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PREDICTION AND PREVENTION OF SPONTANEOUS PRETERM DELIVERY AND PERIPARTUM INFECTIONS BY SCREENING FOR CERVICAL INSULIN-LIKE GROWTH FACTOR-BINDING PROTEIN-1 AND BACTERIAL VAGINOSIS IN PREGNANCY

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ACADEMIC DISSERTATION

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List of original publications

This thesis is based on the following articles, which are referred in the text by the Roman numerals I to IV.

I Kekki M, Kurki T, Pelkonen J, Kurkinen-Räty M, Cacciatore B, Paavonen J. Vaginal clindamycin in preventing preterm birth and peripartal infections in asymptomatic women with bacterial vaginosis: a randomized, controlled trial. Obstet Gynecol 97:643-648, 2001.

II Kekki M, Kurki T, Paavonen J, Rutanen E-M. Insulin-like growth factor-binding protein-1 in cervix as a marker of infectious complications in pregnant women with bacterial vaginosis. Lancet 353;1494, 1999.

III Kekki M, Kurki T, Kärkkäinen T, Hiilesmaa V, Paavonen J, Rutanen E-M. Insulin-like growth factor-binding protein-1 in cervical secretion as a predictor of preterm delivery. Acta Obstet Gynecol Scand 80;546-551, 2001.

IV Kekki M, Kurki T, Kotomäki T, Sintonen H, Paavonen J. Economic evaluation of screening and treatment for bacterial vaginosis in early pregnancy among women at low-risk for preterm birth. Submitted.

Abbreviations

ACTH	adrenocorticotrophic hormone
BV	bacterial vaginosis
Ca^{2+}	calcium
CEE	Central and Eastern Europe
CI	confidence interval
CIS	Commonwealth of Independent States
cPVL	cystic periventricular leukomalacia
CRH	corticoid-releasing hormone
CRP	c-reactive protein
DHEAS	dehydroepiandrosteronesulfate
E_1	estrone
E_2	estradiol
E_3	estriol
ECM	extracellular matrix
ELBW	extremely low birth weight
FasL	Fas ligand
fFN	fetal fibronectin
GBS	group B streptococci
G-CSF	granulocyte colony stimulating factor
hCG	human chorionic gonadotropin
HPA	hypothalamic pituitary adrenal axis
H_2O_2	hydrogen peroxidase
IAI	intraamniotic infection
IEMA	immunoentzymometric assay
IgA	immmunoglobulin A
IGFBP-1	insulin-like growth factor-binding protein-1
IL-1	interleukin 1
IL-1-α	interleukin 1-α
IL-1-β	interleukin 1-β
IL-6	interleukin 6
IL-8	interleukin 8

IL-16	interleukin 16
IUGR	intrauterine growth retardation
IVH	intraventricular hemorrhage
LBW	low birth weight
Mab	monoclonal antibody
MMP-1	matrix metalloprotease 1
MMP-8	matrix metalloprotease 8
MMP-9	matrix metalloprotease 9
mRNA	message ribonucleic acid
NEC	necrotizing enterocolitis
NPV	negative predictive value
PDA	persistent ductus arteriosus
PG	prostaglandin
PPROM	preterm premature rupture of the membranes
PPV	positive predictive value
PROM	premature rupture of the membranes
PTD	preterm delivery
PTL	preterm labour
RANTES	regulated on activation, normal T cell-expressed and secreted
RDS	respiratory distress syndrome
RR	relative risk
TNF-α	tumor necrosis factor-α
VLBW	very low birth weight
WHO	World Health Organization

1 Introduction

One of the most important unresolved issues currently confronting obstetricians is the prevention of preterm birth. It is estimated that up to 90% of all mortality among preterm infants without lethal malformations is due to immaturity (Amon 1999). Preterm birth also accounts for the vast majority of both short-term and long-term perinatal morbidity. The major diseases of the preterm infant are due to organ immaturity, with their incidence and severity inversely related to gestational age (Hakulinen 1992). Preterm birth is, worldwide, the most challenging problem in obstetrics, but the prevention of prematurity has been difficult and ineffective because of its multifactorial and partly still unknown etiology (Romero et al. 1994). However, infections alone may be associated with up to 40% of spontaneous preterm births, especially those taking place at an early gestational age (Gibbs et al. 1992). During the past two decades, the association between maternal genital tract infections and ascending infection in the choriodecidual interface leading to preterm birth has been of special interest (Raivio 1989).

The treatment of preterm labor, preterm delivery, and premature birth are not only major problems in obstetrics and pediatrics but also have major economic, psychological, and social impact. Neonatal intensive care is one of the most expensive health care system interventions. Modern perinatal technology and care has, during the 1980`s, increased the survival rate among extremely low birth weight (ELBW) infants in developed countries from 20% to 60%. This favorable development in mortality has led to a concurrent increase in major neurological sequelae including cerebral palsy and mental retardation as long-term consequences, which occur in 10% to 25% of infants born at an early gestational age (Salokorpi et al. 2001).

To improve the outcome of these very preterm neonates, we need to expand our knowledge of the etiology, prevention, and treatment of preterm labor and preterm delivery. Ideally, we need markers to screen general pregnant women as a part of antenatal care to identify those at risk for preterm delivery and focus preventive care on them. We also need to convince policy-makers by performing health-economic analyses. During the past two decades, we have come somewhat closer to knowing the etiology of spontaneous preterm birth, but we still need better markers to identify women at risk for preterm delivery.

2 Review of the literature

2.1 General aspects of prematurity

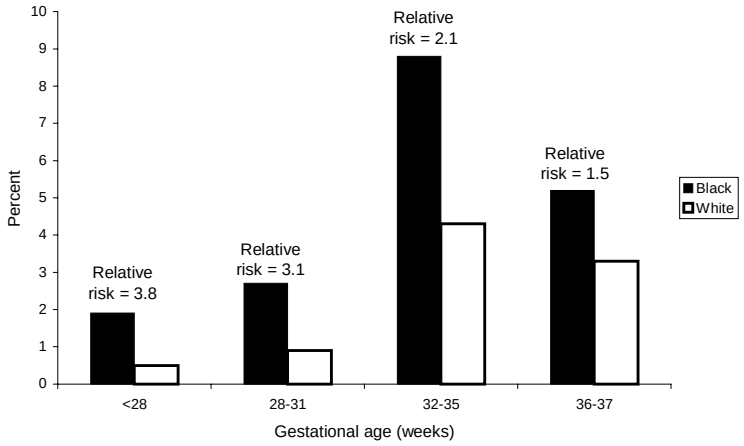
2.1.1 Incidence

The incidence of preterm birth or low birth weight infants varies by country and race and reflects the overall health of a community or nation. Throughout the world, 20% of the mortality among children under 5 years is caused by perinatal conditions (Unicef 2001). Preterm birth is directly responsible for 75% to 90% of all neonatal mortality not caused by congenital malformations (Rush et al. 1976, Amon 1999) and accounts for the vast majority of both short-term and long-term neonatal morbidity. In industrialized countries, only 6% of infants are born with low birth weights, but in the least developed countries 18% (Table 1) (Unicef 2001). In Finland, the incidence of preterm birth in 1998 was 5.3% (Koskinen et al. 1999) and in the United States 11%. Among black women, the rate of preterm deliveries was twice the rate in other women (Blackmore et al. 1995, Guyer et al. 1999). This racial disparity increases by decreasing gestational age (Paneth 1995) (Figure 1). In Mosambique, as an example of an undeveloped country, the rate of preterm deliveries was reported by Osman et al in 2001 to be 15.4% (Osman et al. 2001). The majority of preterm deliveries (80%) happen at 32 weeks of gestation or more, a time when gestational age-specific mortality is 3% to 4%. Neonatal mortality and severe morbidity tend to concentrate in the late second trimester and early third trimester, a period that accounts for only one of six preterm births (Amon 1999).

Table 1. Percent of newborns with low birth weight, 1995-99 (adapted from UNICEF 2001 tables).

Industrial countries	6
CEE/CIS and Baltic States	7
East Asia and Pacific	8
Latin America and Caribbean	9
Middle East and North America	11
Sub-Saharan Africa	15
World	16
Developing countries	17
Least developed countries	18
South Asia	31

Figure 1. Preterm delivery rates in gestational age groupings and by race in the United States in 1991 (reprinted from Paneth, 1995, with permission)



2.1.2 Definitions

According to the The World Health Organization (WHO), preterm labor (PTL) is defined as labor starting before 37 complete weeks of gestation and with intact fetal membranes (WHO 1977). Preterm delivery (PTD) or preterm birth is defined as the birth of a baby before 37 completed weeks of gestation. Rupture of the fetal membranes before the onset of labor is called premature rupture of the fetal membranes (PROM). Using the word preterm (less than 37 week´gestation) (PPROM) or term (more than 37 weeks´gestation) before PROM indicates the presence or absence of fetal maturity at the time of the complication (Romero et al. 1999). Traditionally, pediatricians have defined prematurity as a birth weight of 2,500 g or less; and it is also commonly known as low birth weight (LBW) (Schlesinger and Allaway 1955). This list of definitions has been further expanded with the term ”very preterm birth” (Keirse 1989), or “very low birth weight” (VLBW) which means the birth of a baby before 32 weeks of gestation or at a weight of 1,500 g or less. “Extremely low birth weight” (ELBW) or “very, very low birth weight” (1,000 g or less) also are terms used, and in the literature has also been used the term “incredibly low birth weight” (750 g or less) (Amon 1999). Not all preterm babies are born spontaneously; often labor must be induced before 37 weeks due to maternal or fetomaternal indications: this is defined as “iatrogenic prematurity.”

Of all women giving birth preterm, 30% to 40% experience PROM, 28% to 64% PTL, and 20% to 29% iatrogenic PTD (Meis et al. 1987, Savitz et al. 1991, Romero et al 1999). Furthermore, cervical insufficiency may be associated with 8% to 15% of all preterm births (Parisi 1988). Preterm birth is

a complex syndrome with known or suspected risk factors including biochemical, immunologic, histopathologic, and anatomic factors, and infections (Romero et al. 1994).

2.1.3 Prediction of spontaneous preterm delivery

Traditional methods for identifying women destined to deliver preterm rely on obstetrical history, demographic factors, or symptoms that are neither sensitive nor specific (Main et al. 1985, Newman et al. 1986). Clinical markers commonly used include cervical changes, increasing uterine contraction frequency and vaginal bleeding. These, as well as PTD risk scoring systems based on epidemiological, historical, and clinical risk factors, have proven relatively inaccurate because of poor sensitivity and poor specificity (Copper et al. 1990, Owen et al. 1990, Mercer et al. 1996). More specific and sensitive tools are needed to identify those pregnant women who are at risk for preterm birth in order to better target efforts to prevent PTD. Recent approaches in finding better clinical markers to predict preterm birth have focused on lower genital tract infections ascending to the upper genital tract and leading to intrauterine infections, and have focused on cervical biochemical markers and cervical ultrasound.

2.1.3.1 Risk factors

Traditional risk factors for preterm birth include multiple pregnancy, pre-eclampsia, fetal growth retardation, fetal malformations, and history of previous preterm birth (Keirse et al. 1978, Bakketeig et al. 1979, Hakala 1987, Hartikainen-Sorri and Sorri 1989, Alexander and Keirse 1989, Meis et al. 1995a, Meis et al. 1995b, Mercer et al. 1996) (Table 2). Black women have higher risk than do white women for PTD (Wen et al. 1990, Blackmore et al.1995, Mercer et al. 1996). Significant independent associations with preterm birth have also been found for early- and late-pregnancy bleeding, low maternal weight (<55kg) at 20 weeks of gestation, both low and high maternal age (<18 years and >35 years), nulliparity and multiparity, smoking (dose-dependent), low or high hemoglobin concentration, history of previous abortion (spontaneous or induced), bacteriuria, low social class, drug use and physical trauma, a discrepancy of more than +7 days between menstrual and scan dates in the midtrimester dating scan, maternal stress, heavy or stressful work, prolonged periods of standing, and uterine irritability (Papiernik and Kaminski 1974, Klebanoff et al. 1991, Henriksen et al. 1995, Roberts et al. 1995, Meis et al 1995, Mercer et al. 1996, Copper et al. 1996, Holland et al. 1997, Gardosi and Francis 2000). Spontaneous PTD occurs in 11% to 37% in the

presence of uterine malformation (Heinonen 1997). The etiology of PTD can also in some cases be genetic, as women who themselves have been born preterm have been shown to have an increased risk for PTD (Porter et al. 1997).

Although it is possible to develop graded risk assessment systems that include factors associated with spontaneus PTD, such a system does not identify most women who subsequently develop spontaneous PTD. These complicated risk-scoring systems have relatively low sensitivities (18-24%) and positive predicitive values (PPV) (29-33%) (Mercer et al. 1996). Furthermore, with these traditional risk factors, it is possible to identify only 20% of all preterm births; 35% of women giving birth preterm will exhibit no predisposing factors (Hakala et al. 1989). For example, a history of prior preterm birth or births is known to be one of the strongest risk factors for PTD, with a relative risk of up to 6.7 (Bakketeig et al. 1979), but these women with a history including the identifiable risk factor of previous PTD account for only 10% of the overall prematurity problem (Bloom et al. 2001).

Table 2. General risk factors for preterm birth and for spontaneous preterm birth in Finland (Hartikainen-Sorri 1989, Hakala 1987*).

	Preterm birth in general		Spontaneous preterm birth	
Risk factor	OR	95% CI	OR	95% CI
Previous abortions 1. Two or more 2. Previous induced abortion	1.5 1.4* 1.1	0.8-2.8 1.2-1.7 0.5-2.2	1.3 1.2	0.6-2.6 0.6-2.8
Previous perinatal deaths	1.6 1.6*	0.3-8.3 1.1-2.3	1.3	0.2-12.0
Low social class	1.2 1.2*	0.8-1.8 1.1-1.4	1.2	0.8-2.0
Unmarried status	2.0 1.4*	1.0-4.1 1.2-1.6	1.4	0.6-3.3
Employment	0.9	0.5-1.5	0.9	0.5-1.6
Urinary infection during pregnancy	1.7	0.8-3.7	1.1	0.5-2.5
Medicated hypertension during pregnancy	7.3	2.3-23.6	4.2	0.9-19.2
Current smoking	2.4 1.3*	1.3-4.5 1.1-1.5	3.4	1.6-7.2
Intrauterine growth retardation	3.9	2.0-7.6	2.44	1.1-5.4
Fetal malformation	5.2	2.2-12.2	5.5	1.9-16.0
Preterm contractions	3.5*	3.1-3.9	-	-
Multiple pregnancy	8.4*	6.9-10.3	-	-
Previous premature delivery	3.6*	2.8-4.7	-	-
Bleeding	2.1	1.8-2.5	-	-
Late admission to antenatal care	2.0*	1.6-2.4	-	-
Primiparity	1.3*	1.1-1.4	-	-
Age > 35 years	1.4*	1.1-1.7	-	-
Abnormal growth of the fetus or the uterus	1.7*	1.4-2.1	-	-

2.1.3.2. Clinical examination

2.1.3.2.1 Digital examination of the cervix

Abnormal cervical function during pregnancy may result in a pregnancy loss or premature birth. One universally recognized cause of spontaneus second trimester abortion and premature birth is cervical incompetence, which is divided into primary (congenital weakening) and secondary cervical weakening (acquired weakening of the cervix asscociated with gynecologic and obstetric procedures) (Sonek et al. 1993). Traditionally, diagnosis of cervical incompetence has been done by digital examination and Bishop score, a composite measure that assigns a score of 0 to 3 points to each of five features of the cervix: length, dilatation, position, consistency, and station of the presenting part (Bishop 1964). The Bishop score is widely used and economical but is poorly reproducible, suffering from large interobserver variation (Holocomb and Smeltzer 1991). The prediction of PTD with the Bishop Scoring system has high specificity and high negative predictive value (NPV) in asymptomatic pregnant women but rather low sensitivity (7.9-42.5%) and low positive predictive value (PPV) (9.1-38.5%) (Iams et al. 1996, Iams et al. 2001) (Table 3). Sensitivity (38-83%) in the prediction of PTD with digital examination is, however, better in women with PTL (Table 3), but compared to digital examination of the cervix, the ultrasonographically detected short cervix has higher sensitivity (81-100%) in the prediction of PTD in women with PTL (Iams et al. 1994, Crane et al. 1997).

Table 3. Performance of digital cervical examination in predicting PTD

Reference	Cut-off	Patient	Sensitivity	Specificity	Positive predictive value	Negative predictive value	
Symptomatic women							
Crane et al 1997	Dilatation ≥ 1.5 cm 23-33 wk	136	38%	94%	70%	80%	OR 1.55 (0.63-3.81)
"	Effacement ≥ 50%	136	78%	43%	34%	84%	OR 1.00 (0.97-1.02)
Iams et al 1994	Dilatation ≥ 2 cm 24-35 wk	48	62%	39%	40%	61%	
"	Effacement ≥ 50%	48	83%	39%	48%	78%	
Asymptomatic women							
Iams et al 1996	Bishop score ≥ 6 24 wk Bishop score ≥ 4	2915	8% 28%	99% 91%	39% 12%	96% 97%	
"	Bishop score ≥ 6 28 wk Bishop score ≥ 4	2351	16% 43%	98% 83%	26% 10%	96% 97%	
Iams et al 2001	Bishop score ≥ 4	2107	23%	93%	9%	98%	RR 3.6 (2.1-6.3)

2.1.3.2.2 Examination of the cervix by ultrasound

Attempts to detect cervical changes even prior to the time when changes are evident on digital examination by use of real-time ultrasonography have been relatively successful. Compared with digital examination of the cervix, vaginal ultrasonography is a more accurate, objective and noninvasive method in predicting PTD (Iams et al. 1994, Gomez et al. 1994, Crane et al. 1997). The use of vaginal ultrasonography has made the diagnosis of cervical length more accurate without the confounding influence of bladder filling in transabdominal ultrasonography (Andersen et al. 1990, Soneck et al. 1990). The funneling phenomenon of the cervix has been proven to have some predictive value for PTD with women both symptomatic (sensitivity 22-100%, PPV 44-59.5%) (Timor-Tritsch et al. 1996, Gomez et al. 1994) and asymptomatic for PTD (Iams et al. 1996, Taipale and Hiilesmaa 1998), although the sensitivities (10-32.5%) and PPV´s (11.6-36%) are low in studies of an asymptomatic population.

