PRETERM PRELABOUR RUPTURE OF MEMBRANES AFTER 34 WEEKS – EXPECTANT MANAGEMENT TILL 37 WEEKS VERSUS IMMEDIATE DELIVERY.
A NON INFERIORITY RANDOMISED CONTROL TRIAL COMPARING MATERNAL AND NEONATAL OUTCOMES.

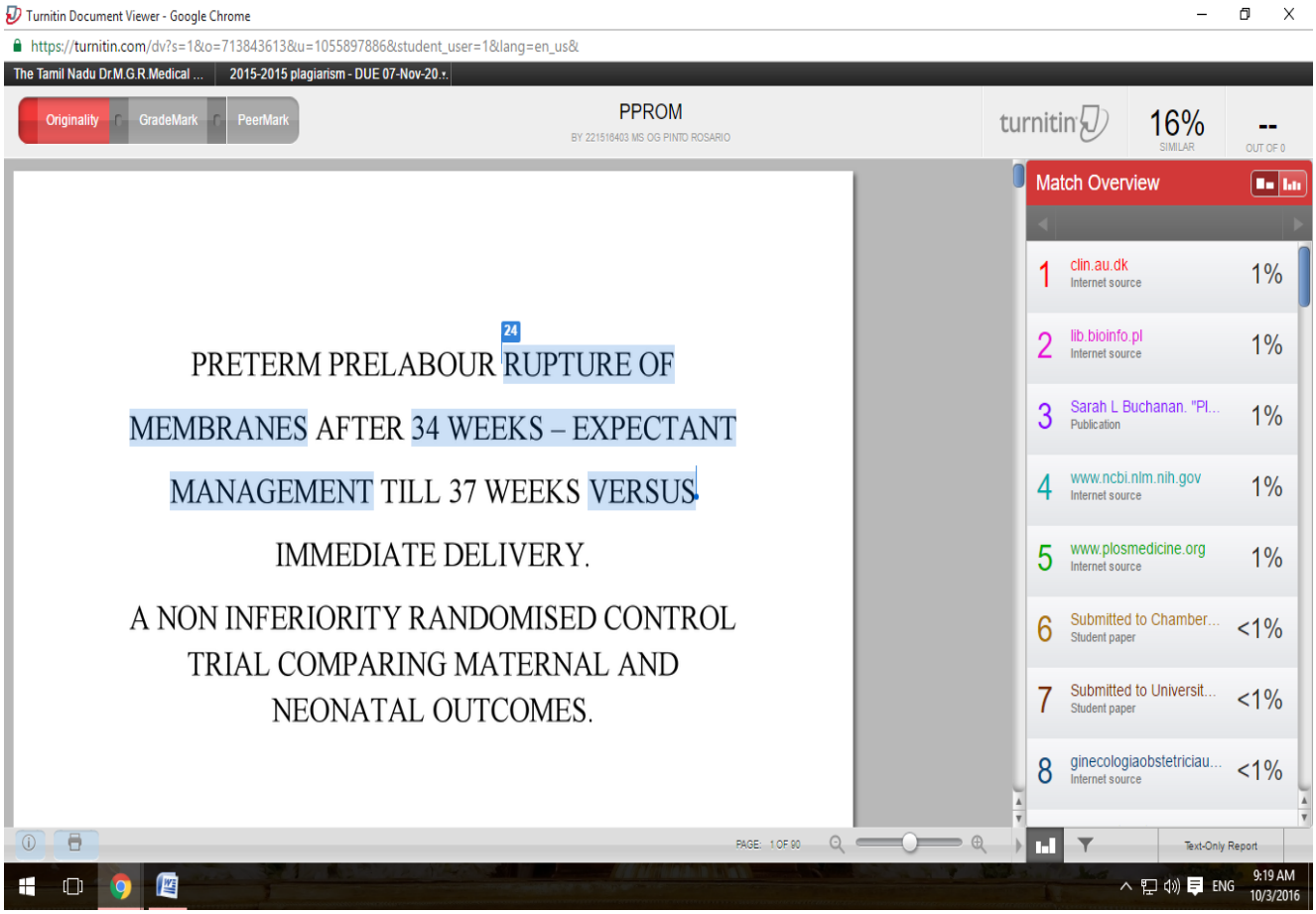
A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE RULES AND REGULATIONS FOR THE MS BRANCH (OBSTETRICS AND GYNAECOLOGY) EXAMINATION OF THE TAMIL NADU DR. M. G. R. MEDICAL UNIVERSITY TO BE HELD IN APRIL 2017

CERTIFICATE

This is to certify that this dissertation entitled "PRETERM PRELABOUR RUPTURE OF MEMBRANES AFTER 34 WEEKS – EXPECTANT MANAGEMENT TILL 37 WEEKS VERSUS IMMEDIATE DELIVERY - A NON INFERIORITY RANDOMISED CONTROL TRIAL COMPARING MATERNAL AND NEONATAL OUTCOMES" is bonafied work done by Dr. Saloni Maria Deepti Pinto Rosario in partial fulfillment of the requirement for the MS branch (Obstetrics and Gynaecology) examination of the Tamil Nadu Dr M.G.R Medical University, Chennai to be held in April 2017.

Signature of the Guide **Signature of the HOD**

Signature of the Principal **Signature of candidate**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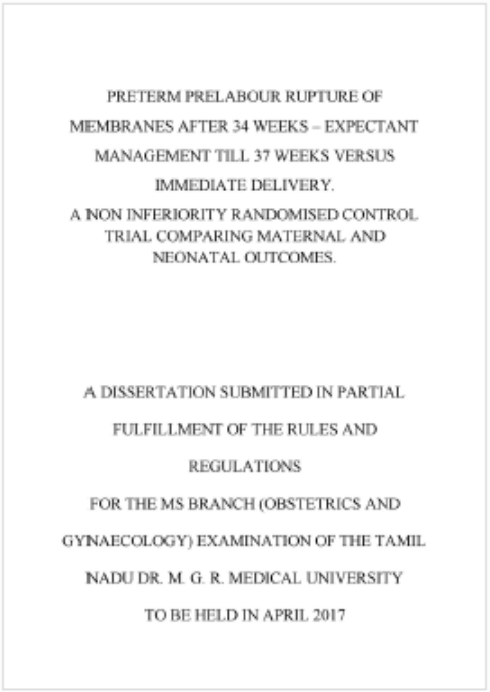

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January 22, 2016

Dr. S. M. Deepti Pinto Rosario
PG Registrar,
Department of Obstetrics and Gynaecology Unit 4,
Christian Medical College,
Vellore 632 004.

Sub: **Fluid Research Funding: New Proposal**
PPROM after 34 weeks – A non inferiority Randomised Controlled Trial for expectant management versus immediate delivery in pregnant women with preterm prelabour rupture of membranes (PPROM)
Dr. S. M. Deepti Pinto Rosario (Employment Number: 20851), , PG Registrar, Obstetrics and Gynaecology Unit 4, Dr. Manisha M. Beck, Obstetrics and Gynaecology Unit IV, Dr. Santhanam Sridhar, Neonatology, Mr. Bijesh Yadav (Employment Number 33244), Biostatistics, Mrs. Gracy Verghese, Biochemistry.

Ref: IRB Min No: 9711 [INTERVEN] dated 28.10.2015

Dear Dr. S. M. Deepti Pinto Rosario,

The Institutional Review Board (Silver, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "A non inferiority Randomised Controlled Trial for expectant management versus immediate delivery in pregnant women with preterm prelabour rupture of membranes (PPROM)" on October 28th 2015.

I enclose the following documents:-

1. Institutional Review Board approval 2. Agreement

Could you please sign the agreement and send it to Dr. Nihal Thomas, Addl. Vice Principal (Research), so that the grant money can be released.

With best wishes,

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
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The Committee reviewed the following documents:

1. IRB Application format
2. Information Sheet and Informed Consent Form (English, Tamil, Bengali)
3. Proforma
4. Cvs of Drs. Santhanam Sridhar, Manisha M. Beck ,Mr. Bijesh Yadav Mrs. Gracy Verghese,
5. No.of documents 1-4

The following Institutional Review Board (Silver, Research & Ethics Committee) members were present at the meeting held on October 28th 2015 in the CREST/SACN Conference Room,Christian Medical College, Bagayam, Vellore 632002.

2 of 5

Dr. George Thomas, D Ortho Ph.D.
Chairperson, Ethics Committee

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Deputy Chairperson,
Secretary, Ethics Committee, IRB
Additional Vice-Principal (Research)

Name	Qualification	Designation	Affiliation
Dr. George Thomas	MBBS, D Ortho, PhD	Orthopaedic Surgeon, St. Isabella Hospital, Chennai, Chairperson, Ethics Committee, IRB, Chennai	External, Clinician
Dr. B. Antonisamy	MSc, PhD, FSMS, FRSS	Professor, Biostatistics, Secretary (Research Committee), IRB, CMC, Vellore	Internal, Statistician
Dr. Prasanna Samuel	MSc, PhD	Lecturer, Biostatistics, CMC, Vellore	Internal, Statistician
Dr. Asha Mary Abraham	MBBS, MD, PhD	Professor, Virology, CMC, Vellore	Internal, Clinician
Dr. Anuradha Bose	MBBS, DCH, MD,MRCP FRCPCH	Professor, Child Health, CMC, Vellore	Internal, Clinician
Dr. B. Poonkuzhali	MSC, PhD	Professor, Haematology, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Suresh Devasahayam	BE, MS, PhD	Professor of Bio-Engineering, CMC, Vellore	Internal, Basic Medical Scientist
Dr. Thambu David	MBBS, MD, DNB	Professor, Medicine, CMC, Vellore	Internal, Clinician
Dr. D. J. Christopher	BSc, MBBS, DTCD DNB, FRCP(Glasg), FCCP(USA)	Professor, Pulmonary Medicine, Associate Director (HR), CMC, Vellore	Internal, Clinician
Dr. Sathya Subramani	MD, PhD	Professor, Physiology, CMC, Vellore	Internal, Clinician
Prof. Keith Gomez	BSc, MA (S.W), M. Phil (Psychiatry Social Work)	Student counselor, Loyola College, Chennai, Deputy Chairperson, Ethics Committee, IRB	External, Lay Person & Social Scientist
Dr. P. Zachariah	MBBS, PhD	Retired Professor, Vellore	External, Clinician
Mr. Samuel Abraham	MA, PGDBA, PGDPM, M. Phil, BL.	Sr. Legal Officer, CMC, Vellore	Internal, Legal Expert

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Mrs. Ruma Nayak	M Sc (Nursing)	Professor, Head of Paediatric Nursing & Deputy Nursing Superintendent, College of Nursing, CMC, Vellore	Internal, Nurse
Dr. Shirley David	MSc, PhD	Professor, Head of Fundamentals Nursing Department, College of Nursing, CMC, Vellore	Internal, Nurse

We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link:

http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html.

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "A non inferiority Randomised Controlled Trial for expectant management versus immediate delivery in pregnant women with preterm prelabour rupture of membranes (PPROM)" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in)

Fluid Grant Allocation:

A sum of 1,00,000/- INR (Rupees One Lakh Only) will be granted for 2 years. 50,000/- INR (Rupees Fifty Thousand only) will be granted for 12 months as an Ist Installment. The rest of the 50,000/- INR (Rupees Fifty Thousand only) each will be released at the end of the first year as 2 nd Installment following the receipt of the Interim progress/Annual report and subsequent submission of it to the IRB

Yours sincerely

Dr. Nihal Thomas
Secretary (Ethics Committee)
Institutional Review Board

Dr. NIHAL THOMAS
MD,MNAMS,DNB(Endo),FRACP(Endo),FRCP(Edin),FRCP(Glasg)
SECRETARY - (ETHICS COMMITTEE)
Institutional Review Board,
Christian Medical College, Vellore - 632 002.

Cc: Dr. Manisha M. Beck, Department of OG, CMC, Vellore.

Acknowledgments

This dissertation, from start to finish, has been a tremendous journey. It has truly been an enriching experience, one for which I am deeply grateful.

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My parents for their constant prayers and worry, and especially for instilling in me the love for Obstetrics and Gynaecology.

To my partner in crime and dear husband, Neeraj. Thank you for all that you do.

Above all, to Him, who watches over me and mine.

CONTENTS

INTRODUCTION

The birth of a baby should always be a joyous time in the lives of its parents and family. There is nothing more satisfying in Obstetrics than to have a healthy mother and baby at the end of gestation. Unfortunately, this is not always the case, and when a baby is born too early this can cause immense financial and emotional trauma to the family.

As we learn more and more about the morbidities and mortality associated with premature births, there is a special group of these infants coming to light, those born between 34+0/7 and 36+6/7 weeks. Now termed 'late preterms,' these babies are at risk of short and long term consequences as a result of their premature birth.

Research has been aimed to decrease the number of babies born at this gestation. One way is to prolong pregnancies complicated by preterm prelabour rupture of membranes (PPROM). When these pregnancies are prolonged, there are risks. Does prolonging pregnancy increase infectious morbidity for the mother and baby? Is the risk of infectious morbidity preventing conservative management?

If this question could be adequately addressed, then more and more late preterm births could be prevented, leading to more healthy, term babies.

AIMS AND OBJECTIVES OF THE STUDY

Aim:

To compare the fetal, neonatal and maternal outcomes in pregnant women presenting with pretermprelabour rupture of membranes with two types of treatment- namely - immediate delivery versus expectant management until 37 completed weeks of gestation.

Objectives:

1. To determine whether rates of neonatal sepsis were similar in babies born to womenpresenting with preterm prelabour rupture of membranes with two types of treatment- namely – immediate delivery versus expectant management until 37 completed weeks of gestation.

2. To determine whether these two approaches will cause significant differences in neonatal and maternal morbidities and mortality.

REVIEW OF LITERATURE

Structure

Introduction – PPROM, Statistics

Pathogenesis of PPROM

The late Preterm Neonate – why worry?

Incidence of PPROM

Clinical course

Predisposing/ Risk Factors for PPROM

Diagnosis of PPROM, including differential diagnosis

Complications of PPROM – Neonatal and Maternal consequences

Management of PPROM

INTRODUCTION

Preterm Prelabour Rupture of membranes (PPROM) is described as rupture of membranes before the onset of labour from the gestational age of 20 to <37 weeks (American College of Obstetricians and Gynecologists, 2013).

Globally, PPROM occurs in 3 to 4.5% of all pregnancies(1). The incidence of PPROM in Indian studies has been shown to be about 7 – 8%. (2) These account for nearly 30 – 40% of all preterm deliveries, and consequently a large proportion of neonatal as wellas maternal morbidity.

According to timing of birth, preterm births can be divided into

- Extremely preterm : Less than 28 weeks
- Very preterm : 28 to <32 weeks
- Moderate preterm : 32 to <34 weeks
- Late Preterm : 34 to 36 + 6 weeks of gestation (3) .

It has recently been noticed that those infants born between 34+0/7 and 36+6/7 weeks have characteristic morbidities and mortalities. It was also observed that those born between 37+0/7 and 38+6/7 weeks of gestation experience more morbidities than those born after 39 completed weeks to 40+6/7 weeks. This latter group has been found to have the lowest infant mortality than babies born in any other period in human gestation (4).

Much of the morbidity/ mortality associated with PPROM are due to the premature nature of the baby, and include those affecting the Respiratory System (eg.Respiratory Distress Syndrome), Gastrointestinal system (eg. Necrotising Enterocolitis), Immunological, Renal, Cardiovascular, Central Nervous System. The incidence of these complications decline the nearer to term that the PPROM

occurs. Hence there may be considerable health benefits to the fetus in continuing a pregnancy after PPROM in the late second and third trimesters. There is emerging evidence that this holds true for late preterm babies as well.

However, there are also problems inherent to PPROM, such as cord prolapse, ascending infection and abruption placentae. Chorioamnionitis is of particular mention, as this can translate to Fetal Inflammatory Response Syndrome (FIRS) and its effects such as periventricular leucomalacia and cerebral palsy are independent of the ill effects of prematurity (8). However most studies include early preterm babies, or those with very low birth weights and it might be difficult to extrapolate the results to our intended study population as the incidence of cerebral palsy in near term/ term infants is lower (maximum reported incidences of 1.9% in the chorioamnionitis group)(7). Mothers affected by chorioamnionitis are also at a greater risk of sepsis and its ill effects.

Hence the ultimate goal of management should be to minimise the immaturity of the fetus, while avoiding harmful effects of remaining in utero.

A recent Cochrane review (5)was undertaken to assess the effect of planned early birth versus expectant management for women with preterm prelabour rupture of the membranes between 24 and 37 weeks' gestation for fetal, infant and maternal well being. There was no significant difference in neonatal sepsis between those babies delivered early and those managed expectantly (risk ratio (RR) 1.33, 95% confidence interval (CI) 0.72 to 2.47.

The incidence of respiratory distress was also not significantly increased in the Induction of Labour (IoL) group, neither was there a difference in overall neonatal or

intrauterine mortality.

There was, however, a non-significant trend towards more neonatal deaths in pregnancies which underwent early IoL and an increase in intrauterine deaths in those who received expectant management. There was one trial (Mercer 1993) which reported on suspected early onset neonatal sepsis. It was found that there was a significant decrease in sepsis associated with early delivery, as well as a decreased need for neonatal antibiotics.

Five studies (Cox 1995; Garite 1981; Iams 1985; Mercer 1993; Naef 1998) reported the number of women who developed chorioamnionitis. Overall, there was no significant difference in the women who developed chorioamnionitis in the early delivery group compared with the expectant management group (RR 0.44, 95% CI 0.17 to 1.14; I2 = 56%; 575 women). There was, however, substantial heterogeneity between the trials in assessing chorioamnionitis (demonstrated by an I2 of 56%.) At the time of the Cochrane review, there was only one study which included the group of our interest, 34 – 37 weeks gestational age (Naef 1998) , therefore the review included only these 120 women. Early delivery resulted in a reduction in chorioamnionitis (RR 0.11, 95% CI 0.01 to 0.84), with no significant increase in caesarean section (RR 1.47, 0.34, 6.30). It was concluded that there was insufficient evidence on the clinical benefits and harms for women and their babies of immediate delivery compared with expectant management for women with PPROM to make recommendations with which to guide clinical practice. The need for further, methodologically sound, adequately powered clinical trials to guide the management of PPROM was stressed upon.

