Neonatal and Maternal Outcome after Conservative Management of Preterm Premature Rupture of Membranes (PPROM) between 24-28 Weeks Gestation

Yasser Mesbah, MD; Mohamed Taman, MD; Hamed Youssef, MD; Hanaa Elsharkawy, MSc; Yasser Abduldayem, MD

Department of Obstetrics and Gynaecology, Mansoura University Hospital, Mansoura Faculty of Medicine, Mansoura, Egypt.

Corresponding author:
Yasser Mesbah, MD
Associate professor
Department of Obstetrics and Gynaecology
Mansoura University Hospital
Mansoura Faculty of Medicine
Mansoura, Egypt
Email: yasermesbah@yahoo.com

Coauthers

Mohamed Taman,MD
Lecturer
Department of Obstetrics and Gynaecology
Mansoura University Hospital
Mansoura Faculty of Medicine
Mansoura, Egypt
Tel.: +200103516395
Email : Dr_mohammed_elsayed@mans.edu.eg

Hamed Youssef, MD
Professor
Department of Obstetrics and Gynaecology
Mansoura University Hospital
Mansoura Faculty of Medicine
Mansoura, Egypt

Hanaa Elsharkawy, MSc
Department of Obstetrics and Gynaecology
Mansoura University Hospital
Mansoura Faculty of Medicine
Mansoura, Egypt
Email:elsharkawy_hanaa@yahoo.com

Yasser Abduldayem
Associate professor
Department of Obstetrics and Gynaecology
Mansoura University Hospital
Mansoura Faculty of Medicine
Mansoura, Egypt

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Abstract

Background: The Incidence of preterm pre mature rupture of membranes ranges from 3.0-10.0% of all deliveries and leads to one third of preterm births. There are several risk factors for PPROM, such as intrauterine infection at early gestational age, sexually transmitted infections, vaginal bleeding, and smoking during pregnancy.

Methods: An observational prospective study included 100 pregnant females with PPROM between the 24th and 28th week's gestation that were admitted to Mansoura University Hospital (MUH) between April 2018 and December 2019. Pregnancies with known fetal malformations, multiple fetuses, stillbirths, placenta previa, pre-eclampsia & Eclampsia and diabetes mellitus were excluded from this study group. Women who deliver within 24 hours of PPROM were also excluded.

Results: Out of 100 pregnant females were eligible for the study only 88 patients continued the study. Data from our study showed that the median gestational age at delivery after conservative management of patient diagnosed to have PPROM was 33 weeks. 85.2% of patients delivered by cesarean section. Recurrent urinary tract infection and Vulvo-vaginitis are the most common associated risk factors (28 %, 24 %) respectively.The percentage of live born neonates was (65.9%) while still birth occurred in (15.9%) and miscarriage occurred in (18.2%) of the females who completed the study. The main neonatal complications reported in the study was 55 out of 58 live birth cases were admitted to NICU (62.5%). Twenty-nine cases developed respiratory distress syndrome (32.9 %), 17 cases developed bronchopulmonary dysplasia (19.3%), 6 cases developed pulmonary hypoplasia (6.8%),47 casesdeveloped neonatal sepsis (53.4%) and 34 cases developed perinatal death after admission to NICU (38.6%). Fourteen neonates were discharged with different degrees of disability (15.9%). The overall survived neonates were 24 cases (27.3%). For maternal complications we noticed that 43 cases developed signs of chorioamnionitis (48.9%). Also cord prolapse was reported in 3 cases (3.4%). After delivery postpartum hemorrhage occurred in 14 cases (15.9%) and 10 cases (11.4%) were in need of blood transfusion. Signs of maternal sepsis developed only in 3 cases (3.4%).

Conclusion: Data from our study showed that after conservative management of patients with PPROM the overall neonatal survival rate was 27.3 %. 3.4% of neonates were discharged without need of NICU, 7.95% of neonates were healthy after being discharged form NICU and 15.9 % of neonates were discharged with different degrees of disability. Most of material complication were not fatal and showed improvement after giving the appropriate care.

Keywords: Preterm labor, neonatal outcome, chorioamnionitis, prematurity, maternal sepsis.