Studies of an asymptomatic general pregnant population have shown shortened cervical length to be predictive for PTD, although with low PPV`s (6- 47.6%) (Tongsong et al. 1995, Iams et al 1996, Taipale and Hiilesmaa 1998, Hassan et al. 2000, Iams et al. 2001) and sensitivities (8.2-69.9%) (Table 4). Shortened cervical length and funneling together at 18 to 22 weeks of gestation in an asymptomatic pregnant population did not better the sensitivity (29%) for PTD < 35 weeks of gestation (Taipale and Hiilesmaa 1998) (Table 4) and might therefore not be useful for screening purposes for the prediction of PTD. In a study, however, of a asymptomatic but high-risk pregnant population with previous PTD < 32 weeks of gestation, shortened cervical length measured with ultrasonography at 16 to 19 weeks of gestation showed a better PPV of 75% but still a rather low sensitivity of 19% (Owen et al. 2001). Studies with women with PTL and shortened cervical length measured with vaginal ultrasonography have been shown better sensitivities (73-100%) and PPV (46-67%) (Gomez et al. 1994, Iams et al. 1994, Crane et al. 1997, Kurkinen-Räty et al. 2001) (Table 5). In a symptomatic pregnant population, the cervical index measured as (funnel length + 1)/cervical length, has also shown itself to be predictive for PTD with sensitivities of 50 to 76% (Gomez et al. 1994, Kurkinen-Räty et al. 2001).

As a conclusion, because in some studies, sensitivities and PPV are low, data on the value of vaginal ultrasonography alone in predicting PTD are inconsistent.

Table 4. Performance of cervical length in predicting PTD among asymptomatic women with single pregnancies.

Reference	Cut-off	Patient	Sensitivity	Specificity	Positive predictive value	Negative predictive value	
Tongsong et al 1995	< 3.5 cm 28-30 wk	730	66%	62%	20%	93%	LR 1.75 PTD < 37 wk
Iams et al 1996	≤ 3.0 cm 24 wk	2915	54%	76%	9%	97%	RR 3.79 (2.32-6.19) PTD < 35 wk
Iams et al 1996	≤ 3.0 cm 28 wk	2531	70%	69%	7%	99%	RR 5.39 (2.82-10.28) PTD < 35 wk
Taipale et Hiilesmaa 1998	≤ 2.9 cm 18-22 wk + funneling	3694	19 % 29%	97% 97%	6% 7%	ND	RR 8 (3-19) PTD < 35 wk RR 11 (5-23)
Owen et al 2001	< 2.5 cm 16-19 wk	183 High-risk population with previous PTD < 32 wk	19%	98%	75%	77%	RR 3.3 (2.1-5.0) PTD < 35 wk
Goldenberg et al 1998	≤ 2.5 cm 22-24 wk	2929	ND	ND	ND	ND	RR 3.5 (2.7-4.6) PTD < 37 wk
Iams et al 2001	≤ 2.5 cm 24 wk Bishop score ≥ 4	2197	39% 14%	93% 99%	14% 27%	98% 97%	RR 6.9 (4.3-11.1) PTD < 35 wk RR 10.3 (5.6-191)
Hassan et al 2000	≤ 1.5 cm 14-24 wk	6877	8%	100%	48%	97%	OR 24.3 (12.9-45.9) PTD < 32 wk

ND=not done

Table 5. Performance of cervical length in predicting PTD among women in PTL with singleton pregnancies.

Reference	Cut off	Patient	Sensitivity	Specificity	Positive predictive value	Negative predictive value	RR
Gomez et al 1994	< 1.8 cm 20-35 wk PTD < 36 wk	59	73%	78%	67%	83%	3.9 (1.8-8.5)
Iams et al 1994	< 3.0 cm 24-35 wk PTD < 36 wk	48	100%	44%	55%	100%	ND
Crane et al 1997	< 3.0 cm 23-33 wk PTD < 37 wk	136	81%	65%	46%	90%	0.85 (0.8-0.91)
Kurkinen-Räty et al 2001	< 2.9 cm 22-36 wk PTD < 37 wk	77	82%	48%	ND	ND	LR+2.7 (0.8-9.7)

ND=not done

2.1.3.2.3 Uterine contractibility

In the literature, the diagnosis of threatening preterm birth is usually based on the presence of painful, regular uterine contractions at least at 8- to 10-minute intervals, accompanied by cervical changes (Kragt and Keirse 1990). On the other hand, uterine irritability can be defined as frequent, usually painful uterine contractions without demonstrable cervical changes in effacement or dilatation (Roberts et al. 1995). The risk for PTD is higher in women with such uterine irritability than in the general obstetric population (Roberts et al. 1995). Prediction of the risk for PTD based on uterine contractions alone is difficult. First, pregnant women can identify only 15% of contractions demonstrable by tocodynamometry (Newman et al. 1986). Second, those contractions known as Braxton-Hicks contractions are common in uncomplicated pregnancies where delivery takes place at term, but it is difficult to discriminate these contractions from true PTL (Copper et al. 1990, Lockwood and Dudenhausen 1994a). It has been reported that 26% of all pregnant women report uterine contractions before 37 weeks of pregnancy, and the adjusted relative risk for PTD, given the occurrence of symptomatic uterine contractions, ranged from 1.2 to 2.9 between 18 and 36 weeks of gestation (Papiernik et al. 1986). On the other hand, with pregnant women at high risk for PTD, no significant difference existed in contractions among women delivering preterm compared to those delivering at term (Copper et al. 1990).

Home uterine-activity monitoring based on tocodynamometry for the evaluation of uterine contractions at home, combined with daily telephone calls from a health-care practitioner has been proposed as a method for predicting preterm birth in high-risk women. However, the largest study involved 2422 women at risk and showed no improvement in outcome (Dyson et al. 1991).

2.1.3.2.4 Pathologic uterine distension

Conditions associated with pathologic uterine distension include abnormal increase in intrauterine volume, such as multiple gestation and polyhydramnion, or uterine anomalies. Increased interleukin-8 and collagenase expression is associated with mechanical stretch of human fetal membranes (El Maradny et al. 1996). In vitro studies have demonstrated that such mechanical stretching increases synthesis of prostaglandin E_2 in cultured human amnion cells (Kanayama and Fukamizu 1989) and raises the maternal plasma level of prostaglandin $F_{2\alpha}$ (Manabe et al. 1985), which influences cervical maturation and the onset and progress of labor.

2.1.3.2.5 Vaginal bleeding

In predicting PTD, vaginal bleeding is associated with relatively low sensitivity but high PPV value. In the first trimester, a two-fold increased relative risk for PTD resulted from vaginal bleeding (Williams et al. 1991). Such bleeding occurring in the first and subsequent trimester was associated with three-fold risk for PTD (Funderburk et al. 1980, Batzofin et al. 1984, Williams et al. 1991). Heavy vaginal bleeding has been associated with an up to 6-fold increase in PTD in women with of advanced maternal age, with previous spontaneous or induced abortion, in those working during pregnancy, and having certain gynecologic conditions (fibroids, cervical inflammation, ovarian cysts) (Strobino and Pantel-Silverman 1989). Futhermore, recurrent vaginal bleeding has been found to carry a 7-fold risk of PPROM (Harger et al. 1990).

2.1.3.2.6 Infections

Abundant clinical, epidemiological, and experimental evidence exists that urogenital tract infections are associated with preterm birth and that amniochorionic-decidual inflammation is a cause of PTD due to both PPROM and PTL (Gibbs et al. 1992). On the basis of meta-analysis, even asymptomatic bacteriuria increases the risk for PTD (Romero et al. 1989a). Evidence for maternal group B streptococcal genital colonization as a cause of PTL or PTD is inconsistent, with five of six studies finding no significant association (Baker et al.1975, Regan et al. 1981, Minkoff et al. 1984, Hastings et al. 1986, Lamont et al. 1986, Martius et al. 1988). Syphilis (Fiumara 1952), untreated gonorrhea (Elliot et al. 1990), and *Chlamydia trachomatis* (Martin et al. 1982) are associated with PTD, and *Trichomonas vaginalis* has been associated with LBW (Hardy et al. 1984). Finally, the association between BV,-- in which normal vaginal lactobacilli flora is replaced by anaerobic bacteria, especially *Gardnerella vaginalis*, *Prevotella spp*, *Mobiluncus spp*, and *Mycoplasma hominis*-- and PTL, preterm birth, and PPROM is solid (Kurki et al. 1992b, Hay et al. 1994). Preterm birth has also been associated with abnormal vaginal flora (”aerobic vaginitis”) other than BV, including aerobic bacteria like *Eschrichia coli*, GBS, and *Staphylococcus aureus* (Donders et al. 1998). Some prospective studies have, however, failed to show any association between prematurity and vaginal or cervical infections caused by *Mycoplasma hominis* (Harrison et al. 1983), *Trichomonas vaginalis* (Meis et al. 1995c), *Ureaplasma urealyticum* (Carey et al. 1991), *Chlamydia trachomatis* (Harrison et al. 1993), or BV (McGregor et al. 1990a).

Histologic chorionamnionitis, defined as inflammation between the chorion and amnion of the placenta, has been consistently linked with prematurity, LBW, and PROM. It has been detected in 19% to 74% of placentas from preterm deliveries and in 4% to 16% in term deliveries (Russel 1979,

Guzick and Winn 1985, Hillier et al. 1988, Mueller-Heubach et al. 1990). In the etiology of histologic chorioamnionitis, the role of infection has been investigated, revealing that in both preterm and term placentas, micro-organisms can be recovered in 51% to 82% of placentas with histologic chorioamnionitis in contrast to 15% to 45% of those without histologic chorioamnionitis (Pankuch et al. 1984, Svensson et al. 1986, Quinn et al. 1987, Hillier et al. 1988, Zlatnick et al. 1990). The relationship between histologic chorioamnionitis and infection (positive cultures) of the chorionamnion is strongest among PTD cases (Hillier et al. 1988), whereas it is less strong in term placentas (Dong et al. 1987). Clinically, the most significant microbes associated with chorioamnionitis are GBS (Regan et al. 1981, Moller et al. 1984, Bobitt et al. 1985), *Escherichia coli, Prevotella spp* (formely *Bacteroides spp*), *Ureaplasma urealyticum, Gardnerella vaginalis, Peptostreptococcus* (Hillier et al. 1988, Hillier et al. 1991, Romero et al. 1991a), *Fusobacterium* (Chaim and Mazor 1992, Watts et al. 1992), and *Listeria monocytogenes* (Valkenburg et al. 1988). In addition, anaerobic Gram-negative rods are ten times as commonly isolated from the placenta as are aerobic bacteria (Miller Jr. and Pastorek 1986, Romero et al. 1988a). Chorioamnionitis is about four times as likely in patients with PROM as in patients without it (Romero et al. 1988b, Seo et al. 1992, Romero et al. 1992d).

Other infections, such as periodontal disease and systemic infections including pyelonephritis, pneumonia, and peritonitis, are associated with PTL or PTD (Offenbacher et al. 1996, Graham et al. 1993, Madinger et al. 1989, Mazze and Kallen 1991), through the release of endotoxins (Iams et al. 1987, Romero et al. 1988c) and other mediators of inflammation (Romero et al. 1991b). Moreover, microbes may themselves release endotoxins (Sjöberg and Håkansson 1991).

2.1.3.3 Biochemical markers

Various biochemical markers have been suggested as useful in distinguishing true PTL from false labor (Table 6). It now seems clear that neither the measurement of serial plasma, saliva, or estradiol/progesterone, nor of maternal and fetal stress-associated factors (CRH) is useful in predicting PTD in practice (Block et al. 1984, Lockwood et al. 1996). Recent targets in the search for biochemical markers of PTL have been various cytokines and the extracellular matrix (ECM) of the fetal membranes, cytotrophoblast, decidua, or cervix.

Table 6. Some biochemical markers serving as predictors for PTD.

Biochemical marker	Source	Sensitivity (%)	Investigators
Estradiol	Plasma	76	Tamby Raja et al. 1974
Placental protein 5	Serum	33	Salem et al. 1981
PGFM	Plasma	71	Weitz et al. 1986
Relaxin	Serum	25	MacLennan et al. 1986
Estriol/progesterone	Saliva	57	Darne et al. 1987
Estriol	Saliva	51	McGregor et al. 1995a
Major basic protein	Serum	92	Coulam et al. 1987
Collagenase	Serum	76	Rajabi et al. 1987
Hematocrit	Serum	42	Lieberman et al. 1988
CRH	Plasma	80	Wolfe et al. 1988
Isoferritin	Serum	72	Maymon et al. 1989
Ceramide lactoside	Amniotic fluid	82	Hallman et al. 1989
Thromboxane B_2	Urine	57	Noort and Keirse 1990
Oxytocin	Plasma	47	Behrens et al. 1991
Microalbumin	Urine	15	Perry et al. 1993
Nitrite/nitrate	Vaginal fluid	78	Nakatsuka et al. 2000
CRP	Plasma	69	Burrus et al. 1995

2.1.3.3.1 Hypothalamic-pituitary-adrenal (HPA) axis

Maternal and fetal stress are associated with both PTD and activation of the hypothalamic-pituitary-adrenal (HPA) axis. This link between maternal stress and PTD is suggested by the increased prevalence of PTD among unmarried mothers (Harger et al. 1990), pregnant women subjected to major stressful events (Newton et al. 1979), pregnant women with elevated psychological scores for anxiety (Omer et al. 1986), and pregnant women subjectively reporting increased stress and anxiety (Lobel et al. 1992). The link between fetal stress and PTD is suggested by the increased occurrence of placental vascular lesions and intrauterine growth retardation (IUGR) among fetuses of patients delivering preterm without infections or pre-eclampsia (Salafia et al. 1992). In addition, several markers of uteroplacental vascular abnormalities and IUGR are also predictive of spontaneous PTD, including elevated maternal serum alpha-fetoprotein (Burton 1988) and human chorionic gonadotropin (hCG) (Gonen et al. 1992).

Corticotropin-releasing hormone (CRH) comes into the portal circulation from the hypothalamus and mediates pituitary adrenocorticotropin (ACTH) secretion; ACTH enhances adrenal cortisol secretion. CRH also mediates the autonomic, immunological, and behavioral responses of mammals to stress. In addition to expression in the central nervous system, CRH is expressed by trophoblasts in placenta and chorion, as well as by amnion and decidual cells (Saijonmaa et al. 1988). Maternal plasma CRH levels rise during the second half of pregnancy, peak during labor, and decline rapidly postpartum (Lockwood et al. 1996). Activation of the fetal or maternal HPA axis results in enhanced placental CRH production (Petralgia et al. 1991). Other mediators of maternal and fetal

stress, including norepinephrine, angiotensin II, and vasopressin, also enhance CRH release by these cells (Jones et al. 1989, Petralgia et al. 1991, Petralgia 1989). Parturition may be induced by CRH enhancement of prostanoid production by isolated amnion, chorion, and decidual cells (Jones and Challis 1990). Prostanoids stimulate CRH release in isolated placental, fetal membrane, and decidual cells (Jones and Challis 1990, Petralgia et al. 1991), establishing a positive feedback loop to potentiate the PTD process. Prostaglandins act as direct uterotonins, and enhance myometrial receptivity by increasing the number of oxytocin receptors (Neulen and Breckwoldt 1994) and by stimulating formation of gap junctions (Grazul-Bilska et al. 1996). Women subsequently delivering preterm or experiencing PTL have exhibited elevated maternal plasma levels of CRH (Kurki et al 1991a). An assessment, however, of maternal plasma CRH levels in asymptomatic pregnant women found no association with preterm birth (Lockwood et al. 1996).

2.1.3.3.2. Estrogens and progesterone

Premature and/or stress-induced activation of the fetal 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 and is converted by the placenta to estriol (E3) (Siiteri and MacDonald 1966). Estrogens interact with myometrium to enhance gap junction formation (Lye et al. 1993), oxytocin receptor mRNA levels (Bale and Dorsa 1997), prostaglandin $F_{2\alpha}$ activity (Windmoller et al. 1983), and expression of myosin light chain kinases and calmodulin (Matsui et al. 1983). Several studies have shown PTD to be predicted by: elevated maternal plasma estriol (Tamby Raja et al. 1974), elevated salivary estriol (McGregor et al 1995), an elevated salivary estriol- to- progesterone ratio (Darne et al. 1987), and elevated plasma and amniotic estradiol (Mazor et al. 1994).

Progesterone antagonizes in general the effects of estrogens, and its levels rise with advancing gestation (Fuchs and Fuchs 1984). Furthermore, progesterone inhibits IL-8 production by choriondecidual and decidual cells (Kelly et al. 1992). Progesterone may, however, act synergistically with estrogen to promote oxytocin and PG-receptor formation in the myometrium (Fuchs et al 1984). These two hormones may thus play an important role in priming the uterus for labor (Haukkamaa and Lähteenmäki 1979).

2.1.3.3.3 Cytokines

Choriodecidual inflammation leads to activation of various cytokines, thus leading to uterine contractions, cervical changes, and rupture of the fetal membranes (Figure 2; adapted from Lockwood and Kuczynski 1999). The amniotic fluid of women with PTD and coexistent intra-amniotic infections (IAI) displays detectable levels of cytokines such as interleukin 1 (IL-1), tumor necrosis factor α (TNF-α), interleukin 16 (IL-16), and RANTES (regulated on activation, normal T cell-expressed and -secreted) (Romero et al. 1989b, Romero et al. 1992a, Romero et al. 1992b, Athayde et al. 1999, Athayde et al. 2000). The effects of IL-1 and TNF-α are greatly amplified by IL-6, which is secreted by cultured decidual and chorionic cells in response to IL-1 and TNF-α (Lockwood and Kuczynski 1999). Levels of these cytokines from the amniotic fluid correlate with histologic chorioamnionitis (Hillier et al. 1993, Potter et al. 1992). Prostanoid production in cultured decidual, chorionic, amniotic, and myometrial cells, and production of endothelin by amniotic and decidual cells are both stimulated by high concentrations of endotoxin and by IL-1 and TNF-α (Lockwood and Kuczynski 1999). Elevated levels of both prostanoids and endothelin as well as of leukotrienes have been found in amniotic fluid in pregnant women with PTD associated with IAI (Gibbs et al 1992, Romero et al. 1992c). Elevated amniotic IL-6 levels expressed as early as 16 weeks` gestation and increased placental IL-6 expression have been associated with PTD, particularly in the presence of IAI (Romero et al. 1990, Wenstrom et al. 1996). The presence of IL-6 in serum, amniotic fluid, and cervical or vaginal secretions has been linked to chorioamnionitis and PTD (Tables 7 and 8). Elevated cervical IL-6 levels were predictive of half the PTDs in a high- risk population (Lockwood et al. 1994b). Elevated cervical and serum IL-6 levels are strongly associated with preterm birth in the presence of IAI (Greig et al. 1997, Murtha et al. 1996, Rizzo et al. 1996a). Elevated cervical levels of a combination of TNF-α and IL-6 as well as IL-6 and fetal fibronectin (fFN) are associated with spontaneous PTD (Inglis et al. 1994, Goepfert et al. 2001).

