obvious symptoms of threatened preterm birth. Kragt et al. described the prognostic value of symptoms relating to spontaneous preterm birth (SPB) and of all pregnant women, who consulted the gynecologist with symptoms of threatened preterm birth.<sup>9</sup> In 35% of the cases the SPB diagnosis was confirmed immediately (26% actually delivered within 48 hours and 9 % had a short delay by tocolytics). In 25% of the patients there was no question of SPB and the women could safely return home. Uncertainty of diagnosis occurred in 40 % of the cases of threatened preterm birth.<sup>9</sup> These patients were admitted to the hospital, and may have received unnecessary tocolytic and/or corticosteroid treatment.

The principle objective of new diagnostic methods is to identify and treat the women at high risk of SPB in time, it is also important to avoid unnecessary interventions. With this background, the guidelines regarding threatened preterm birth are briefly described in the Obstetric Indication List ('VIL').<sup>10</sup> The Dutch College of Obstetrics and Gynecology ('NVOG') provided guidelines in 1997 for using tocolytics and includes a few sentences on methods for predicting SPB.<sup>11</sup> How these guidelines are implemented in clinical practice remain unclear. This study aimed to answer three questions. (1) Do the Dutch obstetrician/gynecologists (further mentioned as 'gynecologists') use new diagnostic methods (fetal fibronectin, bacterial vaginosis and ultrasonographic assessment of the cervical length) to identify the women at high risk of SPB? (2) What are the gynecologists' views regarding appropriate diagnostic methods and interventions for SPB? (3) Are there differences in management approaches by gynecologists from hospitals with residency programs compared to gynecologists from general hospitals without residency programs?

## Methods

*Design.* An observational study was performed.

*Study population.* All representatives from the 118 Dutch gynecological practices.

*Data collection.* Representatives were sent a questionnaire that addressed the following variables:

1. Characteristics of the gynecologists: age, sex, hospital with residency program (yes/no), obstetric experience (number of deliveries per year).
2. In three patient groups with high risk of SPB ('prior preterm birth' 'conization in history' and 'multiple gestation'), was asked which new diagnostic methods were used (ultrasonographic assessment of cervical length, fetal fibronectin testing in cervicovaginal secretions (FFN) and testing of bacterial vaginosis (BV)). Response options were 1: often, 2: only at indication or 3: never. In addition, an open question about the treatment of bacterial vaginosis was asked.
3. In two cases (primigravid who works as a resident and a multigravid with a complicated obstetrical history) with contractions varying in presentation the use of ultrasonographic assessment of cervical length, fetal fibronectin testing and the advise regards working (stop working or continue part-time) was asked.
4. In two cases questions were asked on the management and treatment (admission, tocolytic-, antibiotic- and corticosteroid use) regarding the clinical situations of 'preterm rupture membranes (PROM) without contractions' and 'triplet pregnancy with some contractions' both at 28 weeks gestation.

*Data entry.* Data entry was performed with an 'optical reading' system (Teleform) and the statistical analyses were performed with SPSS. Control of data entry took place with unlogical codes and missing data.

*Analyses.* Frequencies of the characteristics of the responding gynecologists were calculated ( $\bar{x}$ ; sd). The views and management in the written cases were presented according to the main characteristics of the cases (frequencies). The correlation between the personal characteristics of the professionals, their views and management approach were analyzed with the Spearman rang correlation coefficient ( $r_s$ ). Correlations  $\geq .25$  (with a p-value  $< .05$ ) were considered relevant (analogue of the Pearson r: expected variance  $\geq 5\%$ ).

## Results

*Response.* From 118 gynecological practices, 85 (73%) questionnaires were returned. More than half of the gynecologists work in a hospital without a resi-

**Table 1.** Characteristics of gynecologists (n=85).

	Gynecologists (%)	
<b>Hospital</b>		
General (without residency)	59	
General (with residency)	33	
University (with residency)	8	
<b>Sex</b>		
Male	74	
Female	26	
<b>Average age (sd)</b>	48 (7.6)	
<b>Deliveries/year</b>	<b>Self/direct</b>	<b>Indirect</b>
0-29	39	16
30-49	8	12
50-100	14	14
>100	39	58

dency program. One out of four gynecologists were female. Other characteristics are shown in Table 1. About 80% of the gynecologists used ultrasonographic assessment of cervical length for women in all three patient groups at risk for SPB (Table 2). About half of the gynecologists responded that they only used ultrasonography ‘at indication’. Fetal fibronectin (FFN) was used by 10% of the gynecologists, but ‘only at indication’. They often tested for bacterial vaginosis (BV), (50 to 80%, depending on the patient group), especially in patients with a prior preterm birth. The use of a diagnostic method (cervical length measurements, fetal fibronectin testing and bacterial vaginosis) in one patient group was correlated with the use of the same diagnostic method in the two other patient groups at risk for SPB. ( $r_s$  varied from .36 - .66). There was no correlation between the use of these diagnostic methods and practicing in a hospital with or without a residency program.

When the gynecologists looked for vaginal infections, they diagnosed BV by gram stain (63%), by microscopic examination (15%), by a combination of gram stain and microscopic examination (18%), and by the Nugent score with or without

**Table 2.** Frequencies (%) of utilizing modern diagnostic methods (on a regular basis) for (1) pregnant women with an early prior preterm birth, (2) primi-gravid with a conization in history (3) women with a multiple gestation (n=85).

		Often (%)	Only at indication (%)	Never (%)
<b>Cervical length measurements</b>	Prior preterm birth	48	33	19
	Conization in history	39	38	23
	Multiple gestation	24	53	23
<b>Fetal fibronectin testing</b>	Prior preterm birth	-	12	88
	Conization in history	-	8	92
	Multiple gestation	-	7	93
<b>Bacterial vaginosis testing</b>	Prior preterm birth	41	41	18
	Conization in history	4	46	50
	Multiple gestation	15	46	39

combination of microscopic examination (4%).<sup>12</sup> Eighty percent of the gynecologists actually treated BV. First choice antibiotics were metronidazole (71%), clindamycin (13%) amoxicillin/clavulanic acid (9%), amoxicillin (3%), ampicillin (2%), erythromycin (2%). Most respondents did not specify how the drug was administered (oral or local). Treating or not treating BV was associated with the type of hospital where the gynecologists work ( $r_s = .26$ ). Gynecologists practicing in hospitals with a residency program treated BV more frequently than those practicing in hospitals without a residency program. Cervical length measurement was commonly used, however, FFN was rarely used in the two cases of women with contractions (Table 3). For both indication groups (primigravid and multigravid), the gynecologists advised the patients to stop working or go part-time.

All gynecologists reported that they admit to hospital all women with ‘preterm membrane ruptures without contractions’ and 81% admitted ‘triplet pregnancy cases with some contractions’, both at 28 weeks gestation. The management varied greatly after admission (Table 4). Forty percent reported to administer prophyl-

**Table 3.** Frequencies (in %) regarding the management of contractions varying in presentation in (1) a primigravid working as an internal medicine resident in your hospital (2) a multigravid with a complicated obstetrical history (2x immature delivery) and a cerclage in this pregnancy (n=85). (EGA = estimated gestational age.)

		Contractions primigravid (resident)	Contractions multigravid (with cerclage)
		EGA 29 wk	EGA 24 wk
<b>Cervical length measurements</b>	yes	52	82
	no	48	18
<b>Fetal fibronectin testing</b>	yes	1	6
	no	99	94
<b>Advised to stop working or go part-time</b>	yes	part-time 61 stop 26	part-time 16 stop 84
	no	13	-

lactic tocolytics in both above-mentioned cases and 26% routinely treated the first case with antibiotics, but none did so in the latter case. In the case of ‘preterm membrane ruptures without contractions’ almost all the gynecologists prescribed corticosteroids to increase fetal lung maturity; 71% repeated this treatment after 1-2 weeks if women had not yet delivered. They administered prophylactic and repeated corticosteroids to a lesser degree (67% respectively 56%) in women with ‘triplet pregnancy with some contractions’.