INTRODUCTION

Preterm premature rupture of membrane (PPROM) is defined as rupture of foetal membrane before onset of labour at less than 37 weeks of gestation. It was reported that 5 in 1000 women are at risk of developing PPROM (1). Unfortunately, when this happens it will be associated with poor neonatal outcome due to preterm delivery and due to a certain degree of pulmonary hypoplasia as a result of the reduction of amniotic fluid at a very early gestational age.

It is also known that it leads to about one third of preterm deliveries. many risk factors were associated with this condition as multiparity, low socioeconomic standards, smoking, malnutrition, and recurrent vulvo-vaginal infections (2). The mechanism by which PROM happens refers to release of collagenase and phospholipases enzymes that will lead to erosions in the amniotic membranes and leakage of amniotic fluid. These groups of enzymes could be execrated from microorganisms like bacteria or due to malnutrition of bad habits like active or passive smoking. (3).

Many maternal and neonatal complication could happen after PPROM and it differs according to the gestational age of the onset of ROM, the degree of oligohydramnios, the associated maternal comorbidities and the latency period till the onset of labour or delivery (4). The most common maternal complications are the risk of antenatal or postpartum infections. Multiple foetal and neonatal complications also could happen as prematurity, very low birth weight, respiratory distress syndrome, lung hypoplasia, intracerebral haemorrhage, patent ductus arteriosus, neurologic disorders and perineal mortality (2).

The proper management in the event of PPROM is controversial. Expectant management is feasible to decrease the risk of prematurity. Prophylactic antibiotic could help in decreasing the incidence of chorioamnionitis, also administration of corticosteroids could stimulate type II pneumocytes to excrete surfactant to enhance lung maturity and a short course of tocolytic drugs to achieves such target. On the other hand, extending the latency period "duration between the start of rupture of membranes and the onset of labour "may increase the risk of uterine infections, consequently this will lead to harmful neonatal complications. (5). The plan of management of such condition differs from on country to another according to the facility of neonatal care and it should be conducted in a tertiary health care centre to maximize the benefit of this plan. (6). It was generally recommended that if premature rupture of membranes (PROM) happened between 24–31 weeks' gestational age (GA) expectant management could be tried. Labour induction is suggested if lung maturation is confirmed at 32–33 weeks' gestational age (GA). After 33 weeks' GA, it is generally recommended to proceed to delivery (usually by induction) because of the decreased likelihood of respiratory complications (7). We conducted this study to evaluate the efficacy of conservative management of patients with PPROM at Mansoura university hospitals (MUH) and to assess safety of the management plan.

Methods

We conducted a prospective observational cross-sectional and analytical study for a group of pregnant females attending at outpatient clinic and were admitted at Obstetrics and Gynaecology Department, Mansoura University Hospital, Mansoura, Egypt. The study was conducted over the period of 20 months in the period from April 2018 till December 2019.

Study subjects

Participant in the study were 100 pregnant females with PPROM between the 24th and 28th weeks gestation. Diagnosis of PPROM was based on the patient's history of watery vaginal discharge and leakage of amniotic fluid from the cervical os during a sterile speculum examination and decrease in the amniotic fluid index (2) by transabdominal ultrasonic examination.

Exclusion criteria:

1. Confirmed Gestational age other than our inclusion group 24 – 28 weeks' gestation.
2. All pregnancies with known foetal malformations, multiple foetuses, stillbirths, placenta previa, pre-eclampsia & Eclampsia and diabetes mellitus.
3. Intrauterine growth restriction.
4. Women who present with abruptio placenta.
5. Maternal and/or foetal indications for immediate delivery after admission.
6. Clinical signs of chorioamnionitis at presentation with PPROM.
7. Women who deliver within 24 hours of PPROM are also excluded from the study group.

