Prelabour rupture of the membranes at or near term

Clinical and epidemiological studies

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Abstract

Objectives: To study: (1) the risks and benefits for women with prelabour rupture of the membranes (PROM) after 34 weeks of gestation managed with different expectant periods from 24 to 72 hours; (2) perinatal infectious morbidity in the different groups and the association between demographic, intrapartum and postpartum variables and neonatal sepsis; (3) the influence of bath on infectious morbidity in mothers and neonates in women with PROM; (4) the false negative rate using a sterile speculum examination for the diagnosis of rupture of the membranes (ROM) compared to Diamine oxidase (DAO); (5) possible risks for the mother and the baby when the women were allowed to return home without further controls if amniotic fluid was not visible at the speculum examination; (6) the prevalence and risk factors for PROM in an urban Swedish population.

Material and methods: Studies I-III were based on a randomised study comparing two different regimens in women with PROM. Women without contractions within two hours (n=1012) were randomised to induction the following morning after PROM (”early induction group”) or induction two days later (”late induction group”). Digital examination of the cervix was avoided until onset of active labour. Labour was induced with oxytocin if no spontaneous contractions occurred or if chorioamnionitis or fetal distress was detected.

Study IV was based on women admitted for suspected rupture of the membranes after 34 weeks of gestation in which no amniotic fluid was visible at the sterile speculum examination. A test for DAO was performed. No further controls were performed if amniotic fluid was not visible at the speculum examination. Neonatal and obstetric outcome was recorded prospectively. Study V was based on a sample of 2880 women randomly selected from the national population register. They had delivered 2270 times at hospitals in the Göteborg area and 2242 of these case records were found. The case records were systematically analysed for the occurrence of PROM and potential risk factors for PROM. Two thousand two hundred and eight of these deliveries occurred after 34 weeks of gestation. The analyses were based on these 2208 deliveries.

Results: There were no differences in the frequency of neonatal or maternal infections if the mother were randomised to early or late induction. No differences were found in the frequency of caesarean sections between the randomised groups. In nulliparous women ventouse extraction was more often used in the ”early induction group” compared to the ”late induction group”, 14% and 7% respectively ($p<0.05$). There was no difference in the incidence of neonatal infections between the groups. Clinical neonatal sepsis was associated with time from PROM to delivery over 32 hours, caesarean section, parous women and gestational age between 34 and 36 weeks. The false negative rate of a speculum examination of the diagnosis of rupture of the membranes in women without amniotic fluid visible at a speculum examination was 12%. This study did not show any disadvantages for mothers and infants if the women were sent home after a false negative speculum examination. The prevalence of PROM after 34 weeks of gestation in an urban Swedish population was 12.9%. In the multiple stepwise regression analysis risk factors for PROM were age at delivery ≥35 years, primiparity, premature contractions, PROM in a previous pregnancy and bleeding in the first trimester.

Keywords: Amniotic Fluid; Fetal Membranes, Premature Rupture; Diagnosis; Prospective Studies; Apgar Score; Baths; Newborn; Infection; Epidemiology; Time Factors; Labor; Oxytocin; Chorioamnionitis; Endometritis; Risk ;Labor,Induced; Oxytocin; Pregnancy Outcome; Morbidity;

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Contents

List of publications

This thesis is based on studies reported in the following papers, referred to in the text by their Roman numerals.

I Ladfors L, Mattsson LA, Eriksson M, Fall O. A randomised trial of two expectant managements of prelabour rupture of the membranes at 34 to 42 weeks. Br J Obstet Gynaecol 1996; 103:755-762.

II Ladfors L, Tessin I, Mattsson LA, Eriksson M, Seeberg S, Fall O. Risk factors for neonatal sepsis in offspring of women with prelabor rupture of the membranes at 34–42 weeks. Journal of Perinatal Medicine. [in press]

III Eriksson M, Ladfors L, Mattsson LA, Fall O. Warm tub bath during labor. A study of 1385 women with prelabor rupture of the membranes after 34 weeks of gestation. Acta Obstet Gynecol Scand 1996; 75:642-644.

IV Ladfors L, Mattsson LA, Eriksson M, Fall O. Is a speculum examination sufficient for excluding the diagnosis of ruptured fetal membranes? Acta Obstet Gynecol Scand 1997; 76:739-742.

V Ladfors L, Mattsson LA, Eriksson M, Milsom I. Prevalence and risk factors for prelabour rupture of the membranes (PROM) at or near term in an urban Swedish population. [submitted]

Abbreviations

AFP	Alpha-fetoprotein
CI	Confidence interval
CRP	C-reactive protein
CS	Caesarean section
DAO	Diamine oxidase
FHR	Fetal heart rate
FFN	Fetal fibronectin
IGFBP-1	Insuline-like growth factor binding protein-1
MBR	Medical birth register
OR	Odds ratio
pH	Negative logarithm of the hydrogen ion concentration
PROM	Prelabour rupture of the membranes
PPROM	Preterm Prelabour rupture of the membranes
RCT	Randomised controlled trial
ROM	Rupture of the membranes
SD	Standard deviation
SCBU	Special Care Baby Unit
Sens.	Sensitivity
Spec.	Specificity

Introduction

Prelabour rupture of the membranes (PROM) occurs in 6–19% (Grant *et al.* 1989) of all pregnancies. The differences in prevalence are partly a result of differences in study populations (hospital-based or population-based), cut-off points for term (ranging from 34 to 38 weeks) and the specific time interval from rupture of the membranes (ROM) and the onset of contractions the diagnosis is based. Studies in the period 1960–80 showed an increased risk of maternal and perinatal morbidity and mortality when the time interval from rupture of the membranes until delivery was prolonged (Shubeck *et al.* 1966, Russel *et al.* 1962, Lanier *et al.* 1965, Johnson *et al.* 1981, Burchell 1964, Gunn *et al.* 1970, Webb 1967). This fact was the main reason why a policy of immediate induction of labour after PROM at term was adopted. Later studies showed that expectant management resulted in a lower rate of caesarean sections (CS) without an increased risk of maternal or neonatal infections (Kappy *et al.* 1982).

The main objective for the obstetrician and for the woman with suspected PROM is a correct diagnosis of ROM and a management of the delivery that gives a high rate of successful vaginal deliveries without a rise in neonatal and maternal infections. When the diagnosis of ROM is unclear, the pregnancy should be managed to avoid unnecessary check-ups. It is also important that women are well informed and they should be offered the possibility to influence the decision regarding the management of their deliveries. A healthy neonate and mother as well as a satisfied mother are natural aims for the obstetrician.

Early studies of PROM were not prospectively and randomly designed and many of them included both preterm and term patients. A systematic review of controlled trials (Grant *et al.* 1989) revealed that not a single trial could be identified in which women with PROM at term had been assigned to induction of labour or expectant care by a formal process of randomisation. There was a need for properly controlled randomised studies.

Definition of prelabour rupture of the membranes

PROM is defined as the spontaneous leakage of amniotic fluid prior to the onset of labour. This definition has been subcategorised into preterm PROM (PPROM) when the gestational age is less than 37 weeks and term PROM when the gestational age is 37 weeks or more. In the latest version of the Cochrane database (Hannah *et al.* 1997,a), trials in which PROM occurred after week 34 are included in a review called "Prelabour rupture of membranes at or near term". Previously PROM was an abbreviation for *"Premature rupture of the membranes"* but this is not a proper way of describing the clinical entity (Keirse *et al.* 1996).

Diagnosis of rupture of the membranes

There is no golden standard for diagnosing rupture of the membranes. For decades different methods have been tested based on the assumption that there is a need for a specific test besides visualisation of amniotic fluid by speculum examination. As early as in 1932, a report on the use of bromthymol blue as an indicator for ROM was published (Berlind 1932). Since that time results of a number of different methods for the diagnosis of ROM have been published. Such methods include fetal fat, nitrazine, Papanicolaou (cytological test), amniotic fluid crystallisation test, Lanugo hair (cytological test), Nile blue sulphate (cytological test), Pinacyanol (cytological test), Acridine orange (cytological test), Evans blue, diamine oxidase and dye-injection (Smith 1976).

Some questions have to be addressed before a test for ROM is developed and introduced in clinical practice.

1. Is there a need for a test?
2. Are women with PROM with a false negative diagnosis at risk for an increased morbidity?
3. Even if the test was 100% valid, accurate, and reliable, would it influence the neonatal or maternal morbidity?
4. Against which method should the test be evaluated since there is no golden standard for diagnosing ROM?

The observation of amniotic fluid passing through the cervical os and pooling in the posterior vaginal fornix is for most clinicians a useful and definitive diagnostic test. Accordingly a study of a test for ROM should be done on women with suspected but not verified ROM. Most studies have not been performed on this group of women. An overview of the sensitivity and specificity in some of the studies is shown in Table 1. Older studies of methods of diagnosing ROM were based on the assumption that there was an increased risk of neonatal and maternal morbidity/mortality after prolonged rupture of the membranes (Webb 1967, Gunn *et al.* 1970). Nowadays women with PROM as well as the neonates are managed differently and this may have changed the need for a test for ROM in women at or near term. A false positive test may raise problems since it may be followed by an unnecessary and difficult induction of labour. Perhaps a test could be of importance in women with suspected PPROM, though this has not yet been shown in any study.

Maternal infections

Histological chorioamnionitis is defined as an inflammation of the extraplacental membrane. It was detected in 53% of the placentas in preterm delivery and in 16% of the placentas in term deliveries (Hillier *et al.* 1988). PPROM occurred in 66% of the women who delivered preterm and PROM occurred in 20% of the women delivering at term. In both preterm and term placentas microorganisms have been recovered from 51% to 71% of placentas with histological chorioamnionitis and from 23% to 45% of placentas without histological chorioamnionitis (Hillier *et al.* 1988, Pankuch *et al.* 1984, Svensson *et al.* 1986, Quinn *et al.* 1987, Zlatnik *et al.* 1990). The relationship between histological chorioamnionitis and infection (positive cultures) was strongest in preterm deliveries (Hillier *et al.* 1988) while it was less evident in term placentas (Dong *et al.* 1987). In a study, the placentas of 1843 deliveries were examined for the presence of histological chorioamnionitis, which was classified as mild, moderate, or severe (Mueller-Heubach *et al.* 1990). Chorioamnionitis was present in 7.5% of patients who underwent caesarean section before labour and in 18% and 32% of those delivering at term and preterm respectively. Chorioamnionitis was severe in 74% of preterm compared to 15% of term deliveries. Chorioamnionitis was present in 42% of women with PPROM and 15% of patients with PROM (Mueller-Heubach *et al.* 1990). The frequency and severity of chorioamnionitis were inversely related to gestational age at preterm birth. Mothers with histological chorioamnionitis usually have no clinical evidence of infection but their infants have an increased risk of sepsis and death, especially when associated with PPROM. However, histological examination of the placentas is of limited value for the diagnosis of intraamniotic infection prior to delivery (Gibbs *et al.* 1991). A biopsy from the chorioamniotic membranes is neither safe nor practical since the processing of the tissue specimen is relatively expensive and labour intensive and histological inflammation occurs much more commonly than clinical chorioamnionitis. For example, in a high-risk population, histological chorioamnionitis occurred in 11% of all membranes (Dong *et al.* 1987) while clinical chorioamnionitis was reported to be diagnosed in only 0.8% to 4% (Gibbs *et al.* 1980, Koh *et al.* 1979, Newton *et al.* 1989).