Activation of the cytokine network leads to increased placental and membrane apoptosis by a glycoprotein of the Fas ligand (FasL) (Runic et al. 1998). FasL expression is regulated by TNF-α in the human placenta (Guller et al. 1998). Apoptosis of cervical smooth muscle cells appears to play a physiologic role in cervical ripening (Leppert 1995) and takes place in fetal amnion epithelial cells (Lei et al. 1996) and in human fetal membrane cells (Runic et al. 1998), leading to membrane rupture (Fig 2).

Activation of the cytokine network also increases decidual, fetal membrane-, and cervical ECM-degrading protease production. Chorionic and cervical cells activated by IL-1 release collagenases and IL-8 by amniotic, chorionic, decidual, and cervical cells (Fig 2; adapted from Lockwood and

Kuczynski 1999). Both amniotic fluid and cervical IL-8 levels are elevated in PTD, particularly in those with IAIs (Romero et al. 1991b, Potter et al. 1992). IL-8 concentrations in myometrium, decidua, and membranes correlate also with the concentrations of specific collagenases (MMP-8, MMP-9) (Osmers et al. 1995). The combined effect of these proteases is efficient degradation of collagen, laminin, elastin, and fibronectin, which are crucial ECM components of the fetal membranes, decidua, and cervix.

Although markers obtained by amniocentesis, including microbial culture and measurement of cytokines from the amniotic fluid, have better sensitivity and PPV than do the vaginal/cervical IL-6 tests in prediction of PTD, their use is hampered by the fact that amniocentesis is an invasive procedure.

Table 7. Performance of IL-6 in predicting clinical chorioamnionitis

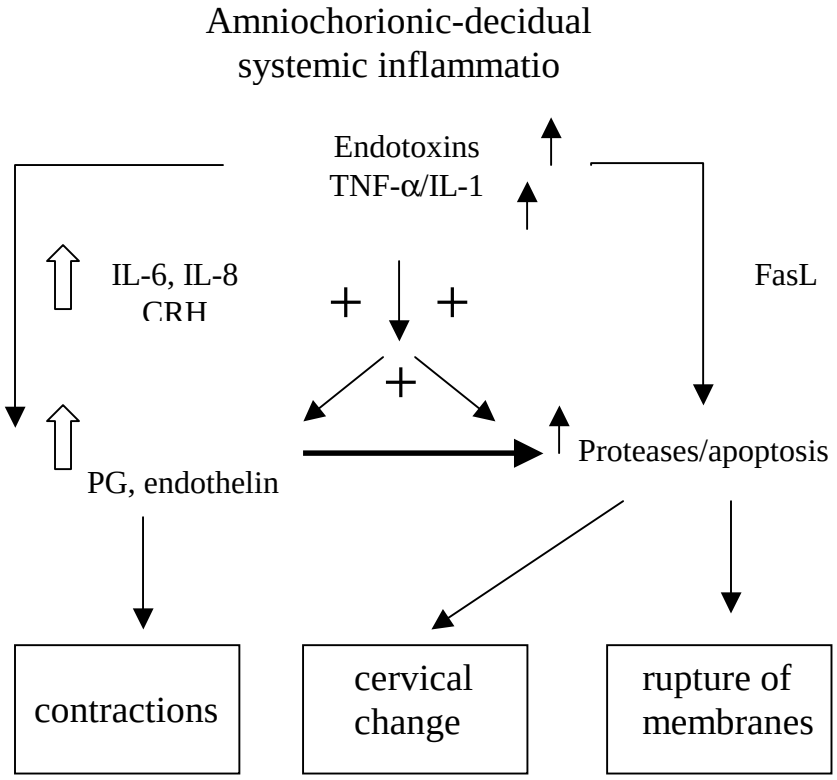
Reference	Patients	Measurements	Sensitivity	Specificity	Positive predictive value	Negative predoctive value	RR
Rizzo et al 1996	N = 92 with PTL, intact membranes	Cervical IL-6 amniotic fluid culture	67%	91%	63%	92%	7.7 (3.3-17.8) for chorioamnionitis
Murtha et al 1996	N = 110 with PPROM 22-34 wk	Serum IL-6	81%	99%	96%	95%	p < 0.0001
Coultrip et al 1994	N = 89 with PTL, intact membranes	Amniocentesis for culture and IL-6 detection	75%	79%	36%	95%	p < 0.005

Table 8. Performance of IL-6 in predicting spontaneous PTD

Reference	Patients	Measurements	Sensitivity	Specificity	Positive predictive value	Negative predoctive value	
Coultrip et al 1994	N = 89 with PTL, intact membranes	Amniotic IL-6 ≥ 6.7 ng/ml	55%	100%	100%	67%	OR 35.07 (3.37-365.4)
Burrus et al 1995	N = 37 with PTL, intact membranes PTD < 34 wk	Cervical fFN > 50 ng/ml Amniotic fluid IL-6 >1500 pg/ml Cervical fFN + amniotic fluid IL-6↑	89% 88% 91%	79% 100% ND	ND	ND	
Lockwood et al 1994a	N = 161 Asymptomatic 24-36 wk	Cervical/vaginal IL-6 < 250 pg/ml	50%	85%	47%	86%	OR 4.8 (1.7-14.3)
Goepfert et al 2001	N = 125 case N = 2929 control asymptomatic 22-26 wk	Cervical IL-6 ↑ Cervical IL-6 + cervicovaginal fFN	20% 20% 32% 8% 23%	90% 92% 92% 98% 96%	SPTD < 35 wk SPTD < 32 wk SPTD < 29 wk PTD < 35 wk PTD < 29 wk	ND	OR 9.4 (1.2-424.0) OR 2.7 (1.0-7.2)

ND=not done

Figure 2. Inflammation leading to activation of the cytokine network, thus leading to uterine contractions, cervical change, and/or rupture of the fetal membranes (adapted from Lockwood and Kuczynski 1999).



2.1.3.3.4 Matrix metalloproteinases and fetal fibronectin

The decidual-amnionchorionic-cervical proteolytic processes induced by inflammation through the activation of the cytokine network lead to breakdown of the ECM of the fetal membranes and cervix. Recently, approaches to the detection of these pathological processes are the release of MMP-1 (Rajabi et al.1987), of MMP-9 (Vadillo-Ortega et al. 1995), and of amnionchorionic fetal fibronectin (fFN).

Fibronectins are glycoproteins found in the plasma and ECM and in amniotic fluid. Plasma fibronectin helps to regulate oncotic pressure, coagulation, and bacterial opsonisation. Fetal fibronectin (fFN) is a unique fibronectin found in the basement membrane near the choriodecidual interface and produced by the fetal membranes. It is an adhesive binding the placenta and membranes to the decidua (Lockwood et al. 1991). Fetal fibronectin can be identified by the monoclonal antibody FDC-6 (Matsuura and Hakomori 1985). As the gestation sac implants and attaches to the inferior of the uterus in the first half of pregnancy, fFN normally occurs in cervicovaginal fluid (Feinberg et al. 1991). On the other hand, after this fusion, the presence of fFN in the cervix or vagina after the 20th week is abnormal and may indicate either mechanical or

inflammatory-mediated disruption of the attachment of membranes to the decidua (Sibille et al. 1986, McGregor et al. 1987). Because fFN is also found in amniotic fluid, its presence in the vagina may also indicate the presence of amniotic fluid in the cervicovaginal secretions (Lockwood et al. 1991, Eriksen et al. 1992). The presence of fFN in cervicovaginal secretions between 20 and 34 weeks` gestation is a strong predictor of PTD in asymptomatic and high-risk women for PTD and in women with PTL (Table 9).

Among low-risk pregnant populations, however, fFN lacks PPV (Goldenberg et al. 1996c) (Table 9). One explanation can be the fact that sperm contains abundant amounts of fFN (Amuller & Riva 1992), and 93% of women have intercourse during pregnancy (Kurki and Ylikorkala 1993). Fetal fibronectin may still be clinically useful, due to the test`s high (96-98%) negative predictive power for both the low and high-risk pregnant population, including women with PTL, in identifying those not in true PTL and therefore not needing admission or treatment (Table 9). The presence of fFN in cervical/vaginal secretions is also predictive of chorioamnionitis related to PTD before 32 weeks´ gestation (Goldenberg et al. 1996d). In the late second trimester, choriodecidual infection is believed to be the major cause of choriodecidual damage, of the subsequent presence of cervicovaginal fFN, and of spontaneous preterm birth (Gibbs et al. 1992, Goldenberg et al. 1996d). The presence of BV-- especially in smokers-- is associated with higher values of cervicovaginal fFN (Goldenberg et al. 1996d, Pastore et al. 1999). As early as between 13 and 22 weeks` gestation, elevated cervicovaginal fFN increases risk for spontaneous PTD, especially in African-Americans with BV (Goldenberg et al. 2000e). Overall, a cervicovaginal fFN value of $\geq$ 50 ng/mL has been used to define women at risk of having PTD, but levels of cervicovaginal fFN as high as 300 ng/mL are associated with increasing risk for spontaneous PTD (Goepfert et al. 2000). Furthermore, the greater the percentage of positive results during gestational weeks 24 to 30, the higher the risk for spontaneous preterm birth (Goldenberg et al. 1997).

Table 9. Performance of fetal fibronectin in predicting spontaneous PTD among asymptomatic women, asymptomatic high-risk women, and women symptomatic for PTD.

Reference	Patients	Measurements	Sensitivity	Specificity	Positive predictive value	Negative predictive value	
Asymptomatic for PTD							
Lockwood et al 1993	N = 429 asymptomatic general population 24-37 wk	PTD < 37 wk Cervical and Vaginal fFN Cut point > 60 ng/ml for cervical > 50 ng/ml for vaginal	73% 68%	72% 80%	25% 30%	95% 95%	OR 8.9 (3.6-22.1) OR 6.0 (2.6-13.7)
Goldenberg et al 1996c	N = 2929 asymptomatic general population	Cervical / vaginal fFN ≥ 50 ng /ml PTD ≤ 34 wk	H 24 23% H 26 22% H 28 20% H 30 29%	97% 97% 97% 96%	25% 20% 17% 18%	96%	RR 8.9 (6.3-12.6) RR51.2 (35.9-97.8)
Goldenberg et al 1996d	N = 2899 asymptomatic general population	Cervical/vaginal fFN ≥ 50 ng /ml every two weeks from 23-24 to 30 wk fFN↑ 4.0%	fFN↑ + PTD <32 wk	100% chorio-amnionitis	ND	ND	OR 16.4 (7.1-37.8)
Faron et al 1997	Asymptomatic, general pregnant population N = 135 at 24-33 wk	Cervical fFN > 50 ng/ml	27%	96%	40%	92%	LR 6.2 (2.0-19.6)
Goldenberg et al 2000b	N = 13 360 asymptomatic general pregnant population at 8-22 wk	Vaginal fFN 13-22 wk ≥ 50 ng /ml for PTD < 28 wk for PTD < 35 wk	 26% 30%	 92% 90%	 ND	 ND	 OR 4.0 (2.6-6.0) OR 2.5 (1.9-3.4)

ND=not done

Asymptomatic, high risk for PTD							
Nageotte et al 1994	High-risk women for preterm birth N = 87 at 24-34 wk	Cervical and vaginal secretion fFN Cut off 50 ng/ml	93%	52%	46%	94%	
Crane et al 1999	Asymptomatic pregnant population 20-24 wk	PTD < 37 wk Vaginal fFN + positive preterm birth risk score	44%	98%	57%	96%	LR 19.4% (5.1-73.8)
Morrison et al 1996	High-risk, asymptomatic women for PTD, N = 145 (multiple gestation, previous PTD, a history of at least two second-trimester abortions, uterine anomaly)	PTD < 34 wk Cervical fFN at 26-28 wk Home uterine contraction assessment + cervical fFN	43% 64%	89% 85%	43% 45%	89% 92%	RR 3.8 (1.5-9.4) RR 5.9 (2.4-14.2)
Symptomatic for PTD							
Iams et al 1995	Women with PTL and intact membranes 24-34 wk, N=192	PTD < 37 wk Cervical / vaginal fFN	44%	86%	60%	76%	ND
Rizzo et al 1996b	Women with PTL and intact membranes 24-36 wk N = 108	PTD < 37 wk cervical fFN ≥ 60 ng / ml Vaginal fFN > 50 ng / ml	81% 74%	84% 87%	79% 81%	85% 81%	OR 21.3 (2.8-42.4)
Bartnicki et al 1996	Women with PTL and intact membranes at 22-35 wk, N = 112	PTD < 37 wk vaginal fFN ≥ 50 ng /ml	67%	90%	79%	83%	OR 19.3 (7.7-48.1)
Peaceman et al 1997	Women with PTL N = 725, singleton pregnancies at 24-35 wk with intact membranes	Cervical fFN ≥ 50 ng /ml Delivery within 7 days 14 days before 37 wk	 90% 88% 44%	 ND	 13% 16% 43%	 100% 99% 87%	 RR 38.8 (9.1-165) RR 31.3 (9.5-103) RR 3.2 (2.4-4.3)

ND=not done

2.1.3.3.5 Insulin-like growth factor-binding protein-1 (IGFBP-1)

Insulin-like growth factor-binding protein-1 (IGFBP-1, previously called placental protein-12 and alpha-1-pregnancy-associated endometrial globulin) is a protein synthesized and secreted by the fetal and adult liver and is a major product of maternal decidualized endometrium (Rutanen et al. 1985, Julkunen et al. 1988). The physiological role of IGFBP-1 in pregnancy may be essential for appropriate endometrial/decidual function and endometrial-trophoblast interaction, both beginning from preimplantation events (Rutanen 1992). Furthermore, IGFs play a role in regulating embryonic and fetal growth and differentation, and IGFBP-1 modulates the actions of IGF in the fetus. In the maternal circulation, the concentration of IGFBP-1 increases during pregnancy and is a major protein in the amniotic fluid (AF) from the second trimester of pregnancy to term (Rutanen 2000). There are negative correlations between cord serum IGFBP-1 and birth weight as well as between maternal serum IGFBP-1 and birth weight (Rutanen 1992).

The phosphorylation status of IGFBP-1 varies among different body fluids and tissues (Jones et al. 1991, Koistinen et al. 1993, Westwood et al. 1994, Martina et al. 1997). In AF, the nonphosphorylated isoform of IGFBP-1 predominates, but all phosphorylated isoforms also exist, except for the highly phosphorylated isoform (Westwood et al. 1994, Martina et al. 1997). The origin of amniotic fluid IGFBP-1 remains unknown. The phosphorylated isoforms of IGFBP-1, including the highly phosphorylated isoform, are predominantly secreted by human decidual cells (Westwood et al. 1994, Martina et al. 1997). Different IGFBP-1 phosphoisoforms and, consequently, the source of IGFBP-1, either decidua or amniotic fluid, can be identified by use of monoclonal antibodies (Rutanen 2000).

Nonphosphorylated and less phosphorylated isoforms of IGFBP-1 in cervical and vaginal samples can be detected by the immunoenzymometric assay using the monoclonal antibody 6305 from Medix Biochemica, Kauniainen, Finland (Rutanen et al. 1996). The detection of these AF isoforms of IGFBP-1 in cervical and vaginal samples is diagnostic for the rupture of fetal membranes (Rutanen et al. 1993, Lockwood et al. 1994c, Rutanen et al. 1996). A rapid strip-test (PROM test, Medix Biochemica) gives a positive test result when AF isoforms of IGFBP-1 in extracted samples are present at concentrations above 25 to 50 μg/L (Rutanen et al. 1996). The highly phosphorylated isoform of IGFBP-1 (phIGFBP-1) is the primary isoform in decidua and is detected by the monoclonal antibody 6303 (Medix Biochemica) (Rutanen et al. 1988). Tissue destruction in the lower uterine segment, whether due to uterine contractions or to infection-induced proteolysis, may cause leakage of choriodecidual products such as fibronectin and IGFBP-1 into the cervix. The presence of these proteins in cervicovaginal secretions may, therefore, be a marker for term and

preterm delivery. In keeping with this hypothesis, i+ncreased levels of decidual phospho-isoforms of IGFBP-1 in the cervical secretion predict cervical ripening at term (Nuutila et al. 1999). In that preliminary study, 10 μg/L was chosen as a cut-off level between positive and negative results after considering the absorption capacity of the dacron swab (150 μg/L) and the extraction efficiency (20-60%) of the protein involved (Nuutila et al. 1999). If the concentration of phosphoisoforms of IGFBP-1 in cervical samples exceeds 100 to 200 μg/L, it probably will give a false-positive PROM test result, and this has to be considered in interpreting the results of the PROM test (Rutanen et al. 1996). Among pregnant women in PTL, elevated levels of cervical phIGFBP-1 predict an increased rate of puerperal and neonatal infectious morbidity (Kurkinen-Räty et al. 2001). As a marker of intrauterine infection, phosphorylated isoforms of IGFBP-1 may predict infection-related problems in pregnancy even more specifically than does fFN, because urine or seminal plasma has only minimal amounts of IGFBP-1 (Rutanen et al. 1993).

2.1.3.4 Combined use of risk factors

The latest achievements in predicting spontaneous PTD have been made by combining obstetrical risk factors with biochemical and clinical markers. For a low-risk asymptomatic primigravid population examined at 22 to 24 week´s gestation, cervical length ≤ 2.5cm detected by ultrasonography and the presence of cervicovaginal fFN ≥ 50 ng/mL showed a sensitivity of 15.6%, a PPV of 50%, a specificity of 99.5%, and a NPV of 94.4% in the prediction of PTD < 35 week´s gestation (Iams et al. 2001). In the same study, cervical length (measured by ultrasonography) < 2.5 cm combined with cervical digital examination evaluated with a Bishop score ≥ 4 had high specificity (98.8%) and NPV (97.4%) but low PPV (27.3%) and sensitivity (14.1%) (Iams et al. 2001). A combination of cervicovaginal fFN ≥ 50 ng/mL and cervical length ≤ 2.5cm detected by ultrasonography at 24 to 26 weeks of gestation with the presence of BV in unselected pregnant women predicted spontaneous PTD before 28 to 30 weeks of gestation in 44% (Goldenberg et al. 2000c). Elevated cervicovaginal fFN levels were associated with elevated cervical IL-6 concentrations and spontaneous PTD in asymptomatic pregnant women (Goepfert et al. 2001).

Of high-risk asymptomatic pregnant women with a history of PTD and a positive cervicovaginal fFN of ≥ 50 ng/mL, combined with a short cervix < 2.5 cm detected by ultrasonography, 65% delivered before 35 week´ gestation (Goldenberg et al. 1998). A combination of these three strongest risk factors (cervical/vaginal fFN, cervical length, and prior PTD) has proven to be

optimal in the prediction of preterm birth, as only 0.5% of women without these risk factors have spontaneous preterm birth before 32 weeks´ gestation (Goldenberg et al. 1998). In asymptomatic high-risk pregnant women, the combination of cervical fFN and home uterine contraction assessment of PTD also improved prediction of PTD before 34 weeks´ gestation (Morrison et al. 1996) (Table 9).