Protocol of management of PPROM:

A thorough clinical evaluation was done for every patient by complete history taking, and the following data were collected demographic data (age, sex and other demographic data, general medical history, associated comorbidities, obstetric history (gravidity, parity and complications of previous pregnancies if present), and accurate estimation of gestational age. Also clinical examination was done to document any signs of chorioamnionitis. Vaginal examination was done as well by inspection and sterile speculum examination to confirm the occurrence of rupture of membranes. Then trans-abdominal ultrasonic examination was done to document the viability of pregnancy, amniotic fluid index (2) and to ensure the gestational age. The following laboratory investigations were requested including complete blood count (CBC) and serum C-reactive protein (CRP). After patients' counselling all patients were put on our local management protocol. All patients were admitted to obstetrics and gynaecology department. A single course of corticosteroids (dexamethasone) was given in two divided doses (24 mg divided into two over 24 hours), simultaneously antibiotic therapy was started (Intravenous ampicillin 1 gm every 12 hours for 2 days, followed oral amoxicillin or erythromycin for another 5 days). Urine samples were taken upon admission for culture and sensitivity testing. Monitoring of patients' vital signs was done on daily basis, also estimation of any abdominal tenderness, recording of foetal movement count and foetal heart rate. Ultrasound

and laboratory assessment were done twice weekly.If patients developed regular and frequent uterine contractions (≥ 3 contractions every 10 min), then vaginal examination was done under complete aseptic conditions. A short term tocolysis was prescribed for 48 hours to gain the effect of enhancing lung maturity by corticosteroids. If 2 or more of the following signs were present (Maternal body temperature ≥ 38°C, Maternal heart rate (≥ 110 beats/min), Persistent increase in foetal heart rate (FHR) (> 160 beats/min) or decrease in FHR (< 110 beats/min), evidence of significant abdominal or uterine tenderness, rising serum levels of CRP, appearance of offensive vaginal discharge, increase in white blood cell count (WBCs) (≥ 15,000 cells/mm3) the diagnosis of chorioamnionitis was confirmed. The decision to deliver is based on the clinical assessment by the supervising obstetrician. Induction of labour is indicated in case of maternal infection or intrauterine death, and for all other cases, once the pregnancy reached 32-34 weeks' gestation. After delivery all patients continued on antibiotic therapy till discharge after at least 48 hours. If any signs of puerperal sepsis or pyrexia were present, the duration of treatment was extended till clinical and laboratory improvements were documented.An outpatient clinic visits were arranged for all patients to discuss their pregnancy events and outcome and to formulate a management plan for subsequent pregnancies.

Outcome measures:

A- Maternal outcome measures included:

- Estimation of gestational age at PPROM.
- Estimation of gestational age at delivery.
- Estimation of Latency period (period between onset of PPROM till the onset of labour or delivery).
- Mode of delivery (vaginal or abdominal).
- Maternal morbidity rates (e.g. postpartum haemorrhage, vaginal or cervical tears, chorioamnionitis and endometritis).

B-Neonatal outcomes included:

- Degree of neonatal distress.
- Foetal birth weight at delivery.
- Apgar scores at the 1 and 5 minutes.
- Rate of admission to neonatal intensive care unit (NICU).
- Rate and type of neonatal infection.
- Major neonatal conditions (including patent ductus arteriosus (PDA), respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH), necrotizing enterocolitis (NEC) and sepsis).
- Congenital malformations.
- Perinatal mortality rate.

Statistical analyses:

The collected data were coded, processed and analysed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA).

Data were tested for normal distribution using the Shapiro Walk test. Quantitative data were expressed as mean ± SD (Standard deviation) or median (range) according to distribution (parametric and non-parametric respectively).

Logistic regression analysis was used to analyse the occurrence of categorical outcome by other variables. Univariate regression analysis was used to test the individual variables for prediction while multivariate regression analysis was used to determine the independent predictor factors.

Results

The study included 100 pregnant females presented with PPROM between 24 and 28 weeks' gestation. As shown in table 1 the mean age of the patients was 27.47 ± 6.17 years. About (54%) of patients had moderate degree level of socioeconomic standards. The majority of the females had no special habits of medical importance, but there were 31 females who were passive smokers. More than 50% of patients were multiparous. Among all patients, there were 11 patients with previous history of PROM, 5 patients with previous history of preterm birth in 7 patients with previous history of still birth. 33 % of patients had past history of intrauterine device (IUD) usage as a method of contraception. Regarding the associated chronic diseases among the females in this study, recurrent UTI and Vulvo-vaginitis were reported in 38 females and 34 females respectively. Diabetes mellitus (DM) was present in 11% of patients, SLE was present in 2% of patients. Also the median gestational age of rupture of membrane in this study was at the 25th

week. The majority of patients did not show significant signs of chorioamnionits either at clinical or laboratory levels at the onset of ROM.