Hence, given the myriad problems that are associated with the late preterm, it is prudent to avoid delivery at this gestation. However, on the other hand, with expectant management there is concern about the risk of ascending infection.

The current management of PPROM is based on the gestational age at which PPROM hasoccured. There is consensus on the management of pregnancies upto 34 weeks complicated by PPROM, with most major Obstetric societies (American Congress of Obstetrics and Gynaecology 2013, Royal College of Obstetricians and Gynaecology – Greentop Guideline Number 44 (6)) advocating expectant management till 34 completed weeks, followed by planned early delivery.

For example the American Congress of Obstetrics and Gynaecology (2013) (7)recommended that all PPROM cases beyond 34 weeks undergo immediate delivery.

Prolonging pregnancies upto 37 weeks may have a significant impact on decreasing composite neonatal morbidity, without increasing rates of neonatal sepsis. With careful maternal fetal monitoring and timely intervention, complications such as chorioamnionitis may be avoidable. This is the clinical question hoped to be answered in this study.

Statistics

United States of America

In the US, preterm births showed an increase from 10.6 in 1990 to 12.8% of all live births in 2006, this was an all time high. This rise was largely attributable to a rise in

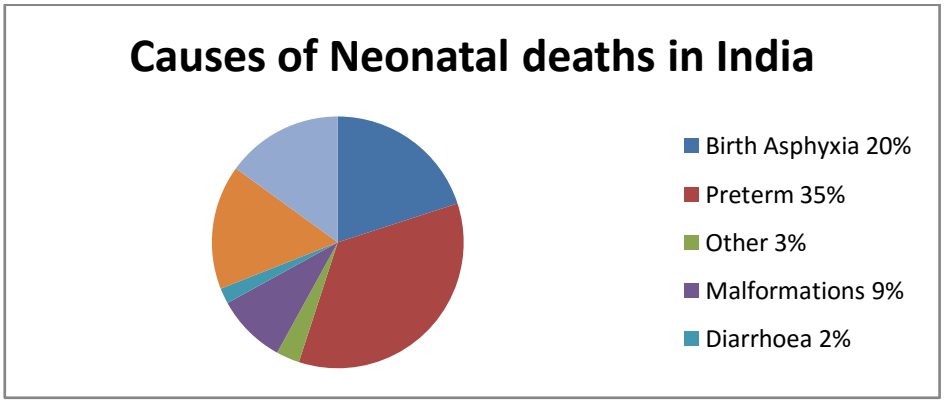
preterm births, as newer modalities of diagnosis and better obstetric care lead to diagnosis of fetal, placental and maternal complications that led to medically indicated late preterm births. The late preterm births rose from 7.3 to 9.1 percent of all live births in 2006, accounting for >250,000 births per year. Preterm birth rates have since fallen, comprising 9.6% of all births in 2014-2015. There was a decline in late preterm births from 9% in 2007 to 6.8% in 2015, indicating real progress in efforts to prevent late preterm births.(8) However, from 2014 to 2015, the US preterm birth rate rose from 9.57% to 9.62%. This increase was mainly in the late preterm (34 to 36 week) group, in whom birth rates increase from 6.82% to 6.87% (9)

Petrini et al (10)found that infants born from 34 to 36 weeks (late preterm), account for

about 70% of all preterm births. 35% of these births were due to PPROM.

India

In India,there has been a significant decrease in the number of neonatal deaths - from 1.35 million in 1990, to around 0.76 million in 2012. (11)The causes of neonatal deaths in India are as follows:



(Source: Liu et al, Lancet 2012 (12) *)*

Worldwide Statistics

There are not many worldwide statistics for preterm labour and PPROM. The Royal College of Obstetrics and Gynaecology cites an incidence of PPROM of 2%, which accounts for 40% of the incidence of preterm deliveries (13). One Nigerian study quotes an incidence of 3.3%, with a perinatal mortality of 7%(14).

Race and Socioeconomic status

Savitz et al (15)demonstrated a higher incidence of PPROM in the black population (5.1% to 12.5%), which contrasted with an incidence of 1.5 – 2.2% in the corresponding white comparision groups. However, other studies such as the Preterm Prediction Study (16) have not confirmed this increased risk in black women to be statistically significant.

Miller et al (17) did not find a statistical difference in the incidence of PPROM between various socioeconomic groups.

Incidence of Chorioamnionitis

Chorioamnionitis is a common complication with PPROM.The incidence of chorioamnionitiswith PPROM has been studied in gestations less than 34 weeks and has been found to be between 19% and 58.6% (18,19). It was found to be higher with decreasing gestational age.

One particular review found the following incidence according to gestation at delivery:

<27 weeks – 41%
28 to 36 weeks – 15%
Term – 2% (20).

PATHOGENESIS OF PPROM

The pathogenesis behind PPROM is of uncertain significance.

1. Cell death, and the breakdown of Collagen

PPROM may be related to increased levels of certain proteases in the amnionic fluid/ membranes, or increased apoptosis of cell membrane components.The tensile strength of the amnionicmembranes has been attributed to extracellular matrix of the amnion as well as type I and III interstitial amnionic collagen. These are produced in mesenchymal cells (21). Hence, the degradation of collagen in the amnion has been an area of research in elucidating the pathogenesis of PPROM.

Matrix Metallo-Proteinases (MMPs) are usually implicated in the degradation of collagen. It has been found that certain types of MMPs, namely MMP-1, MMP-2, MMP-3, MMP-9, are increased in the amnionic fluid of pregnancies with PPROM. Furthermore, inhibitors of MMPs, namely Tissue Inhibitor of Matrix MetalloProteinases (TIMPs), are found to be decreased in the amnionic fluid in such pregnancies (22,23) .

A more recent study done in 2013 by Mogami et al (24) provides a mechanism wherein bacterial endotoxin or TNF causes release of fFN (fetalfibronectin) from amnionic epithelial cells. This fFN then binds to Toll-like receptor 4 which is present in amnionic mesenchymal cells which causes activation of signalling cascades. This causes raised Prostaglandin E2 synthesis and increases activity of MMP 1,2 and 9. PG-E2 incites uterine contractions and causes cervical ripening, while the MMPs allow for collagen to breakdown in the amnion thereby rupturing membranes.

These pregnancies exhibit higher rates of apoptosis markers and a greater degree in

cell death than that of term amnions. In vitro studies have shown that this apoptosis is most likely regulated by TNF, IL-1 and bacterial endotoxin (25).

Proteins involved in the synthesis and maturation of cross-linked collagen, as well as the matrix proteins that are involved in the binding of collagen and promotion of tensile strength seem to be altered in pregnancies with PPROM (26) .

All these observations give strength to the theory that PPROM may result from altered collagen assembly, degradation of collagen and cell death. These could lead to a weakened amnion and early rupture of membranes.

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2. Infection

There is much evidence pointing to infection as a cause of PPROM. A review of 1500 women from 18 studies found that in one third of cases of PPROM, bacteria was isolated from the amnionic fluid (27).

WHY WORRY ABOUT THE LATE PRETERM NEONATE?

The rise in overall preterm births is largely attributable to delivery of late preterm babies. These babies, though sometimes the same size and weight as term neonates, have been found to have a higher morbidity and mortality.

This is attributed to their relative immaturity, both metabolically and physiologically.

The problems with late preterm are as follows:

1. During Hospitalisation at birth
    - Hypothermia
    - Hypoglycemia
    - Respiratory morbidity
    - Apnea
    - Hyperbilirubinemia
    - Feeding difficulties

2. Complications following Post Birth Discharge

3. Long term morbidity
    - Neurodevelopmental consequences
    - Others- Failure to thrive, Respiratory outcome

4. Mortality

1. <u>Morbidity during Hospitalisation at Birth</u>

Petrini et al (10)found that infants born from 34 to 36 weeks (late preterm), account for about 70% of all preterm births. 35% of these births were due to PPROM. Neonatal mortality rates, as well as morbidity indices were significantly increased in each late preterm week compared with those at 39 weeks as the referent. Specifically, the frequency of respiratory morbidity decreased by approximately 50 percent per week from 34 to 37 completed weeks.

A retrospective study by Wang et al studied 90 late preterm and 95 term neonates. Although both had similar length of hospital stays, it was found that late preterm infants had significantly more medical issues than term infants. They had higher rates of respiratory morbidity, temperature instability, evaluation for sepsis, jaundice and incurred higher hospital costs than their term counterparts. Apnea and bradycardia, though rare, were found only in the late preterm group. **(28)**

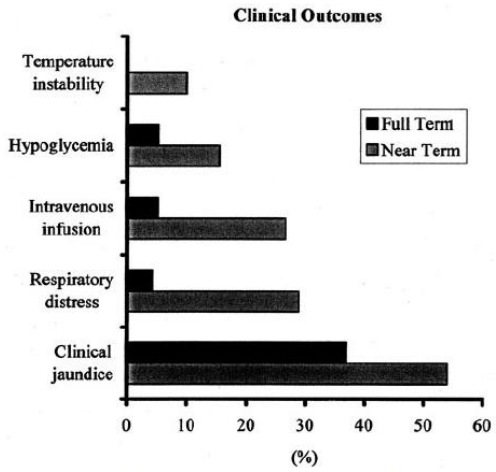


Fig 2. Graph of clinical outcomes in near-term and full-term infants as percentage of patients studied. Near-term newborn data are graphed with gray bars, full-term data with black bars.

(Reproduced from Wang et al, 2004)

2. Post Birth Discharge

Hwang et al demonstrated that late preterm infants were less likely to be discharged early than term infants(29). Cost of hospital care and rehospitalisation rates have also been shown to be higher for these babies. McLaurin et al studied 33,745 term babies and 1683 late preterm babies. On average, term babies were hospitalised for 2.2 days, incurring average costs of $2061. On the other hand late preterms tend to be hospitalised for longer, 8.8 days on average, with an average cost of $26,054. First year costs were also 3 times higher on average for late preterms, $12,247 as compared to $4069 for term infants. Higher rates of rehospitalisation were recorded for late pretems than term infants (15.2% vs 7.9%). There were a subset of late preterm infants with late discharge from hospital at birth that had the highest health care costs and rehospitalisation rates.

This not only shows that late preterm have higher morbidity and health care costs than term infants, but that this difference persists through the first year of life.(30)

3. Long term Morbidity

Long term morbidity will be studied under the following headings

— Neurodevelopmental consequences
— Failure to thrive
— Long term respiratory morbidity

A. Neurodevelopmental consequences:

It has been coming to light that late preterm babies may be at higher risk of more subtle neurological issues, such as inferior performances academically or behavioural issues(31).

Pathogenesis of neurological injury

The possible mechanisms of neurological injury in these babies may be as follows:

1. Prematurity, and complete neurological maturation taking place outside the uterine mileu.
2. Morbidity that is a consequence of late preterm delivery
3. The underlying primary cause of the preterm labour

The last half of pregnancy (including 34 to 36+6 weeks) is considered critical for brain development, with rapid/ dramatic changes in structural, molecular and neurochemical parameters. Brain weight at 34 weeks is just 65% of that of the term brain. Gyral and sulcal formation is incomplete at this stage. Twenty five percent of cerebral development occurs between 34 and 40 weeks, and cortical volume increases by 50% during this time period. Because the relative proportion of both gray and myelinated white matter to total brain volume increases so exponentially during this time, the period between 34 and 40 weeks gestation is critical. The late preterm brain is more vulnerable to free radical mediated injury and glutamate induced injury. This is due to the susceptible nature of the immature oligodendrocytes, as well as the

immaturity of the antioxidant enzymes that regulate stress.

Dendritic arborisation and synaptogenesis are still occurring and therefore incomplete in the late preterm brain. This is more pronounced in the very premature brain (31).

Possible long term neurodevelopmental consequences

The neurodevelopmental consequences can be myriad. There have been significant associations between late preterm births and the following:

- Cerebral palsy

Petrini et al(10) found that children born late preterm were more than 3 times as likely to be diagnosed with cerebral palsy than those born at term (hazard ratio, 3.39; 95% CI, 2.54-4.52)

- Developmental delay/ Mental retardation

A study done in 2009 by Morse et al (32)compared outcomes in prekindergarten and kindergartenbetweenhealthy late preterm and healthy term infants. Investigators found a 36% higher risk for developmental delay or disability for late preterm infants compared with term infants. These late preterm infants had a 19% higher risk of being suspended from kindergarten. Risk of retention in kindergarten was also 19% higher for late preterm infants. The assessment of not being ready to start school was only borderline significant.This study concluded that healthy preterm infants are at a higher risk for school- related problems and developmental delay and school related problems up to the first 5 years of life.

Petrini et al (10)found that the lower the gestational age, the higherthe incidence of developmental delay/ mental retardation. This was found true even for thosebabies

born between 34 and 36 weeks. For these children, an association was found with developmental delay and mental retardation (hazard ratio, 1.25; 95% CI,m1.01-1.54).

On the contrary, a study from the National Institute of Child Health and Development Study of Early Child Care and Youth Development (33)showed no significant difference. This study followed a total of 1298 children, 53 of which were healthy late preterms, the remaining being healthy term babies. These were followed from birth till age 15. Standard outcomes such as social skills, cognition, behavioural and emotional outcomes were studied. No consistent or significant difference was found between the two, indicating that healthy late preterms may not be at a significant disadvantage than their term counterparts.

B. Failure To Thrive

Goyal et al (34)studied 7,866 infants upto 18 months of life. The study population included late preterm and term infants and the main outcome measure at 6,12 and 18 months was a weight-for-age z score of 2 or less. It was found that late preterms had higher adjusted odds ratios of weight-for-age z scores of 2 or less at 6 and 12 months of age. However, at 18 months, there was no significant difference.

C. Long term Respiratory Morbidity

Data are inconsistent, and it is still uncertain whether late preterm babies suffer long term respiratory morbidity compared to term infants.

A Swedish study (35)using a national cohort of 622,616 infants were followed from ages 25 through 35, and it was determined whether medications for asthma were prescribed between 2005 and 2007. They found that very early preterms (born at 23

to 27 weeks of gestation) were 2.4 times more likely to have been prescribed these medications as adults. However, no association was found between later preterms (those born from 28 to 36 weeks).Abe et al(36) showed a modest association between late preterms and physician diagnosed asthma, but this was not found to be statistically significant.

4. Mortality

Tomashek et al(37)used US period linked birth/infant death files from 1995 – 2002, and compared cause- specific and overall early/ late neonatal/ post neonatal and infant mortality rates between singleton infants, both those born late preterm and term. There was a significant decline in mortality rates for both late preterm and term neonates. However, despite this decline, infant mortality rates in the year 2002 were three times higher for late preterm as compared to term infants(7.9 versus 2.4 deaths per 1000 live births. These late preterm infants were four times more likely to die of newborn bacterial sepsis, congenital malformations and complications with regard to placenta, cord and membranes.

Even early, late and postneonatal mortality rates were six, three and two times higher in late preterms respectively.

Authors concluded that late preterm infants have higher mortality rates than their term counterparts all through infancy. These findings again bring to light the need to prevent late preterm births as far as possible.

INCIDENCE OF PPROM

As mentioned before, most western literature quotes PPROM to occur in 1 – 5% of pregnancies. As stated, the incidence of PPROM in Indian studies has been shown to be about 7 – 8%(2). It is the most common factor identifiable with preterm labour.

CLINICAL COURSE

Most studies have studied the clinical course of PPROM before 34 weeks. Most of these cases deliver within one week of membrane rupture. The period of latency was more than 48 hours in about 73.4% of cases(38). Women who delivered earlier than 48 hours tended to have a greater cervical dilatation and were more likely to be nulliparous. Average period of latency was 0 – 59 days, and had an inverse relationship with gestational age at admission ($P< 0.001$)(38). Spontaneous resealing of membranes has been found to be very rare, except in cases of iatrogenic PPROM due to amniocentesis. These women tend to have a more favourable clinical course and outcome and should always be managed conservatively(39).

PREDISPOSING/ RISK FACTORS FOR PPROM

Maternal genetic, physiological and environmental factors most likely contribute, but in most cases no risk factors are found.

1. Prior History of PPROM

Women with prior PPROM are at risk of PPROM / preterm birth without PPROM in subsequent pregnancies. A large prospective study, the Preterm Prediction Study conducted by the National Institute of Child Health and Human Development (NICHD) Maternal-Fetal Medicine Units (MFMU) Network, found that women with

history of PPROM had a 13.5% rate of PPROM in subsequent pregnancies. In those with no such history, the rate was only 4.1% (RR 3.3, 95% CI 2.1-5.2) (16). Asratet al reported a much higher recurrence rate of 32.2% in their study (40).

2. Genital Tract Infection

Infection in PPROM: Cause or Effect? There are very good reasons to presume that infection may be the cause of PPROM, but substantial evidence has yet to come to light. Women with genital tract infections, specially bacterial vaginosis, have a higher incidence of PPROM than uninfected women. Also women with PPROM have significantly higher rates of amniotic fluid cultures being positive, as well as evidence of histologic chorioamnionitis than women who deliver prematurely without history of PPROM (41) .

These organisms may produce substances that incite membrane degradation, as well as induce host inflammatory responses, both of which could lead to premature rupture of membranes and preterm labour.

Predisposing factors for ascending infection of the genital tract may be as follows:

- *Prolonged membrane rupture*
- Prolonged labour
- Multiple digital vaginal examinations
- Nulliparity
- Internal fetal/ uterine monitoring
- Presence of genital tract pathogens
- Tobacco/ alcohol use (42).

3. Antepartum bleeding

First trimester vaginal bleeding has been found to have a small, but significant increase in risk for PPROM (43).

4. Cigarette Smoking

These individuals have a 2 to4 fold increased risk of PPROM compared to non smokers(44,45).

DIAGNOSIS OF PPROM

History: Most women will complain of fluid leaking from the vagina. However, some may have inconsistent historical findings, such as leakage of small amounts of fluid, or a feeling of wetness on the perineum. Williams Obstetrics describes a history of a continuous stream or gush of fluid from the vagina.

Physical Examination: A simple local examination, asking the patient to cough or performvasalva may aid in diagnosis. A sterile speculum examination to grossly visualiseamnionic fluid pooled in the vagina, clear fluid draining from the cervix or both is done (Williams Obstetrics, 24th Edition).