There were correlations between the type of hospital in which gynecologists were practicing and the management approach after admission. Gynecologists in hospitals with residency programs gave less prophylactic tocolytics in comparison to their colleagues in the general hospitals without residency programs ( $r_s = .27$ ), in the first case. Gynecologists who reported to administer tocolytics, repeated corti-

**Table 4.** Frequencies (in %) regarding management of (1) a pregnant woman (G3P2: prior preterm birth (32 weeks) and 1 term pregnancy) with preterm rupture of membranes (PROM) without contractions at 28 weeks and (2) a triplet pregnancy (G1P0) after IVF, with some contractions at 28 weeks. (EGA = estimated gestational age; sd = standard deviation)

		PROM without contractions	Triplet pregnancy with some contractions
		EGA 28 wk	EGA 28 wk
<b>Admission</b>	yes	100	81
	no	-	19
<b>Prophylactic tocolytics</b>	yes	40	38
	no	60	62
(n=29)	until EGA (mean ± sd)	33.3 ± 1.5	33.5 ± 0.9
<b>Routine antibiotics</b>	yes	26	-
	no	74	100
(n=17)	from EGA (mean ± sd)	26.6 ± 2.1	NA
	until EGA (mean ± sd)	32.1 ± 2.6	
<b>Prophylactic corticosteroids</b>	yes	94	67
	no	6	33
<b>Repeated corticosteroids</b>	yes	71	56
	no	29	44
(n=50)	after 1wk	56	50
	after 2 wks	44	50
(n=46)	until EGA (mean ± sd)	32.9 ± 1.3	30.8 ± 1.1

costeroid treatment more frequently ( $r_s = .25$ ). Gynecologists in hospitals with residency programs were less likely to repeat corticosteroid administration in comparison to their colleagues in the general hospitals without residency programs ( $r_s = .28$ ). Corticosteroid administration was also repeated more frequently in women with triplet gestation by gynecologists in general hospitals without residency programs ( $r_s = .37$ ). There was also an association between administering

tocolytics and an initial ( $r_s = .43$ ) or repeat ( $r_s = .38$ ) treatment of corticosteroids. Antibiotics were given more often by younger gynecologists ( $r_s = .28$ ) and by gynecologists in hospitals with residency programs ( $r_s = .29$ ).

## Conclusion

The study contains three key findings. Firstly, there is a variation in management regarding preterm birth; cervical length and bacterial vaginosis were assessed more often in contrast with the fetal fibronectin testing in cervicovaginal secretions. Secondly, the treatment of BV, tocolytics and corticosteroids treatments were used frequently, while only one of the four gynecologists gave antibiotics to women with 'preterm membrane ruptures without contractions'. Thirdly, a clear difference exists in management approach between gynecologists working in hospitals with or without residency programs. Gynecologists in general hospitals without residents administer tocolytics frequently, repeated corticosteroid treatment more often, and gave fewer antibiotics for BV or preterm membrane ruptures.

With this study we aim to give insight into the management approach of Dutch gynecologists concerning the obstetrical problem of spontaneous preterm birth. The response rate from the gynecologists on the questionnaire is satisfying. The responding gynecologists did not differ from the Dutch gynecologists in areas of age, sex, and deliveries per year. The number of responses from the gynecologists of the residency hospitals was slightly higher than from the total group of general hospitals without residency programs.<sup>13</sup> We assume that our study accurately reflects the current situation in the Netherlands.

The Dutch gynecologists frequently measure cervical length with transvaginal ultrasonography. This is understandable since this method has extensively been described in the literature. An inverse association between a short cervical length and an increased risk of spontaneous delivery is shown - both in symptomatic and asymptomatic patients - with singleton gestations.<sup>14-16</sup> Uncertainty exists regarding the therapeutic consequences of this diagnostic method. Currently, only in women with a suspicion of cervical incompetence measurement of the cervical length - and when indicated a cerclage - is considered useful.<sup>17</sup> At this moment a large randomized controlled trial is taking place on the possible therapeutic consequences of a 'accidentally found' short cervix in an uncomplicated population.

A positive contribution of the cervical length measurement to the pregnancy outcome is until now not demonstrated in the indication fields of preterm contractions or multiple gestations. In several studies a cervical length of  $< 30$  mm was found to be the best cut-off for predicting a preterm delivery. For women with risk factors of SPB, a cut-off of 25 mm was often employed. The presence of funneling does not contribute to only measuring the length of the cervix in the prediction of SPB.<sup>16</sup>

Screening of fetal fibronectin (FFN) in cervico-vaginal secretions is infrequent in Dutch obstetrical practice. This is remarkable since the presence of cervico-vaginal fetal fibronectin was found to predict SPB in women with preterm uterine contractions and in asymptomatic patients.<sup>18-20</sup> The high negative predictive value in asymptomatic and symptomatic women is especially important in providing strong reassurance that delivery will not occur within 7 days in more than 99% of the cases and that these women will not give birth for 14 days in 95% of the cases.<sup>20</sup> Several investigators have shown that a negative fetal fibronectin test when presenting with symptoms of threatened preterm birth is associated with a reduction in preterm labor admissions, length of stay, prescriptions for tocolytic agents, and consequently to an overall cost-reduction.<sup>21,22</sup> The clinical utility of this test is obvious: women who are seen for evaluation of possible preterm labor (unspecific abdominal complaints, moderate contractions and a cervical dilatation  $< 3$  cm) may be screened by fetal fibronectin. Those testing positive are then admitted for additional observation and treatment. Our data suggest that patients with a negative test result can be safely observed in the outpatient setting for 7-14 days. A positive FFN-test and a short cervical length ( $< 25$  mm) together seem to be good predictors of SPB.<sup>23</sup>

Dutch gynecologists report high bacterial vaginosis testing and 80% of them start treatment after a positive test result. The treatment of choice is metronidazole and this was used by 7 of the 10 Dutch gynecologists. A standardized scoring system for the diagnosis of BV, the so called Nugent-score is seldom used in the Netherlands.<sup>12</sup> Bacterial vaginosis is seen as a condition in which the normal vaginal microflora and lactobacilli are replaced by a polymicrobial overgrowth of anaerobes and gardnerella. BV is associated with an increased risk of preterm membrane ruptures (odds ratio: 7.3),<sup>24,25</sup> low birthweight,<sup>26</sup> and spontaneous preterm birth (odds ratios ranging from 1.8 to 2.8).<sup>27,28</sup> In some studies, the use of oral antibiotics (metronidazole or clindamycin) to treat women with BV who are



at risk for SPB (e.g. prior PTB) has resulted in a reduction of the SPB rate and in pregnancy-associated morbidity. This does not apply to local treatment.<sup>28-30</sup> Prophylactic treatment in low-risk women or in high-risk women without BV is not indicated because it may change the normal vaginal flora to an intermediate type or to bacterial vaginosis which may increase the risk of preterm birth.<sup>14,30</sup> From the literature, we conclude that, at this moment, it is only recommended to treat women who have had a prior preterm birth with actual presence of BV with oral antibiotics (e.g. metronidazole).

The Dutch gynecologists utilize treatment modalities for threatened preterm birth differently. What was striking is that 40% of the gynecologists administered prophylactic tocolytics in preterm membrane ruptures without contractions. While prophylactic tocolytic use can cause desensitization of the uterus muscle. The gynecologists frequently prescribe (single or repeat courses) corticosteroids to increase fetal lung maturity.<sup>31</sup> More frequently in the case of preterm membrane ruptures than in the triplet pregnancy with some contractions. Another notable point is 1 out of 4 gynecologists gave antibiotics to woman with rupture of membranes. Furthermore, we found correlations between the type of hospital in which the gynecologists practice and the management of the cases after admission. Gynecologists in hospitals with residency programs gave less prophylactic tocolytics and repeated more corticosteroid treatment than their colleagues in the general hospitals without residency programs, who gave more antibiotics for woman with ruptured membranes.

The views regarding corticosteroid use in the Netherlands is quite similar to the other 14 European countries.<sup>32</sup> Antenatal corticosteroid treatment usually takes place between 25 and 34 weeks of gestation. Eighty-seven percent of the European gynecologists use more than one course of the drugs in cases of persisting active labor. The current benefit and risk data are insufficient to support routine use or repeat courses of antenatal corticosteroid in clinical practice.<sup>32</sup> Recently, a randomized trial was published on the use of erythromycin in women with preterm rupture of membranes for prolonging the pregnancy, for reducing maternal infection and for improving neonatal health with a probable reduction in childhood disability.<sup>33</sup> These results were not yet published while our study took place. Although antibiotics for women with preterm rupture of membranes have been used for many years and they seem to prolong the pregnancy and decrease neonatal morbidity, the Cochrane review recommended not to use this

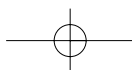
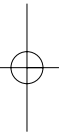
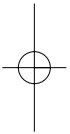


*Chapter 8*

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treatment yet.<sup>34</sup> The gynecologists from the hospitals with a residency program led the way in comparison to the gynecologists in the general hospitals without residency programs.

We conclude that the diagnostic methods and treatment modalities in threatened preterm birth are only slightly standardized. We encourage the Dutch College of Obstetrics and Gynecology ('NVOG') to create new guidelines regarding for predicting and treating threatened preterm birth.



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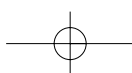
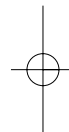
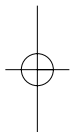
*Chapter 8*

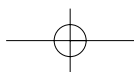
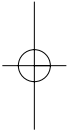
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# 9

## Summary and Discussion

Preterm birth is a leading cause of neonatal morbidity and mortality. It is a major goal in obstetrics to lower the incidence of spontaneous preterm birth (SPB) and related neonatal morbidity and mortality. One of the principal objectives is to discover early markers that would allow us to identify subgroups of patients at high risk of SPB and, secondly, to manage those patients with an appropriate and effective strategy.