Table 1. Tests for the diagnosis of ROM, evaluated methods, recruited patients, "golden standards", sensitivity and specificity

Study	Method	Patients with known status of the membranes (n)	Patients with unknown status of the membranes (n)	"Golden standard"	Sens.	Spec.
Friedmann	History (H)		100	c	90%	88%
1969	Nitrazine(N)		100	c	90%	83%
	Crystallisation(C)		100	c	87%	94%
	H+N+C		100	c	91%	96%
Elmfors 1974	DAO	200		k	100%	100%
Elmfors 1974	DAO		72	d	100%	90%
Mills 1977	Nitrazine	60		k	100%	92%
Gahl 1982	DAO	253		k	99%	99%
	DAO		75	d30h	96%	100%
Rochelson	Alpha-fetoprotein	48		k	98%	
1987	Nitrazine	48		k	77%	
	Crystallisation	48		k	62%	
Garite 1990	Alpha-fetoprotein	45		k	91%	96%
	Nitrazine	45		k	91%	73%
	Crystallisation	45		k	96%	100%
Bank 1991	DAO	145	100	k/c	84%	74%
Salfelder 1992	Fibronectin	133		s	97%	97%
Eriksen 1992	Fibronectin	406		if2	98%	27%
Beckmann	Fibronectin		53	I	100%	90%
1993						
de Haan 1994	Crystallisation	51		k	98%	88%
			100	c	51%	71%
Lockwood 1994	IGFBP-1		105	if2	74%	93%
Gaucherand	Fibronectin	131		k	94%	97%
1995	AFP	131		k	88%	84%
	DAO	131		k	83%	95%
Rutanen 1996	IGFBP-1	130		k	100%	95%
Gaucherand	IGFBP-1	69	31	k/ifG	95%	98%
1997	pH	69	31	k/ifG	91%	77%
	DAO	69	31	k/ifG	84%	100%

k = known from start, I = Indigo carmine, transabdominal injection
d = delivery within three days, d30h = delivery within 30 hours
s = speculum examination, c = "clinical decision"
if2 = if two standard tests were positive: pooling, crystallisation, nitrazine
ifG =if two tests were positive: IGFBP-1, pH, DAO

Intraamniotic infection, also called **clinical chorioamnionitis,** is a cause of maternal morbidity, preterm birth (Hillier *et al.* 1988), neonatal sepsis (Yancey *et al.* 1996) and perinatal mortality (Gibbs *et al.* 1980). An association between clinical chorioamnionitis and cerebral palsy (CP) in infants born preterm has been found (Murphy *et al.* 1997). In a case-control study of 46 children with CP weighing 2500 g or more at birth and 378 selected controls, maternal fever exceeding 38°C or a clinical diagnosis of chorioamnionitis was associated with an increased risk of unexplained CP (Grether *et al.* 1997). Clinical chorioamnionitis has been defined in different ways. Gunn (Gunn *et al.* 1970) presumed that amnionitis was at hand when a woman had a temperature over 38°C in the absence of any other obvious reason for fever. A definite diagnosis was established when purulent amniotic fluid was observed. Gibbs defined chorioamnionitis on the basis of temperature >37.8°C plus two or more of the following conditions: maternal tachycardia, fetal tachycardia, uterine tenderness, foul odour of the amniotic fluid or maternal leucocytosis (Gibbs *et al.* 1982). Clinically, many signs and symptoms may suggest chorioamnionitis. Most of these signs may be sensitive, but very often they are not specific. As a general rule, at least the presence of fever (temperature >38°C) in the absence of any other apparent infection is necessary for the clinical diagnosis of chorioamnionitis. Risk factors for clinical chorioamnionitis at the time of labour are: low parity, increased numbers of cervical examinations in labour, increased duration of labour or membrane rupture and internal fetal monitoring (Newton *et al.* 1989, Soper *et al.* 1989). The management of clinical chorioamnionitis includes treatment with antibiotics and delivery. Caesarean section should be reserved for standard obstetrical indications. However, the rates of delivery by caesarean section are two to three times higher than in pregnant women in general (Duff *et al.* 1983, Silver *et al.* 1986). In women with clinical chorioamnionitis approximately 10% of the neonates will have clinical signs of sepsis (Gunn *et al.* 1970, Duff *et al.* 1984, Wagner *et al.* 1989, Gibbs *et al.* 1991). A few years ago there was debate regarding the timing of antibiotics but studies have shown decreased neonatal sepsis and maternal morbidity when the treatment is started as soon as the diagnosis is made (Gibbs *et al.* 1988).

Endometritis is more properly termed deciduitis because the superficial layer of the endometrium is involved. In its simplest form inflammation occurs in the superficial layers but in more severe forms the infectious process may spread to the adjacent myometrium and if untreated it may eventually progress to the parametria. The diagnosis is based on temperatures of 38°C or greater, documented on two occasions, with no other source of infection, in association with a tender uterus on palpation (Daikoku *et al.* 1982). In women with PROM at or near term the frequency of endometritis has been reported to be between 2% and 9% (Hannah *et al.* 1996, Wagner *et al.* 1989).

Neonatal infections

The diagnosis of neonatal infection is based on clinical suspicion of infection and additional laboratory or radiological criteria. Clinical symptoms are, for example: temperature above 37.8°C, hypotension, poor feeding, necrotising enterocolitis, apnoea, respiratory distress, lethargy, irritability, poor peripheral perfusion or abdominal distension (Yancey *et al.* 1996). To define an infection as bacteriological in a neonate with clinical signs, a bacterial pathogen has to be isolated from a normally sterile fluid such as blood or cerebrospinal fluid (CSF), or from a site of clinical infection such as tracheal aspirate, paranychia or supra-pubically obtained urine (deLouvois *et al.* 1992). The laboratory parameters used to diagnose infections are a serum C-reactive protein (CRP) level of >20mg/l or a band/total neutrophil ratio of >0.2. Another criterion for defining infec-

tion is radiologically confirmed pneumonia or diarrhoea if stool microscopy reveals an excess of leukocytes in the absence of a recognised pathogen.

Neonatal infections could be classified as follows (deLouvois *et al.* 1992):

1. Clinical symptoms and a positive culture from a normally sterile fluid.
2. Clinical symptoms and an elevated CRP or a band/total neutrophil ratio of > 0.2 or a radiologically confirmed pneumonia or diarrhoea.
3. Neonates treated with antibiotics where no findings supported the initial suspicion of infection.

The diagnosis of a neonatal infection depends on the knowledge and personal opinion of the neonatologist.

Pathophysiology

Most studies concerning the pathophysiology of ROM are based on studies of women with PPROM. The mechanisms by which rupture takes place must be related to a weakness in the chorioamniotic membrane. In the third trimester, the amnion consists of a single layer of epithelial cells. The chorion is thicker and consists of four to six cell layers. A basement membrane lies beneath both the amnion and the chorion. Between these layers there is a connective tissue zone, containing collagenous bundles, reticular fibrils and fibroblasts. Morphological studies in patients with PROM at term have shown that the membranes are thinner near the rupture site and the connective tissue layer contains a decreased number of poorly organised collagen fibrils (Bou-Resli *et al.* 1981). With biochemical techniques, it has been shown that there is a decline in the collagen content of the prematurely ruptured amnion (Skinner *et al.* 1981). Some authors suggest that for the majority of women with PROM at term, amniorrhexis most likely occurs as a result of proteolytic enzyme-mediated weakening of the fetal membranes in the region of the cervix or the lower uterine segment (Bou-Resli *et al.* 1981, Polzin *et al.* 1991). Proteolytic enzymes involved in the weakening of the fetal membranes may originate from bacteria present in the lower genital tract, maternal inflammatory cells, or seminal secretions. One of the key proteolytic enzymes implicated in prelabour amniorrhexis is phospholipase A_2, an enzyme produced by microbial organisms, principally anaerobic bacteria. This enzyme catalyses the breakdown of phospholipids to arachidonic acid. Arachidonic acid is then converted into prostaglandins by cyclooxygenase and into leukotrienes by lipooxygenase. The presence of these eicosanoids can lead to uterine contractions with increased intrauterine pressure, localised weakening of the fetal membranes and decreased lubrication between the chorion and amnion, a cascade of events ultimately resulting in rupture of the fetal membranes (Polzin *et al.* 1991).

Cytokines have recently also been implicated in the mechanisms of PROM. Interleukin-1 (IL-1) and tumour necrosis factor (TNF) stimulate the collagenase activity and the prostaglandin production in several cell types, including chorionic cells (Casey *et al.* 1989). These cytokines have been found in the amniotic fluid of women with PROM and intraamniotic infection (Romero *et al.* 1989). Cytokines may also have an effect on the synthesis of glycosaminoglycans. For example, IL-1 increases hyaluronic acid biosynthesis by chorionic cells and an increase in hyaluronic acid may lead to a further reduction in tensile strength of the membranes given its highly hydrophilic nature. This observation is consistent with that of Skinner and Liggins, who found that the membranes from patients with ROM had increased concentrations of hyaluronic acid (Skinner *et al.* 1981).

Risk factors

Many risk factors have been implicated in PROM. However some of these claims have been made on the basis of small and often uncontrolled studies. Since many risk factors can coexist in the same patient, multiple regression analysis is the best way to distinguish primary factors from confounding variables. Infections have been found to be associated with PROM. There is good evidence to support the association between PROM and infection with Chlamydia trachomatis (Harrison *et al.* 1983, Gravett *et al.* 1986, Sweet *et al.* 1987, Alger *et al.* 1988) and Neisseria gonorrhoea (Handsdfield *et al.* 1973, Amstey *et al.* 1976, Edwards *et al.* 1978). A significantly increased incidence of *Trichomonas Vaginalis* and Staphylococci was found among women with PROM (Minkhoff *et al.* 1984). Group B Streptococcus (GBS) carriage was found to be twice as common in women with PROM (Regan *et al.* 1981), but no study has shown that identification and treatment of women colonised with GBS reduced the risk of PROM.

In a randomised prospective study, PROM was more common in women in whom pelvic examinations were done weekly starting at 37 weeks' gestation than in the control group (18% vs. 6%, $p<0.001$) (Lenihan 1984). Women with generalised disease of the connective tissue are at risk for PROM. For women with the Ehlers-Danlos syndrome an 83% risk (15 of 18) was reported (Barabas 1966). One abortion was not associated with an increased incidence of PROM but two or more induced abortions almost doubled the risk for PROM (Linn *et al. 1983).* Antepartum vaginal bleeding was found to be a risk factor for PROM (Ekwo *et al.* 1993). There has been controversy regarding cigarette smoking as a risk factor. Naeye found no association between smoking and PPROM (Naeye 1982) but in a Swedish study such an association was found (Evaldsson *et al.* 1980). Several studies have investigated if sexual intercourse is a risk factor for PROM (Naeye *et al.* 1980, Mills *et al.* 1981) but there is little evidence to implicate coitus during pregnancy in the etiology of PROM. Evaldsson reported that a history of cervical conisation or cervical rupture was more common in patients with PPROM than in controls (Evaldsson *et al.* 1980). Harger found an association between a previous elective abortion or a previous dilatation and curettage and PPROM (Harger *et al.* 1990), but after multiple logistic regression analysis no association could be confirmed. In a rigorous and comprehensive study using multiple logistic regression analysis (Harger *et al.* 1990), three independent risk factors for PPROM were reported: antepartum vaginal bleeding in more than one trimester, current cigarette smoking and previous preterm delivery. The recurrence rate of PPROM has been reported to be 32.2% (Asrat *et al.* 1991).

If a digital examination is undertaken in women with PROM, there is a presumed risk that the clock of infection is started. The potential benefits of digital examinations in women without contractions can be questioned. A prolapsed cord would most probably affect the FHR-tracing. In a retrospective analysis of 321 women with a ROM to delivery interval >24 hours (Schutte *et al.* 1983), a higher incidence of fever was found in women who underwent vaginal examination more than 24 hours prior to delivery (31%) compared to women who were examined only within 24 hours before delivery (12%). In one study including 182 women with PROM, one group was induced with oxytocin immediately and the other was induced 24 hours after randomisation. The delayed induction was associated with an increase of neonatal infectious morbidity (Wagner *et al.* 1989). However, among 18 women with an initial digital vaginal examination who were randomised to the group with delayed induction, five had infections whereas none of the 78 in the group without a digital vaginal examination at admission developed a neonatal infection.

At the annual meeting of the Society of Perinatal Obstetricians (SPO) in 1998 an abstract from a prospective study of women with ROM was presented. A cervical culture was taken before and after a digital cervical examination. The cultures taken after the examination demonstrated that 21 (84%) of the 25 patients had a heavier growth and/or an increased number of different organisms compared to cultures taken before examination (Imseis *et al.* 1998). In a multiple regression analysis of risk factors for clinical chorioamnionitis, an association was found with the number of vaginal examinations (Seaward *et al.* 1997).

Natural history

PROM at term is generally a benign condition. Approximately 80% to 90% of women enter labour spontaneously within 24 to 48 hours without medical intervention (Duff *et al.* 1984, Conway *et al.* 1984, Morales *et al.* 1986). Unfortunately, 5% to 10% of women will not enter labour within 72 hours and 2% to 5% remain undelivered 7 days after PROM at term (Duff *et al.* 1984, Morales *et al.* 1986, Johnson *et al.* 1981). Why some women enter labour shortly after membrane rupture while others have an extended latency period is unclear. One theory, proposed by Yancey, is that in the subgroup of women who experience a short latency period the membranes rupture as a result of the cascade of events associated with the initial stages of parturition (Yancey 1996). The myometrial tissue has enough gap junctions and oxytocin receptors in the myometrium to respond to biochemical uterotonins associated with spontaneous labour. It is also possible that the frequency of uterine contractions increases during the days or weeks preceding delivery, causing the lower uterine segment to become thinner, with further stretching of the membranes. The cervix will coincidentally undergo changes typically referred to as "ripening," representing an increase in water content and disorganisation of collagen bundles. The cervix effaces and softens as the presenting fetus occupies the expanding lower uterine segment. The internal cervical os may dilate to several centimetres and allow further bacterial inoculation of the chorioamniotic membranes. These events may result in localised weakening of the membranes and subsequent rupture with increased uterine activity. The uterus has already undergone the requisite preparatory phases of parturition. Spontaneous labour typically commences within the next few hours and the patient has a labour course similar to that of a parturient in spontaneous labour at term with intact membranes.

A different sequence of PROM events may occur in women in whom the uterus and cervix have not undergone the initial phases of parturition. The myometrial cells are supposed to have few oxytocin receptors and poor gap junction formation (Yancey 1996). The lower uterine segment remains undeveloped and the fetal presenting part is unengaged. Increases in local prostaglandin production after amniorrhexis are insufficient to cause a rapid preparation for labour. While other parts of the uterus remain quiescent, bacteria may ascend into the lower uterine segment and overwhelm local host defences, eventually causing overt chorioamnionitis or maternal/fetal infections. Such cases of PROM can be considered pathological since there is an increased risk of an adverse maternal and/or neonatal outcome.