CONFIRMATION OF DIAGNOSIS

Ferning: A swab is taken from the posterior fornix and swabbed onto a glass slide. This is allowed to dry and then observed under a microscope for about ten minutes. Amniotic fluid produces a ferning pattern, whereas dried cervical mucus will produce a thick, wide arborisation.

Ferning pattern due to amniotic fluid

(Source: Beckmann CRB, Ling FW, Smith RP, et al. Obstetrics and Gynecology, 5th Edition. Philadelphia: Lippincott Williams & Wilkins, 2006.)

False positive can be caused by well estrogenised cervical mucus. False Negatives can be obtained if inadequate amniotic fluid is collected, or there is contamination with vaginal secretions or blood.

Ferning seen with estrogenised cervical mucus

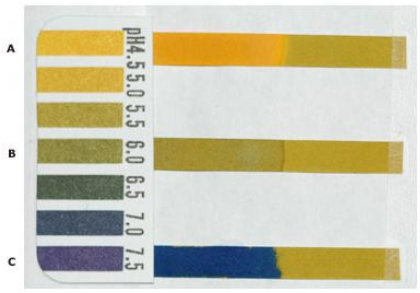
(Source: Scott JR. Danforth's Obstetrics and Gynecology, 6th Edition. Philadelphia: J.B. Lippincott, 1990.)

Ultrasound Examination: This reveals a decreased amniotic fluid index in 50-70% of pregnancies (46).

Laboratory Tests: When history is not forthcoming or uncertain, then one might need to use laboratory tests to confirm the diagnosis of PPROM.

1. Nitrazine test: pH of the amniotic fluid (7 to 7.3) is higher than that of the vagina (3.8 to 4.2). Thus diagnosis can be inferred by testing the pH of the vaginal fluid (47).

pH testing using Nitrazine test



(A) Normal, (B) Bacterial vaginosis, (C) Pregnant woman with premature rupture of membranes.

2. Amniosense: This is an absorbent pad that can be worn as to detect ruptured membranes. Studies show that it is a useful test, negative results can proved assurance of intact membranes and it might helpprevent unnecessary speculum examinations (48).

3. Commercial Tests

Actim PROM: This test is used in the CMC labour room. It is useful in cases where diagnosis is in doubt. It identifies insulin-like growth factor binding protein 1 (IGFBP-1), also known as placental protein 12 (PP12).

This is a protein which is produced by decidual and placenta cells. It is present in very high concentration inamniotic fluid.

A positive test is denoted by the presence of two parallel blue lines. It is unaffected by presence of semen, vaginal fluids, small volumes of blood or urine in the vagina.

It has a sensitivity of 95 to 100 percent, specificity of 93 to 98 percent, and positive predictive value is nearly 98 percent(49) .

ROM Plus (Alpha Fetal Protein and Placental protein 12/insulin-like growth factor binding protein): This test detects both these protein markers in amniotic fluid. It is a mono/polyclonal antibody test. A study comparing the value of this test to Speculum

examination+ Nitrazine + Fern tests showed that this test has a high sensitivity (99 % vs 85%) but a lower specificity (91 vs 98%) (50) .

AmniSure (Placental alpha microglobulin-1 protein): This test, available as a kit, is a rapid test which uses immunochromatography methods to detect placental alpha microglobulin 1 in vaginal fluid.

It is not affected by semen or minute amounts of blood. Sensitivity is about 94 to 98.9%, with a specificity of 87.5 to 100%).The positive predictive value is reported to be100%, and negative predictive value 99.1% (51).

These tests are relatively expensive, and use is limited to cases where physical examination, Nitrazine and fern tests are inconclusive.

FetalFibronectin: A negative test is strongly suggestive that membranes are intact. However, a positive test is an indication that there is disruption between chorion and amnion, which may be the case with intact membranes (52).

Alpha Fetoprotein:Alpha Fetoprotein is present in high proportions in amnionitic fluid. It is present in other bodily secretions, but to a lesser degree. Its presence in the vagina at a level > 3.88 ng/mL is suggested for a diagnosis of rupture of membranes. It is a much more cost effective test, however can produce false positives with the presence of blood in the vagina (53).

DIFFERENTIAL DIAGNOSIS

In cases with uncertain history/ clinical findings, one should consider other diagnoses. These could be urinary incontinence, excessive vaginal secretions or perspiration.

COMPLICATIONS OF PPROM

Pregnancy complications with PPROM

Pregnancy complication	Potential consequences for offspring	Potential maternal consequences
Intrauterine infection	Neonatal sepsis Cerebral palsy, other neurodevelopmental abnormalities	Postpartum endometritis
Oligohydramnios	Umbilical cord compression, Fetal Asphyxia	Cesarean delivery
Fetalmalpresentation	Cord Prolapse - asphyxia	Cesarean delivery
Abruptio placentae	Asphyxia	Cesarean delivery, Coagulopathy
Preterm birth	Morbidity of prematurity, including patent ductusarteriosus , intraventricularhemorrhage, respiratory abnormalities, necrotizing enterocolitis, retinopathy of prematurity,	Failed induction - Cesarean delivery

(Reproduced from UptoDate.com)

1. Risks to Neonate

The fetus and neonate are at risk for complications arising from PPROM. These can be

A. Prematurity related morbidity
B. Exposure to intramniotic infection
C. Cord prolapse
D. Abruptio Placentae and fetal distress
E. Malpresentations
F. Early PPROM and severe oligohydramnios can lead to pulmonary hypoplasia, orthopaedic abnormalities and facial deformation.

2. Risks to Mother

A. Infections: Chorioamnionitis, Endometritis, Sepsis

B. Abruptio Placentae
C. Higher rates of Caesarean section

COMPLICATIONS OF PPROM

A. Exposure to Intramniotic Infection

Intramniotic infection (IAI) is the infection of the amniotic fluid, placenta, membranes and/or decidua.

Pathogenesis: It is usually caused by ascending infection, i.e., organisims from the cervicovaginal flora when there has been a breach in the amniotic membranes. Other rare causes include transplacental migration *(eg. Listeria monocytogenes)* , and iatrogenic causes eg. Inoculation during amniocentesis, fetal blood sampling, chorionic villus sampling or fetal surgeries.

Incidence: Common in labour at term, the frequency is highest in preterm deliveries. The incidence with PPROM has been studied in gestations less than 34 weeks and has been found to be between 19% and 58.6%(18,19). It was found to be higher with decreasing gestational age.

Risk Factors for Chorioamnionitis

Prolonged membrane rupture and prolonged labour are two of the most important risk factors. It is relevant to our study as this is the main worry with expectant management of PPROM. There is a breach of membranes, and every risk of chorioamnionitis. Hence, a careful evaluation to rule out clinical/ subclinical chorioamnionitis was of utmost importance in our study.

Confirmation of clinical suspicion of infection (chorioamnionitis)

Usually in the background of ruptured membranes/ prolonged labour. Can occur with intact membranes.

Common clinical features in chorioamnionitis

Clinical features	**Frequency in Chorioamnionitis (%)**
Fever	95-100
Maternal Tachycardia	50-80
Fetal Tachycardia	40-70
Uterine tenderness/ foul, purulent amniotic fluid	4-25

(Source: Tita et al, ClinPerinatol. 2010 Jun; 37(2): 339–354) (54)

Maternal fever >100.4 degrees F persisting for greater than one hour, or any fever more than 101 degrees in pregnancy needs to be evaluated. Fever is a prerequisite for diagnosis.(54)

Laboratory Tests

1. Leucocytosis

   A total WBC count of >12,000 or >15,000/mm3, or on differential count a shift to the left/ bandemia>9% is present in 70-90% cases of clinical chorioamnionitis. Leucocytosis in the absence of clinical signs has been found to be of limited value as it can be caused by other factors such as prolonged labour and steroid use.

2. C- Reactive Protein

   CRP is an acute phase reactant that is elevated in the presence of inflammation. A review done by Van de Laar et al in 2009 sought to determine the accuracy of CRP in predicting chorioamnionitis and neonatal infection in women with PPROM.The

authors included studies which measures maternal CRP levels in women with PPROM varying from 20 to 36+6/7 weeks.

Outcomes studied were

- Neonatal sepsis (positive blood culture/ clinical signs of infection)
- Suspicion of clinical chorioamnionitis
- Histological chorioamnionitis

Assay used to measure CRP was nephelometry, one study used immunoassay. Diagnostic thresholdsused in the studies ranging from >12 mg/L to 40mg/L, and interval between the determination of CRPranged from 12 to 72 hours.

Results: Five cohort studies with 372 evaluable participants were included. Most studies did not meet the criteria for neonatal sepsis.

A SROC (summary receiver operating characteristic) was constructed for histological chorioamnionitis. However, a reliable SROC could not be estimated for clinical chorioamnionitis due to significant heterogeneityamong studies reporting clinical chorioamnionitis.

Clinical Chorioamnionitis: Prevalence was 25.8% (18 to 50%). Sensitivity of CRP for clinicalchorioamnionitis at a diagnostic threshold of >20mg/L was 55%, and for >12.5 mg/L was 100%. Specificity at a diagnostic threshold of >20mg/L ranged from 55 to 98%.

Histological Chorioamnionitis:Prevalence was 54.6% (21 to 63%). Sensitivity of CRP at a diagnostic threshold of >40mg/L was 37%, and at a threshold of 12.5mg/L was 88%. Specificity was a 100% at a diagnostic threshold of >40mg/L, and 68% at a threshold of >20mg/L.

Conclusion: CRP is moderately predictive of histological chorioamnionitis. The studies that reported clinical chorioamnionitis had too much heterogeneity to pool data. No data was available on CRP as a predictor of neonatal sepsis.

The authors concluded that literature at the time of publication did not support use of CRP in women with PPROM.(55)

However, a study published in 2016 by Caloone et al (56) compared various markers in maternal serum that could possibly predict histological chorioamnionitis in PPROM. The markers studied were C-Reactive Protein (CRP), Interleukin-6 (IL-6), Interleukin-8 (IL-8), Triggering receptor on myeloid cells (TREM-1), InterCellular Adhesion Molecule-1 (ICAM-1), Human Neutrophile Peptides (HNP) and Matrix-Metalloproteinase 8 and 9 (MMP-8, MMP-9). They found that the concentrations of CRP, MMP-9, MMP-8 and HNP were higher in histological chorioamnionitis versus the non-Histological chorioamnionitis group ($P<0.05$). Among these, the ROC curve with the highest area under the curve, and significantly higher than other markers was C-RP. The authors concluded that C-RP was the best maternal marker to predict histological chorioamnionitis.

3. Other Laboratory Tests

Interleukin 6, Lipopolysacharide binding protein (LBP) and soluble intercellular adhesion molecule 1 (sICAM 1). Their clinical utility has not been established.

4. Amniotic Fluid Testing

Culture of amniotic fluid, usually obtained via amniocentesis has been used. However, results may not be available for upto 3 days, and given the invasive nature of the test, is hardly undertaken.

Placental and umbilical cord pathology

Histological chorioamnionitis is diagnosed three times more frequently than clinical chorioamnionitis(57). This is in part because it encapsulates both clinical and sub-clinicalchorioamnionitis. Also, amniotic fluid cultures for genital mycoplasms, which are among the most common organisms causing chorioamnionitis, are not very sensitive.

Histological chorioamnionitis has been defined as presence of acute histological changes on examination of the amniotic membrane and chorion of a placenta. Funisitis is the leucocytic infiltration of the wall of the umbilical vessel or Wharton's jelly (58).

Differential Diagnosis of Chorioamnionitis

Epidural- associated fever, Extra uterine infections: Pyelonephritis, appendicitis, pneumonia, influenza, etc.

Effects on the fetus

Goncalves et al (27) categorized intrauterine infection into 4 stages:

Stage 1 - Bacterial Vaginosis
Stage 2 - Decidual Infection
Stage 3 – Amnionic Infection
Stage 4 – Fetal Systemic Infection

Gomez et al (59) conducted a study to find out the frequency and significance of the fetal inflammatory response syndrome (FIRS) in women with PPROM/ Preterm Labour. They defined FIRS as elevated Interleukin-6 in fetal plasma. Amniocentesis andcordocentesis were performed in157 patients with preterm labour and PPROM. Investigators then cultured the amniotic fluid for aerobic/ anaerobic bacteria/

mycoplasms. Amniotic fluid and fetal plasma Interleukin-6 levels were measured.

Results: 105 patients with preterm labour and 52 patients with PPROM were included. The prevalence of severe neonatal morbidity (defined as Respiratory Distress Syndrome, pneumonia, suspected/ proven neonatal sepsis, intraventricular haemorrhage, necrotizing enterocolitis or periventricular leucomalacia) was 34.8% (54/155).

These neonates had higher levels of IL-6 compared to neonates who did not develop severe neonatal morbidity (median 14.0 pg/mL, range 0.5 to 900 vs median 5.2pg/mL, range 0.3 to 900, respectively; $P < .005$).

In order to trace the relationship between the presence of FIRS and neonatal outcome, a multivariate analysis was performed. The analysis was restricted to those neonates who delivered within 7 days of cordocentesis, in order to maintain a meaningful temporal relationship. In this subset, 39/73 patients had severe neonatal morbidity (53.4%).

A cut of of>11 pg/mL was used to define FIRS, and it was found that those neonates that met this criteriahad a higher rate of severe morbidity than those that did not (77.8% [28/36] vs 29.7% [11/37], respectively; $P < .001$).Stepwise logistic regression showed that fetal plasma IL-6 levels was an independent predictor of severe neonatal morbidity (odds ratio 4.3, 95% confidence interval 1 to 18.5), when adjusted for cause of preterm delivery, gestational age of delivery, presence of clinical chorioamnionitis, amniotic fluid IL-6 results and culture.

Complications of Chorioamnionitis

- Fetal/ Neonatal
  - Asphyxia and Respiratory Distress
  - Sepsis
  - Neurological effects - Cerebral Palsy, Periventricular Leukomalacia
  - Pneumonia
  - Grade 3/4 Intraventricular Haemorrhage
  - Perinatal death
- Maternal
  - Endometritis
  - Postpartum haemorrhage
  - Sepsis

- Neonatal Asphyxia and Respiratory Distress

Alexander et al (60) found that infants exposed to chorioamnionitishad increased risk of low Apgar (3 or less at 5 minutes), umbilical artery cord pH of 7.0 or less and meconium aspiration syndrome. After adjusting for confounders, these babies were significantly more likely to require delivery room intubation.

Yoder et al (61) found that respiratory distress occurred in 20% of term infants in the presence of chorioamnionitis and only 2% when chorioamnionitis was absent.

- Sepsis

Yoder et al (61) found a higher rate of neonatal sepsis in term infants whose mothers were diagnosed with chorioamnionitis.Chorioamnionitis has found to be associated with up to 40% cases of early in onset neonatal sepsis (54).

- Cerebral Palsy and Periventricular Leucomalacia

It has been suggested that Chorioamnionitis leading to FIRS can lead to fetal brain injury which can cause subsequent cerebral palsy (62).

Studies have shown elevated fetal plasma cytokines and elevated amniotic fluid cytokines in children who subsequently developed cerebral palsy (58,63).

A metaanalysis by Wu et al (64) was conducted on studies that studied the association between clinical/ histological chorioamnionitis and the cystic periventricular leucomalacia (cPVL) and cerebral palsy in children.

Findings:

In preterm infants: Clinical chorioamnionitis was significantly associated with both cPVL(RR, 3.0; 95% CI, 2.2-4.0) and cerebral palsy (RR, 1.9; 95% CI, 1.4-2.5). The risk ratio of histologic chorioamnionitis with cerebral palsy was 1.6 (95% CI, 0.9-2.7).

Histologic chorioamnionitis was associated significantly with cPVL (RR, 2.1; 95% CI, 1.5-2.9).

Full term infants: A positive association in full term infants between clinical chorioamnionitis and cerebral palsy was found (RR, 4.7; 95% CI, 1.3-16.2).

Thus, investigators concluded that chorioamnionitis is a risk factor for both cPVL and cerebral palsy.

- IntraventricularHemorrhage (IVH)

Morales et al (65) found a statistically significant increase in rate of IVH in the setting ofchorioamnionitis.

Complications of chorioamnionitis in Pretermversus Term

Preterm infants are at even higher risk of all the complications of chorioamnionitis than term infants.

- Perinatal death (25% vs 6%, preterm vs term)
- Neonatal Sepsis (28% vs 6%)
- Pneumonia (20% vs 3%)
- Grades 3 /4 IVH (24 vs 8%)
- Respiratory Distress (62 vs 35%) (65)

Treatment of Chorioamnionitis

This is done with broad spectrum antibiotics as soon as diagnosis is established to treat mother and baby. Treatment is not complete, however, without complete evacuation of the uterus of the products of conception. Hence, a plan for delivery should be made, either by induction/ augmentation of labour or if other indications, for example fetal distress coexist, caesarean section. The standard antibiotics used are Inj. Ampicillin 2 grams IV every 6 hours, and Inj. Gentamicin 1.5mg/kg every 8 hours.

In case of caesarean delivery, additional coverage with an antibiotic that covers anaerobes (eg. Metronidazole), is required as these patients are at greater risk for post partumendometritis.

The baby also requires a blood culture postnatally and coverage with antibiotics.

Prevention of chorioamnionitis

Central to prevention of chorioamnionitis is the administration of antibiotics to women with PPROM. This strategy prolongs latency, decreases incidence of chorioamnionitis and improves neonatal outcomes.

OTHER COMPLICATIONS OF PPROM

A. Prematurity related morbidity has already been discussed at length.
B. Cord Prolapse

Malpresentations can lead to cord prolapse. Lewis et al (66)conducted a retrospective study of preterm pregnancies, 74 with vertex and 74 with non-vertex presentations.

They found a higher rate of cord prolapse in the non-vertex (n = 8; 10.8%) compared to the vertex group (n = 1; 1.4%). More infants in the non-vertex group had low Apgar scores and cord pH levels than in the vertex group. Five infants underwent a non plannedprecipitous vaginal breech delivery, but with no significant morbidity.

They concluded that after transfer to the antenatal ward, patients with non-vertex pregnancies appeared to have a significantly higher risk of cord prolapse, low Apgars and low cord pH.