Out of 100 pregnant females were eligible for the study, only 88 females completed the routine follow up till delivery. The majority of patients gave rise to live birth neonates (65.9%) while still birth occurred in 14 females (15.9%) and miscarriage occurred in 16 females (18.2%) (table 2). The median gestational age at delivery was 33 weeks. Regarding the mode of delivery, vaginal delivery was conducted in 13 females (14.8%) while caesarean delivery (CD) was conducted in 75 females (85.2%). The average duration of latency period (duration between the onset of ROM and delivery) was about 5 weeks.

For neonatal outcomes, the mean neonatal birth weight was 1406.22 ± 419.42 gm. The median 5-min Apgar score was 5. The following neonatal complications were reported as follows; 62.5% of neonates were admitted to NICU, 32.9 % developed different degrees of respiratory distress syndrome, neonatal sepsis was present in 53.4% of neonates, only one neonate showed signs of intrauterine growth restrictions (IUGR) and the perinatal mortality rate was 38.6% (table 3).

Table 4 showed the different maternal complications occurred for patients who completed the study. Clinical chorioamnionitis was diagnosed in 43 cases (48.9%), cord prolapse was reported in 3 cases (3.4%), postpartum haemorrhage was present in 14 cases (15.9%), and maternal sepsis occurred only in 3 cases (3.4%).

After doing logistic regression analysis, elevated CRP and amniotic fluid index were identified as determinants of development of maternal and neonatal complications, however, by multivariate regression analysis, elevated CRP was detected as an independent determinant of development of complications (table 5).

Discussion

The present study is being planned to describe the course of pregnancies and evaluate neonatal and maternal outcomes with PPROM between 24 and 28 weeks' gestation that are conservatively managed in Mansoura University Hospital (MUH). The overall neonatal survival to discharge rate was 27.3% and it was improved significantly with increasing gestational age at PPROM and gestational age at birth. There were no reported cases of maternal mortality.

In this study, the mean age of the included cases was 27.47 ± 6.2. This is comparable to other studies that found that the commonest age group among PPROM patients were 20-24 years with ranges between 17 to 35 years. (8-11).

In the present study increased cases of PPROM were observed in cases of multigravidas more than primigravida which is in agree with many of the studies, multiparity is a risk factor for PROM due to long standing infection, trauma to cervix and cervical incompetence (12).

The majority of patients developed ROM the 26th week of gestation. In spite of associated many risk factors with occurrence of PPROM we found that the most common associated conditions were recurrent UTI and Vulvo-vaginal infection. Also the laboratory markers of infections did not show a significant elevation with the start of the condition. Also maternal serum CRP concentration was found to be among the most commonly used clinical non-invasive markers to predict infectious-related and inflammatory complications in women with PPROM, in spite of the absence of strong evidence for its use in relation to these indications (13).

In our study, the onset of delivery ranged between 28 and 36 weeks' gestation with the median duration of 33 weeks. And the average duration of latency period was 5 weeks. The latency period between the occurrence of PPROM and delivery is considered an important factor to improve neonatal outcomes. As the managing team succeeded to increase the duration of latency period as the preferable neonatal outcomes are expected (14). On the other hand, this should be performed with caution to prevent any unwanted serious maternal or neonatal complications. Also the neonatal survival rate was found to be about 56% when the onset of PPROM happens in later gestational ages even when the latency period was short (15). In another study, it was found that the neonatal survival rate was about 86 %, in a group of patients who had PPROM between 14 + 0 and 32 + 0 weeks of gestation (16). To achieve this prolongation of la-

tency period, it was found that antibiotics are the key player in the management protocol (17). It was recommended that penicillin is the drug of choice in this situation. Intravenous therapy could be initiated the first 2 days, followed by maintenance therapy using amoxicillin or enteric coated erythromycin for the next 5 days (17).

In our study we found that 85.2% of patients delivered by caesarean section. The increase in Caesarean section rate was largely due to the increased incidence of foetal malpresentations and failed induction in the immediate induction group.