This thesis consisted of two parts. The first part included the etiology and risk assessment of SPB. The aims of the studies described in this part were to evaluate which predictive tests are appropriate to use to identify women at risk for SPB and what factors influence these tests, in particular related to the assessment of cervical length. In the second part we described the strategies which are used regarding threatened SPB in Dutch obstetric care.

### **Part 1. Etiology and risk assessment of spontaneous preterm birth**

In **chapter 2** we present the mechanisms contributing to SPB, which - mainly - have been identified during the past decade.<sup>1</sup> SPB may result from one of the four primary pathogenic mechanisms, or from a combination: (1) activation of the maternal or fetal HPA axis; (2) inflammation (of ascending genital tract, systemic or chorion/decidual); (3) decidual hemorrhage and (4) pathologic distention of the uterus. Recent evidence suggests that the four pathways are active at different gestational periods. The majority of very early (before 30 weeks of gestation) spontaneous preterm births seems to be associated with ascending genital tract infections.<sup>2,3</sup> Later SPB can be caused either by the hormonal pathway, due to decidual hemorrhage, or due to mechanical stretching of the myometrium caused by increase in uterine size. However, SPB is often caused by a combination of factors. Each pathway has a distinct epidemiological profile and biochemical signature, but shares a common final pathway leading to myometrial contractions, rupture of membranes, cervical change and finally to SPB. The observation that several pathways are involved in its pathogenesis may explain why preterm delivery has proven so difficult to predict and prevent. The elaboration of these pathogenic mechanisms has led to the belief that biologic markers associated with the specific pathways involved might be useful predictors of preterm birth. During the past decade, there has been an explosion of research papers that examined the usefulness of mediators (cytokines, hormones, enzymes, proteases) of these diverse biochemical pathways as new predictive tests for SPB.



The review in the second part of **chapter 2** describes the usefulness of new biochemical fluid markers to identify women at risk for SPB and their preferred gestational period of sampling. After looking attentively at various studies, we determined that the predictive value of all described biochemical fluid markers is relatively close to - although often somewhat higher - than that of the ones used until now. The low predictive value of these pathway-specific markers can be explained, in large part, by the multi-factorial pathogenesis of SPB. Markers associated with the common final pathways of SPB - uterine contractions monitoring, fetal fibronectin (FFN) expression and cervical length assessment - have been proposed as another approach to predict SPB. Some of these markers are already used in clinical practice, while their predictive value is not yet established in clinical practice. It is our objective to give recommendations for the clinical practice, both for a general population and the population at risk for SPB.

**General population (without a prior history of SPB or other risk factors for SPB):**

- \* There are no current data to support the use of salivary estriol, home uterine monitoring, or bacterial vaginosis (BV) screening as strategies to identify or prevent preterm birth.
- \* For other biochemical markers (e.g., corticotropin-releasing hormone (CRH), maternal serum alpha-fetoprotein (MSAFP), interleukine-6 (IL-6) and granulocyte colony-stimulating factor (G-CSF)) larger studies are needed.
- \* In the general population no other risk factors than the obstetric history has proven to be effective.

**Population at risk (with risk factors for SPB or symptoms with threatened SPB):**

- \* Transvaginal ultrasonography (TVS) to determine cervical length and FFN testing, or a combination of both is likely to be useful in determining women at high risk for preterm labor. However, their clinical usefulness may rest primarily with their high negative predictive value, thereby avoiding unnecessary intervention.
- \* For other biochemical markers (for instance CRH, MSAFP, IL-6, G-CSF) larger studies are needed.
- \* Only treatment with oral antibiotics (metronidazole with or without erythromycin) of women with BV and with a history of prior SPB might result in a reduction of SPB. Prophylactic treatment in women at risk for SPB, but without BV is not indicated.

Our recommendations are quite similar to the recently published guidelines by the American College of Obstetrics and Gynecology (ACOG).<sup>5,6</sup> It is important to examine the diagnostic value of a test in the population (high risk versus low risk) where the test is used for. In the review of the predictors of SPB, we choose to show the sensitivity, specificity, positive and negative predictive values and when available the likelihood ratio. A limitation of the studies is the use of predictive values to compare studies and tests, because the prevalences can differ greatly between populations. The likelihood ratio indicates by how much a given test result will raise or lower the probability of having the event that the test is designed to predict.<sup>7</sup> We must point out that many authors erroneously conclude that tests have a good diagnostic value. Khan et al. reviewed 14 prospective studies about the prediction of SPB by FFN.<sup>4</sup> They observed that authors' conclusions about the diagnostic value of FFN met the gold standard in only 26% of cases and that 66% of the authors overestimated the diagnostic value of their test. Mainly, because of an inadequate assessment of reliability and validity of new tests. It may also arise from overenthusiastic recommendations by authors of diagnostic test studies. It is not uncommon that new tests (for instance salivary estriol) are widely introduced and then failed as a significant advance in health care.<sup>8</sup>

New markers used in a general or selected population must be easy to test, inexpensive, and reproducible for physicians in daily practice. We recommend for future research to develop a model to predict SPB in which the predictive value of medical history, physical examination and additional diagnostic tests are incorporated. We suggest using various predictors for SPB separately, but also combined. Future research and intervention trials are needed to evaluate which combination of tests through artificial neural networks will be most successful in predicting SPB. By using multiple pathway-specific biochemical markers, we may be able to identify asymptomatic patients destined to deliver preterm, and to identify the precise etiology accounting for their risk to better target therapy. Goldenberg et al. found a small degree of overlap among predictive markers in women who delivered preterm.<sup>9</sup> This confirms our opinion that there are several pathways that lead to spontaneous preterm birth. It suggests that the use of several biologic markers together might be useful in the creation of a multiple-marker test. Furthermore, to provide answers about the utility of new markers, evaluation of the advantages and disadvantages of the use of the diagnostic tests in everyday practice, is needed. The only way to convince practitioners that a new marker is more effective than those they habitually use is to compare their diagnostic values in a prospective study of the same patients.

The usefulness of possible novel markers matrix metalloproteinase (MMP)-1 and MMP-9 in the prediction of SPB was described in **chapter 3**. The final common pathway shows that proteases, which are produced by chorion and decidua, play an important role during cervical dilatation in human parturition. MMP1- and -9 have been studied in various biologic fluids (serum, plasma, amniotic fluid, and urine). We studied for the first time whether cervico-vaginal fluid MMP-1 and MMP-9 levels were different during pregnancy compared with those at term or in preterm labor. Unfortunately cervico-vaginal MMP-1 levels were low and did not change during either preterm or term labor. In contrast, there might be a role for MMP-9 in the mechanisms of labor and rupture of membranes. Indeed, MMP-9 levels increased during term and preterm labor, with highest values in laboring patients with ruptured membranes, but the levels prior to preterm delivery were not significantly increased in comparison to MMP-9 throughout pregnancy. MMP-9 therefore is not a useful predictor of preterm birth. Another research group has recently studied MMP-9 in fetal membranes and they confirmed our findings.<sup>10</sup> We conclude that MMP-9 plays an important role in membrane rupture in the final common pathway model. It will be interesting to study the usefulness of MMP-9 as a confir-

mation test for premature preterm rupture of membranes (PPROM) in the future.

As described in the above-mentioned recommendations, cervical length measurements together with FFN are the most useful markers in the prediction of SPB. The relationship between a short cervix and the risk of SPB is well established. The shorter the cervix the higher the risk and vice versa.<sup>11</sup> Transvaginal ultrasonography (TVS) is a useful diagnostic tool in the detection of changes in gross morphology, but not in discrimination between the different underlying pathologies causing preterm delivery. It is also a diagnostic method that has been used in clinical practice, before the evidence for its usefulness and the adequate frequency of measurements was clear in the prediction of SPB. The cervix is a dynamic organ and that there is a lot of variability in cervical length. We sought to determine (in chapter 4 and 5) which methodological and socio-demographic factors can cause this variability in cervical length measurements. We also aim to develop nomograms. First, it is vital that the technique of measuring cervical length is standardized. In our cervical length studies we used the standardized measurement technique defined by Iams.<sup>11</sup> Secondly, several authors stated that the presence or absence of funneling and fundal pressure needs to be addressed when measuring cervical length.<sup>12-14</sup> However in recent studies the role of funneling in the prediction of SPB does not provide any significant contribution in addition to the cervical length measurement itself.<sup>12,13</sup> In our studies the presence or absence of funneling did not contribute to the prediction of SPB.

In **chapter 4** we assessed the association of sociodemographic factors on the change of cervical length of 125 women with an uncomplicated singleton pregnancy, who delivered at term. The cervical length was sonographically measured at 3 to 4 weeks interval between 20 and 32 weeks' gestation. All women had a slight decrease of cervical length across gestation. Women who were African-American, under stress, or working as skilled manual laborers demonstrated significant shortening of the cervix during gestation. Given that a shorter cervix predisposes to preterm delivery, our findings may give new insights into the well-described association of these psychosocial and sociodemographic factors with an increased risk of preterm delivery.