Earlier studies of PROM

During the 1960s and 1970s, several investigators reported that women with PROM had a substantially higher incidence of serious maternal and neonatal infections, particularly when the latency period was extended beyond 24 hours, compared with those who had intact membranes at the onset of labour (Gunn *et al.* 1970, Johnson *et al.* 1981, Lanier *et al.* 1965, Shubeck *et al.* 1966, Webb 1967). These studies were retrospective and most of them did not differentiate between term and preterm gestations, did not control for management practices and were performed in an era when our understanding of the nature of ascending intrapartum genital tract infections was poor. The treatment of chorioamnionitis often did not include broad-spectrum antimicrobial agents and treatment was occasionally withheld until the fetus had been delivered. Consequently, the perinatal and maternal morbidity and mortality associated with PROM were high, mainly because of infectious complications. Accordingly, early induction of labour and operative delivery if the woman had failed to deliver spontaneously within 24 hours after the onset of PROM were proposed to reduce maternal and neonatal complications.

This management practice was initially challenged by Kappy *et al.* (1979), who performed a retrospective review of women with PROM at term who had an unfavourable cervix. Immediate labour induction had been performed in 19 women, while the remaining 63 deliveries had been expectantly managed. Spontaneous labour began within 24 hours of PROM in 85% of the deliveries managed expectantly. There was a trend toward a reduction in the caesarean section delivery rate associated with expectant management and no statistically significant differences in the incidence of maternal or neonatal infections were observed. In an additional report some years later the same investigators added 72 women to their previous study (Kappy *et al.* 1982). This analysis demonstrated a reduction in the caesarean section delivery rate (13.8% vs. 34.9%, $p<0.05$) in women with PROM at term who had an unfavourable cervix and who were expectantly managed, compared to a similar group of women undergoing immediate induction of labour. No increase in the incidence of maternal or neonatal infections was detected.

About a decade after these retrospective studies by Kappy and colleagues, several prospective trials sought to compare the effects of immediate induction with those of expectant management in women with PROM at term and an unfavourable cervix. One of the first prospective randomised trials in women with PROM at a gestational age of 36 weeks or more who had an unripe cervix (Bishop's score <4) as assessed by a single digital examination was performed by Duff (Duff *et al.* 1984). Patients were randomised either to induction with oxytocin infusion within 12 hours after amniorrhexis or to hospitalisation for expectant management until spontaneous labour occurred or until there was evidence of intraamniotic infection. Women undergoing immediate induction were more likely to require caesarean section delivery (20% vs. 8%, $p<0.05$) and to develop intraamniotic infections (16% vs. 4%, $p<0.05$) compared to women managed expectantly. The majority of caesarean section deliveries in the induction group were performed for failed induction with no change in cervical status after 12 hours of oxytocin infusion.

Randomised studies of PROM with oxytocin

Immediate induction of labour in the woman with PROM at term will result in a decrease in the time interval between rupture of the membranes and delivery of the neonate. Historically, intravenous oxytocin has been utilised as the initial labour induction agent in women with PROM at term. This drug is inexpensive and safe when used

judiciously in carefully monitored patients. In the literature there are 17 randomised studies published to determine the effects of induction of labour with oxytocin versus expectant management for prelabour rupture of membranes (PROM) at or near term (≥34 weeks), evaluating maternal and perinatal morbidity (Alcalay *et al.* 1996, Duff *et al.* 1984, Fayez *et al.* 1978, Grant *et al.* 1992, Hannah *et al.* 1996, Hjertberg *et al.* 1996, Ladfors *et al.* 1996, Morales *et al.* 1986, Natale *et al.* 1994, Ottervanger *et al.* 1996, Ray *et al.* 1992, Rydhström *et al.* 1991, Shalev *et al.* 1995, Sperling *et al.* 1993, Tamsen *et al.* 1990, Van der Walt *et al.* 1989, Wagner *et al.* 1989). An overview of these articles is published in the latest version of the Cochrane Database (Hannah *et al.* 1997,a). The main features of these trials are presented in Table 2. Formal randomisation is a procedure where the patient or the staff do not know in advance what group the women will be randomised to. Other types of randomisation are often referred to as quasi-randomisation because bias is introduced since both the woman and the staff know in advance to which group the woman will belong if she enters the study.

In a large prospective, randomised, multicentre investigation, 5041 women with uncomplicated singleton gestations (in a cephalic presentation) with PROM at term were randomised to one of four treatment arms (Hannah *et al.* 1996): (1) immediate labour induction with oxytocin infusion; (2) immediate labour induction with intravaginal prostaglandin E_2; (3) expectant management for up to 4 days followed by labour induction with oxytocin infusion; or (4) expectant management for up to 4 days followed by labour induction with intravaginal prostaglandin E_2. The primary outcome variable was neonatal sepsis, which was determined by clinicians blinded to the maternal treatment. In spite of the large sample size, there were no statistically significant differences in the caesarean section or neonatal infection rates among the four treatment groups. Maternal infectious morbidity, as measured by the incidence of chorioamnionitis, was lowest in deliveries managed by immediate oxytocin induction. However, a digital vaginal examination at first admission for PROM was done in 37% of the women in the study. There were four perinatal deaths of nonmalformed infants in the expectantly managed groups, versus none in the groups with immediate induction, this difference was not statistically significant. One stillbirth occurred after 14 hours of expectant management. The reason was asphyxia and the other stillbirth occurred after 38 weeks of gestation due to group B streptococcal sepsis. There was one neonatal death due to birth trauma-first forceps and then a difficult caesarean section was performed-and one death occurred after 5 hours of labour in the hospital. The reason was fetal distress. It was not obvious how these patients were observed during the expectancy and during labour. While the findings of this investigation are important, there are several study limitations that deserve consideration when interpreting the results. The lack of information about the cervical examination for a large percentage of the study participants precludes subset analysis of the population of women with an unfavourable cervix. The dose of prostaglandin E_2 utilised in the two prostaglandin arms was 1 or 2 intravaginal doses of 1-2 mg, which are relatively low doses for cervical ripening and labour induction. As many as 72 hospitals participated in that study and conditions in the hospitals differed, as did some parts of the management.

These investigators (Hannah *et al.* 1996) also performed a survey of patient satisfaction in conjunction with this large randomised trial. They found that women who underwent immediate induction were more likely to give a positive evaluation of their treatment than women who were expectantly managed. In an unpublished study based on a random sample of women resident in the city of

Table 2. Characteristics of randomised studies of PROM in which oxytocin was used for induction.

Study	n	Location	Initial digital examination	Parity	Method of randomisation
Fayez 1978	112	Kansas, USA	All	All	Hospital number
Duff 1984	134	Texas, USA	All	All	Day of week
Morales 1986	317	Florida, USA	None	All	Day of week
Van der Walt 1989	40	Pretoria,South Africa	None	All	Open list of numbers
Wagner 1989	182	California, USA	Some	All	Hospital number
Tamsen 1990	93	Uppsala, Sweden	None	All	?
Rydhström 1991	277	Lund, Sweden	All	Nulliparous	**Formal randomisation**
Grant 1992	444	Bellshill, UK	None	Nulliparous	**Formal randomisation**
Ray 1992	100	California,USA	None	All*	**Formal randomisation**
Alcalay 1993	154	Tel Aviv, Israel	None	All	Open list of numbers
Sperling 1993	124	Copenhagen ,DK	All	All*	**Formal randomisation**
Natale 1994	242	Ontario, Canada	All	All	?
Ottervanger 1996	123	The Hague, Netherlands	?	Nulliparous	**Formal randomisation**
Shalev 1995	566	Afula,Israel	None	All	Hospital number
Hannah 1996	2521	Multicentre	Some	All*	**Formal randomisation**
Hjertberg 1996	201	Stockholm, Sweden	All	Nulliparous	?
Ladfors 1996	1012	Göteborg, Sweden	None	All*	**Formal randomisation**

* Separate analysis for nulliparous and parous women
?= not reported

Göteborg, over 40% of women without experience of PROM did not know what they wanted to do if they experienced PROM. Among women with experience of PROM, 69% preferred induction within 24 hours after PROM. In this study only 13% of women with experience of PROM and 5% of women without experience of PROM preferred to await spontaneous contractions for up to 72 hours.

Randomised studies of PROM with prostaglandin versus oxytocin

Labour induction in a patient with an unripe cervix may result in protracted labour and an increased risk of operative vaginal or abdominal delivery. Cervical ripening with prostaglandins prior to labour induction in women with intact membranes may improve the chances of successful labour induction (Keirse *et al. 1993).* Some randomised clinical trials have compared induction of labour with prostaglandins versus induction of labour with oxytocin for PROM (Hannah *et al.* 1996, Lange *et al.* 1981, MacLennan *et al.* 1980, McQueen *et al.* 1990, Möller *et al.* 1987, Ray *et al.* 1992, Sanchez-Ramos *et al.* 1997, Westergaard *et al.* 1983). A meta-analysis of these trials (Hannah *et al.* 1997,b) indicated that induction of labour with prostaglandins increased the risk of maternal infections (chorioamnionitis), maternal inter-

ventions (numerous vaginal examinations; >8) and possibly also of neonatal infections compared to induction of labour with oxytocin. Induction of labour with prostaglandins increased the use of antibiotics in the neonate and admission to the neonatal intensive care >24 hours. There is no evidence from high quality trials that induction of labour with prostaglandins increases or decreases the rate of Caesarean section (Hannah *et al.* 1997,b).

Randomised studies of PROM with prostaglandin versus expectancy

A number of studies comparing induction of labour with prostaglandins versus expectancy have been performed (Chua *et al.* 1995, Chung *et al.* 1992, Davies *et al.* 1991, Gonen *et al.* 1994, Hannah *et al.* 1996, Hauth *et al.* 1977, Herabutya *et al.* 1991, Mahmood *et al.* 1992, Mahmood *et al.* 1995, Ngai *et al.* 1996, Ray *et al.* 1992, Van der Walt *et al.* 1989). An overview was presented in the Cochrane database (Hannah *et al.* 1997,c). Prostaglandin is more expensive than oxytocin and the meta-analysis did not show that prostaglandin was more beneficial than oxytocin. The fact that all these studies have been performed is remarkable since no studies have shown any advantage of using prostaglandin instead of oxytocin.

Bathing in labour after PROM

Water has been used for therapeutic purposes for centuries. The pioneer of the use of water during labour in modern obstetrics was the French obstetrician Michel Odent. He stated that he had never noticed any problems with neonatal infections after bathing (Odent 1983). It was also claimed that a tub bath could reduce pain and might improve cervical dilatation during the first stage of labour (Lenstrup *et al.* 1987). In many delivery wards women in labour are offered a bath for relaxation purposes. The protection from infection offered by the amniotic sac might be removed once the membranes are ruptured. Accordingly, bathing during labour may increase the risk of infection in mothers and newborn infants, especially after PROM, and has been discouraged. However few and small studies have been performed concerning bathing and PROM and conflicting results have been found regarding the neonatal outcome (Waldenström *et al.* 1992, Cammu *et al.* 1994).

Evidence-based medicine

A new paradigm for medical practice has emerged. Evidence-based medicine de-emphasises intuition, unsystematic clinical experience and pathophysiological rationale as sufficient grounds for clinical decision-making, and stresses the examination of evidence from clinical research. Evidence-based medicine requires new skills of the physician, including efficient literature-searching, and the application of formal rules of evidence in evaluating the clinical literature. The influence of evidence-based medicine on clinical practice and medical education is increasing. The Cochrane Library is a regularly updated electronic library designed to give the evidence needed for informed health care decision-making. It is published four times a year and there are many studies in obstetrics in the database. The “golden standard” when studying a clinical problem is the randomised controlled trial (RCT).

Statistical power analysis

When planning a study or evaluating the evidence from a published article, knowledge about power analysis is of importance. Statistical power is the probability of getting a statistically significant result provided that there is a biologically real difference between, for example, two different populations studied. If a particular test of a difference is not statistically significant, is it because there is no effect or because the study design makes it unlikely that a biologically real difference would be detected? Power analysis can distinguish between these alternatives and is therefore a critical component in the design

of experiments and testing of results (Peterman 1990).

The power of a test is the probability of rejecting the null hypothesis given that the alternative hypothesis is true (Muller *et al.* 1992). Power depends on the type of test, increases with sample size, effect size and higher α-level and declines with increasing variance in the population. Effect size is the difference between the null and alternative hypothesis, and can be measured by using either raw or standardised values. Raw measures, such as the slope in a regression analysis or the difference between means in a *t*-test, are closer to the measurements that researchers take and are easier to visualise and interpret. Standardised measures, such as the correlation coefficient or *d*-value (difference in means divided by the standard deviation), are dimensionless and incorporate the sampling variance implicitly, removing the need to specify variance when calculating power.

A power analysis is most useful when planning a study. Such a "prospective" power analysis is usually exploratory in nature, investigating the relationship between the range of sample sizes that are deemed feasible, effect sizes thought to be biologically important, levels of variance that could exist in the population (usually taken from the literature or from data in pilot studies), and desired levels of α . The result is a choice about the sample size and α-level that will be used in the study, and the target effect size that will be "detectable" with the given level of statistical power.