Among women in PTL, combined use of cervical fFN and cervical ultrasonography improves the efficiency of predicting PTD (Rizzo et al. 1996b). Symptomatic pregnant women with elevated cervical fFN and amniotic fluid IL-6 were also more likely to deliver preterm than were those with nondetectable fFN (Burrus et al. 1995) (Table 11). The presence of TNF-α in cervical secretions was associated with a 6-fold increased risk, and the presence of fFN with a 4-fold risk for PTD in women with PTL (Inglis et al. 1994).

Although the combined use of different risk factors might better the prediction of PTD, in clinical practice it is too complicated and expensive.

2.1.4. Prevention of preterm birth

The primary goal in the prevention of PTD is to gain time to improve neonatal outcome by admitting the mother to a tertiary clinic and by giving a full course of glucocorticoid treatment.

2.1.4.1 Surgical

Preterm birth due to suspected cervical insufficiency can be prevented by cervical cerclage, performed either by Shirodkar`s (1955) or MacDonald`s method (1957). In the 1960`s, cerclage resulted in viable live births in 80% to 90% of patients (Seppälä and Vara 1970, Harger 1983). More recent studies have, however, yielded contradictory results. Three studies have reported cerclage as being associated with a significant reduction in the rate of spontaneous preterm birth and with improved neonatal outcome, whereas three other studies have found cerclage to be ineffective (Heath et al. 1998, Berghella et al. 1999, Rust et al. 2000, Hibbard et al. 2000, Novy et al. 2001, Hassan et al. 2001). It is also important to remember that cerclage itself may predispose to complications such as PROM, which may occur in 38% of patients after cerclage (Treadwell et al. 1991, Hassan et al. 2001).

2.1.4.2 Medical

When PTL has begun, the only way to prevent preterm birth is to apply tocolytic therapy. However, tocolytic therapy can only lengthen the pregnancy for up to 48 hours (King et al. 1988, The Canadian Preterm Labor Investigators` Group 1992). Especially women with PTL and increased CRP are less likely to respond to tocolysis than are women with normal or nondetectable serum CRP (Dodds and Iams 1987). Treatment of PTL with antimicrobial therapy is discussed elsewhere (2.2.5)

2.1.4.3 Beta-sympathomimetics

Beta-sympathomimetics include a large group of related compounds such as isoxsuprine, nylidrin, terbutaline, salbutamol, and ritodrine. All of these stimulate myometrial β_2-receptors and thereby inhibit preterm uterine contractions; the most important action is reduction of the availability of intracellular calcium (Lipshitz 1981). All beta-sympathomimetics have the same mode of pharmacological action leading to suppression of preterm uterine contractions in 44 to 86% of cases (Castren et al. 1975, Leveno et al. 1986). In order to achieve adequate serum concentrations, beta-sympathomimetics should be administered by i.v. infusion (Haukkamaa et al. 1985). In patients with an acute episode of PTL, beta-sympathomimetic agents are able to delay delivery for up to 48 hours but do not reduce the incidence of preterm birth or of perinatal morbidity or mortality (King et al. 1988, The Canadian Preterm Labor Investigators` Group 1992). Oral beta-sympathomimetic treatment is of no value in either arresting PTL, improving neonatal outcome, or serving as maintenance tocolytic therapy (Rust et al. 1996). The use of beta-sympathomimetics is associated with maternal cardiovascular side-effects in 24% to 60% of women (Katz et al. 1981). The most severe maternal complications seem to occur when beta-sympathomimetics are infused in association with underlying infection (Hatjis et al. 1988); beta-sympathomimetics can cause fetal side-effects, as well. The most severe side-effects have been reported in newborns with electrocardiographic changes suggestive of myocardial ischemia after having being exposed to as long as 30 days of beta-sympathomimetic tocolysis (Gemelli et al. 1990).

2.1.4.4 Prostaglandin synthetase inhibitors

Large amounts of prostaglandins are synthesized in the fetal membranes, decidua, and myometrium, and some of them are potent oxytotic agents (Mitchell 1981). Prostaglandin synthetase inhibitors are 20% more effective in preventing uterine contractions than are beta-sympathomimetics (Kurki et al. 1991b). Unfortunately, they cross the placenta and may have serious effects on the fetus such as constriction of ductus arteriosus and reduction of the amount of amniotic fluid, limiting the effective use of such inhibitors (Dudley and Hardie 1985).

2.1.4.5 Calcium antagonists

The specific calcium blockers interfere directly with the availability of Ca^{2+} for the contractile process. Calcium-channel blockers include a wide variety of compounds such as nifedipine or verapamil which inhibit or block the influx of extracellular calcium into muscle cells, leading thus to smooth muscle relaxation. Based on a meta-analysis of nine randomized controlled trials, for tocolysis, nifedipine appears to be more effective and better tolerated than beta-agonists, leading to better neonatal outcome (Tsatsaris et al. 2001).

2.1.4.6 Magnesium sulfate

Magnesium sulfate, which acts as a Ca^{2+} antagonist, has been widely used as a tocolytic agent, especially since 1969 in the United States. In Europe, however, magnesium sulfate for arresting preterm contractions has been used very infrequently. Intravenous magnesium sulfate has been shown to halt preterm contractions in 77% of the women treated (Steer & Petrie 1977). Conversely, some data show that magnesium sulfate is no more effective than placebo (Cox et al. 1990). The overall safety and efficacy of magnesium sulfate in term-gestation pre-eclampsia are well established (The Eclampsia Trial Collaborative Group 1995), but recently discussion has arisen as to a possible dose-dependent relationship between fetal toxicity and magnesium used in very preterm labor and mainly as a tocolytic (Mittendorf et al. 1997).

2.1.4.7 Oxytocin antagonists

Oxytocin antagonists block oxytocin receptors competitively without inducing oxytocic effects. Atosiban, an oxytocin receptor antagonist, delays delivery for at least 48 hours longer than does placebo in patients with PTL at a gestational age $\geq$ 28 weeks (Romero et al. 2000). In the same study, the incidence of fetal death at < 24 weeks´ gestation was higher in the atosiban group than in the placebo group. However, an imbalance occurred in the study groups with more women in the atisiban group being of gestational age < 26 weeks and having advanced PTL. Maintenance therapy with atosiban after successful treatment with atosiban of an acute episode of PTL prolonged pregnancy in a placebo-controlled study (Valenzuela et al. 2000). The efficacy of atosiban in the inhibition of PTL is comparable to that of beta-sympathomimetics like terbutaline. In short, the benefit of using atosiban is its placebo-like maternal-fetal side-effect profile compared to that of beta-sympathomimetics (The European Atosiban Study Group 2001).

2.1.5 Neonatal outcome

The major diseases of the preterm infant are due to organ immaturity. These conditions include respiratory distress syndrome (RDS), bronchopulmonary dysplasia, patent ductus arteriosus (PDA), necrotizing enterocolitis (NEC), intraventricular hemorrhage (IVH), hyperbilirubinemia, apnea of prematurity, retinopathy of prematurity, and neonatal sepsis. Their incidence and severity are inversely related to gestational age, which is in general a better predictor of outcome than is birth weight (Keirse 1989, Hakulinen 1992). For accuracy of prediction of infant survival, however, both birth weight and gestational age should be included (Draper et al 1999) (Figure 3).

According to a recent Finnish study, the overall rate of pregnancy complications diagnosed before PTD was 58%, including pre-eclampsia (19%) as an idiopathic cause of PTD, premature rupture of membranes (19%), infection at the time of delivery (30%), and abruptio placentae (7%) (Tommiska et al. 2001). However, infection as a cause of preterm birth may occur at an even higher rate, according to a recent study in which 50% of the neonatal deaths of ELBW infants were ascribed to infections (Barton et al. 1999). Furthermore, intrauterine infection or clinical chorioamnionitis has been implicated as a potential cause of cystic periventricular leukomalacia (cPVL) and the consequent cerebral palsy (Dammann and Leviton 1997, Wu and Colford 2000). Infants at risk for development of brain white matter lesions can be identified by the concentrations of IL-6 and IL-

1β in amniotic fluid (Yoon et al. 1997). Thus prolongation of delivery in cases of intrauterine infection seems to be harmful to the neonate.

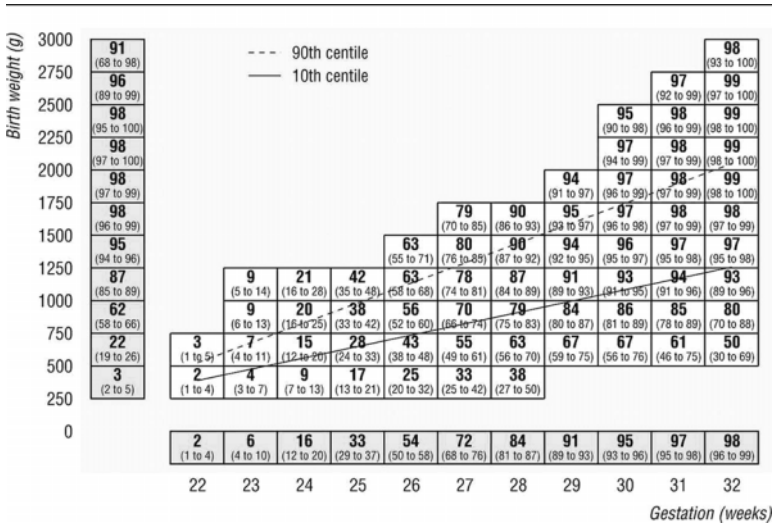
Success in the development of neonatal intensive care for preterm infants in the past 25 years has improved the survival of very low birth-weight infants. Specific therapies to regulate PDA (indomethacin, prostaglandin) and to treat RDS (surfactant therapy) have improved outcomes. A single course of glucocorticoids prior to PTD has led to reduced risk for RDS and incidence of IVH, periventricular leukomalacia, and mortality of the newborn and has improved long-term neurological status (NIH Consensus Development Panel on the Effect of Corticosteroids for Fetal Maturation on Perinatal Outcomes 1995). On the other hand, although the survival of preterm infants (especially EVLBW infants) has improved, the absolute number of neurologically damaged infants has still increased (Stevenson et al. 1998, Vohr et al. 2000).

Place of birth is also important for neonatal outcome, since it is estimated that moving the mother from the standard obstetrical unit to a unit with intensive neonatal care facilities is roughly equivalent to a gain of at least one week in the duration of gestation (Keirse 1989).

Of the preterm infants, 17 to 18% are born ”very preterm,” that is, before 32 weeks´ gestation, including infants of very low birth weight (VLBW), and extremely low birth weight (ELBW). Approximately 82 to 83% are born after 32 weeks` gestation weighing 1,500 g or more (Advance report of final natality statistics 1994). After the introduction of important management strategies in perinatal medicine, such as exogenous surfactant therapy and use of antenatal steroids, the overall survival rate has risen to 80.4% among those born between 22 and 32 weeks´ gestation (Draper et al 1999). According to Draper (1999), the predicted survival of European infants at 22 weeks´ gestation is 2 to 3%, irrespective of size. For those infants of 24 weeks´ gestation, survival ranges from 9% for infants of birth weight 250 to 499 g to 21% for those of 1,000 to 1,249 g. At 27 weeks` gestation, survival ranges from 55% for infants of birth weight 500 to 749 g to 80% for those of 1,250 to 1,499 g (Draper et al. 1999). In a recent Finnish study of ELBW infants weighing < 1,000 g, the survival rate of infants born at 22 to 23 weeks´ gestation was 9% and increased to 60% at 24 to 25 weeks´ gestation (Tommiska et al. 2001). According to that study, birth weight < 600 g and gestational age < 25 are the strongest risk factors for short-term morbidity and death of surviving ELBW infants. With these infants, the incidence rates for RDS, NEC, culture-positive septicemia, IVH, and PDA are 76%, 22%, 22%, 27%, and 46%, respectively. The incidence of IVH as a short-term neurological disorder decreased as gestational age increased, being at 22 to 23 weeks´ gestation 59%, and at 28 to 29 weeks´ gestation 16% (Tommiska et al. 2001). Long-term neurological disorders develop in 60% of ELBW infants up to the age of 4 including 37% with minor

neurological disorders, 19% with cerebral palsy, and 4% with mental retardation (Salokorpi et al. 2001).

Figure 3. Median (95% confidence interval) predicted percentage survival for European infants known to be alive at onset of labor. Values above the 90th centile represent infants large for gestational age, values below the 10th centile infants small for gestational age (reprinted from Draper et al. 1999, with permission).



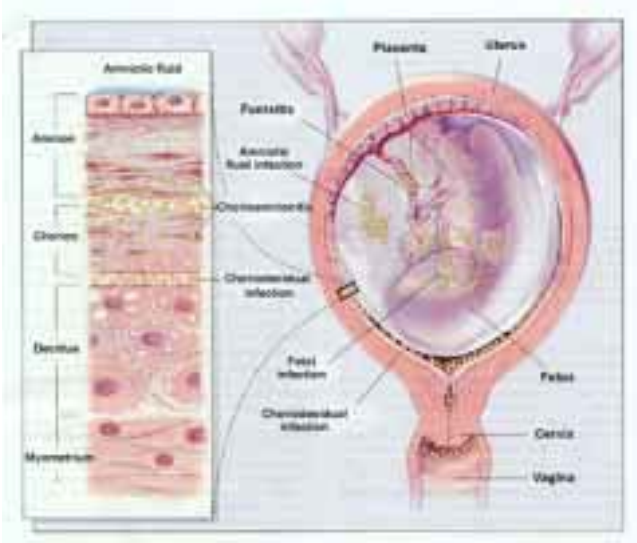
2.2 Infection and prematurity

2.2.1 General

Histologically confirmed bacterial infections within the uterus can occur between the maternal tissues and the fetal membranes (chorioamnionitis), within the placenta (villitis), within the amniotic fluid (amnionitis), or within the umbilical cord or the fetus (funisitis) (Fig. 4) (Goldenberg et al. 2000d). Early data suggest that ascending infection in the maternal genital tract is associated with PROM and PTD (Knox and Hoerner 1950). The first studies linking intrauterine infection to PTD were of *Treponema pallidum* (Fiumara 1952), group-B Streptococci (GBS) (Regan et al. 1981), *Neisseria gonorrhoea* (Amstey and Steadman 1976), *Chlamydia trachomatis* (Martin et al. 1982, Gravett et al. 1986a), *Bacteroides fragilis* (Minkoff et al. 1984), and BV (Gravett et al. 1986b, McGregor et al. 1990b).

Epidemiologically, the risk for PTD is among black women twice that of any other racial group in the United States, with an even greater discrepancy in the rate of very early PTD (Goldenberg et al. 1996a). More black women also have BV (29-41%), histologically or clinically diagnosed chorioamnionitis, and postpartum endometritis (Hay et al. 1994, Fiscella 1995, Goldenberg et al. 1996b, Goldenberg et al. 1998). In all women, infection is also more likely to cause PTD before 30 weeks` gestation than at 34 to 36 weeks` gestation, as shown by histologic examination of the fetal membranes at delivery (Russel 1979, Chellam and Rushton 1985, Mueller-Heubach et al. 1990), and by studies of amniotic fluid from women in labor with intact membranes (Watts et al. 1992) and by studies of fetal membranes from women with intact membranes who undergo Cesarean section (Cassel et al. 1993). Evidence also exists of an association between BV and chronic intrauterine plasma-cell endometritis in nonpregnant women; thus it is possible that the intrauterine colonization associated with spontaneous PTL is present at conception (Korn et al. 1995).

Figure 4. Potential sites of bacterial infection within the uterus (reprinted from Goldenberg et al. 2000d, with permission).



2.2.2 Pathways and mechanisms causing preterm delivery due to infection

It has been calculated that in over 90% of patients with amniotic fluid infection, microbes originate from the vagina and the cervix. However, bacteria may also in 1% to 2% of cases invade the uterus by migration from the abdominal cavity through the fallopian tubes, by inadvertent needle

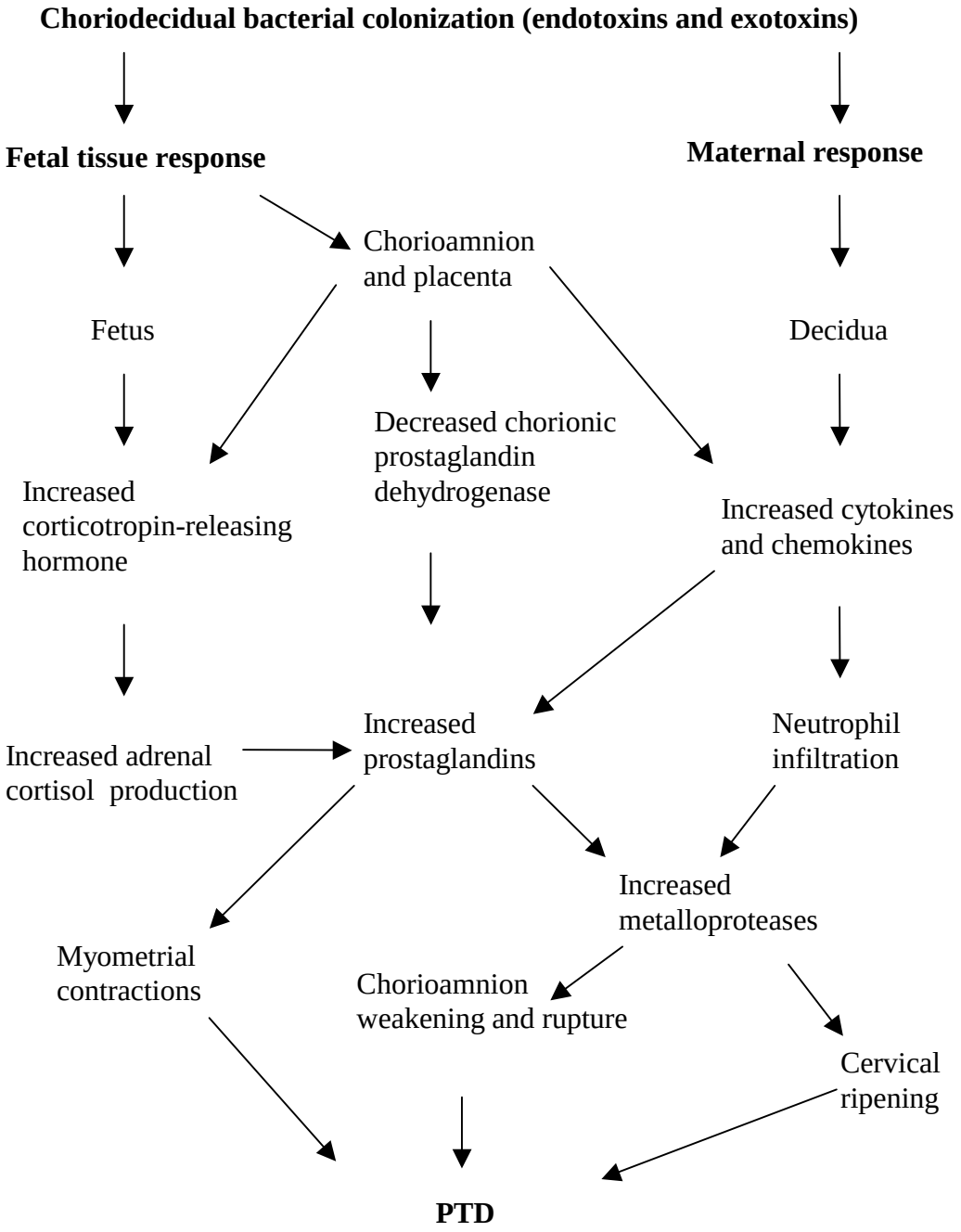
contamination at the time of amniocentesis, or by chorionic-villus sampling and hematogenous spread through the placenta (Romero et al. 1988b).