C. Abruptio Placenta

Abruption is found to occur in 2-5% of pregnancies with PPROM (67,68). This risk was found to be increased seven to nine fold where these pregnancies are complicated by chorioamnionitis or severe oligohydramnios(67,69).

D. Fetalmalpresentations

This can occur frequently, as it is well known that breech presentations are more frequent with decreasing gestational age. Another contributing factor is the decreased amniotic fluid that accompany these cases.

E. Pulmonary hypoplasia, orthopaedic abnormalities and facial deformation

These are rare, and occur with very early, severe, prolonged PPROM.

F. Higher rates of Caesarean Section

This can occur due to higher rate of malpresentations, fetal distress intrapartum due to decreased liquor; or failed induction of labour.

G. Infections

Infections due to rupture of membranes are usuallypolymicrobial. The organisms isolated from amniotic fluid culture are usually enteric/ vaginal flora.

Organisms isolated from amniotic fluid of 404 patients with chorioamnionitis

Organism	Percent	Number
Ureaplasmaurealyticum	47.0	190
Any gram-negative anaerobe	38.4	155
Mycoplasma hominis	30.4	123
Bacteroidsbivius	29.5	119
Gardnerellavaginalis	24.5	99
Group B Streptococcus	14.6	59
Peptostreptococcusspp	9.4	38
Escherichia coli	8.2	33
Enterococci	5.4	22
Fusobacteriumspp Bacteroidesfragilis	5.4	22

(Source: Sperling et al Intraamniotic infection in low-birth-weight infants. J Infect Dis 1988; 157:113.) (70)

MANAGEMENT OF PPROM

Diagnosis of PPROM is first confirmed via history, speculum examination, fern test, Actim PROM as required.The approach to a patient, once the diagnosis of PPROM has been confirmed, is based on the following considerations:

- Gestational age
- Presence or absence of infection
- Presence or absence of labour, Cervical status (by visual inspection)
- Fetal well-being
- Fetal presentation
- Fetal lung maturity
- Availability of neonatal intensive care

PPROM can be managed in two ways: either immediate delivery or expectant management.

Before making this decision, one must rule out contraindications to expectant management. These are

1. The presence of sepsis
2. Cord prolapse/ risk of the same due to unstable lie
3. Non reassuring fetal status
4. Abruptio Placentae

Abruptio Placentae and Cord Prolapse are ruled out via clinical examination.

A thorough clinical examination is done to rule out sepsis, aided by laboratory tests – Total and Differential White Blood Cell Count, C-RP. An ultrasound is performed to rule out growth restriction, confirm presentation, calculate amniotic fluid index and gain a rough estimate of baby weight. Non Stress Test is performed to confirm fetal well being. Neonatal consultation is sought, in the event of early delivery.

If any complications are present, there is no role for expectant management, and one must immediately deliver the patient either vaginally, or if need be, by Caesarean section.

Once complications are ruled out, the woman is administered a course of steroids for fetal lung maturity. She is also given a course of antibiotics, as this has been shown to improve outcomes and prolong latency.Once we have ensured fetal and maternal well being, the decision to deliver immediately or manage expectantly must be made. Before 34 weeks, most experts agree on management, and that is to prolong pregnancy with close monitoring. In the event of any complications, pregnancy is terminated by immediate delivery either via vaginal or caesarean delivery.

Expectant Management

- Administration of Antenatal Corticosteroids:

A landmark paper published in 1972 by Liggins et al demonstrated that administering steroids to women at risk of preterm delivery decreased the respiratory morbidity as well as mortality in offspring (71). Antenatal steroid have been shown to accelerate development of certain key cells in the lungs – type 1 and type 2 pneumocytes – leading to biochemical and structural changes in the lungs. These changes improve lung mechanics (maximal lung volume and compliance) and improve gas exchange (66).

The following adverse outcomes have been shown to decrease in preterm neonates when administered steroids antenatally

- Respiratory Distress Syndrome
- Intra Ventricular Haemorrhage
- Necrotising Enterocolitis
- Neonatal Mortality
- Risk of infection in the first 48 hours (73).

A 2006 Cochrane review by Roberts et al (73) showed significant benefit of Antenatal Corticosteroids when administered from 26 to 34 weeks of gestation. It is usually not administered after 34 weeks, provided one is sure of gestational age.

- Antibiotics:

As previously stated, infection may be the cause, or effect of PPROM. Antibiotics seem to prolong the latency, and treat/ prevent any such infection.

A 2013 Cochrane review (74)of 22 randomised studies involving more than 6800 women studied the use of antibiotics in women before 37 weeks of gestation. Compared to placebo, the use of antibiotics was found to have the following benefits

with significant reductions in

- Babies born within 48 hours (RR 0.71, 95% CI 0.58-0.87) and 7 days (RR 0.79, 95% CI 0.71-0.89) of randomization
- Chorioamnionitis (RR 0.66, 95% CI 0.46-0.96)
- Use of surfactant (RR 0.83, 95% CI 0.72-0.96)
- Neonatal oxygen therapy (RR 0.88, 95% CI 0.81-0.96)
- Neonatal infection (RR 0.67, 95% CI 0.52-0.85) and
- Abnormal cerebral ultrasound scan prior to hospital discharge (RR 0.81, 95% CI 0.68-0.98)

No definite regimen was found to show more benefit than the others, however use of Amoxicillin – Clavulunate was found to be associated with the incidence of necrotisingenterocolitis in the offspring. In CMC, a 5 day course of Tab. Azithromycin 250mg twice a day with Tab. Metronidazole 400 mg thrice a day for a duration of 5 days is used.

- Use of Tocolysis/ Progesterone

Neither of these therapies has been found to be of use in these patients.

- Home care versus Hospitalisation

A Cochrane review was published in 2014 assessing safety and cost for home versus hospital care for women with PPROM (75) . They were able to include only two trials comprising a total of 116 women. These studies did not show a significant difference in neonatal morbidity/ mortality. They found that women who stayed at home were more satisfied with their care, had a shorter duration of hospital stay by approximately 10 days and had fewer costs. However, women who were hospitalised seemed more likely to have caesarean delivery.

The authors concluded that these studies were inadequately powered, and further, larger randomised trials were required before a recommendation could be made.

- Maternal monitoring

This should be done vigilantly for signs of infection. In CMC, a twice weekly blood counts, with CRP is done to monitor for infection, however studies have not found this to be of much use (54).

They should also be warned of complications that may arise, and report any fever, foul smelling lochia, decreased fetal movements, abdominal pain or bleeding per vaginum.

- Fetal Monitoring

Some form of fetal surveillance has to be undertaken to assure fetalwell being(76). No definite method is agreed upon. Some of the methods used are – daily fetal kick count, daily Non Stress Test/ Bio Physical Profile.

- Delivery

Timing of delivery should be decided after discussing the pros and cons of expectant management versus immediate delivery with the patient. Once delivery has been decided upon, if no contraindication to vaginal delivery exists, one can induce labour using Prostaglandin E2, or oxytocin directly as per the Bishops Score.

- Future Pregnancies

The risk of recurrence must be explained, as well as the association with preterm birth. Supplemental progesterone or cervical length monitoring with cerclage placement can be considered in these cases.

Beyond 34 weeks, there is no consensus on key management issues.

ACOG Guidelines 2013

- Patients with PPROM <34 weeks should be managed expectantly if no other contraindications to the same exist (Level A).

- A 7 day course of antibiotics with a combination of Erythromycin or Ampicillin/ Amoxicillin is recommended in women on expectant management <34 weeks, this reduces maternal/ neonatal infections and gestational age dependent morbidity (Level A)

- A single course of antenatal corticosteroids are recommended for these women who are 24 +0/7 to 34 +0/7 weeks and at are risk of delivery.

Greentop Guideline Number 44(6) published in 2006 recognises that the decision to deliver beyond 34 weeks is one that should not be taken lightly. The increased risks associated with perinatal morbidity when a late preterm delivers should be weighed againsttherisks of chorioamnionitis and its effects on baby and mother when one tries to prolong pregnancy. Most studies did not find a difference in major neonatal composite morbidity if delivery occurred at 34 weeks. There was also not enough research done in the subgroup of 34 to 37 weeks.

Hence, it was concluded that delivery be considered at 34 weeks of gestation. Expectant management could also be considered with the caveat of adequate counselling to the mother – the risks of chorioamnionitis versus the benefits of decreased respiratory morbidity.

The following are a list of consequences that must be considered with either line of management.

Pregnancy complications with PPROM

Pregnancy complication	Potential consequences for offspring	Potential maternal consequences
Intrauterine infection	Neonatal sepsis Cerebral palsy, other neurodevelopmental abnormalities	Postpartum endometritis
Oligohydramnios	Umbilical cord compression, Fetal Asphyxia	Cesarean delivery
Fetalmalpresentation	Cord Prolapse - asphyxia	Cesarean delivery
Abruptio placentae	Asphyxia	Cesarean delivery, Coagulopathy
Preterm birth	Morbidity of prematurity, including patent ductusarteriosus , intraventricularhemorrhage, respiratory abnormalities, necrotizing enterocolitis, retinopathy of prematurity,	Failed induction - Cesarean delivery

(Reproduced from UptoDate.com)

The need for more research on this subject has been noted, and there have been randomised control trials on this subject to address these clinical questions.

Two notable studies are - PPROM Expectant Management versus Induction of Labor (PPROMEXIL)(77) and PPROMT trial (Immediate delivery compared with expectant management after preterm pre-labour rupture of the membranes close to term(78)**.**

These trials brought to light the advantages and disadvantages of prolonging pregnancy in late preterms with PPROM.

Advantages of Expectant Management (from 34+0/7 to 37+0/7 weeks)

There does not seem to be an increased risk of neonatal sepsis as previously thought (77,78).

There is a higher probability of vaginal delivery when these patients are carried closer to term (77,78).

There is also less neonatal morbidity when these patients are carried to term. Morris et al demonstrated that those delivering immediately had higher rates of respiratory distress (76 [8%] of 919 vs 47 [5%] of 910, RR 1·6, 95% CI 1·1-2·30; p=0·008) and any mechanical ventilation (114 [12%] of 923 vs 83 [9%] of 912, RR 1·4, 95% CI 1·0-1·8; p=0·02) (78).

In those undergoing immediate delivery, babies spent more time in neonatal intensive care (median 4·0 days [IQR 0·0-10·0] vs 2·0 days [0·0-7·0]; p<0·0001) (78).

Disadvantages of Expectant Management (from 34+0/7 to 37+0/7 weeks)

These women had higher rates of chorioamnionitis and need for intrapartum antibiotics than those undergoing immediate delivery.

Morris et al found that women who undergo expectant management have higher risks of intrapartum/antepartumhemorrhage (RR 0·6, 95% CI 0·4-0·9), occurrence of intrapartum fever (0·4, 0·2-0·9), and the use of postpartum antibiotics (0·8, 0·7-1·0) with a longer hospital stay (p<0·0001) (78).

In the absence of obvious infection, when fetal well being is assured, a policy of expectant management with prudent surveillance of maternal as well as fetal wellbeing should be followed in women with PPROM close to term.

METHODOLOGY

This was a prospective, non inferiority randomised control trial to ascertain whether conservative management of preterm prelabour rupture of membranes had similar neonatal and maternal outcomes in comparison to immediate delivery, in pregnant women after 34 weeks of gestation till 37 completed weeks.

The trial was presented before the Institutional Review Board in Christian Medical College and Hospital (CMCH), and protocol was approved prior to start of recruitment.

All pregnant women admitted to the Christian Medical College Labour ward between 34 +0/7 and 36 +6/7 weeks of gestational age with complaints of leaking per vaginum were screened for eligibility to this trial.

Pregnant womenbooked in CMCH were informed of this study at first antenatal visit, through information sheets given in OPD. If they were willing to be part of this study, informed consent was taken at the next antenatal visit.

Those who subsequently presented with rupture of membranes between 34+0 to 36weeks and 6 days of gestational age were included in this study. All pregnant women reporting to labour room with preterm prelabour rupture of membranes (leaking per vaginum from 34 to 36+6 weeks of gestation) were eligible. Pregnant women who were booked elsewhere , but referred to CMC labour ward and meeting inclusion criteria, were also included in the study after taking informed consent.

After confirmation ofPPROM, by means of definite history of leaking, direct visualization of amniotic fluid in the posterior fornix with speculum examination or using an enzyme-linked immunosorbent assay (ELISA) test to confirm leaking, patients were enrolled into the study. Exclusion criteria were suspected chorioamnionitis (determined by clinical examination , Total WBC count >15,000, C-RP >5, Differential WBC Count with band forms), the presence of labour (presence of uterine contractions and cervical dilatation >=2cms) , severe oligohydramnios (AFI <= 5 cms), malpresentations (transverse lie and footling breech), suspected abruption and fetal compromise. Pregnancies with flexed/ extended breech presentations were included in the trial.

All consenting and eligible women were randomized to either the immediate delivery or conservative management group. In the immediate delivery group, induction of labour/ caesarean section was carried out as per protocol. If randomized to expectant managementgroup, pregnancy was allowed to continue till 36 completed weeks, in the absence of any maternal/ fetal complications, and induction of labour /LSCS was carried out as per protocol at 37 weeks.

In the Expectant Management group, women received a course of oral antibiotics (Tab. Azithromycin/ Tab. Metronidazole) and antepartum surveillance was carried out for fetal and maternal well being. The components of antepartum surveillance are described below:

- Admission of pregnant women to antenatal ward with biweekly ultrasounds for modified biophysical profile.
- Biweekly maternal blood test (CRP) to detect subclinical chorioamnionitis.
- Strict daily clinical monitoring for signs of chorioamnionitis – Maternal fever/ tachycardia, uterine tenderness, foul smelling discharge per vaginum.

Women were discharged after one week if there were no maternal and fetal complications, at the discretion of senior consultant fromthe respective Unit and advised to return to the antenatal clinic for biweekly visits. At discharge, womenwere given instructions to return immediately to labour ward in the event of fever, foul smelling discharge per vaginum, abdominal pain, vaginal bleeding, decreased or absent fetal movements. Antenatal per vaginal examinations in the absence of labour were not carried out. Conservative management was terminated in the presence of chorioamnionitis, fetal compromise,onset of spontaneous labour, suspected abruption or any condition necessitating early delivery.

Blinding was not possible after randomisation due to the inherent nature of the study design.

Baseline data was collected for all patients, which included body mass index, age, socioeconomic status, time and date of rupture of membranes. Additional information was collected after delivery, such as randomisation to delivery interval, data pertaining to the neonate, mode of delivery, post natal course of the mother.

Primary outcome was the occurrence of neonatal sepsis, which was defined as proven neonatal infection with positive blood culture within 48 hours of birth.

Secondary outcomes includedthe

occurrence of neonatal and maternal adverse outcomes. All babies were assessed by a Neonatologist at birth, and need for ICU care/ antibiotics decided by the treating Neonatologist. Neonatal morbidity was also be recorded by the treating neonatologist.

Secondary Neonatal Outcomes

- Mode of delivery
- Apgar score at 0 and 5 minutes
- Need for resuscitation at birth
- Cord pH at the time of delivery (In case of low Apgar)
- Respiratory distress syndrome (RDS)
- Pneumonia
- Meconium aspiration syndrome
- Late onset neonatal sepsis
- Hypoglycaemia
- Necrotizing enterocolitis
- Convulsions
- Intrauterine death/ Neonatal death
- Total length of hospital stay and admission
- Need for admission to neonatal intensive care unit (NICU), and if required, length of stay in NICU
- Need for Readmission

Secondary Maternal Outcomes-

- Clinical chorioamnionitis (defined as fever before or during labor with a temperature greater than 100.4degreesF, requiring antibiotics)
- Maternal sepsis (defined as a temperature greater than 100.4degreesF and a positive blood Culture or circulatory instability requiring intensive care monitoring)
- Antepartum hemorrhage (Bleeding per vaginum after 28 weeks gestation and before the onset of labour)
- Umbilical cord prolapse
- Urinary tract infection treated with antibiotics
- Endometritis (defined as a temperature greater than 100.4 degrees F on two occasions at least 1 h apart after the first 24 h postpartum with associated uterine tenderness),
- Post partum Haemorrhage (Blood loss after delivery >500ml after a vaginal delivery, >1000 ml after a caesarean section)
- Total length of hospital stay
- Admission to the intensive care unit
- Maternal death

SAMPLE SIZE CALCULATION

Non-inferiority - Two Groups - Parallel - Two proportions - Equal Allocation	
Proportion in the standard treatment	0.02
Proportion in the new treatment	0.02
Observed/Expected difference in proportions	0
Non-inferiority margin	-0.02
Power (1- beta) %	80
Alpha Error %	5
Required sample size in each group	606

Assuming an equal incidence of neonatal sepsis in both arms (that is immediate delivery or prolonging pregnancy to 37 weeks), with a non inferiority margin of 20%, the calculated sample size is 606 in each arm.