After the study is completed and the results analysed, a "retrospective" power analysis can also be useful if a statistically non-significant result was obtained (Thomas *et al.* 1996). The actual sample size and α-level are then known, and the variance observed in the sample provides an estimate of the variance in the population. These values are used to calculate power at the minimum effect size thought to be of biological significance, or alternatively the effect size detectable with the minimum desired level of power. Note that it is rarely useful to calculate power using the effect size observed in the sample: such analyses tell us nothing about the ability of the test to detect biologically important results (Thomas 1977).

Example of a power analysis

A "null hypothesis" ($\mathbf{H_0}$) is set up. It states that the treatment and control group would have the same mean if we repeated the experiment a large (infinite) number of times.

An alternative hypothesis **(H_1)** is that one particular mean will be greater than the other (called 1-tailed test) or that two means will be different but the researcher cannot say a priori which will be greater (called 2-tailed test).

A two-tailed test has an α area at each end

A one-tailed test has an α area only in the middle (seldom used in medical research)

$\mathbf{t_1}$: is the break point for $p<0.05$

$\mathbf{H_1}$: a test value obtained >1.96

α**:** the level of significance that is chosen (e.g. 0.05)

β**:** the level is chosen (over 0.70, often 0.80)

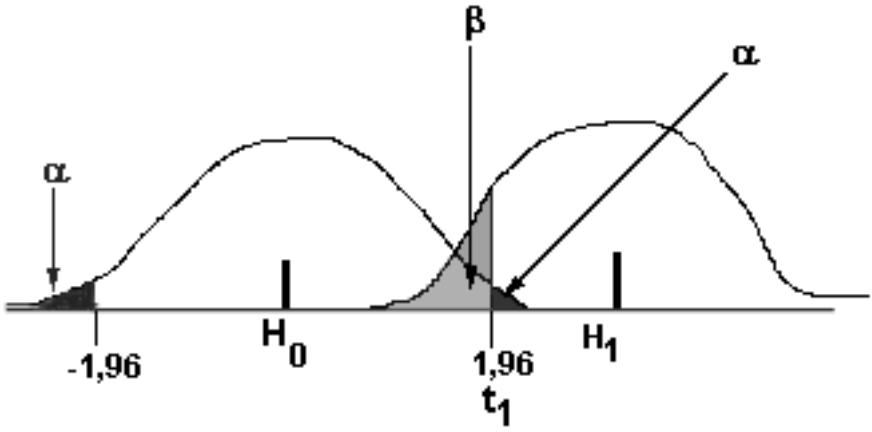
power= $1-\beta$

To reject the null hypothesis when it is true is to make what is called a type **I error** (the result falls in area α).

If we do not reject the null hypothesis when in fact there is a difference between the groups we make what is called a **type II error** (the result falls in area β).

Of all perfectly designed studies where there is a real difference between the populations, with adequate sample size for 80% power, 20% of the studies will fail to show a statistically significant effect.

Fig. 1 Example of a power analysis



Aims of the study

The aims of this study were:

- To evaluate risks and benefits for nulliparous and parous women after 34 weeks of pregnancy with expectant periods from 24 to 72 hours after PROM.
- To compare the perinatal infectious outcome between groups of women with PROM with two different expectant managements and to study the possible associations between demographic, intrapartum and postpartum variables and neonatal sepsis.
- To evaluate the influence of a tub bath on infectious morbidity in mothers and their offspring in women with prelabour rupture of the membranes after 34 weeks of gestation .
- To study the false negative rate using a sterile speculum examination for the diagnosis of ROM using analysis of diamine oxidase as the standard.
- To evaluate possible risks for the mother and the baby if the woman was allowed to return home without any further controls if no amniotic fluid was visible on speculum examination.
- To determine the prevalence and identify risk factors for PROM after 34 weeks of gestation in an urban Swedish population.

Material and methods

Clinical studies

Study I A randomised trial of two expectant managements of prelabour rupture of the membranes at 34 to 42 weeks.

Study II Risk factors for neonatal sepsis in offspring of women with prelabor rupture of the membranes at 34–42 weeks.

Study III Warm tub bath during labor. A study of 1385 women with prelabor rupture of the membranes after 34 weeks of gestation.

Study IV Is a speculum examination sufficient for excluding the diagnosis of ruptured fetal membranes?

Patients

Two thousand and ninety-nine women admitted to the delivery ward on suspicion of rupture of the membranes were examined by sterile speculum examination at admittance. Women with amniotic fluid visible at the speculum examination were included in the randomised studies (Studies I, II and III). Women without amniotic fluid visible at the speculum examination were included in Study IV. Informed consent was always obtained. All women participating in the studies had a normal singleton pregnancy after 34 weeks of gestation.

Study protocols

Randomised study of PROM (Study I, II and III)

At admission, a sterile speculum examination was performed for diagnosis of rupture of the membranes(Fig. 2). If amniotic fluid was visible at the speculum examination cultures from the cervix were performed including Group B streptococcus (GBS), *Candida albicans*, *Gardnerella vaginalis* and Gram-negative enterobacteria. Separate cultures were performed for *Ureaplasma urealyticum* and *Mycoplasma hominis* . The results of the bacteriological analysis were blinded and not available to anyone before the end of the trial. Digital examinations were not allowed before the contractions started or labour was induced.

Patients without contractions during the first two hours after the speculum examination were randomly allocated to either induction within 24 hours (*early induction group)* or induction within 72 hours (*late induction group)*. A computer generated a list of random numbers. A sealed, opaque and sequentially numbered envelope containing the randomisation code was used for each patient. Women with contractions within 2 hours after the speculum examination were also included in the calculations as a *short latency group.* For study purposes, rupture of the membranes was said to occur when amniotic fluid was confirmed by a sterile speculum examination. In the *early induction group* the patients were observed in the antenatal ward awaiting contractions for up to 24 hours. Body temperature was measured twice a day. A strict protocol was followed. Women in the *early induction group* were induced 2–24 hours after randomisation. If rupture of the membranes was diagnosed between midnight and 6:00 a.m. and no contractions had occurred at 8:00 a.m. the same day, induction was started with oxytocin. If rupture of the membranes was diagnosed

between 6:00 a.m. and midnight and contractions were absent at 8:00 a.m. the next day, oxytocin was administered to induce labour. Five units of oxytocin were administered in 500 ml sodium chloride, and the initial dose of oxytocin was 2.5 mU/minute. The infusion rate was raised by 2.5 mU/min. every 30 minute until progress of labour. Women in the *late induction group* were observed at the antenatal ward awaiting contractions for up to 72 hours. Women in the *late induction* group were induced 50–72 hours after randomisation. If rupture of the membranes was diagnosed between midnight and 6:00 a.m. and no contractions had occurred at 8:00 a.m. two days later, oxytocin was administered. On the other hand, if rupture of the membranes was diagnosed between 6:00 a.m. and midnight and no contractions were present at 8:00 a.m. three days later, the patient received oxytocin at that time. During the expectancy a FHR tracing and analysis of C-reactive protein (CRP) were performed each day. Body temperature was measured twice a day. In cases of an abnormal FHR, labour was induced. If chorioamnionitis was detected, the patient received antibiotics (Cefuroxim 1.5 g three times a day) and oxytocin infusion was started. Chorioamnionitis was considered to be present if body temperatures were ≥38°C on two occasions one hour apart without evidence of any other sources of fever or if the CRP was elevated over 40 mg/l. All fetuses had a fetal scalp electrode adapted but no intrauterine pressure catheters were used.

Immediately after the delivery, blood samples were taken from the umbilical cord for CRP and blood gas analysis. A specimen for culture of GBS and *Escherichia coli* was obtained from the external ear canal of the newborn infants immediately after delivery. The results of the CRP and the cultures were blinded for the paediatrician. The newborn infants were observed like other newborn infants, i.e. a paediatrician examined the baby on the day after delivery unaware of the woman's participation in the study. However, the paediatrician had the opportunity to get information from the obstetrical record. No special protocol was used to diagnose neonatal infections. It was thought that the use of such a protocol might lead to over-diagnosis of clinically unimportant conditions. A neonatologist read the files of all the newborn babies admitted to the neonatal care unit. All neonates with any signs of infection were assigned to one of three groups:

1. Proven sepsis: Bacteriologically proven infection, i.e. neonates with clinically suspected infection in which a positive culture from blood, cerebrospinal fluid and/or urine was found.

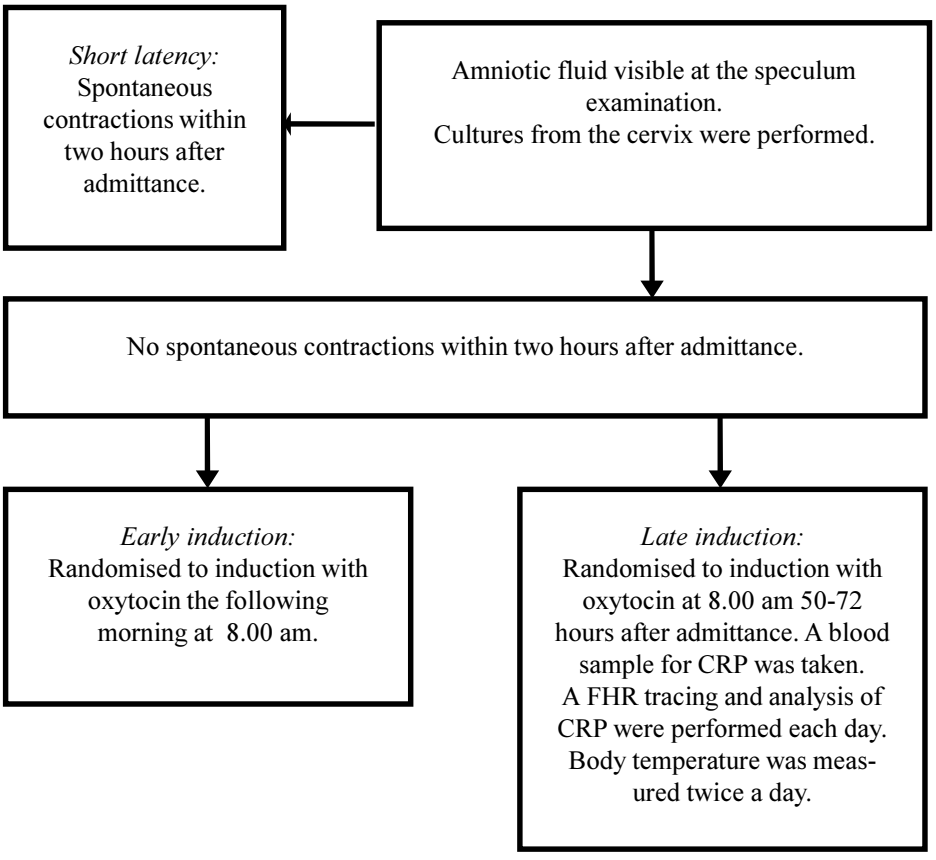
2. Suspected sepsis: Infection diagnosed on clinical grounds, i.e. neonates with clinical signs of infection and a CRP level of >20mg/l in blood taken from the newborn child or a band/total neutrophil ratio of >0.2. The blood samples were taken within 48 hours after symptoms occurred. The clinical signs included respiratory problems, haemodynamic changes, convulsions or temperature ≥38°C.

3. Other neonates treated with antibiotics that did not fulfil the above criteria.

In the analysis, newborn infants with proven or suspected sepsis were classified as **clinical sepsis**.

The main parameters analysed and tested for differences between the randomised groups were proven sepsis and clinical sepsis. Other parameters evaluated as potential risk factors for neonatal infections were: gestational age, parity, smoking, treatment for a lower genital tract infection during pregnancy, spontaneous contractions or induced labour, augmentation of labour, maternal CRP at first admission for PROM, hours after ROM to established labour, time from PROM to delivery, time from established labour until delivery, mode of delivery, maternal infections, CRP in the umbilical cord blood, Apgar score, pH in the umbilical cord

Fig 2. Algorithm for patients in Studies I, II and III.