Based on the results of the previous chapter, we aimed to evaluate the racial variation on cervical length and its association with preterm birth (**chapter 5**) With a prospective cohort among 856 women, we measured serial cervical length at three

different intervals between 20 and 32 weeks' of gestation (65.5% Hispanics, 11.6% Asians 9.5% Caucasians and 13.4% African-Americans). Preterm rates did not significantly differ by race, but African-Americans delivered on average earlier (38.4 weeks) than the other race groups. All pregnancies displayed progressive cervical shortening except Asians. African-American women had shorter cervixes across all 3 gestational age intervals even after controlling for preterm delivery. African-American women who delivered preterm had shorter cervixes at 20-24 weeks' gestation than African-American women that delivered at term. This difference was not significant in the other racial-ethnic groups. At 25-28 weeks only African-American and Hispanic women showed a significant difference of mean cervical length between delivering preterm compared to term. At 29-32 weeks the difference in cervical length between delivering preterm or term were significant in all ethnic groups. It suggests that shortening of the cervix is particularly a risk indicator for preterm birth in African-American women, since they already have shorter cervixes to begin with. Measuring cervical length before 25 weeks gestation might not be of substantial contribution to the prediction of preterm birth in other ethnical groups. It is note worthy that thus far most studies on the importance of cervical length measurement have predominantly included African-American women.

Several authors studied the recurrent risk of preterm delivery.<sup>15-17</sup> Particularly the early prior preterm deliveries give a higher risk of a singleton preterm delivery in the following pregnancy. The African-American women in our study population had a higher rate of prior preterm birth, but after controlling for it, we still confirm that ethnicity has an influence on cervical change across gestation. In our study we report that the mean gestational age of African-American women is significantly shorter (38.4 weeks) in comparison to the other ethnic groups (39.1 weeks). Several authors confirmed these findings that African-American women deliver earlier than for instance Caucasian women.<sup>18,19</sup> The reasons for this difference mentioned in the past were lower socio-economic status among African-Americans; a short-pregnancy interval; a higher prevalence of known risk factors such as hypertension, diabetes, anemia, higher risk of infection. However, in our study, the statistically significant anatomic variation in cervical length, may contribute to the higher rate of preterm births in the African-American population. Our findings of a shorter cervix at 20-24 weeks and a significant shortening of the cervix during gestation among African-Americans might give them a different exposure to other risk factors in comparison with the other ethnic groups. In some

cases shortened cervix becomes an ineffective barrier to ascending infection.<sup>14,20</sup> This might predispose African-Americans to shorter gestations. The cervical length measurements of the African-Americans in our study were not confounded by the above-mentioned socio-economic risk factors.<sup>20,21</sup> When measuring cervical length by transvaginal sonography to assess risk for preterm birth, consideration should be given to racial-ethnic background when interpreting results. It could well be that lower cut-off values in African-American women should be used than in other ethnic groups, but future research needs to clarify this.

We did not focus on cut-off values and frequencies of cervical length measurements needed for the prediction of SPB. However, from our review in chapter 2 we would like to draw a few conclusions for the clinic. The cervical length measured by transvaginal sonography is a tool that is non-invasive, easy and often used in clinical practice. To date, it is unclear what a useful cut-off value is for the prediction of SPB. For singleton pregnancies the international literature mostly suggests to use the cut-off for cervical length of <30 mm to predict SPB in a general population and <25 mm for the population at risk.<sup>11,22</sup> The minimum interval between cervical length measurements necessary to detect cervical shortening in time mostly used in the literature is every 3 weeks. Based on our results we suggest that the predictive value of screening for cervical length early in the pregnancy might only be useful for the African-American population. Blacks have apparently a shorter cervix with less reserve capacity than the other ethnic groups. We recommend future research to determine new cut-off values for African-American women and other ethnic groups. From a practical perspective, our study suggests that the value of measuring cervical length may be limited prior to 25 weeks in racial/ethnic groups other than African American women and before 29 weeks among Caucasian and Asian women; It is questionable if early measurements are cost-effective.

In **chapter 6** we evaluated the role of transvaginal ultrasonographic cervical length measurements for women with cervical incompetence. The study population contained of eighty women at risk for cervical incompetence whose primary physician determined that a prophylactic ( $n = 50$ ) or urgent cerclage ( $n = 30$ ) was indicated. Cervical length measurements took place before and after the cerclage until 32 weeks' gestation. We determined that there was an increase in cervical length after cerclage. However, the degree of lengthening after cerclage was not predictive of term delivery. Our second research question of this study was

whether serial follow-up measurements of cervical length after cerclage were useful in the prediction of pregnancy outcome. We showed that serial cervical length measurement in the late second or early third trimester predicted preterm birth. It gave an earlier warning in women with a prophylactic cerclage than in women with an urgent cerclage.

There remains discussion in the literature regarding the use of transvaginal ultrasonography for women with a cerclage and the frequency of follow-up after cerclage. We confirmed the usefulness of transvaginal ultrasonography with the results from our study that women with progressive shortening of the cervix are at higher risk to deliver preterm (not only  $< 37$  weeks, but also  $< 35$  weeks) in comparison to women whose cervixes decrease slowly across gestation. We suggest that in a woman with cervical incompetence ultrasound follow-up of the cervix should start at the end of the first trimester and continue serially every 3 weeks till 30-32 weeks' gestation.<sup>23-25</sup> The cut-off values for cerclage placement described in the international literature range from 15 to 25 mm.<sup>13,26</sup> Althuisius et al. suggested a (second) therapeutic cerclage and bedrest when a cervix is found  $< 25$  mm before 27-28 weeks' gestation.<sup>27</sup> This gestational period was chosen because the advantages of prolonging pregnancy, outweigh the risk of the cerclage application before the gestational age of about 27-28 weeks.<sup>27,28</sup> In this randomized intervention trial only a minority of the women fulfilled the criteria for the traditional definition of cervical incompetence. 60% of the women with a prophylactic cerclage might not have needed it.<sup>27</sup> Guzman et al. described that women with cervical lengths of  $\leq 15$  mm will benefit the most from cerclage placement. Larger randomized intervention trials are needed in the future, which address the use of a (therapeutic) cerclage versus restriction of physical activity for the short cervix and the follow-up after cerclage by TVS.<sup>13</sup>

## Part 2: Spontaneous preterm birth in Dutch obstetric care.

Since many studies regarding prediction of spontaneous preterm birth have been published in the recent international literature, we are interested how these (new) predictors of SPB are implemented in the Dutch obstetric care. Furthermore, the impression exists that there are different strategies and views regarding diagnosing and treating threatened preterm birth among and between midwives, general practitioners (practicing obstetrics) and obstetrician/gynecologists (further mentioned as gynecologists). Dutch obstetrical care is based on a 'unique' system of

risk selection with the option of home deliveries. First line obstetric care providers are responsible for the obstetric care for low risk women. It is important to know when a woman is at increased risk for SPB for the first line obstetric care providers. So the patient can be referred to a gynecologist in time. Risk selection as to SPB is important and is partly provided by the Obstetric Indication List ('VIL'). Firstly, it is relevant to know the risk factors, the symptoms and the available diagnostic tests to be able to assess the risk per patient on spontaneous SPB. Secondly, it is important to be clear to patients with a prior SPB what the recurrence risk is and what the management will be in a next pregnancy.

A written questionnaire to study opinions and management regarding threatened preterm birth, co-operation and the 'VIL was sent to first line obstetrical practitioners (midwives and general practitioners practicing obstetrics) and gynecologists (chapter 7). There appeared to be consensus among the three professional groups about the way that risk selection takes place. The three professional groups agreed that the problem of SPB has moved from < 37 gestational weeks to < 35 gestational weeks. In our study the three groups agreed that a preterm birth > 34 weeks carries only a small risk on an early SPB in the following pregnancy. In that case prenatal care can be provided by the midwife or general practitioner. This view is in accordance with the fact that reducing late preterm birth, the 50% that occur at 35 and 36 weeks' gestation, is not likely to have major effects on perinatal outcome. Instead, the 1% to 2% infants born before 30 to 32 weeks' gestation account for the major part of the mortality and both short- and long-term neurologic morbidity. The important time period for PTL management is from 24 weeks until 34-35 weeks of gestation.<sup>29</sup> The three professional groups had a positive view on the general 'VIL and to the mutual co-operation. To date, there are, however, no clear guidelines in the Netherlands for the use of the various diagnostic tests for screening and/or prediction of early, moderate or late SPB in the next pregnancy.