Formula

$$m = \frac{\left(z_{1-\alpha} + z_{1-\beta}\right)^2 \left[\pi_S(1-\pi_S) + \pi_T(1-\pi_T)\right]}{\left(\pi_T - \pi_S - \delta\right)^2}$$

Where,

δ : Noninferiority limit of the difference in Proportions

π_T : Proportion in Test Treatment

π_S : Proportion in Standard Treatment

$\pi_T - \pi_S$: Expected difference in proportions

α : Significance level

1- β : Power

Table 1 – Inclusion Criteria

	Inclusion Criteria
1.	PPROM at 34 weeks upto 36 weeks and 6 days of gestation confirmed by definite history/ positive ELISA test for PPROM / Direct visualization of amniotic fluid in the posterior fornix on speculum examination

Table 2 – Exclusion Criteria

	Exclusion Criteria
1.	Preterm labour
2.	Evidence of clinical or subclinical chorioamnionitis
3.	Fetal distress
4.	High risk pregnancy necessitating immediate delivery
5.	Major congenital anomalies of fetus
6.	Oligohydramnios
7.	Malpresentation (transverse lie and footling breech)
8.	Suspected abruption

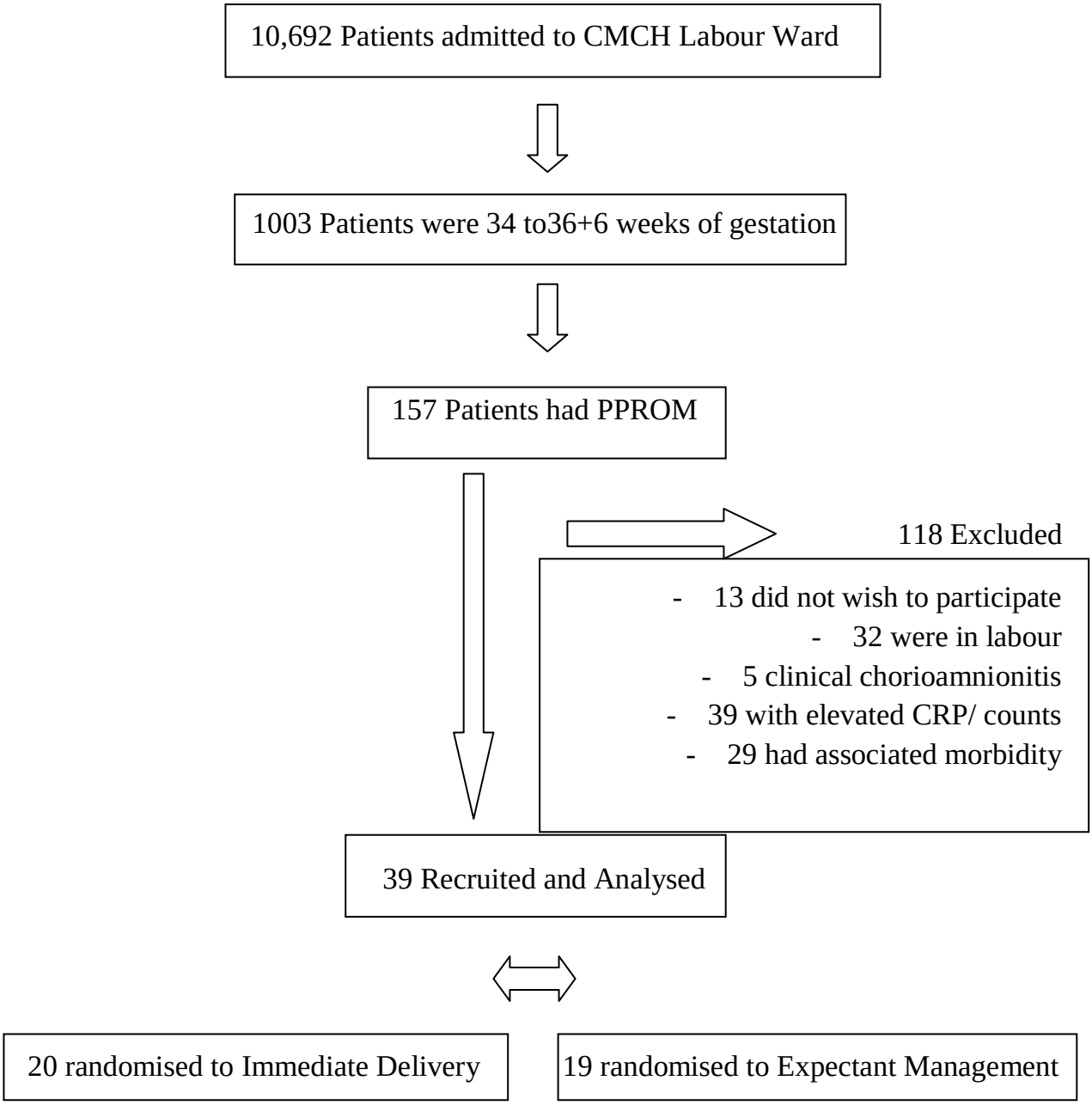
RESULTS

A total of 10,692 patients were admitted to the Christian Medical College Labour ward between December 2015 and August 2016, out of which 1003 were 34 to 36 +6 weeks of gestational age. One hundred and fifty seven (157) of these patients were admitted with complaints of leaking per vaginum and were screened for inclusion in this study. One hundred and eighteen (118) were excluded due to the following reasons. Thirteen patients were unwilling to participate, thirty two had regular contractions with cervical dilatation >= 2 cms, twenty nine could not be recruited due to associated risk factors such as severe preeclampsia. Five patients were induced for clinical chorioamnionitis. Thirty nine patients had elevated CRP/ white blood cell counts that precluded them from the trial.

Table 3 – Patients with PPROM from December 2015 to August 2016

Total	Elevated CRP/ Counts	Clinical Chorioamnionitis	Spontaneous Labour	Associated Risk Factors	Not willing	Recruited
157	39	5	32	29	13	39

Finally, we were able to recruit 39 patients, of which 20 were randomised to immediate delivery and 19 to expectant management.


10,692 Patients admitted to CMCH Labour Ward
1003 Patients were 34 to36+6 weeks of gestation
157 Patients had PPROM
118 Excluded
- 13 did not wish to participate
- 32 were in labour
- 5 clinical chorioamnionitis
- 39 with elevated CRP/ counts
- 29 had associated morbidity
39 Recruited and Analysed
20 randomised to Immediate Delivery
19 randomised to Expectant Management

When we followed up those that were excluded due to increased CRP/ counts, we found that 37 patients had been delivered immediately.

Table 4– Follow up of Patients with elevated CRP/ Counts

	Yes	No
Delivered Immediately	37	1 (9 days gained, had NICUadmission) +1 (3 days gained)
Neonatal Sepsis	2 (suspected)	38 (1 set of twins)
Maternal complications	1 – post partum Fever – UTI	38
NICU Admission	20 +2 – VSD +1 – Anomalous, END	17

NICU – Neonatal Intensive Care Unit, UTI – Urinary Tract Infection, VSD – Ventricular septal defect, END – Early Neonatal Death

Two patients underwent conservative management as decided by the treating consultant. These patients gained a total of 9 days and 3 days respectively, neither patients developed chorioamnionitis/ neonatal sepsis, but one baby needed NICU care for preterm morbidity.

Of all the 40 babies born to these 39 mothers (one was a twin pregnancy), two babies developed suspected sepsis, both needing second line antibiotics. The blood cultures for these babies were sterile. Twenty three babies needed ICU care, of which two had a VSD and one was an anomalous baby that died in the first week of life.
One mother developed fever and was diagnosed with ESBL(Extended Spectrum Beta Lactamase producing) E. Coli positive UTI. There were no other maternal complications.

Baseline Characteristics

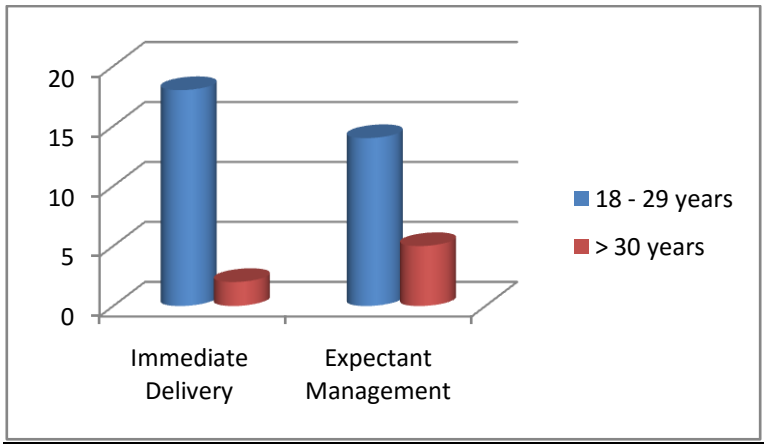
The baseline characteristics are listed in tables 5 and 6.

Table Number 5 – Baseline Characteristics.

Baseline Characteristics	Immediate Delivery Group N = 20	Expectant Management Group N = 19
DEMOGRAPHIC DATA		
1. Age 18-29 >30	 18 (90%) 2 (10%)	 14 (73.7%) 5 (26.3%)
2. Socioeconomic status Wood Kerosene LPG	 0 3 (15%) 17 (85%)	 0 1 (5.3%) 18 (94.7%)
3. Occupation Unskilled labour Skilled worker Professional	 2 (10%) 6 (30%) 12 (60%)	 1 (5.3%) 6 (31.6%) 12 (63.2%)
4. BMI 17-22.9 23-27.9 >28	 7 (35%) 6 (30%) 7 (35%)	 3 (15.8%) 10 (52.6%) 6 (46.2%)
PARITY 1. Primipara 2. Multipara	 15 (75%) 5 (25%)	 11 (57.9%) 8 (42.1%)
ANTENATAL RISK FACTORS		
1. Previous LSCS	0	1 (5.3%)
2. Anemia	1 (5%)	0
3. Gestational Diabetes	3 (15%)	3 (15.8%)
4. Twin Gestation	0	1 (5.3%)

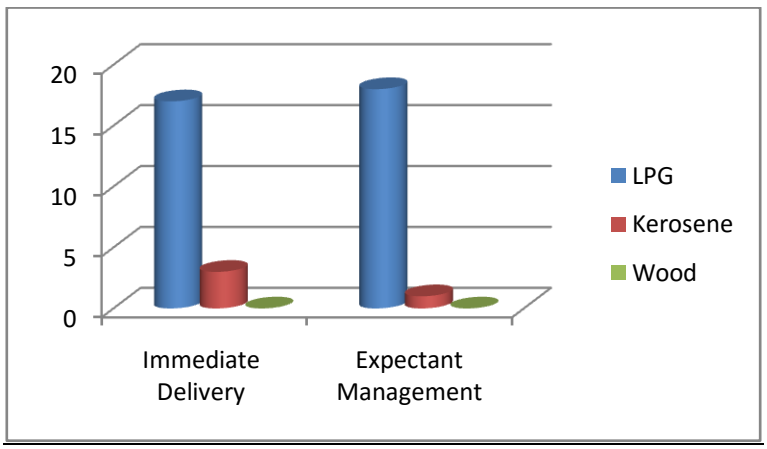
Age:Majority of the patients recruited were in the age group of 18 – 30 years. Two patients in the Immediate Delivery arm and 5 patients from the Expectant Management arm were above 30 years of age. There were no patients at or above the age of 35.

Graph 1 – Age wise Distribution in each arm



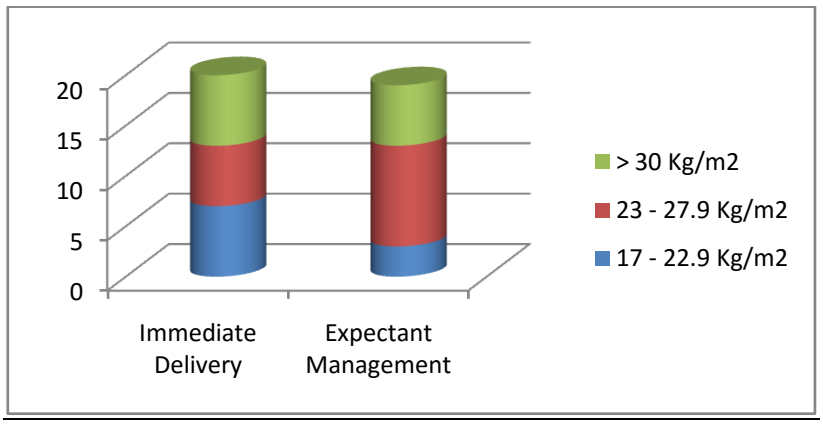
Socioeconomic Status: We asked the patients what fuel they used in the home for cooking as a measure of their socioeconomic status. Majority of our patients used LPG (85% in the Immediate Delivery arm and 94.7% in the Expectant Management arm). The rest of our patients used Kerosene. None of our patients used firewood.

Graph 2 –Socioeconomic Status in each arm



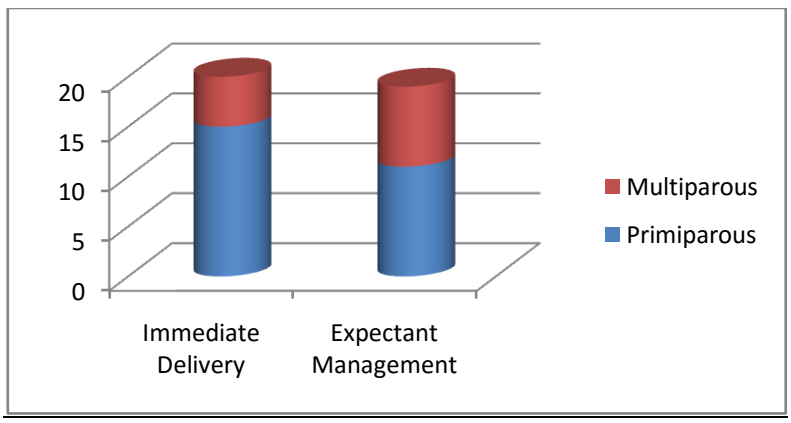
BMI-In the range of 17 to 22.9 kg/m2, there were 7 (35%)patients in the Immediate Delivery Arm and 3 (15.8%) patients in the Expectant Management Arm. In the BMI range of 23 to 27.9 kg/m2 there were patients in the 6(30%) Immediate Delivery Arm and10 (52.6%)patients in the Expectant Management Arm. Above the BMI of 28, there were 7 (30%) patients in the Immediate Delivery Arm and 6 (46.2%) patients in the Expectant Management Arm. There were no morbidly obese patients.

Graph 2 –Patients grouped according to BMI in each arm



Parity- Majority of the patients in the Immediate delivery arm were primigravidas (75%), compared to 57.9% of those in the Expectant Management arm. Twenty five percent in the immediate delivery arm and forty two percent in the expectant management arm were multiparous.

Graph 3 –Patients grouped according to parity in each arm



Antenatal Risk Factors: One patient in the Expectant Management group had a previous LSCS, three in each group were diabetic, while one patient in the Immediate Delivery arm had anemia requiring blood transfusion antenatally.

There was one Diamniotic Dichorionic twin gestation in the Expectant Management arm. Twins with PPROM have not thus far been studied, and this case will be discussed in detail at a later stage.

Graph 4 –Antenatal Risk Factors in each arm

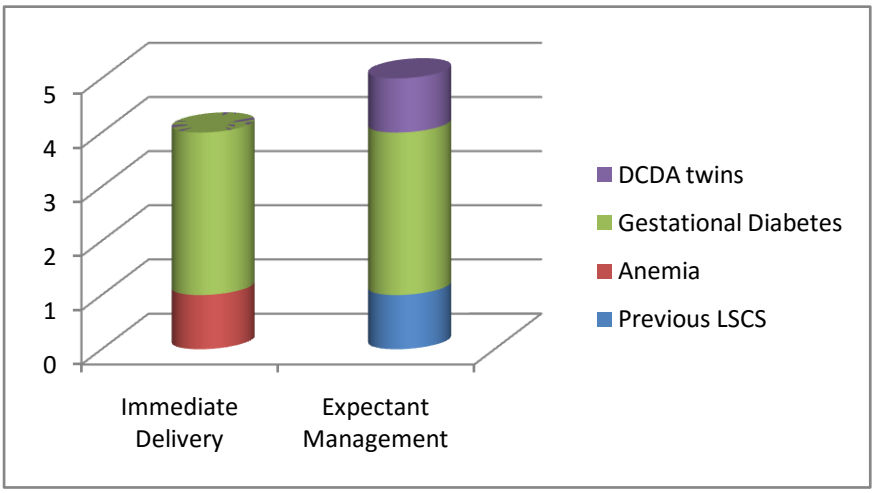


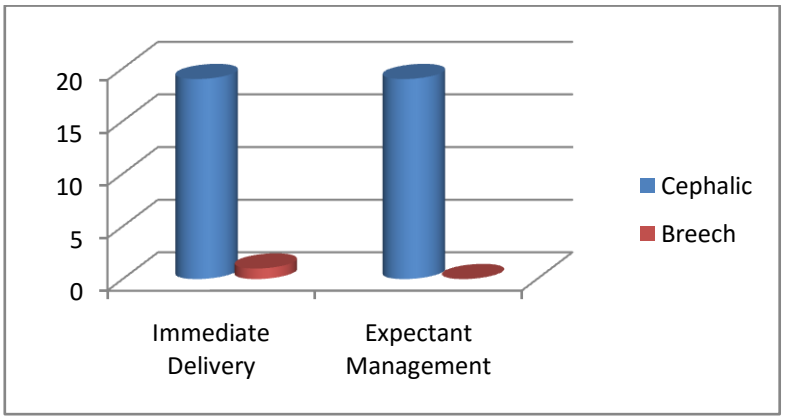
Table 6 - Baseline Characteristics

Baseline Characteristics	Immediate Delivery Group N = 19	Expectant Management Group n = 20
FETAL PRESENTATION 1. Cephalic 2. Breech	 19 (95%) 1 (5%)	 19 (100%) 0
STEROIDS RECEIVED	1 (5%)	0
MODE OF DIAGNOSIS 1. Speculum examination 2. Positive Ferning 3. Definite History 4. ELISA test (Actim PROM)	 18 (90%) 0 0 2 (10%)	 16 (84.2%) 0 3 (15.7%) 0
GESTATIONAL AGE AT PPROM 1. <34 weeks 2. 34+0 to 34 +6 weeks 3. 35 +0 to 35+6 weeks 4. 36+0 to 36+6 weeks	 1 (5%) 3 (15%) 10 (50%) 6 (30%)	 0 7 (36.8%) 6 (31.6%) 6(31.6%)
MEAN GESTATIONAL AGE AT PPROM	35+4 weeks	35+2 weeks
GESTATIONAL AGE AT RECRUITMENT 1. 34+0 to 34 +6 weeks 2. 35 +0 to 35+6 weeks 3. 36+0 to 36+6 weeks	 4 (20%) 10 (50%) 6 (30)	 7 (36.8%) 6 (31.5%) 6 (31.5%)
MEAN GESTATIONAL AGE AT RECRUITMENT	35+4 Weeks	35+1 Weeks
ANTIBIOTICS RECEIVED 1. During Admission (A/F) 2. During Labour (ampicillin)	 14 (70%) 20(100%)	 19 (100%) 19(100%)

Other Baseline Characteristics:

Fetal Presentation: Majority of the babies were cephalic in presentation. One baby in the immediate delivery arm was flexed breech.