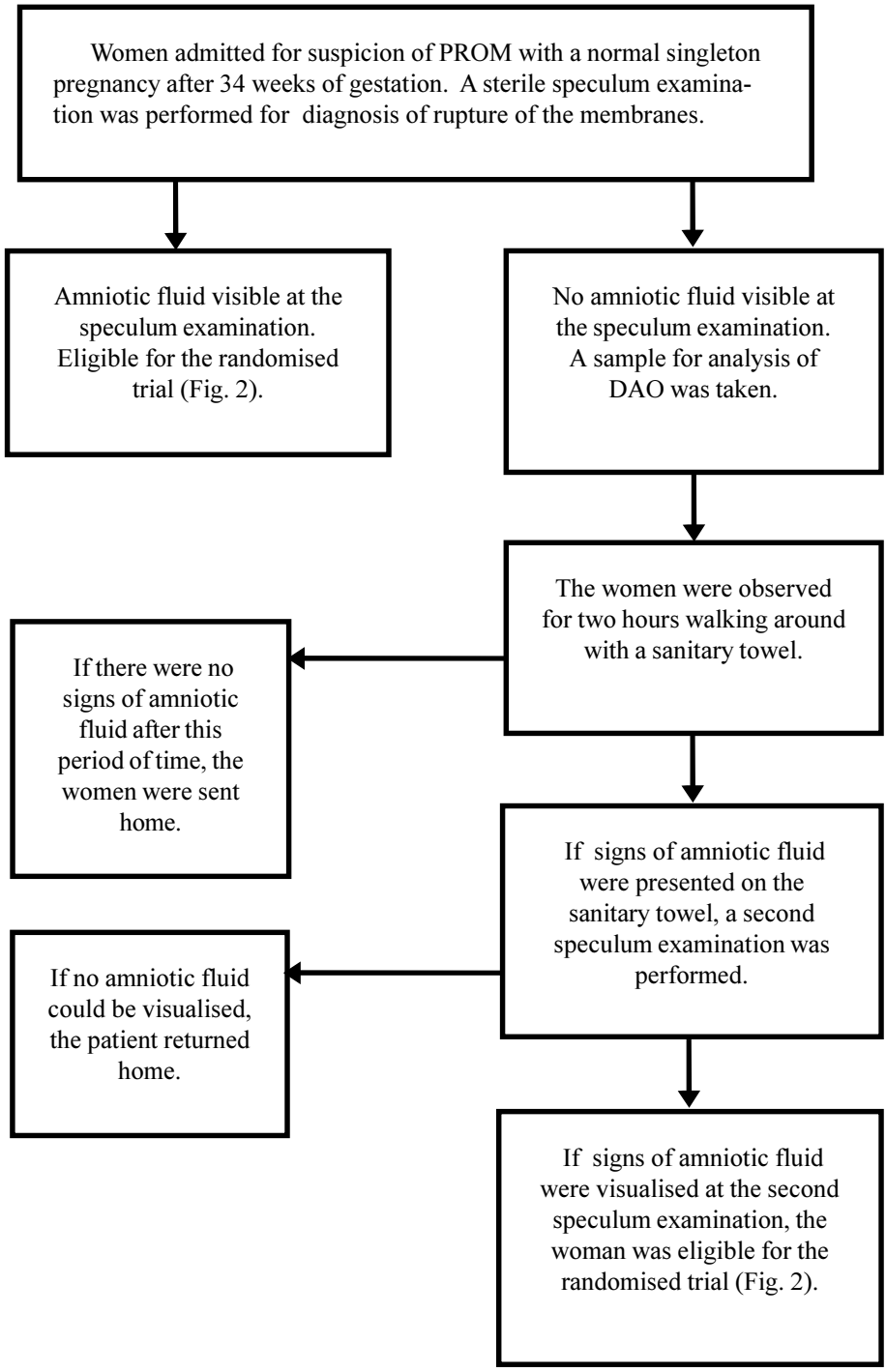


and the results of cervical culture of the mother and culture from the external ear canal of the newborn infant. Endometritis was diagnosed in women with a temperature of 38°C or greater documented on two occasions with no other source of infection in association with a tender uterus on palpation.

Prospective study of women with equivocal rupture of the membranes (Study IV).

At admission, a sterile speculum examination was performed for diagnosis of rupture of the membranes. If no amniotic fluid was visible at the speculum examination a test for diamine oxidase (DAO) was conducted (Fig. 3). Digital examinations of the cervix were avoided until labour. The women were observed for two hours walking around with a sanitary towel. If there were no signs of amniotic fluid after this period of time, the women were sent home. If signs of amniotic fluid were present on the sanitary towel, another speculum examination was performed, but if no amniotic fluid could be visualised, the patient returned home. Clinical data regarding mothers and babies were collected prospectively. Cultures were processed in the Laboratory of Microbiology at Sahlgrenska University Hospital.

Fig 3. Algorithm for patients in Study IV.



Analysis of Diamine Oxidase

A strip of absorbent paper (10 x 65 mm) was introduced into the vagina, and was withdrawn when it was soaked wet and placed in a tube for later analysis. The laboratory analysed the tests continuously but neither the obstetricians nor the women were informed about the results of the DAO tests. The results of the DAO analysis were not available until the trial was finished.

The DAO activity was determined with ^{14}C-Putrescine as the substrate. The strip was placed in a tube and 5 ml of 1/15 M phosphate buffer at pH 7.4 and 2 ml of the extract was warmed to 37°C. Then 100 mikrol. of 0.5 mM ^{14}C-Putrescine was added and the mixture was incubated at 37°C for 15 minutes. After this, 0.2 ml of 10 mM aminoguanide sulphate in 3% (w/v) sodium carbonate solution and 10 ml of scintillation solvent (0.5% w/v, solution of Butyl-PBD in toluene) were added. The tubes were shaken and chilled to –39°C. When the water had frozen the toluene phase was transferred to a counting vial and the radioactivity was measured.

Epidemiological study

Study V: Prevalence and risk factors for prelabour rupture of the membranes (PROM) at or near term in an urban Swedish population.

This study was based on women resident in the city of Göteborg, the second largest city in Sweden (population 454.000). Each year there are approximately 10.000 births in the city of Göteborg, comprising about 10% of all infants born in Sweden. The total female population from the birth cohorts 1955, 1959, 1963, 1967 and 1971 resident in the city of Göteborg at the time of this study (1996) was 18.073. A random sample of approximately 600 women from each of these five birth cohorts was obtained from the population register (n = 2880). All births in Sweden are recorded in the Swedish Medical Birth Register (MBR). The register is based on standardised medical records of maternal, obstetric and neonatal health care from all deliveries in Sweden and includes the hospital code and community affiliation of the mother. Approximately 150 variables are recorded in the MBR. Information from the MBR regarding the present population sample was obtained. In addition, information was obtained directly from the case records of women delivered in Göteborg since the quality of the information in the MBR is low in some variables. From these case records, the following information was obtained: parity, year of delivery, possible complications during delivery such as cervical rupture, PROM in an earlier pregnancy, previous dilatation and curettage or conisation or gynaecological laparotomy, history of sexually transmitted diseases (STD) and occupation. Information was also obtained about the present pregnancy: singleton or multiple pregnancy, body weight at the start and at the end of pregnancy, cigarette smoking, occurrence of a urinary tract infection, enteritis, STD, hospital treatment for premature contractions, vaginal bleeding, the presence of polyhydramnios and the occurrence of PROM and other complications during pregnancy. This information was linked with the data from the MBR.

Statistical methods

The SAS software package (SAS Institute, Cary, N.C.) was used for statistical analysis. Since the frequency of operative deliveries for women with PROM was unknown in our population, an independent consultant statistician performed an interim power analysis after 18 months. The primary efficacy variable was the frequency of operative deliveries in nulliparous women. At that time the frequency was 19.6% in the *early* induction group and 11.5% in the *late* induction group. The sample size required to show a difference between the groups of about 40% and to reach a power of 80 per cent (α= 0.05 and β= 0.20) was 315 patients in each group.

Continuous data were tested for significance with Wilcoxon's rank sum test, Duncan's multiple range test or Tukey's studentised range test HSD. Dichotomous data were tested for significance with Fischer's exact test, and adjustments (multiplication by three) of the p-values due to multiple comparisons were performed by Bonferroni's method. A p-value <0.05, when appropriately adjusted by Bonferroni's method, was considered statistically significant.

Univariate logistic regression was used to study variables correlated to the dependent outcome. Stepwise logistic regression was performed to suggest the predictor variables that consisted of apparently independent and significant predictors of the studied outcome.

Results and discussion

Prevalence of PROM (Study V)

In our hospital-based study the prevalence of PROM was 6% (Study I) and in the cohort study from a representative part of the population the prevalence of PROM was 13% (Study V). In the cohort study, 248 out of 1253 women had experienced PROM, meaning that 20% of all women in the population had experienced PROM in at least one of their deliveries. Reasons for the discrepancy in prevalence could be that some women were not eligible for the randomised study and some of the eligible women were missed. The criteria for diagnosing PROM may also have differed during the years as no specific protocol was followed. These results are in accordance with the finding by Keirse that the prevalence of PROM varied between 6 and 19% depending on whether the study was based on a specific hospital population or on the total population and whether it was a retrospective or a prospective study. The methods used to diagnose ROM and the duration of the latency period chosen between ROM and spontaneous contractions also influenced the prevalence in different studies (Keirse *et al.* 1996).

Risk factors of PROM (Study V)

In the stepwise logistic regression analysis (Study V), risk factors for PROM were primiparity, PROM in a previous pregnancy, bleeding in the first trimester, premature contractions and age ≥35 years at delivery (Table 3). These factors are unfortunately difficult to influence and thus provide no guidance regarding future management aimed at reducing the occurrence of PROM. Differences in risk factors between this study and other studies could be attributed to differences in populations and the fact that few investigators have used multiple regression analysis to determine risk factors. Harger reported three independent risk factors for PPROM: antepartum vaginal bleeding in more than one trimester, current cigarette smoking and previous preterm delivery (Harger *et al.* 1990). In an Italian prospective case-control study also using multiple regression analysis, risk factors for PPROM were low social class, smoking in pregnancy, 1st or 2nd-3rd trimester haemorrhages, cervical incompetence and a documented cervico-vaginal infection during the index pregnancy (Spinillo *et al.* 1994). Some of the risk factors found in our study performed at or near term were also found in their studies performed in women with PPROM. Thus, the etiology of PROM at or near term may not differ greatly from the etiology of PPROM. However there were differences between these studies and our study regarding the influence of cigarette smoking and cervico-vaginal infections. In the present study, we were unable to find an association between PROM and cigarette smoking.

Table 3. Stepwise multiple logistic regression analysis of antenatal risk factors for PROM. A comparison of 268 deliveries with PROM and 1652 deliveries without PROM from the population study.

	Odds ratio (95% CI)	p
Primiparity	2.06 (1.57, 2.70)	0.0001
PROM in a previous pregnancy	2.95 (1.59,5.48)	0.0001
Bleeding in first trimester	3.11 (1.61, 5.99)	0.0004
Premature contractions	2.23 (1.22, 4.09)	0.0091
Age at delivery ≥35 years	1.61 (1.06, 2.45)	0.0253

Diagnosis of ROM and management of equivocal PROM (Study IV)

In this study, a speculum examination was used as the only method to diagnose ROM. Only the visualisation of pooling of amniotic fluid on speculum examination was accepted as diagnostic of ROM (Study I, II and III). In 4% (51/1385) of the women amniotomy was performed at the delivery. Whether the reason for this was an incomplete ROM or a false positive diagnosis remains unclear. Another way of selecting patients would have been to include women with pooling of amniotic fluid at the speculum examination together with a positive nitrazine test. It is possible that some false positive diagnoses could have been avoided by doing this. However, no study has demonstrated the need for a test for ROM and for that reason we found no reason to add a method for diagnosing ROM in this study.

In 25% (519/2099) of the women admitted for suspected PROM fluid could not be visualised at the speculum examination. Kragt and Keirse (1990) found in their study in preterm gestations that 20% of women admitted for suspected ROM did not have ROM.

Among 27502 deliveries there were 519 women admitted for suspected ROM in whom fluid could not be visualised at the speculum examination. The frequency of equivocal PROM of the total deliveries in that period was 519 out of 27502 (1.9%). Diamine oxidase was analysed in all cases of equivocal PROM (Study IV) since there are some reports of high sensitivity and specificity for that test, at least when used in women with known status of the membranes (Elmfors *et al.* 1974, Gahl *et al.* 1982). Another advantage of using DAO in the present study was that the test was not analysed at the delivery ward and for that reason information on the test results did not influence the management of the patients. A positive DAO was only used in an effort to analyse the false negatives from the speculum examination. Sixty-three women out of 519 had a positive DAO in spite of the fact that no amniotic fluid was visible at admittance. The proportion of these patients in relation to all deliveries at the clinics during the study period was 0.2% (63 out of 27502). To detect an increase in neonatal clinical sepsis from 2% to 4% (power 0.80, alpha=0.05), a study with about 1130 women in each group would have been needed. If the frequency of false negatives is 0.2%, the total number of deliveries has to be 565 000 to find 1130 with a false negative speculum examination. No such study has been reported and it could be questioned if there is a need for a test of PROM if the frequency of equivocal PROM is as low as in the present population and a speculum examination is used for the diagnosis of ROM. In our protocol, women admitted for suspected PROM with normal pregnancies were sent home without any further controls if no amniotic fluid was visualised at the speculum examination. In our study, no disadvantages could be found with this management (Study IV) and we are not aware of any studies reporting a risk for these women if they are sent home. To our knowledge, only a few studies have focused on women with equivocal PROM. Fetal fibronectin (FFN) was evaluated in women with a history of prelabour ROM at term but without visible amniotic fluid leakage. No significant difference was found in the time interval between presumed ROM and delivery between those with a negative fibronectin test and those with a positive test (Nisell *et al.* 1996). The investigators' conclusion was that determination of fetal fibronectin in cervical secretion was of limited value in the clinical management of equivocal rupture of the membranes. At the National Maternity Hospital in Dublin, an evaluation was made of the value of ultrasound amniotic fluid quantitation in the diagnosis and management of PROM. The deepest vertical pool was measured in 151 consecutive patients

with a history of suspected PROM for at least 10 h before labour. In 100 patients the diagnosis of PROM was confirmed by the collection of amniotic fluid at the vulva. No difference in the mean depth of amniotic fluid could be found in 100 women with confirmed PROM, compared to those in whom PROM was not confirmed (48.5 mm S.D. 16.4 vs. 60.1 mm S.D. 16.5). The frequency of oligohydramnion (fluid depth less than 30 mm) was 5.0% and 5.8% respectively (Robson *et al.* 1990). There was no relationship between amniotic fluid quantitation by ultrasound and the onset of labour, the duration of labour or the frequency of oxytocin augmentation in labour. The results showed that ultrasound quantitation of amniotic fluid was of no value in the diagnosis and conservative management of PROM at term. In 65% of institutions in the United States ROM is diagnosed by inserting a gloved hand into the introitus to obtain specimens for crystallisation and nitrazine testing (Atterbury *et al.* 1998,a). It was claimed that this procedure had not undergone reliability testing. Considering both the ease with which a sterile speculum examination can be performed and the possible sequelae of a digital examination after PROM, the benefit of using methods other than a sterile speculum examination to diagnose PROM was questioned (Atterbury *et al.* 1998,b).