Bacterial invasion of the choriodecidual space, acting in part through release of endotoxins and exotoxins, activates the decidua and the fetal membranes to produce a number of cytokines, including TNF-α, interleukin-1-α (IL-1-α), interleukin-1-β (IL-1-β), interleukin-6 (IL-6), interleukin-8 (IL-8), and granulocyte colony-stimulating factor (G-CSF) (Lockwood and Kuczynski 1999, Goldenberg et al. 2000d) (Fig. 5). Furthermore, cytokines, endotoxins, and exotoxins stimulate prostaglandin synthesis and release and also initiate neutrophil chemotaxis, infiltration, and activation, culminating in the synthesis and release of metalloproteases and other bioactive substances. The prostaglandins stimulate uterine contractions, while the metalloproteases attack chorioamniotic membranes, leading to rupture of these fetal membranes. The metalloproteases also remodel the collagen in the cervix by softening it (Goldenberg et al. 2000d).

Prostaglandin dehydrogenases in chorionic tissue inactivate prostaglandins produced in the amnion, preventing them from reaching the myometrium and there causing contractions. Under infectious conditions in the chorion, an increasing amount of prostaglandins reaches the myometrium, causing contractions (Fig. 5) (Goldenberg et al. 2000d).

With infected fetuses, an increase in both fetal hypothalamic and placental production of corticotropin-releasing hormone causes an increase in fetal corticotropin secretion, leading to increasing fetal adrenal production of cortisol. The increase in cortisol secretion in turn increases the production of prostaglandins, leading to myometrial contractions (Yoon et al. 1998). Time to delivery has been shown to be 48 to 72 hours in 88% of the cases in which the fetus is infected and fetal production of cytokines is increased (Romero et al. 1998).

Figure 5. Potential pathways from choriodecidual bacterial colonization to PTD (adapted from Goldenberg et al. 2000d).



2.2.3 Microbiology

2.2.3.1 Bacterial vaginosis

Bacterial vaginosis (BV) is defined as a significant change in the vaginal ecosystem balance due to polymicrobial overgrowth of bacteria in the vagina and a decrease in hydrogen peroxidase (H_2O_2)-producing *Lactobacilli* species. BV can cause local genital symptoms (amine odor and increased

amounts of discharge) and upper reproductive tract infections (Spiegel et al. 1980, Amsel et al. 1983, Paavonen et al. 1987, Eschenbach et al. 1988). Normally H_2O_2-producing *Lactobacilli* spp. predominate in the vaginal flora, and other bacteria account for only 10% of the vaginal bacterial species, including facultative aerobes such as *Staphylococcus epidermidis*, *Streptococcus* spp., and *Gardnerella vaginalis, Mycoplasma hominis,* and *Ureaplasma urealyticum* as aerobes, and anaerobic organisms including *Prevotella* spp. (formely *Bacteroides* spp.) and *Peptostreptococcus* spp. (Spiegel et al. 1980, Amsel et al. 1983, Paavonen 1983, Giorgi et al. 1987, Eschenbach 1989, Mårdh 1991, Spiegel 1991, Hillier and Holmes 1999). H_2O_2-producing lactobacilli are toxic to *Gardnerella vaginalis* and *Prevotella,* thus playing an important role in maintaining a healthy vaginal ecosystem (Mårdh and Soltez 1983, Redondo-Lopez et al. 1990).

BV is characterized by 1) decreased or absent *Lactobacillus* spp., 2) increased concentrations of *Gardnerella vaginalis,* and 3) increased concentrations of potentially pathogenic bacteria, including *Prevotella* spp., *Peptostreptococcus* spp., *Porphomonas* spp., *Mobiluncus* spp., *Ureaplasma urealyticum,* and *Mycoplasma hominis* (Spiegel et al. 1980, Paavonen et al. 1983, Eschenbach 1989, Spiegel 1991, Hillier and Holmes 1999).

BV is associated with elevated vaginal pH and increased vaginal fluid concentrations of diamines, polyamines, and organic acids (Chen et al. 1979, Amsel et al. 1983, Pybus and Onderdonk 1997, Hillier and Holmes 1999). Increased pH tends to displace lactobacilli from vaginal epithelial cell receptor sites and to maximize adherence of *Gardnerella vaginalis* (Mårdh and Soltez 1983, Peeters and Piot 1985, Redondo-Lopez et al. 1990). Amino acids produced by *Gardnerella vaginalis* are utilized by *Prevotella spp.* to produce ammonia and short-chain fatty acids such as succinate and isovalerate. This synergistic relationship between *Gardnerella vaginalis* and BV-associated anaerobic bacteria is demonstrated by increased production of amines, putrescine, cadaverine, and trimethylamine (Chen et al. 1979). The growth of *Gardnerella vaginalis* is further enhanced by the presence of ammonia which is produced during growth by *Prevotella spp* (Pybus and Onderdonk 1997).

In the vaginal fluid of women with BV, a number of bacterial virulence factors occur in high concentrations, including endotoxin (lipopolysaccharide), mucinases, sialidase, IgA proteases, collagenase, nonspecific proteases, and phospholipase A_2 and C, as well as host inflammatory products including interleukin-1α, and the prostaglandins E_2 and $F_2\alpha$ (McGregor et al. 1986, Glasson and Woods 1988, McGregor et al. 1991, McGregor et al. 1992, Platz-Christensen et al. 1992, Platz-Christensen et al. 1993, McGregor et al. 1994). Mucinase and sialidase may disrupt cervical mucus and promote bacterial attachment, facilitating possible passage of microorganisms

and their products into the upper reproductive tract (Glasson and Woods 1988, McGregor et al. 1994). During pregnancy, phospholipase A_2 and C as well as nonspecific proteases may act on cervical and amnionchorion connective tissue and promote cervical ripening and focal amnionchorion weakening (McGregor et al. 1991, McGregor et al. 1992).

BV is a well-documented risk factor for preterm birth. Multiple case-control, cross-sectional, prospective cohort studies demonstrate in the presence of BV an increased risk for PTL with an odds ratio of 1.5 to 2.6, for PPROM with an odds ratio up to 2.7 to 6.9, and for preterm birth with an odds ratio of 1.4 to 7.3 (Table 10). BV is most strongly associated with preterm birth at a low gestational age (Hillier et al. 1988). This finding is further supported by associations between BV and second-trimester pregnancy loss (Hay et al. 1994, Llahi-Camp et al. 1996). Furthermore, according to recent studies, women with findings of BV at 16 to 20 weeks´ gestation were at increased risk for preterm birth, even if BV resolved spontaneously (Joesoef et al. 1993, Gratacos et al. 1998).

Table 10. Summary of prospective studies linking BV with preterm birth, preterm premature rupture of membranes, or preterm labor.

Outcome	Study	Weeks of gestation at enrollment	Relative risk (95% CI)
Preterm birth	Kurki et al, 1992b	13 (mean)	7.3 (1.8-29.4)
	Hay et al, 1994	8-17	2.3 (1.0-5.5)
	Fischbach et al, 1988	<16	5.3 (2.0-13.5)
	Joesoef et al, 1993	16-26	5.6 (ND)
	McGregor et al, 1994	16-20	2.0 (1.0-3.9)
	McGregor et al, 1991	16-26	3.8 (1.2-9.1)
	Hay et al, 1994	20-34	3.2 (1.1-9.6)
	McDonald et al, 1992	<24	3.3 (1.5-7.4)
	Hauth et al, 1995	22-28	1.8 (1.0-3.2)
	Hillier et al, 1995	22.9	1.6 (1.3-2.0)
	Meis et al, 1995c	23-26	1.4 (1.2-1.7)
	Meis et al, 1995c	24	1.4 (0.9-2.0)
	Meis et al, 1995c	28	1.8 (1.2-3.0)
	McGregor et al, 1990a	26-30	NS
	Joesoef et al, 1993	28-32	1.5 (0.7-3.0)
Preterm PROM	Kurki et al, 1992b	8-17	6.9 (2.5-18.8)
	Minkoff et al, 1984	13 (mean)	1.5 (0.9-2.6)
	McGregor et al, 1994	16-26	5.7 (0.9-36.1)
	Hillier et al, 1995	23-26	1.1 (0.8-1.6)
	McDonald et al, 1992	22-28	2.7 (1.1-6.5)
Preterm labor	Minkoff et al, 1984	13 (mean)	1.5 (0.8-2.8)
	Gravett et al, 1986a	32(mean)	2.2 (1.3-3.8)
	McGregor et al, 1990a	24 (mean)	2.6 (1.1-6.5)
	Kurki et al, 1992b	8-17	2.6 (1.3-4.9)
	McGregor et al, 1994	16-26	1.5 (0.8-2.6)

CI=confidence interval; ND=not done; NS=not significant

2.2.3.2 Other micro-organisms

In women with spontaneous PTL with intact fetal membranes, the most commonly identified organisms are *Ureaplasma urealyticum*, *Mycoplasma hominis*, peptostreptococci, and *Prevotella spp*, as well as *Gardnerella vaginalis* (Hillier et al. 1988, Gibbs et al. 1992, Andrews et al. 1995, Krohn et al. 1995, Hauth et al. 1998). The micro-organisms that are detected from the placenta and are most often associated with chorioamnionitis after fetal membrane rupture are group B streptococci and *Escherichia coli* (Regan et al. 1981, Moller et al. 1984, Thomsen et al 1987), as well as *Fusobacterium* (Chaim and Mazor 1992, Watts et al. 1992) and *Listeria monocytogenes* (Valkenburg et al. 1988). Polymicrobial infection is present in 32% to 41% of preterm chorioamnionitis cases (Romero et al. 1988a, Romero et al. 1988b, Hillier et al. 1988, Hillier et al. 1991). *N. gonorrhoea* is associated with both PTD and PROM (Amstey and Steadman 1976). The presence of *C. trachomatis* in the cervix has been associated with spontaneous abortion, PTD, PROM, and LBW (Martin et al. 1982, Gravett et al. 1986a, Martius et al. 1988). Other studies have failed to confirm the association between *C. trachomatis* infection and adverse pregnancy outcome (Harrison et al. 1983, Hardy et al. 1984). Studies of whether *T. vaginalis* is associated with preterm birth are conflicting as well, some of them showing a significant increase in PTD, others showing no association (Minkoff et al. 1984, Meis et al. 1995c). Monilial infections are not associated with preterm birth (Meis et al. 1995c). Intrauterine viral infections (adenovirus, cytomegalovirus, Herpes simplex virus, parvovirus) are probably not common causes of spontaneous PTD (Wenstrom et al. 1998).

2.2.4 Markers of infection

Intrauterine infection is often chronic and is usually asymptomatic until labor begins or the membranes rupture. Even during labor, most women who are later shown to have chorioamnionitis (by histologic findings or culture) have no symptoms other than PTL. One of the major challenges in obstetrics, therefore, is identifying women with intrauterine infection. Numerous attempts have been made to find a marker of infection among women at risk for PTD in order to focus efforts on preventing PTD (Table 11).

The best-studied site of infection is the amniotic fluid. As well as containing bacteria, amniotic fluid from women with intrauterine infections has lower glucose concentrations, higher white cell counts, and higher concentrations of complement C3 and various cytokines than those of uninfected women

(Romero et al. 1993a, Elimian et al. 1998). However, detecting bacteria or measuring cytokines and other substances in amniotic fluid requires amniocentesis, and it is not appropriate to obtain amniotic fluid routinely to test for intrauterine infection in women who are not in labor. Obtaining cervical or vaginal secretions is much easier and far safer. BV can be diagnosed reliably by Gram stain (Spiegel et al. 1983, Nugent et al. 1991) or by use of Amsel`s criteria by which BV is diagnosed when at least three of the four criteria are present (homogenous vaginal discharge, white cells ringed by bacteria, an amine odor when vaginal fluid is combined with potassium hydroxide, and pH above 4.5) (Amsell et al. 1983). Choriodecidual basement membrane damage results in leakage of fFN into the cervix and vagina. This protein has high sensitivity but rather low PPV in predicting spontaneous PTD (Table 9). Cytokines (IL-1, IL-6, TNF-α, IL-8, RANTES, IL-16), as well-- as a result of an intrauterine inflammatory process-- have been detectable in vaginal and cervical secretions predicting PTD (Romero et al. 1992a, Inglis et al. 1994, Rizzo et al. 1996a, Rizzo et al. 1998, Athayde et al. 1999, Athayde et al. 2000). High levels of IL-6, TNF-α, and IL-8 in maternal serum have also been shown to predict PTD (Romero et al. 1991b, Inglis et al. 1994, Murtha et al. 1998). High concentrations of granulocyte colony-stimulating factor (G-CSF) in serum in asymptomatic pregnant women have also been found before onset of PTL (Goldenberg et al. 2000b). Other markers of infection include serum C-reactive protein with a sensitivity of 85% in predicting PTD within one week in women with PTL, serum ferritine with an OR of 2.99 for spontaneous PTD, and cervical lactoferrin- although this has very low sensitivity ($p<0.03$) (Dodds and Iams 1987, Tamura et al. 1996, Goldenberg et al. 2000a).

Despite these numerous observations of possible markers in the prediction of PTD, only screening and treatment of BV in pregnancy for those women at high risk for PTD has proven a useful strategy to reduce prematurity (Morales et al. 1994, Hauth et al. 1995, McDonald et al. 1997). According to preliminary findings, screening of BV also in an unselected pregnant population by self-measurement with vaginal gloves to identify increased vaginal pH and subsequent treatment with lactobacilli or clindamycin cream can reduce the rate of PTD, particularly before 32 weeks of gestation ($p<0.01$) (Hoyme et al 2001).

Table 11. Potential markers of intrauterine infection during pregnancy (adapted from Goldenberg et al. 2000d).

Women in labor		
Amniotic fluid	*Cervix or vagina*	*Serum*
Bacteria	Bacterial vaginosis	High G-CSF
Low glucose	High G-CSF	High interleukin-6
High white cell count	High TNF-α	High TNF-α
High G-CSF	High interleukin-1	High C-reactive protein
High TNF-α	High interleukin-6	
High interleukin-1	High interleukin-8	
High interleukin-6	High fetal fibronectin	
Asymptomatic women attending routine prenatal care		
Amniotic fluid	*Cervix or vagina*	*Serum*
High interleukin-6	Bacterial vaginosis	High G-CSF
	High interleukin-6	High ferritin
	High ferritin	
	High fetal fibronectin	

2.2.5 Value of antibiotics in preterm labor, preterm delivery, and neonatal outcome

Preterm PROM (PPROM) precedes preterm birth in 30% to 40% of cases (Romero et al. 1999). According to the Cochrane review of trials of antibiotics in PPROM, antibiotics seem to be of benefit in delaying delivery and in reducting the rate of maternal infection, the rate of neonatal infection, and the numbers of babies requiring neonatal intensive care and ventilation for more than 28 days. They also reduce the need for surfactant (Kenyon et al. 2002). There was also a significant reduction in the number of babies diagnosed with normal cerebral ultrasound scans prior to discharge from the hospital. The most recent trial of antibiotics in PPROM reported that erythromycin seems to be of benefit compared to placebo in the delay of delivery within 48 hours ($p=0.004$), in reducing the rate of neonatal treatment with surfactant ($p=0.05$), reducing oxygen dependence at 28 days of age and older ($p=0.02$), reducing major cerebral abnormalities in ultrasonography before discharge ($p=0.36$), and causing a decrease in positive blood cultures ($p=0.02$) (Kenyon et al. 2001a). Furthermore, treatment with amoxillin and clavulanic acid alone or combined with erythromycin reduced the figures for delivery within 48 hours, but the rate of NEC rose with the use of these antibiotics ($p=0.001$-0.004) (Kenyon et al. 2001a). That study does not, therefore, recommend amoxillin and clavulanic acid for treatment of PPROM, as this antibiotic is known to select for *Clostridium difficile,* a cause of pseudomembranous colitis in adults. Further, the neonatal immature gut is able to absorb any exotoxins that are produced intact, which results in mucosal damage and the initiation of necrotising enterocolitis.

For women with intact fetal membranes and with symptoms of PTD, antibiotic treatment does not usually delay delivery (Oyarzun et al. 1998) or improve neonatal outcome (Gibbs et al. 1997,

Kenyon et al. 2001b). In some other studies, however, antibiotic treatment prolonged the time to delivery and lowered neonatal morbidity as well as maternal infectious morbidity (Norman et al. 1994, Svare et al. 1997, Oyarzun et al. 1998, Kenyon et al. 2001b). A Cochrane meta-analysis of the use of antibiotics with pregnant women in spontaneous PTD with intact fetal membranes showed a decrease in necrotising enterocolitis and a prolonged time to delivery and reduced neonatal sepsis and intraventricular hemorrhage, but also showed a trend towards increase in RDS and overall perinatal mortality (King and Flenady 2002). Thus, antimicrobial treatment for PTD with intact membranes can not be currently recommended for routine practice.

Treatment of BV to reduce the rate of PTD has proven to be succesful in women with a history of PTD and BV diagnosed in the second trimester (Morales et al. 1994, Hauth et al. 1995, McDonald et al. 1997) (Table 12). Successful treatment for these high-risk women has been one week or more on oral metronidazole or oral erythromycin. In an unselected population, treatment of BV with oral clindamycin 300 mg daily for a week was also succesful in reducing the rate of PTD (McGregor et al. 1995b). However, there was no reduction in PTD in women at low risk for PTD when antibiotics were administrated vaginally, or when shorter courses of antibiotics have been used (oral metronidazole two 2-g doses within 48 hours or 400 mg twice a day for 2 days) (McGregor et al. 1994, Joesoef et al. 1995, McDonald et al. 1997, Carey et al. 2000). Two studies show even higher rates of preterm births among BV-positive women treated with intravaginal clindamycin between 16 and 26 weeks of gestation than among placebo-receiving BV-positive women, despite apparently adequate treatment of BV (McGregor et al. 1994, Joesoef et al. 1995). The route and timing of treatment seem to be important factors in preventing preterm birth associated with BV.