In **chapter 8** we assessed the use of 'modern' diagnostic methods such as transvaginal sonographic measurements of cervical length, examination of bacterial vaginosis (BV) and fetal fibronectin (FFN) by Dutch gynecologists. Cervical length measurements are used by most of the Dutch gynecologists, even as testing and treating for BV. Fetal fibronectin testing - according to literature the best marker available now - is seldomly been used. Gynecologists in general hospitals without residency programs prescribe tocolytics and repeat corticosteroid treat-



ment more often compared to the gynecologists in hospitals with residency programs. They prescribe less antibiotics for women with threatened preterm birth. Apparently 40% of Dutch gynecologists 'treat' preterm premature rupture of membranes (PPROM) with tocolytics while there are no contractions. With the results from the 'ORACLE' trial the limited use of antibiotics by the Dutch gynecologists in women with PPRM is striking.<sup>30,31</sup> However, our questionnaire was held before the results of the 'oracle' study. Apparently, the management of gynecologists from general hospitals is more traditional, while the gynecologists from hospitals with residency programs seem to react more quickly to new developments. This regards especially the use of antibiotics for women with PPRM, repeated corticosteroid treatment and the use of tocolytics. We discovered an interesting discrepancy between the use of FFN and measuring cervical length with ultrasound. The reason might be that the 'ultrasound-equipment' was already available in the gynecologist's practice, while for FFN a new system needs to be installed. On some points the disciplines involved in obstetric care should adopt their guidelines to use the evidence from the literature. Use of FFN in the Dutch setting should be evaluated in the future.

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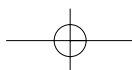
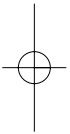
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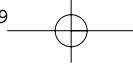


*Chapter 9*

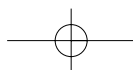
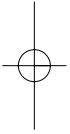
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## Samenvatting en Nabeschuwing



Vroeggeboorte wordt door de Wereld Gezondheidsorganisatie (WHO) gedefinieerd als een bevalling voor 37 complete zwangerschapsweken. Vroeggeboorte is een van de voornaamste oorzaken van neonatale sterfte en een belangrijke oorzaak van lichamelijke en mentale beperkingen op de lange termijn. Op dit moment is de incidentie van vroeggeboorte in de westerse samenleving 7 tot 11 % en dit percentage lijkt internationaal iets te stijgen. De belangrijkste redenen hiervoor zijn (1) toename van meerlingzwangerschappen door fertiliteitsbevorderende behandelingen en (2) hogere leeftijd waarop vrouwen kinderen krijgen, (3) tendens tot eerder ingrijpen (d.m.v. inleiding of keizersnede) bij probleem-zwangerschappen en (4) betere registratie van zowel de zwangerschapsduur (door vroege echoscopie) als van extreme vroeggeboortes op de grens van levensvatbaarheid.

In dit proefschrift concentreren wij ons op de spontane vroeggeboorte. Dit omvat zowel premature (voortijdige) contracties als het voortijdig breken van de vliezen. Het spreekt voor zich dat verlaging van de incidentie van vroeggeboorte door middel van preventie en het op tijd diagnosticeren en behandelen van dreigende vroeggeboorte een belangrijk doel is in de verloskunde. Verder is het van belang te voorkomen dat patiënten onnodig behandeld worden. Internationaal wordt veel onderzoek gedaan naar methoden die ons in staat stellen vrouwen met een verhoogd risico op vroeggeboorte tijdig te identificeren en effectief te behandelen.

In dit proefschrift worden de volgende onderzoeksvragen behandeld:

- Welke ontstaansmechanismen en voorspellende testen van spontane vroeggeboorte zijn tot nu toe beschreven in de literatuur? En welke testen zijn zinvol voor de klinische praktijk?
- In hoeverre kunnen de nieuwe markers matrix metalloproteinase -1 en -9 worden gebruikt om spontane vroeggeboorte te voorspellen?
- Wat is het normale beloop van de cervix (baarmoedermond) lengte gedurende de zwangerschap en welke (socio-demografische) factoren beïnvloeden deze lengte bij een voldragen zwangerschap en bij vroeggeboorte?
- Is het gebruik van cervixlengte metingen na een cerclage (bandje om baarmoedermond) zinvol en wat is de voorspellende waarde hiervan voor spontane vroeggeboorte?
- Wat is de werkwijze met betrekking tot het beleid bij dreigende vroeggeboorte onder de Nederlandse verloskundige hulpverleners?

## Deel 1. Oorzaken van vroeggeboorte en methoden om het te voorspellen.

Het ontstaansmechanisme van vroeggeboorte wordt in **hoofdstuk 2** beschreven. Vroeggeboorte kan worden veroorzaakt door 4 primaire oorzaken, of een combinatie hiervan: (1) activatie van de hypothalamus-hypofyse-bijnier-as (HPA) door stress van zowel moeder als kind; (2) ontsteking (opstijgende infectie vanuit vagina, systemisch of op grens vliezen/placenta (moederkoek)); (3) vaginale bloeding (vanuit placenta) en (4) forse uitzetting van de baarmoeder. De vier beschreven ontstaansmechanismen zijn actief in verschillende perioden van de zwangerschap. Het grootste deel van de extreme vroeggeboortes lijkt in verband te staan met opstijgende infecties vanuit de vagina. Een infectie of bloeding kan irritatie of beschadiging veroorzaken op de overgang van vliezen en placenta. Als gevolg van ontstekingsreacties komen stoffen vrij (enzymen, proteases en collagenases) waardoor prostaglandine productie op gang komt. Dit kan leiden tot voortijdige ontsluiting, contracties en het breken van de vliezen en uiteindelijk tot vroeggeboorte.

Op het moment wordt veel onderzoek gedaan naar de vraag of de biologische stoffen die geassocieerd zijn met de verschillende ontstaansmechanismen (ontstekingsmediatoren, hormonen, enzymen), gebruikt kunnen worden als voorspellers voor vroeggeboorte. In hoofdstuk 2 volgt een overzicht van de literatuur over het gebruik van nieuwe biochemische markers als voorspellende testen voor vroeggeboorte. Hierin staat ook aangegeven wat de beste zwangerschapsduur is waarop de verschillende testen uitgevoerd dienen te worden om vrouwen met een verhoogd risico op vroeggeboorte te identificeren. Uit dit overzicht blijkt dat de voorspellende waarde van nieuwe biochemische markers gemiddeld gezien lager of gelijk is - soms iets hoger - dan die van reeds in de kliniek gebruikte testen. De lage voorspellende waarde van deze specifiek aan ontstaansmechanismen gerelateerde markers, kan mogelijk verklaard worden door het multi-factoriële karakter van vroeggeboorte. Methoden die reeds worden gebruikt om vroeggeboorte te voorspellen zijn: het monitoren van contracties, het testen van een eiwit foetaal fibronectine en het beoordelen van de cervixlengte. Zowel het bepalen van cervixlengte (met vaginale echoscopie) als foetaal fibronectine zijn van belang in de voorspelling van vroeggeboorte in symptomatische en asymptotische patiënten. De relatie tussen een korte cervix en het risico van vroeggeboorte is bevestigd. Hoe korter de cervix hoe hoger het risico en vice versa. Foetaal fibronectine heeft met name een hoge negatief voorspellende waarde. Afwezigheid van foetaal fibronectine in vagina slijm voorspelt met een betrouwbaarheid van 95% dat een bevalling niet binnen 2 weken plaatsvindt.



Aanbevelingen die op grond van de literatuur gegeven kunnen worden, zijn:

**Algemene populatie** (zonder risicofactoren voor vroeggeboorte en zonder eerdere vroeggeboorte):

- Er zijn onvoldoende gegevens bekend om het hormoon estriol bepaald in speeksel, (thuis) monitoren van contracties of het testen van bacteriële vaginosis te gebruiken om vroeggeboorte te identificeren of te voorkomen.
- Voor andere biochemische markers (bijv. corticotropine-vrijkomend hormoon (CRH), moederlijk serum a-foetoproteïn (MSAFP), interleukine-6 (Il-6) en granulocyt colonie-stimulerende factor (G-CSF)) zijn grotere studies geïndiceerd, alvorens conclusies kunnen worden getrokken omtrent hun functie bij het voorspellen van vroeggeboorte.
- In de algemene populatie zijn er behoudens, de verloskundige voorgeschiedenis, geen risicofactoren effectief gebleken bij het voorspellen van vroeggeboorte.

**Populatie met verhoogde kans op vroeggeboorte** (risicofactoren voor vroeggeboorte, of symptomen van dreigende vroeggeboorte aanwezig):

- Om te bepalen welke vrouwen een hoog risico hebben op vroeggeboorte zijn vaginale echoscopische meting van cervixlengte, foetaal fibronectine onderzoek, of een combinatie van beide testen zinvol gebleken. Met name de hoge negatief voorspellende waarde van beide testen is voor de algemene praktijk van belang om onnodige interventies te voorkomen.
- Voor andere biochemische markers (bijvoorbeeld CRH, MSAFP, Il-6, G-CSF) zijn grotere studies noodzakelijk, alvorens conclusies kunnen worden getrokken omtrent hun functie bij het voorspellen van vroeggeboorte.
- Aanwezigheid van bacteriële vaginosis verhoogt de kans op vroeggeboorte. Er heerst echter discussie of behandeling met orale antibiotica (metronidazol met of zonder erytromycine) de kans op vroeggeboorte reduceert. Met de bewijsvoering tot op heden, wordt alleen bij zwangeren met een vroeggeboorte in de voorgeschiedenis behandeling geadviseerd. Profylactische behandeling van vrouwen met een risico op vroeggeboorte, maar zonder bacteriële vaginosis, is niet zinvol.