In spite of achieving high survival rates in some studies, it was found that the neonatal morbidity could reach up to 75% in certain situations. This was found to be due to the impact of medications used for treatment and lengthy admission period in the NICU (18). In our study, the majority of the females gave rise to live birth neonates (65.9%) while still birth occurred in 14 females (15.9%) and miscarriage occurred in 16 females (18.2 %). The mean birth weight of the live birth was 1406.2 ± 419.4 gm. 62.5% of neonates were admitted to NICU and the perinatal mortality rate was 38.6%. In another study, Al-Riyami et al. (2013) reported that the live birth rate was 55%. For those neonates Apgar scores at 1 and 5 minutes were found to be 8.7 and 10, respectively. Also the mean weight of neonates was 2.2 kg. Sixty-four percent of neonates were born having very low birth weight. The majority (79%) of the live born neonates developed different degrees of respiratory distress syndrome. Neonatal sepsis occurred in 50% of the NICU admitted neonates. On the other hand, the miscarriage rate was 20% and the stillbirth rate 9%. Seven percent of the live born neonates had early neonatal death in the first day after delivery (19).

A high perinatal mortality rate was reported (67.7%) among group of pregnant females who developed PPROM between 24 and 26 weeks of gestation. They reported also lower survival rate (13%) when the onset of PPROM was below 23 weeks. It was increased up to 50% if the onset of PPROM was between 24-26 weeks (20). In another study the live birth rate was 25%, and the rate of maternal complications was 58.5% (21). Also after studying a cohort of 73 pregnant females, it was found that the main determinant of the neonatal and maternal complications is the age of onset of PPROM (22). They found poor neonatal outcomes when the age of onset of PPROM was between 16-23 weeks of gestation. This was totally different when comparing the neonatal outcome when PPROM happened after 24 weeks of gestations. The most common neonatal complications in the previous studies were respiratory distress syndrome (79.2 %) and bronchopulmonary hypoplasia (68.4%). It was found that the neonatal complication rates varies among many studies (22-24). Also these variations were reported for the live birth rates. Verma and colleagues reported a live birth rate of 18.3 % when they followed a group of pregnant females had PPROM between 18-23 weeks of gestations (25). On the other hand, Loeb and colleagues reported an overall survival rate of 6.25 % when they studied a group of pregnant females had PPROM between 20-24 weeks of gestation (26). Different survival rates were reported by Farooqi and colleagues when PPROM happened at different gestational ages (40, 92 and 100 % for those who developed PPROM at 14–19, 20–25 and 26–28 weeks respectively). (27). Newman and colleagues reported higher perinatal mortality rate (98.8 %) in a group of pregnant females developed PPROM between 23–24 weeks and it was decreased up to 36.6 % when PPROM occurred between 25–27weeks (28). The neonatal mortality rate was found to be of 82 % when patients developed PPROM before 22 weeks of gestation (29). Margato and colleagues also reported very low live birth rate when PPROM occurred before 20 weeks of gestation (30). In spite of the heterogeneity of data a recent meta-analysis concluded that most of the adverse neonatal complications that are responsible for neonatal morbidity are related to the degree of oligohydramnios that happens after PPROM (31)

However, we did not report any case if maternal mortality in our study, clinical chorioamnionitis was the most common maternal complication as it was present in (48.9%) of cases. In our study, with the logistic regression analysis, elevated CRP and amniotic fluid index were identified as determinants of development of maternal and neonatal complications, however, by multivariate regression analysis, elevated CRP was detected as an independent determinant of development of complications.

Conclusion

Data from our study showed that after conservative management of patients with PPROM the overall neonatal survival rate was 27.3 %. 3.4% of neonates were discharged without need of NICU, 7.95% of neonates were healthy after being discharged form NICU and 15.9 % of neonates were discharged with different degrees of disability. Most of material complication were not fatal and showed improvement after giving the appropriate care. Clinical chorioamnionitis was the most common maternal morbidity followed by Bleeding after PROM

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Disclosure

All authors disclose no conflict of interest.