Nor has antibiotic treatment for asymptomatic, BV-negative, but high-risk women with a history of PTD with vaginal clindamycin been effective in preventing PTD. Vermeulen et al. have reported even higher rates of preterm births and neonatal infectious morbidity in two studies, suggesting that topical clindamycin can change normal vaginal flora to an intermediate type or lead to BV by suppression of lactobacilli. (Vermeulen et al. 1999, Vermeulen et al. 2001).

Table 12. Summary of controlled BV-treatment trials in prevention of adverse pregnancy outcome

Patients	Outcome	Treated	Control	Relative risk (95% CI)	Reference
Oral antibiotic treatments					
Unselected antenatal patients	Preterm birth	9.8%	18.8%	0.52 (0.3-0.9)	McGregor et al. 1995b
	Preterm labor	1.8%	8.8%	0.2 (0.1-0.7)	McGregor et al. 1995b
	Preterm PROM	3.5%	6.9%	0.5 (0.2-1.4)	McGregor et al. 1995b
	Preterm birth	4.9%	6.1%	0.79 (0.4-1.5)	McDonald et al. 1997
	Preterm PROM	3.1%	3.6%	0.87 (0.37-2.02)	McDonald et al. 1997
	Preterm labor			1.0 (0-81.2)	Carey et al. 2000
Selected patients					
Prior preterm birth	Preterm birth	18%	39%	0.4 (0.2-0.8)	Morales et al. 1994
	Preterm PROM	5%	33%	0.14 (0.03-0.6)	Morales et al. 1994
Prior preterm birth	Preterm birth	9.1%	41.7%	0.14 (0.01-0.84)	McDonald et al. 1997
Prior preterm birth	Preterm birth	39%	57%	0.67 (0.5-0.91)	Hauth et al. 1995
Maternal weight <50 kg	Preterm birth	14%	33%	0.42 (0.18-1.0)	Hauth et al. 1995
Intravaginal antibiotic treatments					
Unselected patients	Preterm birth	15%	7.2%	2.0 (0.7-5.8)	McGregor et al. 1994
	Preterm PROM	5%	4.4%	1.1 (0.2-5.4)	McGregor et al. 1994
	Preterm labor	21.7%	14.5%	1.5 (0.7-3.2)	McGregor et al. 1994
	Preterm birth	15%	13.5%	1.1 (0.7-1.7)	Joesoef et al. 1995

2.3 General aspects of peripartum infections

2.3.1 Incidence and risk factors

The frequency of peripartum infections varies by mode of delivery and by population. In the United States, infectious morbidity including postpartum endometritis and wound infections after Cesarean section range from 36% to 65% and after vaginal delivery from 2.6% to 5.0% (Eschenbach and Wager 1980). In the Nordic countries, the incidence of peripartum infections is lower than reported elsewhere: 5.2% to 9% of parturients after elective Cesarean operations, 16.4% to 25% after unplanned cesaren operations, and 1.5% to 2.4% after vaginal delivery (Rehu and Haukkamaa 1980, Rehu 1981, Hägglund et al. 1983, Guldholt and Espersen 1987). The rate of postpartum endometritis after vaginal twin delivery in Finland was 2.6% vs. 13.1% after Cesarean section (Suonio and Huttunen 1994).

Despite the presence of a wound at a contaminated site, an episiotomy infection is uncommon (Sweet and Ledger 1973). Reports of episiotomy infections are relatively few, ranging from 0.09% to 0.3%, although these rates are probably too low, since mild or late infections that occur after discharge from hospital have not been included. Risk factors related to puerperal infections may be

divided into factors related to general risk for infection, to labor events, and to surgical risk factors (Table 13).

Table 13. Known risk factors for puerperal infection

Related to general infection risk
Anemia
Poor nutrition
Lack of prenatal care
Obesity
Low socioeconomic status
Sexual intercourse during pregnancy
Related to labor events
Prolonged rupture of membranes
Chorioamnionitis
Intrauterine fetal monitoring
Number of vaginal exams during labor
Related to surgical risk factors
Cesarean section
General anesthesia
Urgency of operation
Manual placental removal
Hemorrhage
Forceps delivery
Episiotomy
Lacerations

2.3.2 Definitions, diagnosis, microbiology, and treatment

Puerperal endometritis has generally been defined by the clinical criteria of body temperature $\geq$ 38^0C on two occasions, the first at least 4 hours after delivery, and occurring for at least one day with uterine tenderness or foul-smelling lochia and with no other apparent source of fever (Charles and Larsen 1989, Kurki 1992a, Romero et al. 1993b). However, as many as 44% of cases with puerperal endometritis fail to meet this criterion (Sweet and Ledger 1973). It is also presumed that the pathogenesis and etiology of postpartum endometritis differ by type of delivery and delivery-to-infection interval. Most endometritis among women who deliver by Cesarean section develops within 48 hours postpartum (early-onset endometritis), whereas endometritis in women who deliver vaginally develops later in the puerperium, from 3 days to 6 weeks after delivery (late-onset endometritis) (Wager et al. 1980, Hoyme et al. 1986). Early-onset endometritis is a complex polymicrobial infection in 80% of the cases and is caused almost exclusively by bacteria present normally in the lower genital tract. These microbes include facultative and anaerobic vaginal bacteria, and diseases are most often related to contamination of amniotic fluid and the endometrial cavity with these organisms during labor and delivery (Miller et al. 1980, Romero et al. 1992c,

Soper 1993). *Gardnerella vaginalis* and certain anaerobic bacteria (*Prevotella spp* and *Peptostreptococcus spp*.) have been recovered from the endometrium of 60% of women with early postpartum endometritis (Watts et al. 1989). The presence of BV at the time of delivery has been shown to increase risk for postpartum endometritis six-fold (Watts et al. 1990). In contrast, late postpartum endometritis is more likely to result from ascending infection by *Chlamydia trachomatis*, *Mycoplasma hominis*, or *Ureaplasma urealyticum* (Hoyme et al. 1986). Although endometritis is usually a mild infection responding within few days to antibiotic therapy, infectious complications may result, such as septicemia or septic pelvic thrombophlebitis. Bacteremia has been reported to occur in 2% to 8% of parturients with postcaesarean infection (Spandorfer et al. 1996, Kankuri et al.in press).

Wound infection after Cesarean section is defined as evident redness and tenderness around the skin wound with or without pus formation. Serious complications of abdominal wound infection are bacterial gangrene, necrotizing fascitis, and wound dehiscence (Monga and Oshiro 1993). The organisms most commonly involved in abdominal infections include staphylococci, *E coli*, *Proteus*, anaerobic bacteria, and occasionally group A β-hemolytic streptococci. Treatment includes antibiotics and surgical interventions for serious complications.

Puerperal soft tissue perineal infections are grouped according to depth of infection. A simple episiotomy infection is localized to the skin and superficial fascia within the immediate area of the episiotomy. The wound often opens because of edema and infection; however, the skin erythema and edema occur only adjacent to the episiotomy. Therapy includes surgical debridement of the necrotic fascia and antibiotics. Optimal antibiotic combinations must inhibit both aerobic and anaerobic bacteria (Duff 1993).

2.3.3 Biochemical markers of peripartum infections

So far, very few studies concern biochemical markers and peripartum infections. The presence of fFN in cervix or vagina was not associated with peripartum infections detected at 23 to 24 weeks´ gestation (Goldenberg et al. 1996d). However, the presence of BV was associated with the presence of fFN in cervicovaginal secretions (Goldenberg et al. 1996d). The presence of phosphorylated insulin-like growth factor-binding protein (IGFBP-1) in the cervix has been associated with peripartum infections (Kurkinen-Räty et al. 2001).

2.4 Health economic evaluation

The aim of any health care system is to maximize health and save resources (Drummond et al. 1997). When making decisions about care of individual patients, clinicians need to weigh the benefits and risks as well as consider whether these benefits will be worth the health care resources consumed. Clinicians have to convince colleagues and health care policymakers alike that the benefits of their interventions justify the costs. To become informed about these decisions, clinicians need economic analysis of clinical practices.

Economic analyses have been used in comparing alternative strategies with respect to their resource use and their expected outcomes (Eisenberg 1989, Detsky and Naglie 1990) and in determining regional or national policies (Russell et al. 1996). Ideally, an economic analysis should be perfomed simultaneously with a randomized controlled trial evaluating the clinical effectiveness of a new procedure or treatment (Robinson 1993a). In addition to data from randomized trials as to the efficacy of treatment, estimates from several other studies must usually be included in the analysis. Given the preventive nature of much of obstetrics, many interventions, particularly in the area of prenatal care, have been evaluated to assess their economic utility as well as their clinical effectiveness (Ion 1995). Different methods can be used depending on how outcomes have been assessed (Table 14). In all methods, costs are expressed in monetary units, but the types of analysis differ in their measurement of health consequences.

There are essentially four methods of economic evaluation: cost-minimisation, cost-effectiveness, cost-utility, and cost-benefit analyses (Table 14). Cost-minimisation analysis, the simplest form of cost analysis, compares treatment strategies that have been judged to be similar in their effectiveness. For example one study compared the costs of three alternative hysterectomy methods: abdominal-, vaginal-, and laparoscopically assisted vaginal hysterectomy, the last one being the most expensive (Dorsey et al. 1996).

The principal method of economic evaluation of health care treatments and procedures has become cost-effectiveness analysis (Eddy 1992). This analysis is a method for evaluating the health outcomes and resource costs of health interventions, its central function being to show the relative value of alternative interventions for improving health (Robinson 1993a). The results of cost-effectiveness analysis are expressed as the monetary costs of the program per desired health outcome, for example dollars per pain-free day gained. For cost-effectiveness analysis, it is often useful to construct a decision tree including data on the costs and health outcomes of two or more competing strategies (Sintonen et al. 1997). For example, a cost-effective alternative to

hysterectomy in treating women with essential menorrhagia has been the Levonorgestrel releasing intrauterine system (Hurskainen et al. 2001).

Cost-utility analysis is a special variant of cost-effectiveness analysis. A cost-utility analysis is performed in a fashion similar to cost-effectiveness analysis, but the primary outcome is usually quality-adjusted life years (QALYs) gained, which combines the changes in length and quality of life (Sintonen et al. 1997). This, in theory, allows for comparison of cost-effectiveness ratios across all kinds of conditions and interventions, and also for calculation of the total societal value of different health plans (Nord 1999). Often economic evaluations combine both cost-effectiveness and cost-utility, for example in economic evaluation of the neonatal intensive care of very low birth weight infants (Boyle et al. 1983). In that study, the costs per life year gained had to be included as well as the quality of life, because many of the survivors have permanent handicaps.

In cost-benefit analysis, all costs and health outcomes are valued in monetary terms (Robinson 1993b). This can be problematic, especially in medicine, because of ethical issues in assigning a monetary value to quality of life. Another problem with the application of cost-benefit analysis to medicine is that the economic benefits gained usually are less than the costs of a health program. Health care is expensive and is usually not cost-saving. There are, however, some exceptions to this, involving screening and prevention programs. For example, according to a cost-benefit analysis of smoking cessation programs for pregnant women, for every US dollar spent for smoking cessation in pregnancy, 3.41 USD dollars would be saved (Marks et al. 1990). Similarly, screening for chlamydial infections by a PCR test on first-void urine specimens was cost-saving even in low-prevalence populations (Paavonen et al. 1998).

The quality of analyses varies widely, and attempts to standardize methods have been proposed to enhance the validity of results and to reduce bias (Drummond et al. 1996, Russel et al. 1996, Weinstein et al. 1996). From these sources have come six major and four minor methodologic principles that should be addressed in studies of cost effectiveness or cost benefit (Table 15) (Smith et al. 1998). Cost-effectiveness and cost-benefit analyses are comparative in nature and must include information on the alternatives considered. They must also include the perspective from which the analysis is performed (society, the health care payer, the individual). The outcome measure must be defined to show on what the effectiveness is based. The source and time horizon over which costs are provided must be stated. Inclusion of long-term costs and health outcomes discounting should be used whenever costs and health outcomes occur at any time other than during the base year of analysis. The summary measure that quantifies cost and benefit as a single measure representing the value of an intervention should also be included. All economic analyses are based on estimates of

outcomes and costs, and all have some degree of uncertainty. Performing sensitivity analyses is one method of quantifying the uncertainty of the estimates and should be included in analyses. The purpose of economic analyses is to understand the relative value of one intervention compared with an alternative. Calculating an incremental cost-effectiveness ratio allows for direct comparison of the costs and outcomes of using one strategy, relative to its alternatives (Smith et al. 1998).

Table 14. Types of cost evaluations

Analyses	Basis	Advantages	Disadvantages
Cost minimisation	Compares costs of strategies when treatment outcomes are equivalent	Shows cheaper strategy	Compares only strategies of equivalent efficacy
Cost effectiveness	Compares strategies with different treatment efficacies	Uses costs per outcome e.g. cost per life year saved	Cannot combine morbidity and mortality into one measure
Cost utility	Evaluates treatment strategies by quality of life scales	Measures both morbidity and mortality	Requires empirical judgement of the quality of a patient's life
Cost benefit	Places monetary value on both the costs and benefits of a treatment strategy	Most comprehensive form of economic analysis	Placing monetary value on medical benefits is often difficult

Table 15. The methodological principles of economic evaluations

Major principles
1. Description of comparative options 2. Statement of perspective of analysis 3. Outcome measure defined 4. Cost data provided 5. Inclusion of the summary measure (cost-effectiveness ratio, cost-benefit equation) 6. Assessment of uncertainty performed. Use of sensitivity analysis.
Minor principles
1. Source of cost data provided 2. Inclusion of long-term costs 3. Quantifying time value of money and health outcomes (discounting) at any time other than in the base year of the analysis 4. Calculation of incremental cost-effectiveness ratio

3 Aims of the study

The present studies were conducted to:

1. Investigate the efficacy of intravaginal clindamycin in the treatment of BV and learn whether it reduces the rates of preterm birth and peripartum infections in a low-risk population during pregnancy (I)
2. Study the phosphorylated isoform of IGFBP-1 (phIGFBP-1) in the cervix as a predictor of preterm birth and puerperal infectious complications among asymptomatic pregnant women with bacterial vaginosis (II)
3. Study the phosphorylated isoform of IGFBP-1 (phIGFBP-1) in the cervix as a marker of chorion-decidual tissue damage and a predictor of preterm delivery in women with threatening preterm labor (III)
4. Perform a health economic analysis of screening and treatment of BV during pregnancy in a low-risk-population (IV)

4 Patients and methods

4.1 Patients

In Studies I, II, and IV a total of 5432 pregnant women at low risk for PTD (those women with a history of PTD or with present multiple pregnancy were excluded) were screened for BV during the first antenatal clinic visit at 10 to 17 weeks` gestation between November 1994 and August 1998. Gestational age was confirmed by early pregnancy ultrasound examination. The study centers were the Departments of Obstetrics and Gynecology, University of Helsinki and University of Oulu (17 antenatal clinics), the Health Centers of the City Health Department of Helsinki (7 antenatal clinics) and the County of Vihti (4 antenatal clinics). Of the 565 BV-positive women, 375 signed an informed consent to take part in a randomized, placebo-controlled, double-blind study of treatment of symptomless BV with vaginal clindamycin. The characteristics of the study population are shown in Study I, Table 1, p.645.

Study II included the first 180 consecutive BV-positive pregnant women randomized to this study of BV (I) who provided cervical samples for phIGFBP-1 before any treatment.

Study III included 72 pregnant women who presented at the Department of Obstetrics and Gynecology, Helsinki University Central Hospital, with symptoms of PTL, and 58 asymptomatic women without any history of PTD attending a single antenatal clinic in the County of Vihti. The study took place between November 1995 and March 1996. The characteristics of the study population are shown in Study III, Table I, p. 548.

Study IV concerned probabilities of the BV-positive pregnant women randomized to the placebo-controlled treatment trial (375) and consecutive BV-negative pregnant women (629) screened for BV during the randomized controlled trial. Data on the unscreened pregnant population were collected from three sources. First, the probability of PTD was calculated as a weight probability of the BV-negative (629), and the untreated BV-positive pregnant women (placebo group, 188). The probabilities of most other outcomes were derived from the Finnish Perinatal Statistics 1997 to 1998 (Koskinen et al. 1999) (56 504 parturients). Since the probabilities of the peripartum infections diagnosed after women`s discharge from the hospital are not included in the Finnish Perinatal Statistics, data on peripartum infections in the unscreened population were collected from the records of women who delivered in the county of Vihti in 1999 (210 parturients) to reflect the incidence of late-onset peripartum infections.

4.2 Samples

4.2.1 Bacterial samples (I, II, IV)

During the first antenatal visit between 10 and 17 weeks` gestation, a vaginal smear to detect BV was taken from the posterior vaginal fornix with a cotton swab and Gram stained. During the same visit, cervical specimens for *C. trachomatis* and *N. gonorrhoea* were taken. A repeat vaginal Gram stain was taken one week after the treatment, and again during the third trimester (range 30-36 weeks`gestation).

4.2.2 Biochemical samples (II, III)

Cervical dacron swab samples were taken from the BV-positive pregnant women and women with preterm uterine contractions as well as from asymptomatic pregnant women for a quantitative assay of phosphorylated IGFBP-1 (phIGFBP-1). Cervical dacron swab samples were also taken for the rapid strip-test of amniotic fluid IGFBP-1 (PROM-test) to exclude rupture of fetal membranes among the women with preterm uterine contractions.

4.3. Methods

4.3.1 Microbiological assessment

The slides were examined under oil immersion (x 1000) for Gram stain. Bacteria were quantified according to Spiegel et al. (1983): Scanty (1+) (<1 to 5 bacteria per field), moderate (2+) (6 to 30 bacteria per field) and abundant (3+) (more than 30 bacteria per field). Stain findings were classified into three categories: 1) Normal: The bacteria consisted totally (3+) or mainly (2+) of non-sporing gram-positive rods (Lactobacillus-morphotype), 2) Bacterial vaginosis: Lactobacillus morphotypes were absent or their number was diminished (1+) as compared to other bacteria, especially Gram-negative and Gram-variable rods (Gardnerella-morphotype). 3) Undefinable: Total number of bacteria was small (1+), or bacteria comprised a mixture of different morphotypes, with none dominating. Yeast cells, 2+ or more, were also included in this category.