Graph 5 - Fetal Presentation in each arm

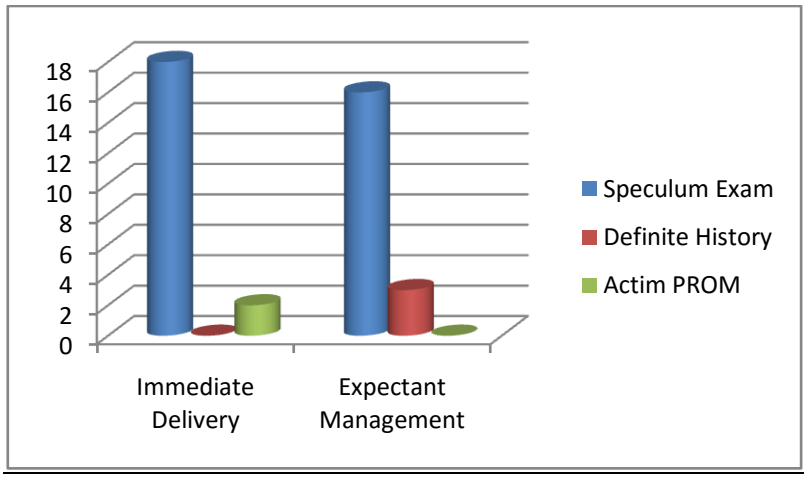


Steroid Course: As per hospital policy, only women with <34 weeks of pregnancy receive steroids for lung maturity. There was only one such patient that presented before 34 weeks, and was subsequently recruited into the immediate delivery arm.

D osing PPROMf diagn

Metho:Ninety percent of patients in the immediate delivery arm were diagnosed by direct visualisation of liqour in the posterior vaginal fornix on speculum examination, as compared to 84.2 % of the Expectant Management arm. On the other hand, 15.7% of those in the Expectant Management arm were diagnosed by a definite history of leaking per vaginum, corroborated by a senior obstetrician, as compared to none in the Immediate Delivery arm. Ten percent of those in the Immediate Delivery arm were diagnosed by the ELSIA test, Actim PROM.

Graph 6 – Mode of Diagnosis

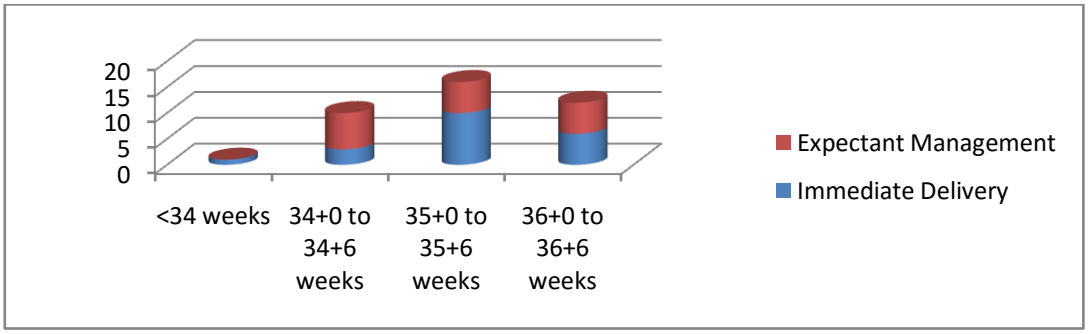


Gestational Age at PPROM

Most of the patients in the Immediate Delivery arm had rupture of membranes at 35+0/7 to 35+6/7 weeks (50% of patients). Thirty percent and fifteen percent ruptured membranes in their 36th and 34th week respectively. One patient had of membranes at < 34 weeks (33 weeks and 2 days of gestation).The mean gestational age at rupture of membranes for this group was 35+4 weeks.

In the Expectant management arm, patients had a more or less uniform distribution of rupture of membranes from 34 to 36+6/7 weeks. There were no patients that had rupture of membranes before 34 weeks. The mean gestational age at rupture of membranes for this group was 35+2 weeks.

Graph 7 – Gestation at Rupture of Membranes

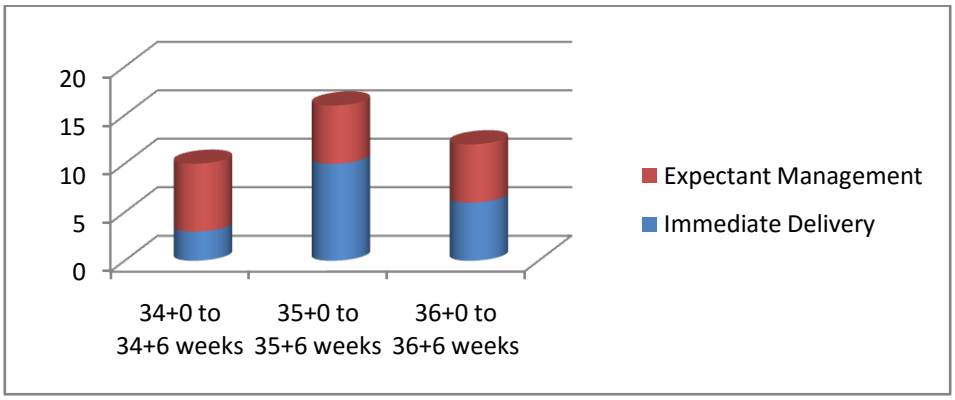


Gestational Age at Recruitment

In the Immediate Delivery arm, 50% of patients were recruited between 35+0 to 35+6 weeks, 20% from 34 to 34+6 weeks and 30% from 36 to 36+6 weeks. The mean gestational age at recruitment in this group was 35+4 weeks.

In the Expectant Management, 36.8% were recruited at 34 to 34+6 weeks, and 31.5% each were recruited in their 34th and 36th week of gestation. The mean gestational age at recruitment in this group was 35+1 weeks.

Graph 8 – Gestational age at Recruitment



Antibiotics received by mother: All patients in the Immediate Delivery group received IV antibiotics in labour (Inj. Ampicillin) for prophylaxis against Neonatal Group B Streptococcal infection. All patients in the Expectant Management received a full 5 day course of oral antibiotics (Tab. Azithromycin and Tab. Metronidazole) and received IV antibiotics if they delivered before 37 weeks gestation.

PRIMARY OUTCOME

Table 7 – Incidence of Neonatal Sepsis

Outcome Measure	Immediate Delivery Group	Expectant Management Group	'p'value	Total
1. Neonatal Sepsis - Culture Proven - Probable sepsis (late onset)	 1 (5%) 1 (5%)	 0 0	0.25	2 (10%)

There were two patients in the Immediate Delivery arm that were diagnosed with sepsis. One baby's blood culture at birth was positive, with significant growth of ESBL E.Coli. This baby was born at 35+6 weeks, with a birth weight of 2080 grams. There was no evidence of chorioamnionitis in the mother, either antenatally or during labour. This baby also had a low Apgar score at birth (5, 8). Cord pH, however, was normal. The baby spent 9 days in the Neonatal ICU on IV Antibiotics, but did not need ventilatory support. The baby was well at discharge.

The second baby was born at 35+6 weeks, with a birth weight of 2220grams. This baby was diagnosed with imperforate anus, cleft palate and patent foramen ovale post natally. The baby underwent sigmoid loop colostomy. Initial blood cultures were negative, however baby was diagnosed with probable sepsis on Day 17. In consultation with senior Neonatologist, the authors agree that this diagnosis is unrelated to the preterm rupture of membranes.

None of the babies in the Expectant management arm developed sepsis.
The p value for neonatal sepsis was 0.2, therefore not significant. However, due to the small numbers obtained, this should be interpreted with caution.

SECONDARY OUTCOMES

Table 8 - Details of Labour

Outcome Measure	Immediate Delivery Group N= 20	Expectant Management Group N = 19	'p'value	Total
1. Onset of labour -Spontaneous labour -Induction of labour -Caesarean Section	 - 19 (95%) 1 (5%)	 9(47.3%) 10 (52.6%) -		39
2. Chorioamnionitis	0	1 (5.2%)	0.2	1 (2.5%)
3. Mode of delivery - Vaginal, spontaneous - Vaginal, instrumental - LSCS	 15 (75%) 3 (15%) 2 (10%)	 13 (68.4%) 2 (10.5%) 4 (21.1%)	 0.6	39
Indication of LSCS - Fetal Distress - Failed Induction	1 (5%) 1 (5%)	2 (10.5%) 2 (10.5%)		
4. Antepartum hemorrhage	0	0	-	
5. Umbilical cord prolapse	0	0	-	
6. Post partum Haemorrhage	1 (5%)	0	0.2	1

Onset of Labour:Nineteen of the twenty patients in the immediate delivery arm underwent induction of labour.One patient had a breech presentation, and underwent LSCS for fetal distress.

Ten patients in the Expectant Management group underwent induction of labour for various reasons. Nine patients went into spontaneous labour.

Chorioamnionitis: One patient in the Expectant Management arm developed chorioamnionitis 24 hours after recruitment and needed induction of labour. Post natal period for both mother and baby were uneventful. There were no patients in the Immediate Management group that developed chorioamnionitis. The p value was 0.2, insignificant, but must be interpreted with caution due to the low numbers obtained thus far in this study.

Mode of Delivery: Almost equal numbers of patients in both arms underwent spontaneous vaginal/ instrumental deliveries. Four patients in the Expectant management underwent LSCS as compared to two patients in the Immediate Delivery arm. The p value was 0.6, there was no statistical significant difference found between the groups.

Graph 9 – Mode of delivery in both groups

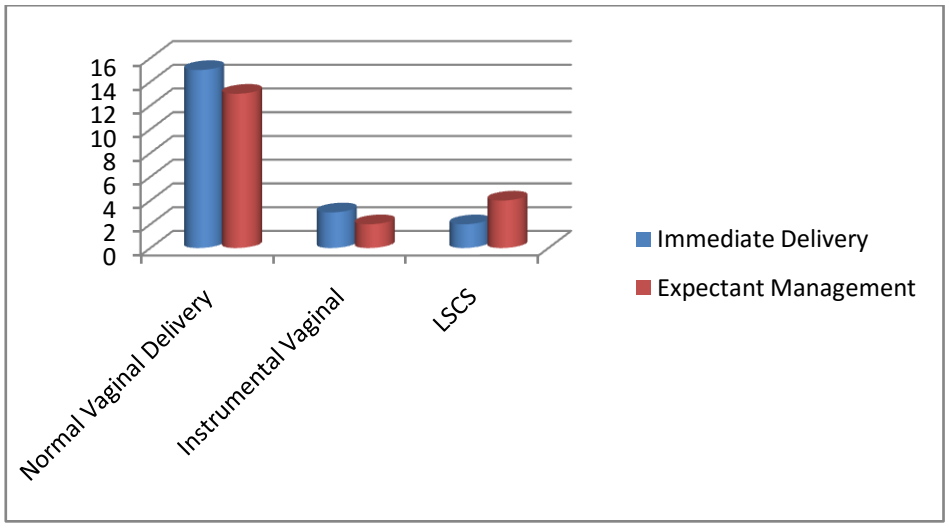
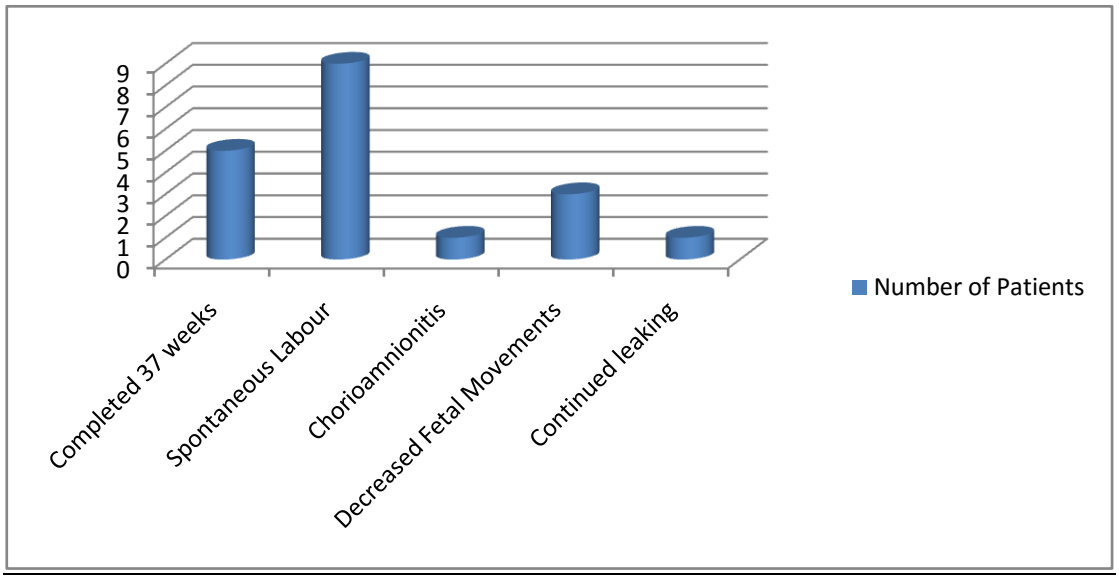


Table 9 - Outcomes withExpectant Management

	Expectant Management	Total
1. Reason for termination of Expectant Management		
- Completed 37 weeks	5 (26.3%)	
- Spontaneous Labour	9 (47.3%)	19
- Chorioamnionitis	1 (5.2%)	
- Decreased fetal movements	3 (15.7%)	
- Continued leaking and low Amniotic Fluid Index	1 (5.3%)	
2. Time gained		
- <1 day	2 (10.5%)	
- 2 – 6 days	10 (52.6%)	19
- 1 – 2 weeks	4 (21.05%)	
- 2 – 3 weeks	1 (5.2%)	
- >3 weeks	2 (10.5%)	

Reasons for Termination of Expectant Management: Nine (47.3%) of these patients went into spontaneous labour after recruitment. Five patients (26.3%) completed 37 weeks and were subsequently induced. One patient developed chorioamnionitis, three complained of decreased fetal movements and one patient had continued leaking with severe oligohydramnios necessitating termination of expectant management.

Graph 10– Reasons for Termination of Expectant Management



Time gained by expectant management: Two patients went into spontaneous labour within twenty four hours of recruitment. Ten (52.6%) patients gained between 2 – 6 days after recruitment. Four (21%) patients gained between 1 and 2 weeks. One patient crossed 2 weeks after recruitment, and two patients gained over 3 weeks. We were able to continue five pregnancies till term.

The minimum randomisation to delivery interval was 3 hours and 32 minutes. The maximum time gained was 33 days and 50 minutes, after which the patient was induced.

Graph 11 – Time gained with Expectant Management

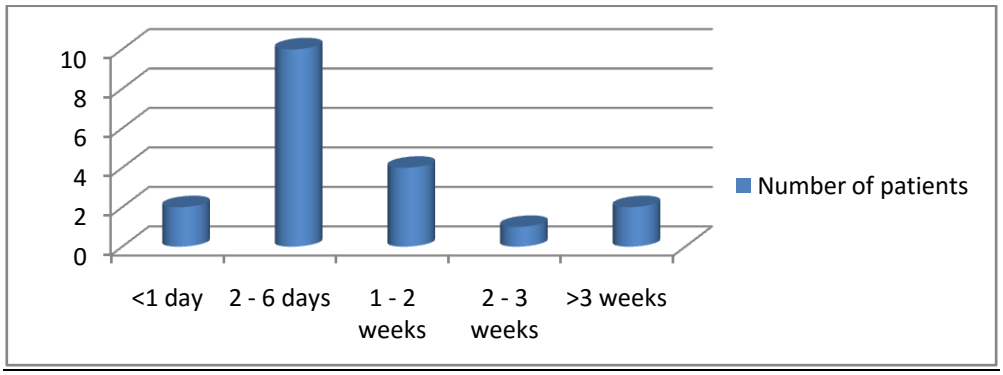


Table 10 – Randomisation to delivery interval in both arms

	Immediate Delivery Arm	Expectant Management Arm	P value
Randomisation to delivery interval (hours) Mean and SD	12 hours 20 mins +/- 7 hours 30 mins	18 hours 29 mins +/- 29 hours 51 minutes	0.04

The mean randomisation to delivery interval in the Immediate Delivery arm was 12 hours and 20 minutes, with a standard deviation of 7 hours and 30 minutes as compared to 18 hours and 29 minutes , with a standard deviation of 29 hours and 51 minutes in the expectant management arm. This difference was statistically significant (p value 0.04).

Table 11 - Patients managed as Inpatient vs Outpatient

	Managed as Inpatient	Managed as outpatient	Total
Number of patients (expectant management arm)	11 (57.8%)	8 (42.09%)	19
Mean days of antenatal hospitalisation	2.1 days	3.1 days	--

In the Expectant Management arm, there were a total of 11 patients managed on an inpatient basis. The mean number of days of hospitalisation with these patients was 2.1 days. Eight patients (42%) were managed on an outpatient basis at time of delivery. The mean duration of antenatal hospitalisation was 3.1 days.

Table 12 - Neonatal Complications

Outcome Measure	Immediate Delivery Group N= 20	Expectant Management Group N = 20	'p'value	Total
1. Gestation at delivery 34 +0 to 34+6 weeks 35+0 to 35 +6 weeks 36+0 to 36+6 weeks >37 weeks	 3 (15%) 10 (50%) 7 (35%) 0	 2 (10%) 4 (20%) 9 (45%) 5 (25%)	 0.2 	 5 (12.5%) 14 (35%) 16 (40%) 5 (12.5%)
2. Apgar <= 5,8	 1	 0		 1 (2.5%)
3. Need for resuscitation	2	1		3 (7.6%)
4. Asphyxia (cord pH<7.2)	0	0		-
5. Necrotizing enterocolitis (+Patent DuctusArteriosus)	1	0		1 (2.5%)
6. Hyperbilirubinemia	2	0		2 (5%)
7. Hypoglycaemia	5	5		10 (25.6%)
8. Polycythemia requiring exchange transfusion	1	0		1 (2.5%)
9. Convulsions not attributable to asphyxia (Probable viral encephalitis)	1	0		1 (2.5%)
10. Neonatal Death/ Intrauterine death	0	0		-
11. Meconium aspiration syndrome, Respiratory distress syndrome (RDS), Pneumonia, Late onset sepsis	0	0		-
12. Infant death (2 months and 11 days)	1	0		1 (2.5%)

13. Discharged against Medical Advice				
- Baby with anomalies, post surgery in critical condition	1	0		1 (2.5%)
- >10% Weight loss	0	1		1 (2.5%)

Neonatal Outcomes:

The most common complication was hypoglycaemia, affecting 5 babies in each group.