Onze aanbevelingen komen vrijwel overeen met de recent gepubliceerde richtlijnen van het Amerikaanse college voor verloskunde en gynaecologie (ACOG).





**Hoofdstuk 3** beschrijft de resultaten van een onderzoek naar de voorspellende waarde van de nieuwe markers matrix metalloproteïnase (MMP)-1 en MMP-9. Het bindweefsel (collageen) in de baarmoedermond zorgt ervoor dat deze tijdens de zwangerschap gesloten blijft. Afbraak van dit bindweefsel leidt tot verkorting en verweking van de cervix en kan tot (vroeg)geboorte leiden. Door de afbraak van collageen, komen proteases (bijvoorbeeld matrix metalloproteïnes) vrij. De voorspellende waarde van MMP-1 en -9 voor vroeggeboorte zijn tot op heden alleen bestudeerd in bloed, vruchtwater en urine. Wij hebben voor het eerst de concentratie van MMP-1 en MMP-9 in cervix en vagina slijm bestudeerd bij 32 vrouwen die uiteindelijk preterm (te vroeg) en 80 vrouwen die a term (op tijd) bevielden. MMP-1 en -9 werden gemeten tussen 20 en 32 weken, een week voor de bevalling, en tijdens de (te vroeg of op tijd plaatsvindende) bevalling. Helaas bleek de hoeveelheid MMP-1 in cervix en vagina slijm laag, en steeg de concentratie niet voorafgaande of tijdens de bevalling. MMP-9 speelt mogelijk wel een rol bij het ontstaan van contracties en breken van de vliezen. De concentratie is namelijk significant hoger tijdens de bevalling dan daarvoor, dit geldt zowel voor de preterm als op tijd komende bevalling. De hoogste waarden worden gevonden bij vrouwen met gebroken vliezen. De concentratie van MMP-9 een week voor de bevalling was niet significant hoger dan die tijdens de zwangerschap. Ook MMP-9 kan daarom niet gebruikt worden als een voorspellende test voor vroeggeboorte. Wel blijkt MMP-9 een belangrijke rol te spelen bij het breken van de vliezen. Onderzoek naar het gebruik van MMP-9 ter bevestiging van het al dan niet gebroken zijn van de vliezen is interessant voor de toekomst.

In de hoofdstukken 4 en 5 hebben we de invloed van socio-demografische factoren onderzocht op de lengte van de cervix. De cervix is een dynamisch orgaan en uit de literatuur blijkt variabiliteit in cervixlengte. Bij het meten van cervixlengte is standaardisatie van de techniek van groot belang. Wij hebben gebruikt gemaakt van de standaardisatie van de meettechniek zoals gedefinieerd door Iams en anderen. Verscheidene auteurs hebben beschreven dat rekening gehouden moet worden met de aan- of afwezigheid van funneling bij het meten van de cervixlengte. Het al dan niet aanwezig zijn van funneling blijkt echter geen toegevoegde waarde te hebben in de voorspelling van vroeggeboorte, als aanvulling op het meten van de lengte van de cervix zelf.

**Hoofdstuk 4** beschrijft normaalwaarden van de cervixlengte en de invloed van socio-demografische factoren hierop. De studiepopulatie bestond uit 125 vrouwen met een ongecompliceerde eenlingzwangerschap, die rond de uitgerekende datum bevielden. De lengte van de cervix werd elke 3 tot 4 weken met transvaginale echografie bepaald tussen 20 en 32 weken zwangerschapsduur. Bij alle vrouwen vond een geringe verkorting van de lengte van de cervix plaats in het verloop van de zwangerschap. Een significante verkorting trad op bij de negroïde vrouwen, bij vrouwen onder stress, cq vrouwen die zware lichamelijke arbeid verrichten. Het is bekend dat deze factoren predisponeren tot vroeggeboorte. De verkorting van de cervix zou een verklaring kunnen zijn voor het verband tussen bovengenoemde psychosociale en socio-demografische factoren en het verhoogde risico op vroeggeboorte.

In **hoofdstuk 5** wordt de invloed van ethnische achtergronden op de cervixlengte en op een eventuele associatie met vroeggeboorte onderzocht bij 856 vrouwen. In een prospectieve cohort werd de cervixlengte gemeten in drie verschillende tijdsperioden tussen 20 en 32 weken zwangerschapsduur. Twee derde van de onderzoekspopulatie was Hispaans van origine, en verder was er een vrijwel gelijke verdeling van Aziatische, blanke en negroïde vrouwen. Het percentage vroeggeboorte verschilde niet significant per ras, hoewel de negroïde vrouwen gemiddeld iets eerder bevielden (38.4 weken) dan de vrouwen met een andere ethnische achtergrond (39.1 weken). Met uitzondering van de Aziatische vrouwen was bij alle groepen sprake van een progressieve verkorting van de cervix. De negroïde vrouwen hadden in alle drie zwangerschapsperioden een kortere cervixlengte dan de andere groepen, ook als gecontroleerd werd voor vroeggeboorte. Negroïde vrouwen die prematuur bevielden hadden bij 20-24 weken een significant kortere cervixlengte dan negroïde vrouwen die tijdens de uitgerekende periode bevielden. Dit verschil bleef ook significant na uitsluiting van risicovrouwen met vroeggeboorte in de voorgeschiedenis. Bij de andere ethnische groepen was dit verschil bij 20-24 weken niet significant. Bij 25-28 weken was de gemiddelde cervixlengte zowel bij negroïde als bij Hispaanse vrouwen die te vroeg bevielden significant korter en dit verschil was bij 29-32 weken significant bij alle vier ethnische groepen. Negroïde vrouwen hebben dus blijkbaar een kortere cervixlengte tussen 20 en 32 weken dan vrouwen met een andere ethnische achtergrond. Verkorting van de cervixlengte blijkt bij hen dan ook eerder een effect te hebben op het voorkómen van vroeggeboorte. Ons onderzoek suggereert dat screening op verhoogde kans op vroeggeboorte bij negroïde vrouwen vanaf 20-

24 weken zinvol is, terwijl dit voor vrouwen met een andere ethnische achtergrond pas later een toegevoegde waarde heeft. Het is vermeldenswaard dat de meeste onderzoekspopulaties waarin het belang van cervixlengte metingen voor het voorspellen van vroeggeboorte werd bestudeerd voornamelijk bestonden uit negroïde vrouwen.

Onze bevinding dat de negroïde vrouwen gemiddeld iets eerder bevallen dan andere ethnische groepen wordt bevestigd in de literatuur. De redenen die hiervoor genoemd zijn, zijn een gemiddeld lagere sociaal-economische klasse; een korter interval tussen de zwangerschappen; hogere prevalentie van bekende risicofactoren als hoge bloeddruk, suikerziekte, bloedarmoede en een verhoogd risico op infectie. Echter, de significant kortere cervix zou het hogere percentage vroeggeboorte onder de negroïde populatie kunnen verklaren. Dit zou hen ook kwetsbaarder kunnen maken voor andere risicofactoren. Zo biedt een kortere cervix een minder effectieve bescherming tegen opstijgende infecties. Het is vooralsnog onduidelijk of deze kortere cervix het gevolg is van aangeboren anatomische verschillen, ontstaat door een ander hormonaal milieu tijdens de zwangerschap, of op zich weer het gevolg is van andere risicofactoren (zoals infectie). Concluderend is het bij het interpreteren van de echoscopisch gemeten cervixlengte voor het voorspellen van vroeggeboorte van belang om rekening te houden met de ethnische achtergrond van de patiënt. Enerzijds is de voorspellende waarde voor het optreden van vroeggeboorte bij negroïde vrouwen al vroeger aanwezig dan bij andere rassen. Anderzijds hebben negroïde vrouwen überhaupt een kortere cervix en zijn mogelijk lagere normaalwaarden op zijn plaats. We verwachten in de toekomst, met een uitbreiding van de studiepopulatie, hierover meer duidelijkheid te verkrijgen.

Het meten van de cervix is een gemakkelijk en slechts beperkt invasief diagnostisch hulpmiddel, dat inmiddels te pas (en te onpas) in de kliniek wordt gebruikt. Vooral de hoge negatief voorspellende waarde is van belang bij onderzoek bij risico-zwangerschappen. Nut voor de algemene populatie is nog niet aangetoond, hoewel ons onderzoek suggereert dat vroege screening bij negroïde vrouwen zinvol zou kunnen zijn. Onderzoek bij risicopopulaties zou volgens de literatuur met een tijdsinterval van circa 3 weken plaats dienen te vinden. De ondergrens voor een toegenomen kans op vroeggeboorte is volgens enkelen 25 mm en volgens anderen 30 mm. Het is vooralsnog de vraag of cervixlengte metingen (vroeg) in het tweede trimester kosten-effectief zijn. Nader onderzoek in een grote populatie

en onderscheid tussen de vrouwen met of zonder verhoogd risico op vroeggeboorte is aangewezen. Dit om een adequaat en efficiënt beleid te kunnen formuleren ten aanzien van de toegevoegde waarde van cervixlengte metingen bij diagnostiek en preventie van (dreigende) vroeggeboorte.