Cervical swabs were tested by the MicroTrak II Chlamydia EIA (Behring Diagnostics Inc., Cupertino, CA, USA) antigen test for *C. trachomatis*. All enzyme immunoassay-positive samples were confirmed by the direct fluorescent antibody Syva MicroTrak *C. trachomatis* Direct Specimen Test (Behring Diagnostics Inc.).

Cervical swab samples were placed in transpocult media (Transpocult, Oriola Oy, Helsinki, Finland) and cultured for *N. gonorrhoea*.

4.3.2 Immunoenzymometric assays

Two immunoezymometric assays (IEMAs) employing different monoclonal antibodies (Mab) were used to detect different phosphoisoforms of IGFBP-1. Mab 6305 (Rutanen et al. 1988) (IGFBP-1 IEMA TEST, Medix) detects the nonphosphorylated isoforms of IGFBP-1, i.e., those predominating in AF (Rutanen et al. 1996, Martina et al. 1997), and Mab 6303 (Rutanen et al. 1988) (Medix) recognizes the highly phosphorylated isoform of IGFBP-1, the primary isoform in decidua but one not present in AF (Westwood et al. 1994, Martina et al. 1997). Both antibodies bind the lesser phosphorylated IGFBP-1 isoforms (Westwood et al. 1994, Martina et al. 1997).

For these measurements during the cervical examination, two dacron swabs were kept in the cervix for about 15 seconds. Thereafter, each swab was placed in a test tube containing 0.5 ml of extraction buffer and rinsed in this buffer for about 15 seconds (Rutanen et al. 1996). One swab was then withdrawn, and the specimen was used immediately for the immunoezymonetric assay, with monoclonal antibody 6305 as the detecting antibody (PROM test, Medix) (Rutanen et al. 1988, Rutanen et al. 1996): the result was read in 2 to 5 minutes (III). The other specimen was frozen and stored at -20^{o}C until the phIGFBP-1 concentrations were measured (II, III). The dacron swab absorbs about 150μL fluid when saturated, indicating that the average dilution of cervical sample in the buffer is about one to five (Rutanen et al. 1996). The concentraton of phIGFBP-1 in cervicovaginal secretion was measured by immunoezymetric assay with monoclonal antibody 6303 as the detecting antibody (Biochemica) (Rutanen et al. 1988). The detection limit was 0.3μg/L and the intra- and interassay coefficients of variation were 4.6% and 6.4% respectively. All samples were measured in duplicate, with internal controls included in each assay. Considering the absorption capacity of the dacron swab and the extraction efficiency (20-60%) of the protein from it, a concentration of 10μg/L was chosen in preliminary experiments as the cut-off point between a positive and a negative result (Nuutila et al. 1999).

4.4 Outcomes

In this thesis the same diagnostic criteria were employed for prematurity as recommended by WHO (1977). Peripartum infection was defined as postpartum endometritis, postpartum sepsis, Cesarean wound infection, or episiotomy wound infection, all of these diagnosed by standard clinical criteria (Charles and Larsen 1989) and necessitating systemic antimicrobial treatment.

For economic evaluation of the screening and treatment of BV in early pregnancy, only direct costs were included in the model, and unit costs in the decision-tree analysis were calculated in US dollars. The source of unit costs was the Hospital Pricing List of the Helsinki and Uusimaa Hospital District in 2000. The cost of vaginal clindamycin was obtained from the catalogue of Pharmaca Fennica of Finland 2000.

4.5 Drugs

Clindamycin 2% phosphate vaginal cream (Dalacin®, Pharmacia & Upjohn) or an identical-appearing placebo vaginal cream was administered at home once daily for 7 days (I, II, IV).

4.6 Statistical analyses

In Studies I, II, and IV, power analysis showed that approximately 180 patients were needed for each treatment arm to show a three-fold difference in the number of preterm births (i.e., 4% compared with 12%; two-sided test) with 80% power at a P level of 0.05. Odds ratios (ORs) with 95% confidence intervals (CI) were calculated (Morris and Gardner 1989). The treatment results were analyzed according to the intention-to-treat principle (Hollis and Cambell 1999). The interobserver agreement of the Gram stain diagnosis of BV between the study centers was 93%, as tested by kappa statistics (I, II, IV).

In Study III, continuous variables were tested by the Mann-Whitney test. Four-fold tables were analyzed by Fisher`s exact probability test. All tests were two-sided. Multiple logistic regression analysis was applied, with PTD as the dependent variable. The phIGFBP-1 results with several potential confounding variables were entered in the regression model, and the adjusted ORs were calculated. NCSS 2000 software (NCSS Inc., Kaysville, UT, USA) served for these computations.

In Study IV, sensitivity analyses were carried out by changing selected baseline parameter values. The main type of sensitivity analysis was threshold analysis, done by varying the values of one variable with the other variables at their baseline values until the alternative decision strategies (screening vs no-screening) are found to have equal outcomes (e.g., direct costs), with no benefit of one alternative over the other. The values of twelve key variables were varied. In addition, a scenario was created in which screening and treatment would be routine practices.

5 Results

5.1 Vaginal clindamycin in preventing preterm birth and peripartum infections in women with bacterial vaginosis (Study I)

Of the total of 5432 women screened for BV by Gram-stain during their first antenatal clinic visit at 10 to17 weeks´ gestation, the prevalence of BV was 565 of 5432 (10.4%). Altogether 375 BV-positive women were randomized to a double-blind, placebo-controlled trial to receive either 2% clindamycin phosphate vaginal cream or identical-appearing placebo cream once daily for 7 days. At the randomization visit, cervical specimens for *C. trachomatis* and *N. gonorrhoea* were taken. A repeat Gram-stain was done one week after treatment and again at 30 to 36 weeks´ gestation. Overall, 171 women refused to participate in the study, and 19 were excluded for various other reasons: multiple pregnancies (n = 2), history of preterm birth (4), move to another city (8), or induced (1) or spontaneous abortion (4) (Study I, Fig. 1, p. 644)

Ten (3%) of the randomized BV-positive women were positive for *C.trachomatis*. None had *N.gonorrhoea.* The cure rate one week after treatment was 66% (119 of 181) in the clindamycin group. In the placebo group, 34% (62 of 181) cleared spontaneously (OR 1.9, 95% CI 1.3, 2.8).

The overall rate of PTD was 4% (16 of 375): 5% (9 of 187) in the clindamycin group and 4% (7 of 188) in the placebo group (OR 1.3, 95% CI 0.5, 3.5). The overall rate of peripartum infections was 14% (54 of 375). The rate of peripartum infections was 11% (21 of 187) in the clindamycin group and 18% (33 of 188) in the placebo group (OR 1.6, 95% CI 0.9, 2.8) (Study I, Table 1, p. 645).

Bacterial vaginosis persisted in 31% (115 of 375) and recurred in 7% (26 of 375) of the study population. The overall rate of PTD and peripartum infections was almost three times as high in the study groups in which BV persisted or recurred during the pregnancy (40 of 141, 28%) as in the group in which BV was cured (12 of 121, 10%) (OR 2.9, 95% CI 1.3, 5.2). There was, however, no difference between the clindamycin and placebo arms (Study I, Table 2, p. 646). Furthermore, in subgroup analysis among women who completed both follow-up visits, the rate of PTD was 15% (4 of 26) for those in whom BV recurred, but only 2% for those in whom BV did not recur (OR 9.3, 95% CI 1.6, 53.5) (Study I, Table 3, p. 646).

5.2 Insulin-like growth factor-binding protein-1 as a marker of infectious complications in pregnant women with bacterial vaginosis (Study II)

As a part of the randomized placebo-controlled, double-blind study of treatment of symptomless BV with vaginal clindamycin during pregnancy (Study I), cervical swab samples were taken for the detection of phIGFBP-1 before any treatment from 180 consecutive BV-positive women at 10-17 weeks´ gestation. Concentrations of phIGFBP-1 were measured by immunoenzymetric assay, and a concentration of 10μg/L was used as a cut-off for a positive test.

Of the 180 BV-positive women, 42 had a positive test result and 138 a negative test result for phIGFBP-1 in cervical swabs. The rate of peripartum infections, including one with a preterm birth, was 33% (14 of 42) in phIGFBP-1-positive women and 12% (16 of 138) (without preterm birth) in phIGFBP-1-negative women (OR 2.9, 95% CI 1.3, 6.4). Among the women in whom BV was cured, but who had a positive cervical phIGFBP-1 test result before treatment, infectious morbidity was 35% (6 of 17), compared with 4% (2 of 47) among women with negative pretreatment cervical phIGFBP-1 (OR 8.3, 95% CI 1.5, 45). Among the women in whom BV was not cured (persistent or recurrent BV) and who had positive cervical phIGFBP-1, the infectious morbidity rate was 32% (8 of 25), compared with 15% (12 of 91) among women with negative cervical phIGFBP-1 (OR 2.1, 95% CI 0.8, 5.5).

Treatment with vaginal clindamycin had no effect on outcome. If cervical phIGFBP-1 was positive, infectious complications occurred in 33% (7 of 21) in both the clindamycin and the placebo group. If cervical phIGFBP-1 was negative, infectious complications occurred in 8% (6 of 71) and in 15% (10 of 67) in the clindamycin and placebo groups, respectively (OR 0.6, 95% CI 0.2, 1.6).

5.3 Insulin-like growth factor-binding protein-1 as a predictor of preterm delivery (Study III)

The study population included 72 pregnant women who presented with preterm uterine contractions before 37 weeks´ gestation at the Department of Obstetrics and Gynecology, Helsinki University Central Hospital. Speculum examination was performed to check for signs of infection and obtain cervical dacron swab samples for a assay of phIGFBP-1 and for the rapid strip-test of amniotic fluid IGFBP-1 (PROM-test), to exclude rupture of fetal membranes. Cervical swab samples for the detection of phIGFBP-1 were also taken from 58 asymptomatic women with no history of PTD. A

concentration of 10μg/L was chosen as a cut-off level between positive and negative results. The samples from the patients and controls were taken at the same gestational weeks.

Of the total of 72 women with PTL, the PROM test was positive in 9, and these were excluded from further analysis. Of the remaining 63 women with preterm uterine contractions and intact fetal membranes, 17 (27%) showed a positive phIGFBP-1 result (range 10-95μg/L) and 46 (73%) a negative result. In the asymptomatic control population, of the 58, 3 (5%) had a positive phIGFBP-1 result (range 13.8-22μg/L) and 55 (95%) a negative result.

There was a total of 10 spontaneous PTD´s in the study population. Three (30%) of these PTD´s were twins. Of the 17 women with a positive cervical IGFBP-1 result, 7 (41%) had PTD (Study III, Fig. 1, p. 548). Among the 46 study women with a negative phIGFBP-1 result for their cervical secretions, three delivered preterm (6.5%) (OR 10, 95% CI 2.2, 47) (Study III, Table II, p. 549). In the phIGFBP-1-positive group, all the PTD´s occurred before 35 weeks + 0 days of gestation (Study III, Fig. 1,p. 548). Two of the PTD´s were twins. In the phIGFBP-1 negative group, the three PTD´s, including one pair of twins, occurred after 35 weeks´ gestation.

Of the 63 women with preterm uterine contractions, 20 (32%) were admitted to hospital either because of cervical changes or of clinical signs of infection and were treated with tocolytics and antibiotics. Of these 20 women, 11 (55%) had a positive cervical phIGFBP-1 test result, and 9 (45%) a negative test result. Of the 20 admitted women, 8 (40%) delivered preterm, and 7 (88%) of these had a positive phIGFBP-1 result. Of the remaining 12 women whose pregnancies continued to term, 4 (33%) had a positive phIGFBP-1 test result and 8 (67%) a negative result.

In the asymptomatic control population, none of the women with a positive cervical phIGFBP-1 test result (3 of 58, 5%) had PTD, whereas among the women with a negative cervical phIGFBP-1 test result (55 of 58, 95%), one woman delivered preterm (1 of 55, 2%).

Of the 63 women, a genital tract infection was diagnosed in 6. In 4 of them (67%), the cervical phIGFBP-1 test result was positive, and all 4 had PTD (100%). In 2 patients with genital tract infections, cervical phIGFBP-1 was negative, and neither of them delivered preterm. The OR for presence of infection was 26 (95% CI 3.9, 167).

After multiple logistic regression, the variables remaining as statistically significant independent predictors of PTD were: positive phIGFBP-1 test result, infection, hospitalization, and twin pregnancy. In contrast, many of the generally accepted risk factors such as previous PTD and nulliparity had no predictive value (Study III, Table II, p. 549).

In the study group, the median number of weeks between first presentation with preterm contractions, and delivery, was 10.2 in the phIGFBP-1-negative group compared with 8.9 in the phIGFBP-1-positive group (P=0.04) (Study III, Fig. 2, p. 549).

5.4 Economic evaluation of screening and treatment for bacterial vaginosis in pregnancy (Study IV)

A decision-tree model was developed to conduct an economic evaluation of screening and treatment of BV in early pregnancy. The decision tree shows the paths to eventual outcomes in the screening and no-screening situations (Study IV, Fig. 1, p. 17). The baseline probabilities used in the decision-tree analysis are shown in Study IV, Table 1, p. 14.

The average ages of the pregnant women in the BV-positive (n=375), BV-negative (n=629) and unscreened general population (n=210) were 28.8, 28.2, and 30.3 years, respectively, and the mean parity was 1.9, 2.0, and 1.9. Thus, characteristics of the groups were similar.

According to the trial base case, the probability of preterm birth was 2.7% in the screening strategy and 2.6% in the no-screening strategy. The probability of preterm birth was 2.5% among BV-negative women compared with 4.6% among BV-positive women. However, the probability of preterm birth was 4.9% among BV-positive women who were treated with vaginal clindamycin and 4% among BV-positive women treated with placebo.

The probability of peripartum infections and postpartum complications was 12.7% in the screening strategy, compared to 15.1% in the no-screening strategy. The probabilities of these complications were 12.5% among the BV-negative women and 14.5% among the BV-positive. Among the women who received vaginal clindamycin for the treatment of BV, the probability of these complications was 11.7%, versus 20.1% in the placebo group.

The expected average cost per case (pregnant women) was 1883 USD for the screening strategy and 1812 USD for the no-screening strategy, 1.2% (21 USD) higher for the screening strategy (Study IV, Table 3, p. 16).

Threshold analysis showed that the screening strategy is less costly if the prevalence of BV is less than 3% or if the probability of PTD in the low-risk population is higher than 3%, with no other change in other base-case values. No threshold was found for the proportion of BV-positive treated within the range of 49.9 to 100%. For cost variables, several thresholds emerged. If the unit cost of a Cesarean section with atonic complications exceeds 15 501 USD, or the cost of vaginal delivery

with atonic complications 3784 USD, or that of vaginal delivery with infectious complications 3211 USD, with the other parameters at their base case values, the screening strategy is less costly compared to no-screening strategy. However, these unit costs are 4.1, 2.2, and 1.8 times as high as their respective base case values. For other unit costs in Study IV, Table 2, p. 15 (except travel costs and costs of clindamycin treatment) no threshold was found in the range of 150 USD to 30 000 USD.

In the scenario in which screening and treatment would be routine practice, a higher percentage of BV-positive women was assumed to be treated (83%), which probably better reflects the real life situation outside any clinical study. In this situation, the cost per pregnant woman would be 1834 USD. The model predicts further that the probability of peripartum infections and postpartum complications is 12.6% among all pregnant women (12.7% for the base case) and 13.1% among BV-positive women (14.5% for the base case) The probability of PTD would be 4.7% among BV-positive women (4.6% for the base case); otherwise the probabilities of other outcomes remain the same as for the base case.

6 Discussion

Preterm birth is the most challenging problem in obstetrics woldwide and causes major morbidity and mortality in neonates. In Finland, the incidence of PTD has remained quite stable during the last 10 years (5.3%, Stakes 1998). However, the rate of PTD is much higher and has even increased in other parts of the world (USA, 11%; Guyer et al. 1999).

Although the rate of preterm birth has not decreased, the survival of extremely low birth weight infants has increased in the last 25 years from 20% to 60%. At the same time, there has been an increase in major neurological disorders from 10% to 25% (Stevenson et al. 1998, Vohr et al. 2000, Salokorpi et al. 2001).

Prevention of prematurity is difficult and ineffective because of the clinical heterogenity of PTD (Romero et al. 1994). From data on numerous risk factors related to PTD, it is possible to identify only the minority of women who will deliver preterm, the majority of pregnant women exbiting no predisposing factor for PTD. Thus, new tools to identify women at risk for PTD are urgently needed. In recent years, attempts to predict preterm birth have included research into ultrasonographic measurement of the cervix and the use of biochemical markers.

Perhaps the most important finding regarding the etiological factors of PTD during the most recent two decades is the relationship between vaginal infections and intrauterine infection. Comprehensive studies have shown that infection is associated with up to 40% of preterm births (Romero and Mazor 1988, Gibbs et al. 1992). Furthermore, nearly 85% of the earliest preterm births are associated with an intrauterine infection prior to membrane rupture (Goldenberg et al. 2000d). Single microbes such as group B *Streptococcus, Neisseria gonorrhoeae,* and *Chlamydia trachomatis* are known infectious risk factors for PTD. However, BV as a common and usually asymptomatic cause of abnormality in the vaginal microbial ecology has proven to be more important than any single microbe in predisposing to preterm birth (Hillier et al. 1995).

PTL, PTD, and preterm infants, as well as infectious peripartal complications are responsible for major costs to health care systems worldwide. To find markers to identify the women at greatest risk for PTD could be of remarkable economic benefit.

6.1 Treatment of bacterial vaginosis with clindamycin in early pregnancy

Bacterial vaginosis in pregnancy seems to be the most important single infectious risk factor for PTD with an odds ratio ranging from 1.4 to 7.3 (Gravett et al. 1986, Gravett et al. 1986, Kurki et al. 1992, Minkoff et al. 1984, Hay et al. 1994, Meis et al. 1995, Hillier et al. 1995). There exists, however, conflicting evidence on the effect of treatment of BV in preventing preterm birth. Randomized controlled trials in high-risk populations for PTD have provided some evidence that treatment of BV during pregnancy can reduce the rate of PTD (Morales et al. 1994, McGregor et al. 1995, Hauth et al. 1995, McDonald et al. 1997), although, studies conducted among women at moderate risk for preterm birth have shown no reduction in PTD´s if BV was treated (McDonald et al. 1997, Carey et al. 2000). Furthermore, randomized studies in entirely low-risk populations for preterm birth have been thus far missing.