Expectant management Group

Five babies (25% of patients) were delivered at term in the Expectant Management group. Another nine babies (45%) were delivered between 36 to 36+6/7 weeks. Four babies (20%) were delivered between 35 to 35+6/7 weeks. Two babies (10%) weredelivered between 34 + 34+6/7 weeks.

One baby required resuscitation at birth since Apgar was low. Cord pH, however, was normal. Five babies had hypoglycaemia, none of the babies had hyperbilirubinemia. One patient who was advised continued admission due to >10% weight loss was discharged against medical advice.

Immediate Delivery Group

In the Immediate Delivery group, 50% of the babies (10 babies) delivered between 35 and 35+6/7 weeks, 35% (7 babies) were above 36 weeks and 15% (3 babies) delivered at<34 weeks.

Two babies in the Immediate delivery group needed resuscitation, one of which had a low Apgar (score of 5,8). Cord pH at birth in these babies was normal.

Two babies had hyperbilirubinemia and five babies had hypoglycaemia. One baby hadpolycythemia and required exchange transfusion.

One baby was born at 35+4 weeks with a birth weight of 2390 grams and Apgar of 9 and 10. This baby developed probable sepsis and convulsions on day 4 of life requiring prolonged ICU care and readmission. MRI brain done on day 10 showed extensive deep white matter hyperintensities and restricted diffusion and multiple micro and macro haemorrhagic foci and symmetrical hyperintensity and restricted diffusion of parahippocampal gyri and medial temporal lobes with findings suggestive of neurotropic viral etiology.

Another baby, born at 35 weeks was initially well with negative blood cultures. However, this baby was eventually diagnosed with necrotising enterocolitis (NEC) and a patent ductus arteriosus. The baby underwent laparotomy and reanastomosis for the NEC as well as thoracotomy for the PDA. This baby was initially discharged well, but was readmitted with anastomotic leak, sepsis and shock. The baby succumbed to its illness at 2 months and 10 days of life.

One baby was born with anomalies which were not detected antenatally – cleft palate, imperforate anus and patent foramen ovale. This baby underwent laparotomy and sigmoid loop colostomy and discharged in a stable condition. A few days later baby was readmiited with septic shock and guarded prognosis explained to the patients . The baby was eventually discharged against medical advice.

Table 13 – Mean birth weight in each group

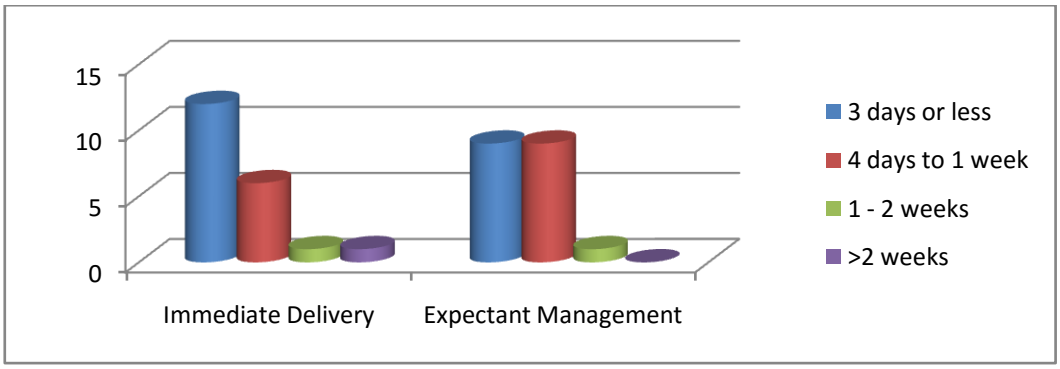
	Weight in gms with standard deviation	p value
Immediate Delivery arm	2400 +/- 370	0.10
Expectant Management arm	2643 +/- 327	

Birth weight in each group - Mean birth weight in Immediate Group was 2400 gms with a standard deviation of 370 gms. The mean birth weight in the Expectant Management group is 2643 gms with a standard deviation of 327 gms. This difference was not statistically significant.

Table 14-Postnatal Stay in Hospital– Maternal

	Immediate Delivery Arm	Expectant Management	p value	Total
Number of women who had prolonged stay postnatally (>3 days)	8 (40%)	10 (52.6%)	0.46	18 (46.15%)
Reason for prolonged stay - Baby's sake - Maternal	 8 0	 10 0		 18 (46.15%)
Length of postnatalstay in Hospital (median)	5.5 days	6 days		

Graph 12– Number of days of Hospitalisation for mother

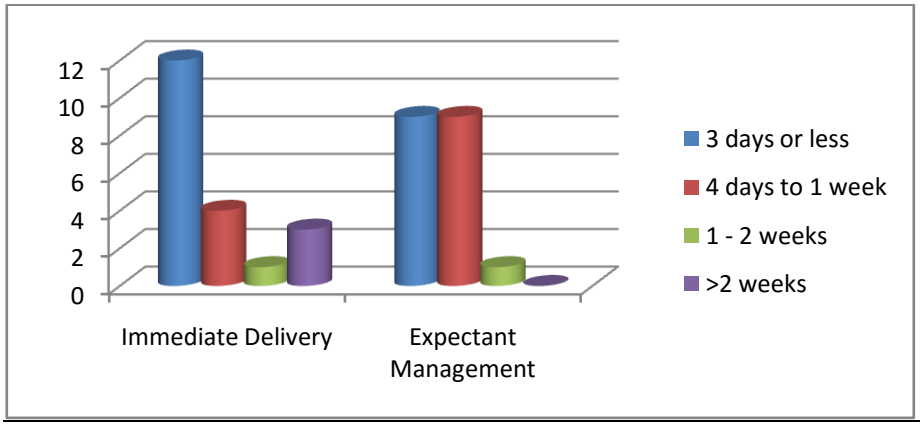


More patients in the Expectant management arm had prolonged hospital stay (10 vs 8). All these prolonged admissions were for the babys sake. There were no significant maternal complications in either group.

Table 15 - Stay in Hospital– Baby

	Immediate Delivery Arm	Expectant Management	p value	Total
Number of babies who had prolonged stay (>3 days)	8 (40%)	10 (52.6%)	0.46	17 (43.5%)
Length of stay in Hospital (median)	8days	6 days		
NICU admission	**8**	**2**		
- Lethargy, poor feeding	1	0		
- Hyperbilirubinemia	1	0		
- Depressed at birth	1	0		
- Hypoglycaemia	0	2		
- Necrotising Enterocolitis, Patent DuctusArteriosus	1	0	0.03	10 (25.6%)
- Polycythemia for exchange transfusion	1	0		
- Anomalies (cleft palate, imperforate anus)	1	0		
- Sepsis	1	0		
- Seizures: Suspected Viral Encephalitis	1	0		
Readmission	2	0		2 (5.12%)
Hospital Bill (mean with standard deviation)	Rs. 27,078 +/- 51,357	Rs. 7,505+/- 2,866	0.3	

Graph 13 – Hospital Stay for Babies in days



Eighteen babies needed hospitalisation for more than 3 days, ten babies (52.6%) from the Expectant management arm and eight babies (%) from the Immediate Delivery

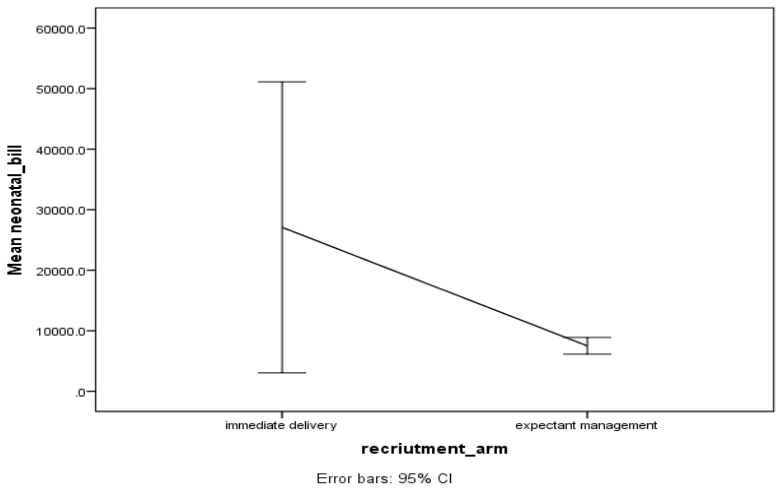
arm. The median duration of stay was six days in the EM arm and eight days in the ID arm.

Stay in NICU (Neonatal Intensive Care) was needed for eight babies in the ID arm and only 2 babies in the Expectant Management arm. This difference was statistically significant (p value of 0.03).

Two of the Immediate Delivery arm babies required readmission as discussed earlier. One of these succumbed to its illness, while the other was discharged at request in a critical condition.

The hospital bills (mean) in the Immediate Delivery arm was Rs. 27,078 and in the Expectant Management arm was Rs. 7,505. This difference did not show a significant statistical difference. However, the babies in the Immediate Delivery arm had a wide range of Hospital Bills, from Rs. 3,985 to a maximum of Rs. 2,03,284. The babies in the Expectant management arm had bills ranging from Rs. 4,105 to Rs. 13,062 at maximum.

Graph 14 – Hospital Bill for Babies in each arm



DISCUSSION

Our study screened 157 patients with preterm prelabour rupture of membranes for eligibility, and 39 patients were recruited into the trial. Of these, 20 patients were randomised to the Immediate Delivery arm and 19 patients were randomised to the Expectant Management arm.

Baseline characteristics were similar in both groups. Ninetypercent of patients in the Immediate Delivery arm and seventy three percent of patients in the Expectant management arm were in the age group of 18 – 30 years, the rest were above the age of 30 years. There were no patients over 35 years of age in either arm. Most of our patients used LPG as a means of fuel and were in the middle socioeconomic class. Sixty percent of patients in both groups were college educated and had jobs in a professional capacity, while the rest worked as skilled/ unskilled labour.

Seventy five percent of patients in the Immediate Delivery arm and about fifty eight percent of patients in the Expectant Management arm were primigravidas. The rest were multiparous.

One patient had a previous Caesarean delivery, one patient was anemic requiring blood transfusion antenatally, and three in each arm had gestational diabetes.

One patient had diamniotic dichorionic twins. She was a 29 year old primigravida who presented to us at 34+6 weeks of gestation with leaking per vaginum which was confirmed on speculum examination. Ultrasound done ruled out selective growth restriction or growth discordancy. Leading twin was in vertex presentation. She agreed to be part of the trial, was discharged and managed on an outpatient basis twice

a week. She presented in spontaneous labour ten days after recruitment. Labour was augmented, and she delivered vaginally at 36+3 weeks, two healthy babies weighing 2770gms and 2280 gms each. Post natal period was uneventful for both mother and babies.

The mean gestational age at rupture of membranes was 35+4 weeks in the Immediate Delivery arm and 35+2 weeks in the Expectant Management arm. The mean gestational age at recruitment was 35+4 weeks in the Immediate Delivery arm and 35+1 weeks in the Expectant Management arm. One baby in the Immediate Delivery arm was breech, the rest were cephalic at presentation. Ninety percent of patients in the Immediate delivery arm were diagnosed by per speculum examination, while 84.2 percent of patients in the Expectant Management arm were diagnosed by a definite history of leaking per vaginum. All patients received either oral or intravenous antibiotics.

Primary outcome looked at was neonatal sepsis. There were two patients in the Immediate delivery arm whose babies developed neonatal sepsis, in comparison to none in the Expectant Management arm. One baby had suspected late onset sepsis , not related to events during intrapartum period or delivery. Even so, this difference was not statistically significant. Other studies also did not find a statistically significant difference in neonatal sepsis when patients were delivered immediately or after expectant management in PPROM.

Nineteen of twenty patients in the Immediate Delivery arm had induction of labour. One patient underwent LSCS as she developed fetal distress and the baby was breech.

Of the Nineteen patients in the Expectant Management arm, we were able to continue five pregnancies to term, at which time they were induced. The maximum time gained was 33 days and 50 minutes. Nine patients went into spontaneous labour before 37 weeks. In five patients , expectant management had to be terminated due to chorioamnionitis, decreased fetal movements or ongoing leaking.

The mean time gained in utero in the Expectant Management group was 18 hrs and 29 minutes with a standard deviation of 29 hours and 51 minutes, compared to the Immediate Delivery arm where mean randomisation to delivery interval was 12 hours 20 minutes with a standard deviation of 7 hours 30 mins. This difference was statistically significant (p value 0.04).

Eleven patients were managed as inpatient up till delivery. Eight patients (42%) were initially managed as inpatient and then discharged at discretion of senior consultant. They were then managed on an outpatient basis till time of delivery. This included a mother with diamniotic dichorionic twins. There was no difference in maternal/ neonatal outcomes with either modality of management. There have been two randomised trials(79,80) which studied home versus hospital care in patients with PPROM. A Cochrane metaanalysis(75)found no difference in maternal or neonatal outcomes with either modality of care, but the studies were not adequately powered to show a significant statistical difference.

One patient developed chorioamnionitis in the Expectant Management group, and Labour had to be induced for the same. No patients in the Immediate Management

group developed chorioamnionitis after randomisation. This difference was not statistically significant. The PPROMEXIL trial found that immediate delivery decreased the risk of chorioamnionitis (22% in the immediate delivery group versus 32% in the expectant management group) . However this was not statistically significant (p value of 0.4). The PPROMT trial also found that women managed expectantly had a higher incidence of intrapartum fever, however, this difference was not statistically significant (p value 0.4). These trials had larger numbers, 532 in the PPROMEXIL trial and 1,835 in the PPROMT trial.

Seventy five percent of women in the Immediate Delivery arm had normal vaginal deliveries, compared with sixty eight percent in the Expectant Management arm. Twenty five percent of women in the Immediate Delivery arm underwent LSCS/ Instrumental delivery compared with thirty one percent in the Expectant Management group. The difference between both groups with respect to mode of delivery was not statistically significant.Our sample size was small, hence results need to be interpreted with caution. Larger studies like the PPROMT trial found a significantly higher rate of LSCS in their Immediate Delivery arm compared to Expectant Management (p value 0.0001). However, other trials (PROMEXIL and TERMPROM) did not demonstrate this difference.

None of our patients in either arm had antepartum haemorrhage or cord prolapse. In the PPROMT trial, authors found a significantly higher rate of ante/intrapartum haemorrhage in the Expectant Management arm, but no difference in the rate of cord prolapse which occurred<1% of the time in both arms.

Neonatal outcomes

Hypoglycaemia was found to be equal in both groups. There were two babies with hyperbilirubinemia in the Immediate Delivery group, and none in the Expectant Management group.The PPROMEXIL study found a statistically significant higher rate of both these complications in their Immediate Delivery arm as compared to the Expectant Management arm.

The number of babies who required prolonged stay (>3 days) was actually higher in the Expectant Management group than the Immediate Delivery group (10 babies versus 8 babies). However, more babies in the Immediate delivery arm required intensive care, had more morbidity and ultimately higher hospital bills than their counterparts in the Expectant Management arm. Despite our small numbers,we were able to demonstrate a statistically significant difference in the rates of neonatal ICU admissions in the Immediate Delivery arm compared to the Expectant Management arm (8 versus 2 babies, p value of 0.03).

The cost of stay for the babies post natally was much higher in the Immediate Delivery group with costs ranging from Rs. 3,985 to Rs. 2,03,284 with a mean of Rs. 27,078. By contrast the babies in the Expectant Management arm had bills ranging from 4,105 to a maximum of 13,062 with a mean of Rs. 7,505.Although the mean cost of hospital stay in immediate delivery group is more than thrice in the expectant management group, this was not found to be statistically significant . This could be explained by the small sample size of our study

.

A major drawback of our study is that we were unable to obtain a larger sample size. This was mostly due to patients that were excluded due to elevated C-RP and WBC counts. Other similar trials such as PPROMEXIL and PPROMT did not use specific cut offs of CRP and counts for excluding patients from recruitment, whereas we used specific cut offs for the same, based on our hospital policy. The cut offs we used were a CRP of 5mg/L and 15,000 cells/mm3 for C-RP and WBC counts respectively. Looking at the meta analysis conducted by Van der Laar et al (55), the five studies included used a cut off ranging from >12mg/L to >40mg/L. Reported Sensitivities for a cut off of >12 mg/L for clinical chorioamnionitis and histological chorioamnionitis were100% and 88% respectively. Specificities for clinical chorioamnionitis ranged from 55% at a cut off of 20 mg/L to 98% at a cut off of >20mg/L. For histological chorioamnionitis, specificity ranged from 68% at a cut off of >20mg/L to 100% when this was raised to 40mg/L.

We therefore propose to increase our diagnostic threshold for chorioamnionitis to CRP levels of 12 mg/L and above, as this will increase our yield of cases. There is a theoretical risk of missing a few cases of chorioamnionitis, but given the above evidence, this is unlikely.

CONCLUSIONS

In pregnant women presenting with Preterm Prelabour Rupture of Membranes between 34 and 36+6 weeks, the risk of Neonatal sepsis does not increase with Expectant Management upto 37 weeks compared to Immediate Delivery in carefully selected patients. Maternal morbidity/ mortality is not affected by either Immediate Delivery or Expectant Management. Mode of delivery does not differ with either line of management.

Immediate delivery may lead to higher rates of admission to Neonatal ICU, greater morbidity to the baby and higher hospital costs and emotional anxiety for the parents. Impact of both modalities of treatment on long term neurodevelopmental outcome of babies will require study with a larger sample size with long term follow up of infants at least upto 5 years of age.

LIMITATIONS

The main limitation of this study is that we were unable to reach our sample size, leaving this study grossly underpowered. However we plan to continue this study, and ultimately reach target sample size.

Due to inherent study design we were unable to blind either caregiver or patient to arm of recruitment.