De voorspellende waarde van cervixlengte metingen voor het optreden van vroeggeboorte bij vrouwen met een cerclage op basis van cervixinsufficiëntie wordt in **hoofdstuk 6** onderzocht. De onderzoeks populatie bestond uit tachtig vrouwen die in verband met een risico op cervixinsufficiëntie een cerclage hadden gekregen (50 profylactisch en 30 therapeutisch). Vóór en na de cerclage werden cervixlengte metingen verricht tot 32 zwangerschapsweken. De lengte van de cervix werd langer direct na het plaatsen van de cerclage. Deze lengte bleek echter niet voorspellend voor de uitkomst van de zwangerschap. Wel hadden de follow-up metingen aan het einde van het tweede en het begin van het derde trimester een voorspellende waarde voor het al dan niet optreden van vroeggeboorte.

Bij vrouwen met een verhoogde kans op cervixinsufficiëntie wordt echoscopische seriële follow-up van de cervix aanbevolen vanaf het einde van het eerste trimester. Dit wordt bevestigd door Althuisius e.a. die in een prospectief gerandomiseerd onderzoek aangetoond heeft dat echoscopische follow-up van de cervixlengte - met een therapeutische cerclage bij een verkorting van de cervix tot onder de 25 mm - een goed alternatief is voor de traditionele profylactische cerclage. Anderen vinden dat vrouwen met een cervixlengte van  $< 15$  mm de meeste baat hebben bij een cerclage.

## Deel 2. Spontane vroeggeboorte in de Nederlandse verloskundige zorg.

De Nederlandse verloskundige zorg is uniek in vergelijking met andere westerse landen, aangezien zwangeren met een laag risico (80%) door eerstelijns verloskundige hulpverleners (verloskundigen en verloskundig actieve huisartsen) worden begeleid. Uitgangspunt daarbij is dat de eerstelijns verloskundige zorgverlener tijdig een betrouwbare inschatting kan maken om bij te verwachten medische of verloskundige problemen, hetzij zelf de bevalling in het ziekenhuis te begeleiden, hetzij de patiënt (voor, tijdens of na de bevalling) naar de gynaecoloog te verwijzen. De Verloskundige Indicatie Lijst ('VIL') is een hulpmiddel voor risicoselectie in de verloskunde. De richtlijnen ten aanzien van vroeggeboorte zijn echter summier beschreven. Verder bestaat de indruk dat er uiteenlopende meningen zijn ten aanzien van diagnostiek en beleid bij dreigende vroeggeboorte tussen en binnen de drie beroepsgroepen. Om in de toekomst nieuwe mogelijkheden voor overleg op dit gebied tussen de eerste en tweede lijn te bieden, hebben we een vragenlijst ontwikkeld om de werkwijze, taakafbakening en opvattingen ten aanzien van dreigende vroeggeboorte te inventariseren. Ook worden de opvattingen ten aanzien van de onderlinge samenwerking tussen de eerstelijns verloskundige hulpverleners en de gynaecologen en de acceptatie van de 'VIL' bestudeerd.

In hoofdstuk 7 worden de resultaten van deze vragenlijst gepresenteerd. Er bleek in grote lijnen overeenstemming te bestaan over het beleid bij dreigende vroeggeboorte onder de drie beroepsgroepen. Bij symptomen van dreigende vroeggeboorte bij > 35 weken werd minder naar de tweede lijn verwezen dan eerder in de zwangerschap. Het beleid bij vrouwen met 'contracties', bij 'verdenking op cervixinsufficiëntie' en bij een 'conisatie in de voorgeschiedenis' bleek bij 25-30 zwangerschapsweken minder eenduidigheid. De meerderheid van de drie beroepsgroepen was van mening dat de begeleiding van een volgende zwangerschap niet in de tweede lijn hoefde plaats te vinden, indien een eerdere vroeggeboorte tussen 34 en 37 zwangerschapsweken had plaatsgevonden. Er bleek overeenstemming over het feit dat het probleem van vroeggeboorte een zwangerschapsduur van minder dan 35 weken betreft en niet meer alle zwangerschappen < 37 weken. Deze bevindingen komen overeen met de literatuur. Enerzijds blijkt dat het herhalingsrisico op vroeggeboorte veel lager is indien de eerste vroeggeboorte na 32-34 weken heeft plaatsgevonden. Anderzijds blijkt dat preventie van late vroeggeboorte tussen 35 en 37 weken - in totaal 50 % van alle vroeggeboortes - nauwelijks effect heeft op de perinatale

uitkomst. Vroeggeboorte, voorspelling en preventie, is vooral van belang vóór 34-35 weken.

Een goede risicoselectie is van belang voor de instandhouding van het Nederlandse verloskundige systeem met de mogelijkheid van thuisbevallingen; een systeem dat op dit moment onder druk staat. Uit ons onderzoek blijkt dat de drie beroepsgroepen actief in de verloskundige zorg in Nederland de (gehele) verloskundige indicatielijst positief waarderen en ook was men in grote lijnen tevreden over de onderlinge samenwerking. De acceptatie van de verloskundige indicatielijst is nu veel groter dan 10 jaar geleden. Het is een uitdaging voor verloskundigen, verloskundig actieve huisartsen, gynaecologen en beleidsmakers om het goede en unieke systeem van de Nederlandse verloskunde te behouden.

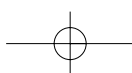
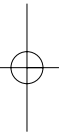
Op dit moment zijn er in Nederland nog geen specifieke richtlijnen voor het gebruik van de verschillende diagnostische testen voor het voorspellen van vroeggeboorte in de (volgende) zwangerschap. Na de vele studies die over het voorspellen van vroeggeboorte in de internationale literatuur zijn verschenen, zijn we geïnteresseerd hoe de (nieuwe) voorspellende testen voor vroeggeboorte in de Nederlandse verloskundige zorg zijn geïmplementeerd.

Het gebruik onder Nederlandse gynaecologen van 'nieuwe' diagnostische testen, zoals echoscopische meting van de cervixlengte, onderzoek naar bacteriële vaginosis en foetaal fibronectine, wordt in **hoofdstuk 8** beschreven. Er bleek een grote variatie in werkwijze te bestaan bij dreigende vroeggeboorte. Cervixlengte metingen en onderzoek naar bacteriële vaginosis werden door 50-80% van de gynaecologen toegepast. Bacteriële vaginosis werd door 80% van de gynaecologen behandeld. Foetaal fibronectine in vagina-of cervix slijm - volgens de literatuur op dit moment de beste voorspeller voor vroeggeboorte - werd daarentegen nauwelijks gebruikt. Weeënremming en corticosteroiden werden vaak gegeven bij zwangeren met prematuur gebroken vliezen zonder weeënactiviteit, terwijl antibiotica slechts bij 25% werd voorgeschreven. Gynaecologen werkzaam in perifere ziekenhuizen gaven aan vaker weeënremming voor te schrijven en corticosteroiden behandeling te herhalen dan gynaecologen in opleidingsziekenhuizen. Antibiotica werden daarentegen vaker voorgeschreven bij prematuur gebroken vliezen door gynaecologen werkzaam in opleidingsziekenhuizen. Recent is gebleken dat erythromycine bij preterm gebroken vliezen niet alleen de zwangerschapsduur significant verlengd, maar ook de neonatale morbiditeit significant



verlaagt. Ten tijde van de enquête was bovengenoemde studie echter nog niet gepubliceerd. Hoewel er al enkele jaren aanwijzingen zijn dat bij preterm gebroken vliezen antibiotica de zwangerschapsduur verlengen en neonatale morbiditeit verlagen, was het advies van de Cochrane Collaboration om deze behandeling nog niet toe te passen. De opleidingsklinieken liepen dus blijkbaar vooruit op het definitieve bewijs en algemene ziekenhuizen waren wat terughoudender. Al met al, blijkt onder Nederlandse gynaecologen slechts in geringe mate sprake van standaardisatie in het gebruik van ‘moderne’ diagnostische hulpmiddelen en behandelingsmodaliteiten voor dreigende vroeggeboorte.