Study I was perfomed entirely in a sample comprising a homogeneous white population with singleton pregnancies and no history of preterm birth, reflecting a low-risk population for preterm birth and thus differing from subjects in most other studies. The overall prevalence of BV was 10% (range 7-14% in different study centers), which is lower than in an earlier study in Finland with nulliparous women (21%, Kurki et al. 1992), although the same diagnostic criteria were used in both studies. This difference is difficult to explain, but may indicate some biologic fluctuation over time in the prevalence of BV.

The efficacy of intravaginal clindamycin has been reported to be up to 90% and is similar to that of oral metronidazole in the treatment of BV in non-pregnant women (Hillier et al. 1990, Andres et al. 1992). In the recent study by Carey et al. (2000), the efficacy of oral metronidazole in the treatment of BV in pregnant women was 78%. We wanted to study the efficacy of vaginal clindamycin in the treatment of BV in pregnant women, because the topical manner of treatment is generally better accepted during pregnancy. In our study, the efficacy of intravaginal clindamycin for BV in pregnancy was 66%, somewhat lower than expected. BV resolved spontaneously in 34% of cases in the placebo arm, in accordance with earlier findings (Hillier et al. 1992, Hay et al. 1994).

Topical clindamycin was effective in reducing neither the rate of PTD nor of peripartum infections, although it was given earlier-- at 10-17 weeks´ gestation-- than in most other studies (McGregor et al. 1994, Joesoef et al. 1995). In fact, intravaginal clindamycin was not only ineffective in reducing the rate of PTD, but seemed to increase the rate. This failure suggests that infection may already be present in the choriodecidual interface or in the upper genital tract, even in early pregnancy or perhaps even before pregnancy (Korn et al. 1995), and thus is unreachable by topical treatment. It

has also been suggested that intravaginal clindamycin may select for *Escherichia coli* and other virulent Gram-negative bacteria in the vagina, which can actually increase risk for PTD (Hillier et al. 1990b). This was not suprising in light of reports from moderate-risk or high-risk populations (Morales et al. 1994, McGregor et al. 1995, Hauth et al. 1995, McDonald et al. 1997, Carey et al. 2000). This finding is also in accordance with that of another study showing that topical treatment in early pregnancy reduced only vaginal fluid mucinase and sialidase activities; it did not reduce the rate of preterm births (McGregor et al 1994). However, systemic antibiotic treatment of pregnant women has also failed to reduce the rate of preterm births, suggesting that eradication of BV during pregnancy is difficult (McDonald et al 1997, Carey et al. 2000). Furthermore, the fact that BV seems to resolve spontaneously in up to 50% of cases during pregnancy (Hay et al. 1994), is in accordance with our findings according to which BV resolved spontaneously in a third of subjects in the placebo arm. This suggests that BV does not necessarily persist throughout pregnancy. Single screening in early pregnancy may not be the best diagnostic strategy. On the other hand, the the overall recurrence rate of BV was 7%, and the infectious morbidity in this subgroup was strikingly high. In fact, recurrent BV increased the risk for PTD nine-fold when compared with that of women who remained BV-negative after the treatment throughout the rest of the gestation. Thus, the timing of screening and the timing of treatment, as well as type of treatment and the most appropriate intervals for follow-up in the treatment of BV in pregnancy are important areas of study.

In this respect, other strategies for treatment of BV are clearly needed. Can BV be treated during pregnancy to achieve better pregnancy outcome, or should BV be treated even before pregnancy has begun? Would it be possible to identify, for example with a biochemical marker, those BV-positive pregnant women with the highest risk for infectious complications in order to target all the possible care available to lengthen the pregnancy? Alternatively, BV may be just one surrogate risk marker of another yet undefined and more specific risk factor for PTD.

6.2 Insulin-like growth factor-binding protein-1 as a marker of peripartum infections and preterm delivery

Bacterial vaginosis is associated with preterm birth, late miscarriage, and postpartum infections (Watts et al. 1990, Kurki et al. 1992b, Hay et al. 1994, Goldenberg et al. 1996d). Randomized controlled trials have not, however, provided evidence that treatment of BV in pregnancy prevents such complications, especially among low-risk populations. Furthermore, among BV-positive women there probably exist individuals more sensitive to BV-related infectious complications (Hay et al. 1994). It would be of great importance to find a marker to identify those women at increased risk for BV-associated complications to target all possible care and treatment at those who benefit from it. Fetal fibronectin has been widely studied (Lockwood et al. 1991), and in some series PTD has been detected at a sensitivity of up to 90% (Nageotte et al. 1994). Nevertheless, other studies have shown that fFN lacks PPV, probably due to the fact that sperm contains abundant amounts of fetal fibronectin (Amuller & Riva 1992) and that most women have intercourse during pregnancy (Kurki et al. 1993). Insulin-like growth factor-binding protein-1 is a protein of human decidua and its highly phosphorylated isoform (phIGFBP-1), which is produced by decidua but is not present in amniotic fluid, may act as an indicator of tissue damage in the choriodecidual interface in pregnant women and as a marker of an increased risk for infectious complications of BV. In contrast to fFN, only minimal amounts of IGFBP-1 are present in urine and seminal plasma. This means that recent intercourse does not limit use of the phIGFBP-1 test among patients with preterm contractions, and urine, which may mimic amniotic fluid in the vagina, does not interfere with this measurement. PhIGFBP-1 was studied in the cervical secretions of low-risk women with asymptomatic BV as part of a randomized placebo-controlled study of treatment of BV with vaginal clindamycin (II) and of women with preterm uterine contractions (III).

Study II showed an up to three-fold increased risk for infectious morbidity in women with BV and positive cervical phIGFBP-1 compared to those with BV and negative cervical phIGFBP-1. However, treatment with vaginal clindamycin had no effect on outcome. Infectious complications were equally common in the clindamycin and placebo groups. Compared with those women whose cervical phIGFBP-1 was negative in early pregnancy, the presence of phIGFBP-1 in the cervix in early pregnancy with BV increased the rate of infectious morbidity eight-fold, even if BV was later cured. In that respect, leakage of this decidual protein into the cervix may indicate tissue damage in the choriodecidual interface. Especially, during the first trimester of pregnancy, the route is open for

microbes to reach the choriodecidual interface, because the layers of the decidua (decidua capsularis and decidua parietalis) have not yet been fused. Infection in the choriodecidual interface can remain subclinical for weeks and activate later in pregnancy, leading to PTD. Furthermore, once the infection has reached the upper genital tract, topical treatment is ineffective. BV may temporarily be suppressed with topical treatment, while infection remains in the choriodecidual interface.This is in accordance with the findings in Study I where topical treatment was ineffective in reducing the rate of PTD or peripartum infections. In fact, the rate of PTD and peripartum infectious complications were the highest in that group of Study I in which BV was cured after the treatment but recurred later in pregnancy. This is also in accordance with the findings in Study I, where recurrence of BV seemed to be the most harmful, with the highest rates of PTD. In Study II, cervical phIGFBP-1 was a useful marker in predicting infectious complications in women with BV. Because the overall prevalence of PTD in our low-risk pregnant study population was low, we could show no increased rate of PTD as a consequence of the presence of cervical phIGFBP-1. However, the only case with PTD occurred in the positive cervical phIGFBP-1 group.

In Study III, cervical phIGFBP-1 was tested in women with PTL but with intact membranes. It is well known that neither uterine contractions nor digital examination of the cervix predicts PTD sufficiently well. We would need additional tools to examine women with symptoms of PTL to select those women with true PTL and the need for admission with all available care to prevent PTD and to gain time to prepare the fetus for preterm birth. On the other hand, those whose contractions are not harmful would not benefit from such special attention. Study III showed that some women with preterm uterine contractions but intact fetal membranes have increased concentrations of phIGFBP-1 in their cervical secretions (27%); these women had a 10-fold increased risk for PTD. Furthermore, women with genital tract infections and preterm uterine contractions were more likely to have a positive cervical phIGFBP-1 concentration (67%), and all of them delivered preterm. On the other hand, among the asymptomatic control population, positive cervical phIGFBP-1 appeared in 5% of the women, and none of them delivered preterm. Among the women with a negative cervical phIGFBP-1 test result, one delivered preterm (2%). Elevated concentrations of cervical phIGFBP-1 as a sign of choriodecidual damage may thus be useful to predict PTD. The data in Study III, although based on a relatively small number of patients, shows that the detection of phIGFBP-1 in cervical secretion during mid- and late gestation is an additional factor which can independently predict risk for PTD in patients with PTL.

6.3 Economic evaluation of screening and treatment of bacterial vaginosis in early pregnancy among women at low risk for preterm birth

Bacterial vaginosis may be responsible for many adverse health sequelae in women and their infants. Several studies have shown a solid link between BV and PPROM, PTL, PTD (Kurki et al. 1992b), chorioamnionitis (Hillier et al. 1988), postpartum endometritis (Watts et al. 1989), and postpartum infant complications (Dammann and Leviton 1997). Treatment of BV has, however, failed to reduce the rate of preterm birth, especially in low-risk populations. Gaining a more comprehensive view of screening for BV at a population level required an economic analysis. In addition to preterm births and maternal peripartum infections, data on other delivery-associated complications such as atonic bleeding and placental retention were included, as well as mode of delivery. The study was of a homogenous low-risk pregnant population, with no pregnant women at high risk for PTD. In addition to the baseline probabilities derived from our randomized trial, a routine practice scenario with a high percentage of BV-positive women treated (83%) was tested in order to make the results more appropriate to non-experimental circumstances.

We found that the strategy for screening and treatment of BV in early pregnancy was not cost-saving based on the baseline probabilities in the decision-tree model, not even when a higher percentage of the BV-positive were treated. This was not unexpected, considering our randomized trial showing that treatment of BV with topical clindamycin in early pregnancy was ineffective in reducing PTD´s, although it reduced to some extent the rate of peripartum infections. However, the savings due to reduced infections were not high enough to compensate for the incremental costs of screening and treatment of BV. Treatment with clindamycin even marginally elevated the rate of PTD in the treatment arm. This latter phenomenon may explain why the sensitivity analysis showed that the screening strategy would become cost-saving at a BV prevalence of less than 3% or at a rate of PTD higher than 3%. We would have expected the savings to increase with increasing prevalence of BV and increasing rate of preterm births. This would probably be the case if a more effective treatment for BV were available. More studies are therefore needed to discover more effective treatment for BV in pregnancy.

Finding a more effective treatment would be important, since in many other studies from other countries, the prevalence of BV has been much higher in more mixed populations (Hay et al. 1994, Meis et al. 1995, Goldenberg et al. 1998, Royce et al 1999). Similarly, the rate of PTD in many other countries is much higher as well. For instance, in the U.S the rate of PTD has increased from

9.5% in 1980 to 11% in 1998 (Guyer et al. 1999). These rates are not calculated, however, based on low-risk pregnant populations. In any case, BV-associated pregnancy complications have been estimated to cost 1.4 billion USD annually in the USA (Oleen-Burkey and Hillier 1995). Our analysis suggests that in those circumstances, a BV-screening and treatment strategy might be cost-saving, assuming that our results are applicable to other than Finnish clinical settings.

The rate of PTD was lowest (2.5%) among the BV-negative pregnant women, meaning that these women represent the true low-risk pregnant population for infectious complications. Although these women did not differ significantly from the unscreened Finnish general population in terms of average age or mean parity, the very low rate of PTD in this group suggests that this group is not necessarily representative of the low-risk unscreened general BV-negative pregnant population. However, due to lack of data, we were unable to address this issue in more detail.

BV may act as a risk marker for multiple problems during pregnancy and peripartum period. The solid evidence linking BV to pregnancy complications worldwide suggests a need for early pregnancy or even pre-pregnancy screening and treatment. Even a marginal reduction in the rate of PTD reduces the high costs associated with neonatal intensive care. BV-associated infectious complications including PTD and peripartum infections also prolong the need for hospitalizations and increase the need for medical interventions and antimicrobial treatment, thus causing further costs to the health care system. It was, therefore, surprising that according to our model, screening and treatment of BV did not reduce costs. This result was, however, mainly driven by the underlying clinical trial showing that the treatment did not reduce the rate of PTD in such a low-risk population. The screening strategy may, nonetheless, be cost-saving in clinical settings in which the rate of PTD is higher.

7 Conclusions and future prospects

This study suggests that vaginal clindamycin for the treatment of BV in early pregnancy was not effective in reducing the rate of PTD or peripartum infections. On the contrary, the rate of PTD in the clindamycin group tended to increase. Two possible explanations for this exist. First, clindamycin may select for virulent Gram-negative bacteria while eradicating BV-associated microbes. Second, subclinical infection may already exist in the upper genital tract and thus be unreachable by topical treatment. Topical treatment may even temporarily suppress BV, leaving the upper genital tract untreated. According to the study, the highest rate of PTD occurred in women with recurrent BV.

IGFBP-1 was studied as a potential candidate for a more specific and sensitive marker for pregnancy-associated infectious complications. The highly phosphorylated isoform of IGFBP-1 is a specific protein of the decidua and its leakage into cervical secretions may reflect tissue damage in the choriodecidual interface. Increased concentrations of phIGFBP-1 in cervical secretions among asymptomatic pregnant women with BV was associated with an 8-fold increase in pregnancy-related infectious morbidity and an up to 10-fold increase in the risk for PTD in women with threatened PTL. To support the theory of BV-associated microbes capable of ascending to the upper genital tract even early in pregnancy, increased concentrations of phIGFBP-1 in cervical secretions in early pregnancy were predictive of pregnancy-related infectious complications, even if BV was subsequently cured. BV should therefore be treated very early in pregnancy or perhaps even before pregnancy has begun. PhIGFBP-1 as a specific decidual protein, present in no other fluids in vagina such as seminal plasma or amniotic fluid, may offer a more specific tool to diagnose tissue damage in the choriodecidual interface. Searching for increased concentrations of cervical phIGFBP-1 in women with BV may be a useful clinical method to select those BV-positive women at increased risk for pregnancy-related infectious complications. It could also become a useful clinical method for differentiating women with a ”true” threat of PTD from those without.

Several studies have shown the efficacy of treating BV to prevent PTD only among high-risk pregnant women. To look at this on a population level, we created a decision-tree model for an economic analysis among pregnant women at low risk for PTD, and considered not only PTD but also peripartum infections and other less common delivery-associated complications. In our study including only a pregnant population at low-risk for PTD, screening and treatment of BV was not cost-saving. This result, however, complements our parallel clinical trial results showing that the

treatment considered (vaginal clindamycin) was ineffective in reducing the rate of PTD. More studies are therefore needed to find proper treatment and timing both to treat BV to reduce BV-associated and pregnancy-related infectious complications. Additionally, the screening strategy considered may be cost-saving in circumstances where the rate of PTD is higher than in our study settings.

To improve the search for the etiology of PTD for each individual and to have the possibility to counsel a woman who has delivered preterm about her following pregnancies, a specific session should be offered to women after delivery. As the etiology of PTD is multifactorial, this kind of session would serve not only in improving the diagnostics of PTD with the woman who has delivered preterm but also overall by leading to better understanding of the phenomenon of PTD.

One of the most important issues in the future is to create a consensus as to how to handle an infected preterm fetus: Delivery or treatment with antimicrobial therapy? Studies on elevated concentration of cytokines in amniotic fluid as a marker for intrauterine infection, and on the correlation between amniotic inflammatory cytokines and cerebral palsy in neonates suggest that the obstetrician must be more active in diagnosing intrauterine infection and acceleration of delivery of the fetus.

8 Summary

The present study was undertaken to investigate the effect of vaginal clindamycin in preventing preterm birth and peripartum infections in pregnant women with BV. As a marker of tissue damage in the upper genital tract, cervical phosphorylated insulin-like growth factor-binding protein-1 (IGFBP-1) was measured in cervical secretions to discover whether it can serve as a biochemical marker to predict PTD and peripartal infectious complications among asymptomatic pregnant women who have BV and women with threatened PTL.

Study I included a homogenous Caucasian population at low risk for preterm birth. The efficacy of vaginal clindamycin for BV was 66%. It was ineffective in preventing PTD and peripartum infections when used in early pregnancy. In fact, the rate of PTD in the clindamycin group increased. This suggests that the infection had already ascended to the upper genital tract, thus being unreachable by topical treatment. Another explanation may be the selection for virulent Gram-negative bacteria (for example *Escherichia coli*) during the use of intravaginal clindamycin. Furthermore, recurrence of BV seemed to be the most harmful, increasing the risk for PTD nine-fold.

As part of our randomized placebo-controlled study of treatment of symptomless BV with vaginal clindamycin among low-risk pregnant women, cervical phIGFBP-1 was measured before treatment (Study II). The rate of peripartum infections was increased almost three-fold among those women whose cervical phIGFBP-1 was elevated compared to those women with negative cervical phIGFBP-1. Treatment with vaginal clindamycin had no effect on the outcome; if cervical phIGFBP-1 was elevated, treatment with vaginal clindamycin did not change the infectious morbidity compared to that of women who received placebo. The highest rate of infectious morbidity was among women in whom BV was cured, but who had elevated cervical phIGFBP-1, an infectious morbidity of 35% compared to that of women with negative cervical phIGFBP-1 (4%) (OR 8.3, 1.5, 45). The results of this study are in accordance with the conclusions in Study I indicating that BV may cause an invasive infection ascending to the upper genital tract early in pregnancy. Although BV was suppressed temporarily, the infection underlying in the choriodecidual interface continued, and as a marker of this tissue damage, phIGFBP-1 was detected in cervical secretions.

Cervical swab samples for the detection of phIGFBP-1 were also obtained from symptomatic women in PTL. The women with elevated concentrations of phIGFBP-1 in their cervical secretions

had a ten-fold risk of PTD compared with risk in women with a negative cervical phIGFBP-1. Cervical phIGFBP-1 was also elevated significantly more often in those women showing signs of genital tract infection and preterm uterine contractions. The measurement of phIGFBP-1 in cervical secretion thus may provide an additional tool to distinguish between women with or without true PTD.

Several studies have shown the efficacy of the treatment of BV in reducing the rate of preterm birth among high-risk pregnant populations. However, treatment of BV among women at moderate or low risk for preterm birth has had no major effect on the rate of preterm birth. Nevertheless, the overall costs of preterm birth are high, and BV-associated maternal morbidity further adds to the costs. An economic evaluation based on our randomized trial was created to gain a more comprehensive view of BV-associated morbidity and costs to the health care system on a population level. Reference groups comprised the general population of pregnant low-risk women not screened for BV as well as BV-negative pregnant low-risk women screened for BV in early pregnancy. The strategy for screening and treatment of BV in early pregnancy under these circumstances was not cost-saving. This result, however, is mainly due to the findings of the underlying clinical trial during which vaginal clindamycin was ineffective in reducing the rate of PTD. More studies are therefore needed to find the proper timing and a more effective treatment of BV in pregnancy. However, a BV-screening strategy may be cost-saving in settings in which the rate of PTD is higher.

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