GLOSSARY OF ACRONYMS

PPROM – Preterm Prelabour Rupture of Membranes

CRP – C Reactive Protein

NICU – Neonatal Intensive Care Unit

UTI – Urinary Tract Infection

VSD – Ventricular septal defect

END – Early Neonatal Death

SROC - Summary Receiver Operating Characteristic

ESBL E. Coli – Extended Spectrum Beta Lactamase producing E. Coli

LSCS – Lower Segment Caesarean

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ANNEXURE
PROFORMA PPROM

Date:

DEMOGRAPHIC DATA

1. Name	_____	
3. Hospital Number		
4. Age (in years)		
5.BMI		
6.Socio economic status	1.Wood	2.Kerosene
7. Occupation	1. Unskilled worker	2. Skilled labour

OBSTETRIC DATA

8.Obstetric score	1.parity-0	2.para-1
9. Gestational age in weeks		
10. Date of rupture of membranes		
11. Time of of rupture of membranes		
12. Mode of diagnosis	1. Definite History	2. Speculum exam
13. Gestation at rupture of membranes		
14. Azithro/ Flagyl received (If no, skip to Question 18)	1. Yes	2. No
15. Course of A/F completed (If yes, skip to Question 18)	1. Yes	2. No
16. Number of doses of A received		
17. Number of doses of F received		
18. Steroids received	1. Yes	2. Yes, partly
19. Presentation of baby	1. Cephalic	2. Breech

20. Maternal Risk factors	1. PIH	2. GDM
21. Arm into which recruited	1. Immediate delivery	2. Expectant Management
22. Duration of antenatal hospitalisation of mother in days		
23. Duration from randomisation to delivery in hours		
24. Duration from randomisation to delivery in weeks		

DELIVERY

25. If expectant management- Indication of delivery	1. 37 completed weeks	2.Chorioamnionitis
26. Chorioamnionitis after recruitment	1. Yes, intrapartum	2. Yes, before delivery
27. Mode of delivery	1. SVD	2. Instrument
28. Indication of LSCS	1. Breech	2. NRFS
29. Duration of labour		
30. Number of PVs		
31. Number of doses of Ampicillin received		
32. PPH	1. Atonic	2. Traumatic

POSTNATAL COURSE

33. Duration of Postnatal hospitalisation of mother in days		
34. If more than 3 days, reason for prolonged stay	1. Babys sake	2. Maternal fever

35. If maternal fever, focus of infection	1. Endometritis	2. UTI
36. Admission to ICU for mother	1. Yes	2. No
NEONATAL OUTCOMES		
37. Gestational age at delivery		
38. Birthweight in grams		
39. Neonatal sepsis	1. Culture Proven	2. Probable sepsis
40. Need for resuscitation	1. Yes	2. No
41. Apgar score at 0 and 5 mins		
42. Cord pH		
43. Pneumonia	1. Yes	2. No
44. MAS	1. Yes	2. No
45. RDS	1. Yes	2. No
47. Necrotizing enterocolitis	1. Yes	2. No
48. Hypoglycaemia	1. Yes	2. No
49. Hyperbilirubinemia	1. Yes	2. No
50. Convulsions	1. Yes	2. No
51. Need for ICU Care	1. Yes	2. No
52. Duration of ICU care in days		
55. Duration of hospital stay in days		
56. Cost of Hospital Stay for baby		

Informed Consent form to participate in a research study

Study Title: **PPROM**

Study Number:

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age:_____

Please initial box

(Subject)

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am

free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s) [ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date: _____/_____/_____

Signatory's Name: _____

Signature of the Investigator: _____

Date: _____/_____/_____

Study Investigator's Name: _____

Signature of the Witness: _____

Date:_____/_____/_____

Name of the Witness: _____

PPROM STUDY INFORMATION SHEET

At some point before you complete 9 months of pregnancy, there is a possibility that there may be premature leakage of water from the bag surrounding the baby during pregnancy.

In the scenario, we will try to continue your pregnancy for as long as possible. The benefits to your baby of staying in the uterus are many. Early delivery could sometimes lead to breathing problems, mental and developmental problems in the future, feeding problems. All these may occur as the baby has not grown fully and is as yet immature.

On the other hand, there are some small and unusual risks of continuing pregnancy ,once the bag has broken . This includes infection for yourself or your baby, premature separation of the placenta that nourishes the baby in the womb and rarely, the umbilical cord coming out of the vagina.

At the present time, the protocol that is followed is that, arrangements are made for the delivery of the premature baby either by Caesarian or normal delivery, depending on the associated complications.

A study done in our department showed that most of the babies born out of premature prelabour rupture of membranes are born beyond 8 and a half months of pregnancy. However, there is evidence to prove that prolonging pregnancy upto 9 months may have considerable long and short term benefits to your baby- less jaundice, less chances of ICU admission. There is greater opportunity for development and maturity of organs for example the brain and lungs of the baby.

We invite you to be part of a study, where we will compare between two different types of treatment. One treatment is immediate delivery at 34 weeks. The second is trying to prolong your pregnancy for as long as possible till 9 months (37 weeks), and then delivery of the baby. If you receive the second treatment option, a close watch will be kept on you and your baby for any complications like infection or bleeding. You might require hospitalisation at this time. If you need prolonged admission you can be discharged and evaluated in the outpatient clinic which you will need to visit twice a week. You must keep a close watch on your babys fetal movements. In case of fever,

excess leaking per vaginum, bleeding per vaginum, foul smelling discharge per vaginum, abdominal pain, decreased fetal movements you must inform your doctor immediately. You can contact one of the numbers listed below, or immediately come to the CMC Labour Room where you will be evaluated. If complications arise, you will be delivered immediately. If not, the process of labour will be initiated at 37 weeks.

If you fall into the" waiting group", you may have the benefit of not delivering prematurely. There will be no increased risk by being part of this study. However, for some reason if you do not choose to be part of this study you will have no disadvantage. You always have the option of withdrawing from the study without your medical care being affected.

In case of any queries, kindly contact

Dr. Deepti Pinto, OG IV Mob. 9626776226 Tel. No. 0416 2286185

Dr. Manisha, OG IV Mob. 9787892640 Tel. No. 0416 2286185

SPSS DATA ENTRY VARIABLES

name hospital no age BMI socioeconimic_status occupation obstetric_score mode_of_diagnosis gestation_at_ROM oral_antibiotics_received course_oral_antib_completed steroids_given fetal_presentation maternal_risk_factors recriutment_arm duration_antenatal_hosp_days duration_randomisation_delivery_hrs duration_randomisation_delivery_weeks duration_randomisation_delivery_months ind_of_delivery_if_expectant_arm mode_of_delivery ind_for_lscs duration_labor_hrs no_of_pv no_of_ampi_doses pph postnatal_stay_hospi_days reason_long_hospi_stay cause_maternal_fever mother_sicu_admission baby_delivered_gest_age birth_wt_gm neonatal_sepsis need_for_resuscitation apgar cord_ph neonatal_complication NICU_admission days_NICU_stay days_hospital_stay readmission_mother neonatal_bill hyperbilirubinemia chorioamnionitis gest_age_at_recruitment gest_age_recruit twins

durga		985461f		22	3	3	3	1	2	35.6	2
3	2	2	3	1	1	2.52	0.00	0.00	4	3	2
6.30	1	1	3	3	1	4	2	35.6	2080	1	1
5.80	2	8	1	9	9	2	12780.0		2	2	
35.6	2	2									
rubini		993076f		26	3	3	3	1	2	35.5	1
2	2	1	3	2	1	30.20	0.00	0.00	2	3	4
15.50	3	8	3	3	1	4	2	35.6	2420	3	2
9.10	3	8	2	0	3	2	4670.02		2	35.0	2
2											
rajkumari		894911d		33	3	3	2	3	3	35.5	1
2	2	1	3	1	1	2.48	0.00	0.00	4	1	5
6.30	5	3	3	24	1	4	2	36.0	2390	3	2
9.10	3	5	1	0	28	1	203284.0		2	2	
35.5	2	2									
zehra fatima		383799f		22	2	3	3	3	2	34.3	1
1	2	1	3	2	3	509.42	0.00	0.00	1	1	5
6.42	1	2	3	3	1	4	2	37.4	3465	3	2
9.10	3	8	2	0	3	2	5285.02		2	34.3	1
2											
revathi		743668d		29	2	2	1	4	2	35.3	2
3	2	1	3	1	2	7.22	0.00	0.00	4	1	5
7.22	1	1	3	2	1	4	2	35.3	2350	3	2
9.10	3	8	2	0	2	2	5280.02		2	35.3	2
2											
shaheeda parvee		332599g		30	3	3	3	1	2	35.2	1
2	2	1	2	2	1	22.05	0.00	0.00	5	1	5
6.20	1	2	3	7	1	4	2	35.3	2680	3	2
9.10	3	5	1	6	7	2	12830.0		2	2	
35.2	2	2									

mythili		424509g		31	2	3	3	1	2	36.1	1
2	2	1	3	2	1	23.51	0.00	0.00	4	2	5
6.00	1	1	3	5	1	4	2	36.2	2370	3	2
9.10	3	8	2	5	6	2	5640.02		2	36.1	3
2											
umma salma		308301g		19	2	3	2	1	2	36.5	2
3	2	1	3	1	1	4.00	0.00	0.00	4	1	5
3.52	1	1	3	3	1	4	2	36.6	3000	3	2
9.10	3	8	2	0	3	2	4865.02		2	36.5	3
2											
esther rani		996577f		27	4	3	3	2	2	34.3	1
1	2	1	4	2	1	3.32	0.00	0.00	4	3	2
3.22	1	1	3	5	1	4	2	34.3	2400	3	2
9.10	3	8	2	0	4	2	5685.02		2	34.3	1
2											
aisha		265014f		25	4	3	3	2	2	35.4	1
2	2	1	3	1	1	13.08	0.00	0.00	4	1	5
11.15	2	2	3	21	1	4	2	35.6	2220	2	2
9.10	3	6	1	21	22	2	62980.0		2	2	
35.5	2	2									
sandhya		335369f		29	4	3	3	2	2	34.6	1
1	2	1	5	2	12	259.15	0.00	0.00	4	1	5
6.00	2	2	3	6	1	4	2	36.3	2780	3	2
9.10	3	8	2	0	6	2	9190.02		2	34.6	1
1											
chitra		727666f		24	4	3	1	1	2	35.4	1
2	2	1	2	1	1	14.12	0.00	0.00	4	2	5
8.42	3	2	3	3	1	4	2	35.5	2170	3	2
9.10	3	8	2	0	3	2	5234.02		2	35.4	2
2											
soundarya		319950g		22	4	3	3	1	2	35.5	2
3	2	1	3	1	1	28.53	0.00	0.00	4	3	4
26.38	5	4	3	6	2	4	2	35.6	2420	3	2
9.10	3	5	2	0	3	2	9360.02		2	35.5	2
2											
hina afreen		334819g		25	3	3	3	1	2	36.3	1
1	2	1	3	2	5	122.23	0.00	0.00	1	1	5
8.00	2	4	3	2	1	4	2	37.1	2685	3	2
9.10	3	8	2	0	2	2	4105.02		2	36.3	3
2											
priyadarshini		084542f		28	3	3	3	2	2	36.5	1
2	2	1	2	1	1	11.30	0.00	0.00	4	1	5
5.50	4	2	3	3	1	4	2	35.2	2005	3	2
8.90	3	5	2	0	3	2	12585.0		2	2	
35.1	2	2									

preethi		352895g		24	3	3	3	1	2	35.1	1
2	2	1	3	2	3	74.10	0.00	0.00	5	1	5
5.25	3	1	3	4	1	4	2	35.4	2510	3	2
9.10	3	8	2	0	4	2	6465.02		2	35.1	2
2											
chamundeswari		238031g		34	3	3	3	1	2	36.2	1
2	2	1	2	2	2	44.38	0.00	0.00	5	1	5
4.38	1	5	3	4	1	4	2	36.4	2500	3	2
9.10	3	5	2	0	5	2	13062.0		2	2	
36.2	3	2									
madhumathy		343979g		29	3	3	3	1	2	34.5	1
2	2	1	3	1	1	8.55	0.00	0.00	4	1	5
8.40	1	1	3	5	1	4	2	34.5	2700	3	2
9.10	3	8	1	5	6	2	8060.02		2	34.5	1
2											
aswini		977659f		23	2	3	3	1	2	34.6	1
2	2	1	3	1	1	10.51	0.00	0.00	4	1	5
10.51	2	2	3	3	1	4	2	35.0	1680	3	2
9.10	3	4	1	19	20	2	134440.0		2	2	
34.6	1	2									
preeti		984904f		25	3	3	3	1	2	36.3	1
2	2	1	3	2	1	34.30	0.00	0.00	5	1	5
4.25	1	1	3	2	1	4	2	36.5	2330	3	2
9.10	3	8	2	0	2	2	4192.02		2	36.3	3
2											
bhuvaneswari		458540g		26	3	3	3	1	3	36.4	1
2	2	1	2	1	1	5.41	0.00	0.00	4	2	5
5.41	2	1	1	4	1	4	2	36.5	2630	3	2
9.10	3	5	1	4	5	2	6820.02		2	36.4	3
2											
lavanya		304904f		28	3	2	1	2	2	34.6	1
1	2	1	3	2	0	297.49	0.00	0.00	4	1	5
5.40	1	1	3	3	1	4	2	36.5	2900	3	2
9.10	3	5	2	0	3	2	5432.02		2	34.6	1
2											
subashini		502067g		21	2	3	3	1	2	35.0	1
2	2	1	3	1	1	3.15	0.00	0.00	4	1	5
3.00	1	1	3	3	1	4	2	35.0	2620	3	2
9.10	3	8	2	0	3	2	5285.02		2	35.0	2
2											
nalini		338698g		32	3	3	2	1	2	34.0	1
2	2	1	3	2	1	24.10	0.00	0.00	4	3	2
8.10	3	1	3	3	1	4	2	34.4	2080	3	2
9.10	3	5	1	7	8	2	10435.0		2	2	
34.2	1	2									

naimunnisa		100700d		30	4	3	2	2	2	35.3	1	
2	2	1	3	2	2	139.00	0.00	0.00	4	1	5	
7.10	2	1	3	3	1	4	2	36.1	2580	3	2	
9.10	3	8	2	0	3	2	5285.0	2		2	35.3	2
najum kousar		507076g		22	2	3	3	1	2	36.3	2	
3	2	1	3	1	1	22.15	0.00	0.00	5	1	5	
13.10	2	2	3	2	1	4	2	36.5	2860	3	2	
9.10	3	8	2	0	2	2	3985.0	2		2	36.3	3
anupriya		507100g		23	4	2	2	1	2	36.5	2	
3	2	1	3	1	1	10.39	0.00	0.00	5	1	5	
10.10	2	2	3	3	1	4	2	36.5	3100	3	2	
9.10	3	8	2	0	3	2	6020.0	2		2	36.5	3
suriyakala		209385f		32	4	3	3	2	1	35.3	1	
1	2	1	3	2	2	389.42	0.00	0.00	1	1	5	
5.00	2	1	3	4	1	4	2	37.4	2850	3	2	
9.10	3	5	2	0	4	2	7897.0	2		2	35.3	2
neelema		883430d		31	4	3	3	2	2	35.3	1	
2	2	1	3	1	1	22.21	0.00	0.00	4	2	5	
9.06	5	2	3	7	1	4	2	35.5	1870	3	1	
5.80	3	8	1	7	8	2	11660.0	2		2		
35.5	2	2										
manjula		507958g		33	3	3	2	1	2	35.2	1	
1	2	1	3	2	4	163.00	0.00	0.00	4	2	5	
10.00	3	2	3	7	1	4	2	36.3	2340	3	2	
9.10	3	8	2	0	7	2	10545.0	2		2		
35.2	2	2										
gayatri		428416g		18	3	2	2	1	2	34.3	1	
2	2	1	3	1	1	21.47	0.00	0.00	5	1	5	
8.20	4	1	3	2	1	4	2	34.4	2250	3	2	
9.10	3	8	1	5	5	2	9460.0	1		2	34.3	1
2												
sheerin		941533d		22	3	3	2	2	2	36.0	1	
1	2	1	3	2	2	269.50	0.00	0.00	1	1	5	
5.10	1	1	3	3	1	4	2	37.0	2800	3	2	
9.10	3	8	2	0	3	2	5285.0	2		2	36.0	3
2												
shabana		513072g		23	4	3	3	1	2	35.3	1	
2	2	1	3	1	1	15.38	0.00	0.00	5	1	5	
11.40	3	2	3	9	1	4	2	35.4	2750	3	2	
9.10	3	8	2	0	3	2	17676.0		1	2		
35.3	2	2										

kashita		416702g		25	4	3	2	1	1	34.2	1
1	2	1	2	2	2	205.00	0.00	0.00	4	3	4
12.30	3	3	3	8	1	4	2	35.4	2440	3	1
5.90	2	4	2	0	8	2	8275.0	2		2	34.2	1
2											
abirami		397694g		20	4	3	3	1	2	36.3	1
2	2	1	3	1	1	12.25	0.00	0.00	5	1	5
8.25	2	2	3	3	1	4	2	36.3	2290	3	2
9.10	3	5	2	0	3	2	5285.0	2		2	36.3	3
2											
jagatheswari		469597g		30	4	3	2	1	2	36.0	1
2	2	1	3	2	1	27.46	0.00	0.00	2	1	5
6.25	2	2	3	5	1	4	2	36.1	3060	3	2
9.10	3	8	2	5	5	2	10620.0	2		1	
36.0	3	2									
ashwini		801247d		28	2	3	3	3	1	34.4	1
1	2	1	3	2	2	792.15	0.00	0.00	1	1	5
3.50	1	1	3	3	1	4	2	38.2	3030	3	2
9.10	3	8	2	0	3	2	7715.0	2		2	34.4	1
2											
sandhiya		519053g		19	2	3	2	1	2	33.2	1
2	1	1	3	1	2	2.13	0.00	0.00	5	1	5
2.13	1	1	3	3	1	4	2	34.0	2190	3	2
9.10	3	8	2	0	3	2	12195.0	2		2	
34.0	1	2									
farheen		436450g		23	2	3	2	1	2	35.1	1
2	2	1	3	1	1	23.30	0.00	0.00	5	1	5
10.34	4	3	3	3	1	4	2	36.3	2440	3	2
9.10	3	8	2	0	3	2	4320.0	2		2	36.2	3
2											