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Table (1): Demographic data and base line characteristics and initial laboratory investigations of the patients included in the study

Variables	Whole study group (N= 100)
Age (years) [Mean ± SD]	27.47 ± 6.17
Gravidity [Median (range)]	2 (1 – 5)
Parity[Median (range)]	1 (0 – 3)
Socioeconomic level [n (%)]	
High	21 (21%)
Moderate	54 (54%)
Low	25 (25%)
Special habits [n (%)]	
No	69 (69%)
Passive Smoking	31 (31%)
Previous PROM[n (%)]	11 (11%)
Previous preterm birth[n (%)]	5 (5%)
Use of contraception[n (%)]	
No	39 (39%)
Intrauterine device (IUD)	33 (33%)
Associated chronic condition[n (%)]	11 (11%)
Diabetes mellitus (DM)	2 (2%)
Systemic lupus erythematosus (SLE)	38 (28%)
Recurrent urinary tract infection (UTI)	34 (24%)
Vulvo-vaginitis	
GA at onset of ROM [Median (range)]	26 (24 – 28)
WBCs (× 10^3) [Mean ± SD]	10.91± 4.31
CRP (mg/L)[Mean ± SD]	17.36± 3.26

SD: slandered deviation PROM: premature rupture of membranes n: Number
WBCs: white blood cells CRP:C-reactive protein GA: gestational age
ROM: rupture of membranes

Table (2): Analysis of the outcomes of pregnancy after PROM

VariablesFemales completed the study	(N=88)
Outcome of pregnancy [n (%)]	
Miscarriage	16 (18.2%)
Still birth	14 (15.9%)
Live birth	64 (72.7%)
GA at delivery (weeks)	
Median (range)33 (28-36)	
Mode of delivery [n (%)]	
Vaginal	13 (14.8%)
CS	75 (85.2%)
Latency period (weeks)	
Median (range):	6 (1-9) weeks

n: Number GA: gestational age CS: caesarean section

Table (3): Analysis of the neonatal outcome in cases of live birth

Variables	Female with live birth (n=58)
Birth weight	
Mean ± SD 1406.22 ± 419.42	
5 min ARGAR score	
Median (min-max) 5 (3 - 7)	
NICU [n (%)]	55 (62.5%)
RDS [n (%)]	29 (32.9%)
BPD [n (%)]	17 (19.3%)
Pulmonary hypoplasia[n (%)]	6 (6.8%)
Neonatal sepsis [n (%)]	47 (53.4%)
Perinatal death [n (%)]	34 (38.6%)
ROP[n (%)]	5 (5.7%)
NEC[n (%)]	3 (3.4%)
HIE [n (%)]	2 (2.3%)
Limb contractures[n (%)]	1 (1.1%)
IUGR[n (%)]	1 (1.1%)
IVH[n (%)]	1 (1.1%)
PDA[n (%)]	1 (1.1%)
Healthy neonates who didn't need NICU[n (%)]	3 (3.4%)
Healthy neonates discharged from NICU[n (%)]	7 (7.95%)
Neonates discharged with morbidity[n (%)]	14 (15.9%)
Over all survived neonates [n (%)]	24 (27.3%)

SD: slandered deviation NICU: neonatal intensive care unit n: Number
RDS: Respiratory distress syndrome NEC: necrotizing enterocolitis
HIE: hypoxic ischemic encephalopathy IUGR: intrauterine growth restriction
ROP: Retinopathy of prematurity IVH: intraventricular haemorrhage
PDA: patent ductus arteriosus

Table (4): Analysis of the maternal complications:

Variables	Females completed the study (N=88)
Clinical chorioamnionitis [n (%)]	43 (48.9%)
Bleeding after PROM [n (%)]	27 (30.7%)
Cord prolapse [n (%)]	3 (3.4%)
Postpartum hemorrhage [n (%)]	14 (15.9%)
Blood transfusion [n (%)]	10 (11.4%)
Maternal sepsis [n (%)]	3 (3.4%)
DVT [n (%)]	1 (1.14%)

PROM: premature rupture of membranes n: Number DVT: deep vein thrombosis

Table (5): determinants of development of maternal and neonatal complications.

Variables	Univariate analysis	Multivariate analysis		
		B	95% CI	P value
Chronic diseases	0.763			
Previous PROM	0.706			
WBCs	0.706			
CRP	0.015*	3.26	2.93 – 3.72	0.043*
Amniotic fluid index	0.034*	1.054	0.756 – 1.375	0.534

* Statistically significant when P value less than 0.05
PROM: premature rupture of membranes CI: confidence interval
WBCs: white blood cells CRP:C-reactive protein