A problem with tests for PROM is the low sensitivity and specificity found when the test is applied in women with equivocal PROM compared to if the test is used in women with known status of the membrane (Table 1). For example, one evaluation of the Ferning test showed a sensitivity of 51% and a specificity of 71% when the test was performed in women with equivocal ROM (De Haan *et al.* 1994).

Before new and costly methods of diagnosing ROM are introduced, there must be studies showing the clinical benefit for such a test. Studies involving a sufficient number of women to show the possible benefits are warranted. We are not aware of any such studies and we believe that the companies and doctors introducing methods for diagnosing ROM have a responsibility to perform such studies before a test is commercially introduced.

Management of PROM (Study I)

In our protocol, estimation of the cervical dilatation was done at admission. In 99% of the cases the cervix was estimated to be open 0-2 cm and it could be questioned whether a speculum examination for evaluating the ripeness of cervix is of any use. One problem is the fact that digital examination of the cervix is the only available method to find women with a Bishop Score <3, and that a digital examination may start the clock of infection (Schutte *et al.* 1983). Among the 27502 deliveries from March 1989 until March 1993, we identified 1580 women who had a normal singleton pregnancy with the fetus in cephalic presentation and rupture of the membranes confirmed by a sterile speculum examination. Altogether 1385 women entered the trial (Study I). Spontaneous contractions within 2 hours after the speculum examination occurred in 373 women and these were included in the calculations as a short latency group. Women without contractions two hours after admittance were randomised to the early induction group (n=502) or to the late induction group (n=510). The women in the short latency group and late induction group who had the opportunity to await spontaneous contractions provided information about the time interval from rupture of the membranes to spontaneous labour (Table 4).

The frequency of spontaneous vaginal deliveries differed between nulliparous and parous women ($p<0.001$) and the obstetrical outcome in nulliparous and parous women is presented separately. This may be an important finding and could motivate different management in parous and nulliparous women. Some authors have only included

Table 4. Hours from diagnosis of PROM until spontaneous contractions and delivery (cumulative frequency,%).

Hours ≤	ROM to spontaneous contractions	ROM to delivery
6	52%	11%
12	68%	37%
18	75%	55%
24	78%	68%
32	83%	75%
38	86%	80%
44	88%	83%
48	89%	85%

nulliparous women (Grant *et al.* 1992. Hjertberg *et al.* 1996, Ottervanger *et al.* 1996, Rydhström *et al.* 1991), but in most studies results from nulliparous and parous women have been mixed. Our findings of differences between nulliparous and parous women are similar to the results in a recent multicentre trial (Hannah *et al.* 1996). The rate of spontaneous vaginal deliveries in their study was 59% for nulliparous and 87% for parous women ($p<0.001$). Accordingly, we propose that an adequate analysis of a trial of PROM at or near term regarding the obstetrical outcome should be subdivided according to parity.

In this study the women were all hospitalised. The possible benefits of having the women at home during the expectant period are a higher satisfaction with the care, avoidance of hospital-acquired infections and lower costs. The negative effect could be that in cases of complications, e.g. an abruptio placenta, the time delay would be longer if the mother is at home. In our study, a FHR tracing once a day and maternal temperature measurements twice a day were sufficient to detect the few cases of complications found. Daily measurement of CRP was of no value. This may imply that these women could be cared for at home during the expectancy period with daily check-ups at the hospital. In the multicentre trial (DiCecco R *et al.* 1998), altogether 2520 women were randomised to expectant management but only in 1670 cases was there information about whether the woman was partially or completely cared for at home during the latency period. One thousand and seventeen women were cared for in hospital and 653 women were cared for partially or completely at home. Multiple regression analysis showed that women cared for at home had a higher risk of use of antibiotics in the mother and the neonate (Hannah, pers. comm.). However, women were more satisfied with their care if they had received their care partially or completely at home. Since this part of the study was not randomised and data were missing for 40% of the women, it is difficult to draw conclusions. No prospective randomised study of adequate size has been performed to provide the final answer to this question.

Obstetrical outcome in nulliparous women (Study I)

In the early induction group, 38 per cent of the women were induced, compared to eleven per cent of the women in the late induction group ($p<0.001$) because no contractions occurred during the latency period. The rate of spontaneous deliveries was 89% in the late induction group, compared to 81% in the early induction group. Ventouse extraction was more often used in the early induction group compared to the late induction group (Fig. 3). Altogether 18 women (6%) in the early induction group were delivered by ventouse, compared to 6 (2%) in the late induction group due to an abnormal fetal heart rate tracing. Insufficient contractions in the second stage was the reason for ventouse extractions in 25 women (8%) in the early induction group vs. 16 women (5%) in the late induction group. Two ventouse extractions were performed because of exhausted mothers in the early induction group and one in the late induction group. For nul-

Fig 3. Mode of delivery in the randomised groups, nulliparous women (n=640)

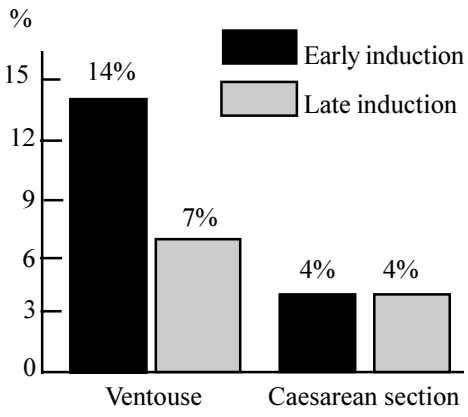
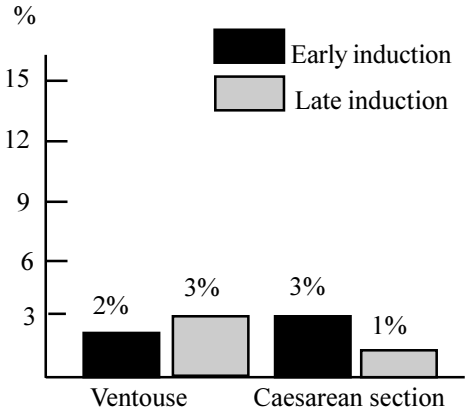


Fig 4. Mode of delivery in the randomised groups, parous women (n=372)



liparous women there was a greater chance of spontaneous vaginal delivery with expectant management (OR=0.57, 95% CI 0.36 to 0.88). To avoid one operative vaginal delivery, fourteen nulliparous women must be managed with delayed induction (Table 5). If the risk of a third or fourth degree perineal tear after operative vaginal delivery is 10.6%, compared to 4.1% after spontaneous vaginal delivery (Hagberg H. pers. comm.), about one out of 220 nulliparous women will avoid a severe perineal laceration with late instead of early induction.

An analysis of randomised studies with nulliparous women (Table 6) showed a higher rate of spontaneous vaginal deliveries with expectant compared to active management. Only two studies of nulliparous women did not find such a difference (Rydhström *et al.* 1991, Hjertberg *et al.* 1996). However, the sizes of these two studies were too small to detect a possible difference at 40% level, which was the difference used in our study. These findings are important since they imply that nulliparous women may benefit from expectant management since a lower frequency of ventouse or forceps extractions may reduce the risk of third or fourth degree perineal lacerations (Hagberg H. pers. comm.). No difference in the frequency of caesarean sections among nulliparous women managed actively or expectantly was found in our study or in an extended analysis of other studies (Table 7). Another finding from these overviews is the differences in the frequency of operative deliveries (10-48%) and CS-rate (3-17%) between different studies. These findings focus on differences in how the delivery wards are organised, how labour is managed and how ROM is diagnosed.

A group of special interest was the nulliparous women (n=32) in the late induction group, in which spontaneous contractions did not occur before the time limit ran out. These women were induced with oxytocin and when compared with nulliparous women

Table 5. Analysis of the influence of late compared to early induction on operative vaginal deliveries in nulliparous woman.

Absolute Risk Reduction	0.07
Relative Risk	1.99
Relative Risk Reduction	0.50
Prevalence (baseline risk)	7%
Number Needed to Treat	14

Table 6. Operative delivery rate in randomised studies of PROM, nulliparous women.

Study	n	Operative deliveries active management	Operative deliveries expectant management	OR (95% CI)
Rydhström 1991	277	12.2%	18.8%	0.61(0.32,1.16)
Grant 1992	444	48.4%	37.3%	1.57(1.08,2.29)
Ottervanger 1995	123	23.0%	9.7%	2.63(1.01,6.83)
Hannah 1996	1493	39.2%	28.7%	1.60(1.29,1.99)
Hjertberg 1996	201	24.8%	25.0%	0.99(0.52,1.87)
Ladfors 1996	640	18.6%	11.5%	1.77(1.14,2.76)
Total:	3178	32.4%	24.6%	1.47(1.26,1.72)

with spontaneous contractions in the late induction group no differences in the mode of delivery could be detected. However the small size of this subgroup means that the analysis lacks enough power to be conclusive.

In a stepwise multiple regression analysis predictors of caesarean section in nulliparous women were: occiput posterior position, chorioamnionitis, epidural analgesia, Bishop score <3 at the start of the delivery, birth weight ≥4000 gram, active labour >8 hours and established labour ≥12 hours after PROM (Table 8).

When the obstetrical outcome for nulliparous women was analysed in relation to the Bishop Score at the start of delivery, only small differences could be detected between women with different scores. However, women with a Bishop Score of one or two (n=47) had a caesarean section rate of 15%, whereas in all the other groups the CS rate

Table 7. Caesarean section rate in randomised studies of PROM, nulliparous women.

Study	n	Caesarean section active management	Caesarean section expectant management	OR (95% CI)
Rydhström 1991	277	2.9%	3.6%	0.79 (0.21,3.00)
Grant 1992	444	17.4%	11.1%	1.68 (0.98,2.88)
Ottervanger 1995	123	6.6%	3.2%	2.11 (0.38,11.62)
Hannah 1996	1493	14.1%	13.7%	1.03 (0.77,1.39)
Hjertberg 1996	201	4.0%	4.0%	0.99 (0.24,4.09)
Ladfors 1996	640	4.4%	4.3%	1.02 (0.4,2.18)
Total:	3178	10.7%	9.6%	1.13 (0.90,1.43)

Table 8. Stepwise logistic regression analyses of predictors of caesarean section in nulliparous women.

	Caesarean section OR (95% CI)	p
Occiput posterior	21.82 (7.1,66.9)	0.0001
Chorioamnionitis	25.70 (3.6,184.3)	0.0001
Epidural analgesia	3.69 (1.62,8.40)	0.0001
Bishop score <3	7.18 (2.41,21.35)	0.0001
Birth weight ≥4000 gram	4.26 (1.75,10.41)	0.0031
Active labour >8 hours	4.22 (1.46,12.16)	0.0076
Established labour ≥12 hours after PROM	2.38 (1.03,5.50)	0.0140

was 2–4% (OR=5.62, 95% CI 2.51 to12.57). Nulliparous women with a Bishop Score <3 are the group of interest for further research. In the multicentre study (Hannah *et al.* 1996) no information was collected on Bishop Score at the start of delivery and no earlier study has been able to detect at what Bishop Score nulliparous women are at an increased risk of CS. We believe that it is important in future studies of different methods of induction to include only nulliparous women with a Bishop Score of 0-2. If Bishop Score 0-2 occurs with a frequency of 0.17%, as in our trial, and if a study is to be able to detect a reduction in the CS rate from 15% to 7.5%, 280 women have to be randomised to each group. Accordingly, there have to be altogether 164.000 deliveries at the institutions involved to find these 560 nulliparous women. In this group, other drugs than oxytocin may be beneficial. Although this is a quantitatively small problem, it is clinically important. The role of preinduction cervical ripening with prostaglandins in the woman with PROM at or near term remains unclear. Based on current literature (Hannah *et al.* 1996, Hannah *et al.* 1997,b), it appear that women in whom immediate labour was induced would not derive any substantial benefit from preinduction cervical ripening with several doses of intravaginal prostaglandin E_2 gel or suppositories. Further research may define a role for prostaglandin E_2 in carefully selected patients and misoprostol may be an alternative (Sanchez-Ramos *et al.* 1997). Until such investigations demonstrate a substantial clinical benefit from agents used for cervical ripening, it is recommended that women with PROM receive oxytocin intravenously for labour induction.