Voor **referenties** zie engelstalige samenvatting



## Abbreviations and Appendix

ACOG	American College of Obstetricians and Gynecologists
ACTH	Adrenocorticotrophic hormone
AF	Amniotic fluid
ANOVA	Analysis of variance
BSA-TBS	Bovine serum albumin in Tris buffer
BV	Bacterial vaginosis
CI	Confidence interval
CRH	Corticotropin-releasing hormone
CV	Coefficient of variability
CVS	Cervicovaginal secretions
DES	Diethylstilbestrol
DHEAS	Dehydroepiandrosterone sulfate
E1-3	Estriol 1-3
ECM	Extra cellular matrix
EGA	Estimated gestational age
ELISA	Enzyme-linked immunosorbent assay
FBM	Fetal breathing movements
FDA	Food and Drug Administration
FFN	Fetal fibronectin
G-CSF	Granulocyte stimulating factor
HCG	Human chorionic gonadotropin
HPA	Hypothalamic pituitary adrenal (axis)
HUAM	Home uterine activity monitoring
IAI	Intra amniotic infection
IL	Interleukine
IUGR	Intrauterine growth retardation
MOM	Multiples of the median
MMP	Matrix metalloproteinase
MSAFP	Maternal serum alpha-fetoprotein
NIH	National Institute of Health
NPV	Negative predictive value
PA	Plasmin activator
PG	Prostaglandin
PMSF	Phenolmethylsulfonylfloride
PPROM	Preterm premature rupture of membranes



PPV	Positive predictive value
PTB	Preterm birth
PTL	Preterm labor
SD	Standard deviation
SPB	Spontaneous preterm birth (= PTL + PPROM)
TAT	Thrombin-antithrombin III complex levels
TIMP	Tissue inhibitor of metalloproteinases
TNF	Tumor necrosis factor
TVS	Transvaginal ultrasonography
VIL	Verloskundige Indicatie Lijst (Obstetric Indication List)
VWS	Volksgezondheid, welzijn en sport (Health and Sports)

## **Appendix**

Since the questionnaires used for chapter 4 and 5 and the 2 Dutch questionnaires used for the studies in chapter 7 and 8 are quite comprehensive, we choose not to publish it in the thesis.

An English or Dutch version of these questionnaires are available by mailing to the author. (karoliendijkstra@hotmail.com)

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## Acknowledgments

The 'naked' women of Matisse, who dance 'united' on the globe, represent in a symbolic way the completion of my thesis. 'United' represents the fact that two different worlds were connected (New York and Utrecht) on the one hand, and two medical fields were united (General Practice and Obstetrics/Gynecology) on the other. The 'naked' women are pure, but also vulnerable, when they are about to deliver premature. The colorful painting style of Matisse fascinates me, as the problem of spontaneous premature birth does. It was a great pleasure to work together with many people who I would like to acknowledge for their part in the realization of this thesis.

First of all, I would like to thank Frank van Bel, who asked me the interesting and challenging question in April 1998 at a preterm birth symposium in Berlin: "if you have already so much research data, why don't you write a thesis; 4 or 5 articles as a first author, introduction, summary, a few staples and you are finished". At that time I could only think: "if it's to be, it's up to me, if not now, when?"

New York City was a wonderful place to initiate my research activities. Professor Lockwood, dear Charles, your enthusiasm for and your extensive knowledge of this particular field of research has been a tremendous support for me throughout the last 6 years. Your easy accessibility and hospitality at your department of New York University made it great fun to not only start this project but, even more importantly, to also finish it. After I told Professor Visser about my research data from New York, he turned into a great initiator and supporter to finish this thesis under his supervision. Dear Gerard, you were always enthusiastic with a clear and positive approach, which was very encouraging. At the end of '98 I decided to become a general practitioner (also active in the field of obstetrics) instead of a straightforward gynecologist and received a lot of support from Professor Verheij and Dr. Ron Pieters to continue my research activities. Dear Theo, your pragmatic, smooth and critical view have always been very much appreciated. Dear Ron, I would like to thank you for facilitating my research activities during and after my training to become a general practitioner.

A majority of my activities took place at the clinic of Bellevue Hospital with the diverse population representing New York City. All staff members, research nurses, colleagues in the laboratories, residents, students and patients I worked with, thanks to all of you for your support, participation and interest in my research project. They

are all the base of the clinical research and the thesis in front of you. I would like to thank in particular Ed Kuczynski, Ed Funai, Men-Jean Lee, Rosemary Wein and Lorraine O'Neill for your pleasant and supporting co-operation.

The second major part of my research took place at the University Medical Center of Utrecht and the Julius Center for general practice and patient oriented research. I would like to thank all participating Dutch gynecologists, midwives and general practitioners for their contribution by filling out my questionnaire. Marijke Kuyvenhoven, I would like to thank you for the methodological support to my research. Although you often had a full agenda, your door was always open and I enjoyed your concrete advises and pleasant co-operation. I will also thank the research assistants and Peter Zuithoff, for being my coach while struggling with SPSS and other statistical challenges.

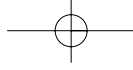
My room mates Lia, Marco, Inge and later on Ayten and Anneloes, thanks for our close co-operation. Dear roommates, we spent a lot of time together throughout my last few months before the finish of this thesis. All your help, advises and support for my thesis and private life has been very much appreciated. Thank you very much for the good time and creating a stimulating, cozy working atmosphere.

I would like to mention three friends in particular. Dear Felicie, Ingrid and later Tjarda, It started back in Groningen, Fauve, Oosterstraat, blue spaghetti and it continued later on in Amsterdam. Thanks for your unconditional interest, warmth and willingness to listen and support. I am sure that our friendship will last forever! Ing, I hope you will be with us today while breastfeeding. Fee, you will be a wonderful paranimf today. Tjarda, great that you came all the way from Baltimore to be my paranimf and I wish you all the best with finishing your own thesis. I would like to thanks my friends, family and brothers for their interest in my research and their support and confidence over the last few years. I would like to thank my parents in particular. Your love and trust have always supported me throughout the years. Lastly, dear Paul, together we took the challenge to live and work in New York, you were at the base, and you have always encouraged me to get to the finish today. This is not the end, this is not the beginning of the end, this is just the end of the beginning! I would like to thank you for all you have given me.

Karolien Dijkstra  
Utrecht, mei 2002

## Curriculum Vitae

Karolien Dijkstra was born in Varsseveld (the Netherlands) on September 9, 1968. She finished her high school (V.W.O.) at the Gemeentelijke Scholengemeenschap Doetinchem in 1987. She started medical school at the University of Groningen in 1988 and throughout her years at medical school she got more familiar with scientific research in the field of obstetrics and gynecology. After finishing medical school in 1993 she followed her internships at the Free University of Amsterdam, which lead to her final medical degree in March 1996. In the meantime she had initiated research activities at the New York University Medical Center with Prof. Dr. C.J. Lockwood as principal investigator. This two-year research period in New York also meant her first step towards this thesis. Between January and July 1998 she worked (as AGNIO) at the department of Obstetrics and Gynecology of the University Medical Center Utrecht. In September 1998 she started her training to become a General Practitioner and registration was obtained in June 2001. Throughout her training for General Practitioner her research activities in the field of preterm birth were never stopped and finally lead to this thesis. Karolien Dijkstra is currently active as (locum) General Practitioner with obstetrics as one of the activities.



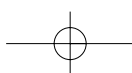
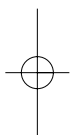
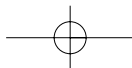
# Stellingen

Behorend bij het proefschrift

“Prediction of Spontaneous Preterm Birth”

Utrecht, 28 mei 2002

Karolien Dijkstra





1. Het is opvallend dat 40% procent van de Nederlandse gynaecologen weeënremmers geeft bij te vroeg gebroken vliezen *zonder* weeën (dit proefschrift)
2. Het langer worden van de cervix na cerclage is niet voorspellend voor een betere uitkomst van de zwangerschap (dit proefschrift)
3. De hogere incidentie van vroeggeboorte bij de negroïde populatie kan mogelijk verklaard worden door een kortere cervixlengte (dit proefschrift)
4. Gynaecologen houden meer van mooie plaatjes dan van biochemische tests; daarom wint de cervixlengte meting van de foetaal fibronectine bepaling (dit proefschrift) en de nekplooi meting van de triple test
5. Vroeg gemeenschap verhoogt de kans op vroeg ouderschap
6. Het consumeren van 1 keer per week vis beschermt vrouwen tegen vroeggeboorte
7. Het aanmoedigen van de verloskundige vaardigheden voor startende huisartsen staat in schril contrast met het ontmoedigen van huisartsen om verloskundig actief te blijven
8. The world is too diverse and beautiful to see it only during your holidays
9. De naam huisarts lijkt - in de 21<sup>e</sup> eeuw - de lading niet meer te dekken; een naamswijziging naar 'eerstelijns gezondheids coach voor allen' is gewenst
10. Te vroeg is nooit te laat
11. Het vervangen van het woord 'spreekuur' in de 'e-mailminuut' is prematuur zolang directe interactie tussen huisarts en patiënt nog gewenst is
12. Het onderscheid tussen luisteren en horen is een wereld van verschil
13. Gezien het feit dat velen New York beschouwen als hemel op aarde, zal 'ground zero' altijd een wolkenkrabber blijven