Another positive effect observed after delayed induction in nulliparous women was a lower frequency of oxytocin-induced labour, 11% versus 38% in the early induction group, OR=0.20 (95% CI 0.13 to 0.30). However 66.9% of the nulliparous women in the late induction group received oxytocin during delivery, compared to 75.7% in the early induction group (OR=0.65, 95% CI 0.46 to 0.92). In the short latency group, 55% received oxytocin. Our protocol for timing of induction of labour in the early induction group was the same as Grant *et al.*(1992) used in their group of expectantly managed women. They showed that nulliparous women had a lower frequency of operative deliveries if they were expectantly managed. They concluded that their results supported a policy of expectant management until the next morning in nulliparous women with PROM. Their study was not designed to answer the question if a longer latency would be beneficial. In our study, no differences were found in the use of analgesia between the randomised groups, with an epidural analgesia rate of 19-22% for the nulliparous

women. In Grant's study (Grant *et al.* 1992) women managed expectantly had an epidural rate of 57%, vs. 70% in women immediately induced. This may imply that it is beneficial for nulliparous women to delay induction until the next morning but a further delay is not beneficial in terms of a less painful labour. In the trial from the United Kingdom (Grant *et al.* 1992), there was a high rate of operative deliveries compared to the Swedish investigations (Rydhström *et al.* 1991, Hjertberg *et al.* 1996).

It is well known that different social factors, the infectious panorama and management of labour have an influence on the modes of delivery. The results from the different trials of PROM report variable frequencies of operative deliveries and infectious complications. For a nulliparous woman, the odds ratio for a caesarean section was 4.10 (2.88 to 5.83) when the multicentre trial (Hannah *et al.* 1996) was compared with our study. The main problem in interpreting results from the multicentre trial is that the 72 institutions in six countries (Canada, UK, Australia, Israel, Sweden and Denmark) varied in many respects regarding clinical management other than randomisation and the management was left to the discretion of the attending nurse, nurse-midwife or physician. It is not easy to explain the big differences in the rates of operative deliveries between institutions. However, a number of differences in the management of labour, organisation of the delivery ward, populations and perhaps also legislation could be explanatory factors. It is obvious that the time of expectancy is not the only factor affecting the frequency of operative deliveries.

Obstetrical outcome in parous women (Study I)

The delivery started with spontaneous contractions in 61% in the early induction group compared to 89% of the patients in the late induction group. This frequency was similar to the findings among nulliparous women. Spontaneous vaginal deliveries were achieved in 95–96% of the parous women (Fig. 4). There was no difference in the operative delivery rate between parous women in the expectantly and actively managed groups. The frequency of operative deliveries was 5%, compared to 13% in the multicentre trial (Hannah *et al.* 1996). A low frequency of CS was found in parous women, without differences between the groups, 2% in this trial and 4% in the study by Hannah and co-workers. In a stepwise multiple regression analysis predictors of caesarean section in parous women were: previous CS (OR=9.15, 95% CI 2.1 to 40.1), meconium-stained amniotic fluid (OR=13.61, 95% CI 2.18 to 85.11) and induction of labour (OR=8.44, 95% CI 1.95 to 36.57)**.** There was a lower rate of oxytocin use in the expectantly managed group, 37% vs. 59%, OR=0.42 (95% CI 0.28 to 0.63). In parous women, no association could be detected between Bishop Score at the start of labour and risk of caesarean section. Similar use of analgesia was recorded in the early induction group and in the late induction group.

Maternal infections (Study I)

Four women in the early induction group, nine women in the late induction group and two women in the short latency group experienced chorioamnionitis and/or endometritis. The infectious morbidity was low in all groups and there was no statistically significant difference between the groups. Since there is a lack of a validated golden standard for the diagnosis of clinical chorioamnionitis, it is difficult to compare results between studies (Table 9).

The frequency of chorioamnionitis before or during delivery was 2 out of 502 (0.4%) in the early induction group vs. 7 out of 510 (1.4%) in the late expectancy group, OR=0.29 (95% CI 0.06 to 1.39). In the multicentre study (Hannah *et al.* 1996), a frequency of chorioamnionitis of 4.0% vs. 8.6%

Table 9. Chorioamnionitis in randomised studies of PROM.

	n	Chorioamnionitis active management	Chorioamnionitis expectant management	OR (95% CI)
Fayez 1978	112	3.8%	11.9%	0.34 (0.09,1.31)
Duff 1984	134	11.9%	4.0%	3.10 (0.85,11.28)
Morales 1986	317	8.0%	3.0%	2.67 (1.01,7.10)
Wagner 1989	182	0.0%	0.0%	
Tamsen 1990	93	0.0%	2.0%	0.16 (0.00,7.93)
Rydhström 1991	277	7.2%	10.9%	0.64 (0.28,1.45)
Ray 1992	100	7.3%	13.3%	0.51 (0.14,1.93)
Shalev 1995	566	11.7%	12.7%	0.92 (0.55,1.52)
Ottervanger 1995	123	1.6%	3.2%	0.52 (0.05,5.06)
Hannah 1996	3782	4.0%	8.6%	0.44 (0.31,0.61)
Ladfors 1996	1012	0.4%	1.4%	0.29 (0.06,1.39)

was found in the actively and in the expectantly managed groups respectively. In their study, a digital cervical examination was sometimes performed at admission and they used a temperature cut-off of 37.5°C to define fever. To exclude a difference in chorioamnionitis between 0.4% and 1.4%, a study including 2700 women would be needed. Since clinical chorioamnionitis in modern obstetrics with modern antibiotics is a small clinical problem, it could be questioned if it is really meaningful to design a study for this purpose.

Neonatal outcome (Study II)

No difference was detected in the number of children admitted to the Special Care Baby Unit (SCBU) between the early induction group and the late induction group. A difference regarding SCBU admittance was detected among children born in gestational weeks 34–36 compared to weeks 37–42. Neonates born in gestational week 34-36 were more often admitted to the SCBU, 34% vs. 10% ($p<0.001$), and the medium length of stay at the SCBU also differed, 7.4 vs. 4.1 days ($p<0.001$). Four neonates in the early induction group had a proven sepsis. Three of these cases had coagulase-negative staphylococci and in one case *Streptococcus pneumoniae* were isolated. One neonate in the short latency group had clinical signs of infection and a positive blood culture with coagulase-negative staphylococci. All five neonates had a CRP over 33 mg/l within two days after clinical onset of infection. However, it is possible that the positive coagulase-negative staphylococci cultures represented cutaneous contamination. The difference between the early induction group and the late induction group did not reach statistical significance ($p=0.06$, Fishers' exact test, Bonferroni's correction not used). Twenty-six (1.9%) of the newborn infants had clinical sepsis, including the five neonates with a positive blood culture. No differences between the groups with regard to clinical sepsis were found (Table 10). The odds ratio was not calculated for proven sepsis because of the small number of neonates with proven sepsis. In the multicentre trial (Hannah *et al.* 1996), no differences were found in the rates of neonatal infections between the groups. The infection rate was 2.0-3.0%, which is similar to our figures. Altogether 61 (4.4%) of the neonates received antibiotics in our study without any differences between the groups. In Hannah's trial, 11.1% of the neonates received antibiotics and one reason for this difference could be that blood samples

Table 10. Neonatal infectious outcome

	Proven sepsis Incidence (%)	Clinical sepsis* Incidence (%)	Clinical sepsis* OR (95% CI)
Short latency group	1/373 (0.27%)	4/373 (1.1%)	1.0
Early induction group	4/502 (0.80%)	11/502 (2.2%)	2.06 (0.64,6.70)
Late induction group	0/510	11/510 (2.2%)	2.03 (0.63,6.59)

* Neonates with proven sepsis or suspected sepsis are classified as clinical sepsis

were taken for culture in 80% of their neonates. In Rydhström's study (Rydhström *et al.* 1991), a neonatal infection was diagnosed when the neonate had pneumonia, meningitis, sepsis, pemphigus or impetigo. They found six infections in the expectantly managed group and one in the actively managed group (OR=6.27, 95% CI 0.75 to 52.80). In the randomised studies in which an initial digital examination was avoided, no differences in neonatal infection were found between actively and expectantly managed groups (Table 11). However, in studies in which some or all patients had an initial digital examination there was an increased incidence of neonatal infections in the expectantly managed group (Table 12).

Table 11 . Incidence of neonatal infection in randomised studies in which an initial digital examination was avoided at admittance.

Study	n	Active management	Expectant management	OR (95% CI)
Morales	317	0.0%	0.0%	-
Van der Walt	40	5.3%	0.0%	3.15 (0.12,82.17)
Tamsen	93	0.0%	4.2%	0.22 (0.01,4.77)
Grant	444	0.0%	0.4%	0.34 (0.01,8.41)
Alcalay	154	1.3%	1.4%	0.92 (0.06,15.05)
Shalev	566	2.1%	0.8%	2.73 (0.55,13.66)
Ladfors	1012	2.2%	2.2%	1.02 (0.44,2.37)
Total:	2626	1.5%	1.3%	1.12 (0.58,2.17)

Table 12 . Incidence of neonatal infection in randomised studies in which an initial digital examination was done at admittance.

Study	n	Active management	Expectant management	OR (95% CI)
Fayez	112	0.0%	5.4%	0.15 (0.01,2.99)
Duff	134	1.7%	0.0%	3.87 (0.16,96.78)
Wagner	182	0.0%	5.5%	0.10 (0.01,1.77)
Rydhström	277	0.7%	4.5%	0.16 (0.02,1.34)
Sperling	124	0.0%	0.0%	
Hannah	3782	2.0%	2.9%	0.71 (0.45,1.13)
Total:	4611	1.7%	2.9%	0.57 (0.37,0.87)

Predictors of neonatal sepsis (Study II)

CRP was taken at admission in 482 women in the late induction group and a CRP over 40 mg/l was found in three women. In two of these women clinical sepsis was found in their offspring. The other nine cases of neonatal clinical sepsis were found among offspring of women with a CRP below 10 mg/l at admission. Univariate analyses showed a significant association between clinical sepsis and: induction of labour (OR=2.94, 95% CI 1.30 to 6.68), established labour 24.1-32 hours after ROM (OR=5.89, 95% CI 1.68 to 20.63), established labour >32 hours after ROM (OR=4.59, 95% CI 1.52 to 13.87), time from ROM to delivery >32 hours (OR=5.07, 95% CI 1.40 to 18.39), caesarean section (OR=11.03, 95% CI 4.10 to 29.68), chorioamnionitis before or during delivery (OR=27.14, 95% CI 2.38 to 309.16), endometritis (OR=18.08, 95% CI 1.82 to 179.87), CRP over 20 mg/l in the umbilical cord (OR=17.12, 95% CI 5.68 to 52.12) and Apgar score <7 after 1, 5 or 10 minutes. In a stepwise logistic regression analysis, a significant association was found between clinical sepsis and caesarean section, time from ROM to delivery >32 h, gestational age 34-36 weeks and parous women (Table 13).

In women who were delivered 0-32 hours after ROM, no differences between the randomised groups in the frequency of neonatal clinical sepsis were found. Clinical sepsis was recorded in six out of 458 (1.3%) in the early induction group and in five out of 339 (1.5%) in the late induction group. However, in women who were delivered after a duration of ROM >32 hours five neonates out of 44 (11.4%) had clinical sepsis in the early induction group compared to 6 out of 171 (3.5%) in the late induction group.

In women from a high-risk population (Yancey *et al.* 1996), a stepwise logistic regression analysis was used to find risk factors for neonatal sepsis. In that study, risk factors were chorioamnionitis, preterm delivery, ROM >12 hours, endometritis, Group B streptococcus and age. Similar results were found in this study but there was no association between a positive cervical culture for GBS and neonatal sepsis. The reason for the differences could be the difference in populations.

GBS and PROM (Study II)

In 1317 out of 1385 newborn infants an ear canal culture was taken. A positive external ear canal culture for GBS was found in 10.0% of the neonates. No difference in the GBS colonisation was found between the newborn infants born to mothers in the short latency, early induction and late induction group. Three out of 132 (2.3%) newborn infants with a positive GBS culture from the external ear had clinical sepsis and in 22 out of 1185 (1.9%) newborn infants a negative culture and clinical sepsis was found (OR=1.23, 95% CI 0.36 to 4.16).

Table 13. Stepwise logistic regression analyses of antenatal risk factors for clinical sepsis

	Clinical sepsis*
	OR (95% CI)
Caesarean section	10.08 (3.26-31.20)
Time from ROM to delivery >32 hours	3.74 (1.62-8.62)
Gestational age 34-36 weeks	3.16 (1.11-8.96)
Parous women	2.41 (1.04- 5.57)

* Neonates with proven sepsis or suspected sepsis are classified as clinical sepsis

In 1356 out of 1385 women vaginal culture was performed. A positive vaginal culture for GBS was found in 10.3% of the women, without any differences between the three groups. In 85% of the women there was a negative cervical culture for GBS and a negative culture for GBS in the external ear of the newborn child. A positive culture in the cervix and in the neonate was found in 5%. Accordingly, the results of GBS culture differed between the mother and the neonate in 10% of the cases. Univariate logistic regression did not show any association between any sort of positive culture from the cervix or the external ear and clinical sepsis. Stepwise logistic regression did not show any association between any of the possible combinations of cultures and neonatal infections. In our population we could not find any indication for cervical cultures in women with PROM after 34 weeks. In the study from 72 centres (Hannah *et al.* 1996), vaginal or introital swabs were taken for GBS. Cervical cultures for GBS were positive in 10.7% of the women. The results of the analysis were not blinded and there was no common protocol for taking care of women with a positive culture.

No group B streptococcal neonatal sepsis was found in our study but in Hannah's study there were 10 cases and one of them was fatal. The incidence of GBS sepsis is about 3-5 cases in 1000 births and neither our study nor Hannah's had the power to answer the question of how serious GBS colonisation is in women with PROM. However, Hannah *et al (*Hannah *et al.* 1997,d) recommended that the best management for women with a positive culture was immediate induction with oxytocin, and they recommended that all women who considered expectant management should be screened for GBS in week 35-37 of their pregnancy. There is a problem when the results from Hannah's study are compared with ours because of the fact that 37.0% of the women in their study had had a digital vaginal examination performed before entry. They also found an association between the number of digital vaginal examinations and chorioamnionitis (Seaward *et al.* 1997).

Neonatal CRP, Apgar Score and acid-base status (Study II)

A blood sample from the umbilical cord for CRP analysis was taken in 1116 cases. CRP in the umbilical cord was 20 mg/l or more in 29 neonates (Table 14). CRP had a sensitivity of 28% and specificity of 98% in detecting neonatal sepsis**.** The low sensitivity

Table 14. Univariate analyses of CRP in the umbilical cord and Apgar score in relation to infectious morbidity.

	Proven sepsis Incidence (%)	Clinical sepsis* Incidence (%)	Clinical sepsis* OR (95% CI)
CRP in the umbilical cord			
CRP < 20	3/1087 (0.3%)	13 /1087 (1.2%)	1.0
CRP ≥20	1/29 (3.5%)	5/29 (17.2%)	17.12 (5.7-52.1)
Apgar score			
Apgar score ≥7 after 1 min.	4/1336 (0.3%)	22/1336 (1.7%)	1.0
Apgar score <7 after 1 min.	1/49 (2.0%)	4/49 (8.2%)	5.3(1.8-16.0)
Apgar score ≥7 after 5 min.	5/1372 (0.4%)	23/1372 (1.7%)	1.0
Apgar score <7 after 5 min.	0/13	3/13 (23.1%)	17.60(4.5-68.1)
Apgar score ≥7 after 10 min.	5/1379 (0.4%)	24/1379 (1.7%)	1.0
Apgar score <7 after 10 min.	0/6	2/6 (33.3%)	28.2 (4.9-161.6)

* Neonates with proven or suspected sepsis are classified as clinical sepsis

of the test and the low prevalence of neonatal sepsis are arguments against using CRP in the umbilical cord as a screening tool for neonatal sepsis. There was no significant difference in the frequency of low Apgar scores in the different groups. Apgar score less than 7 after 5 minutes was found in 6 (1.2%) neonates in the early induction group, 6 (1.2%) in the late induction group and in 1 (0.3) in the short latency group. There was a correlation between an Apgar score less than 7 at 1, 2 or 10 minutes and clinical sepsis (Table 14). The specificity for an Apgar score <7 after 10 minutes in predicting neonatal sepsis was high (99.7%), but the sensitivity was low (8%).

In a case-control study of 113 cases of neonatal sepsis and 347 randomly selected controls a strong association of an Apgar score <7 at five minutes (OR = 36.25, 95% CI 16.0 to 82.2) with neonatal sepsis suggested the possibility of routine sepsis evaluation in such neonates (Soman *et al.* 1985).

A sample for analysis of venous pH was taken from 918 umbilical cords and a sample from the umbilical artery was taken in 766 cases. The incidence of a low pH in the umbilical cord did not differ between the groups. An arterial pH below 7.10 was found in five neonates (1.7%) in the early induction group, versus five (1.7%) in the late induction group and three (1.6%) in the short latency group. A venous pH <7.20 was found in 22 (8.1%) in the early induction group, 25 (7.6%) in the late induction group and 1(0.5%) in the short latency group. No neonate with an arterial pH <7.10 had clinical sepsis.

Warm tub bathing in women with PROM (Study III)

Among the 1385 women who entered the study (Study I), 538 chose to bathe in a warm bath tub during labour for relaxation. Three women were not eligible for bathing since they developed a chorioamnionitis before labour started. Thus 844 women did not bathe. We analysed our material from this aspect although the study was not designed as a randomised trial of bathing or non-bathing. No differences in the frequency of bathing in the three groups were found, 37%-42%. There was a trend towards a higher incidence of chorioamnionitis and/or endometritis among bathing woman (Table 15). No increased neonatal infectious morbidity could be detected (Table 15). In another Swedish study, a significantly lower five minutes Apgar score was reported in infants born more than 24 hours after PROM if the mothers had bathed during labour (Waldenström *et al.* 1992) and the Swedish National Board of Health and Welfare recommended that women with PROM should bathe with caution during labour.

Table 15. Bathing during delivery

	Bath group n=538	Reference group n=844	OR (95% CI)
Chorioamnionitis/Endometritis	9/538 (1.7%)	4/844 (0.5%)	2.30 (0.87, 6.54)
Clinical neonatal sepsis	8/538 (1.5%)	18/844 (2.1%)	0.70 (0.30, 1.60)

Conclusions

- Parous women with PROM after 34 weeks of gestation had the same rate of operative deliveries irrespectively of whether they were induced with oxytocin within 24 hours or within 72 hours after PROM.

- A lower frequency of operative deliveries was found in nulliparous women if they were induced with oxytocin within 72 hours compared to within 24 hours after PROM.

- No differences were found in the frequency of neonatal sepsis between induction with oxytocin within 24 hours and within 72 hours after PROM.

- Risk factors for neonatal sepsis in women with PROM were: time from PROM until delivery exceeding 32 hours, caesarean section, parous women and gestational age between 34 and 36 weeks.

- No association was found between bathing during labour and neonatal infectious morbidity.

- If PROM was diagnosed only when pooling of amniotic fluid was visualised on speculum examination, 75% of the women admitted for suspected PROM were actually diagnosed as PROM.

- Among 519 women where no pooling was visible, the test for diamine oxidase was positive in 63 women. These women were sent home without further controls and no increased morbidity could be detected in this group.

- The prevalence of PROM in the population-based study was 12.9%

- Risk factors for PROM in the population study were age ≥35 years at delivery, nulliparity, premature contractions and bleeding in the first trimester.

Management of PROM at or near term - Clinical recommendations

Women who present with a history suggesting PROM at or near term should undergo a speculum examination for confirmation of amniorrhexis. The management of PROM at or near term is primarily determined by whether the woman has pregnancy complications or not. PROM in a patient whose pregnancy is complicated by, for example, multiple gestation, noncephalic presentation, hypertensive disorders, thick meconium-stained amniotic fluid or abnormal vaginal bleeding warrants special consideration for possible immediate delivery by an appropriate route and method. Digital cervical examination should be avoided before labour since there is no evidence that it would give any additional clinically useful information and it may increase the incidence of ascending genital tract infections. In parous women, induction with oxytocin infusion in the morning not more than 24 hours after PROM has been diagnosed is recommended. If the woman prefers to wait for spontaneous contractions, she will have a lower risk of receiving oxytocin without raising the risk of neonatal infections. In nulliparous women induction with oxytocin should be offered within 72 hours and this may lower the risk of an operative vaginal delivery. Regardless of the woman's parity, the clinician should always discuss the relative risks and benefits of immediate labour induction and expectant management with the patient so that they can develop a mutually acceptable treatment plan. After being counseled, the women who choose labour induction should receive an oxytocin infusion with appropriate continuous maternal and fetal surveillance. Clinicians and midwives should minimise digital cervical examinations in an effort to reduce the risk of chorioamnionitis. Labour should be managed efficiently to achieve spontaneous vaginal delivery. During the expectancy, the maternal temperature and fetal heart rate should be assessed every day. In cases of suspected clinical endometritis (maternal fever ≥38°C), prompt appropriate broad-spectrum antibiotic therapy and immediate labour induction should be started. No study has answered the question if women with PROM at or near term managed expectantly may continue as outpatients until either spontaneous labour occurs or signs of intraamniotic infection develop. Active management should probably not be delayed until more than 72 hours after ROM.

Management of PROM at or near term has become less of a clinical dilemma than in previous decades, largely because of an enhanced understanding of the mechanisms and microbiology of ascending peripartal genital tract infections as well as alterations in intrapartum management techniques aimed at reducing the risk of intraamniotic infection. For the majority of women with PROM at or near term, the condition is benign, and spontaneous labour begins within the first day after amniorrhexis.

Need for further research about PROM

There is still some controversy about how to manage PROM at or near term. The main questions are: If expectant management is preferred, for how many hours should the woman await spontaneous contractions before labour is induced? Should the woman wait until spontaneous contractions occur irrespective of time? Should women with PROM have hospital or outpatient care during the expectancy period? Which examinations should be performed at these check-ups during the expectancy period? Is there a need for a test for ROM besides a sterile speculum examination? What endpoint should be used for the evaluation of a test for ROM? How should nulliparous women with a Bishop score less than three be managed? Are there any indications for using prostaglandins in women with PROM? And if so, what drug and what dosage should be used? Are there any risk factors for ROM that could be influenced? Should the same policy be used worldwide independent of setting and routines at the delivery wards?

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Sammanfattning på Svenska (Summary in Swedish)

Normalt startar en förlossning med värkarbete vilket senare under förlossningen följs av vattenavgång. Vid ca 13% av förlossningarna blir det vattenavgång innan värkarbetet kommer igång. Man har under många år diskuterat hur dessa patienter skall handläggas. Ett flertal metoder, t.ex. biokemiska och cytologiska, har använts för att diagnostisera vattenavgång. Eventuellt kan det räcka med enbart en spekulumundersökning för att diagnostisera vattenavgång. För kvinnor med säkerställd vattenavgång efter 34 fulla graviditetsveckor har man haft olika uppfattningar om det varit en fördel eller en nackdel att relativt snart inducera förlossningen med ett värkförstärkande dropp. Det man vill undvika är infektioner hos mor och barn, onödiga induktioner och operativa förlossningar.

Vid en journalgenomgång av 2208 journaler som utgjorde ett representativt urval av befolkningen fann man att vattenavgång utan värkar förekom i 12.9% av alla förlossningar efter vecka 34. Följande kvinnor hade ökad risk för vattenavgång: äldre än 34 år vid förlossningen, förstföderskor, kvinnor sjukhusvårdade p.g.a. för tidiga värkar, vattenavgång utan värkar i en tidigare graviditet och blödning under graviditeten.

Dessutom genomfördes en studie där kvinnor med vattenavgång utan värkar lottades till induktion påföljande morgon eller induktion två dygn senare. Oxytocin (Syntocinon®) användes för att stimulera värkarbetet. Ingen skillnad i infektionsutfall kunde noteras hos mor eller barn om modern randomiserades till induktion av förlossningen påföljande morgon eller om man avvaktade i ytterligare två dygn. Omföderskor uppvisade ingen skillnad i frekvens kejsarsnitt eller sugklockor mellan grupperna. Förstföderskor hade samma kejsarsnittsfrekvens men däremot en högre frekvens av sugklockor i den grupp som inducerades påföljande morgon jämfört med dom som fick möjlighet att komma igång med ett spontant värkarbete under ytterligare två dygn. Följande faktorer ökade risken för infektion hos det nyfödda barnet: tid från vattenavgång till förlossning, graviditetslängd 34-36 veckor, kejsarsnitt och om kvinnan var omföderska. Bad under förlossningen påverkade inte infektionsfrekvensen.

Vi studerade också kvinnor som kom till förlossningen med misstänkt vattenavgång utan att man kunde se något fostervatten vid spekulumundersökningen. På dessa togs ett prov för vattenavgång(DAO-test) och patienterna gick sedan hem utan ytterligare kontroller. Om man diagnostiserade vattenavgång enbart vid synligt fostervatten vid spekulumundersökning var 12% falskt negativa om man jämförde med DAO-test. Ingen ökad sjuklighet hos mor eller barn förelåg hos kvinnor med en falskt negativ diagnos av vattenavgång jämfört med kvinnor med en negativ DAO-test.

Sammanfattningsvis har vi inte kunnat visa på någon nytta av att använda DAO vid diagnostik av vattenavgång hos kvinnor där man ej såg fostervatten vid spekulumundersökning. Vi ifrågasätter därför behovet av speciella undersökningar förutom spekulumundersökning för att diagnostisera vattenavgång efter graviditesvecka 34. Vi fann inte någon ökad infektionsrisk för mor eller barn om modern lottades till att få ett värkförstärkande dropp påföljande morgon jämfört med två dygn senare. Förstföderskor som avvaktade upp till 72 timmar innan de fick ett värkförstärkande dropp förlöstes oftare utan användning av sugklocka än de som fick ett värkförstärkande dropp påföljande morgon. Förhoppningen är att resultaten från dessa studier skall leda till bättre kunskap om hur vi skall informera och handlägga kvinnor med normal graviditet och vattenavgång utan värkar vid eller nära fullgången tid.

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