Diplomarbeit

Neonatal and long-term neurodevelopmental outcome after extreme preterm premature rupture of membranes (pPROM)

eingereicht von

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Ort, Datum …….. (Unterschrift)

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Zusammenfassung

Einleitung

Ein früher vorzeitiger Blasensprung gilt als einer der Hauptgründe für extreme Frühgeburten, die in der westlichen Welt stetig ansteigen. Ziel dieser Studie war es, die unmittelbaren und langfristigen Auswirkungen eines Blasensprunges auf die betroffenen Kinder zu analysieren und zu untersuchen.

Material und Methoden

Es wurde eine retrospektive Analyse von geburtshilflichen und pädiatrischen Daten der klinikinternen Datenbanken PIA und Medocs aus den Jahren 2003 bis 2010 an der klinischen Abteilung für Geburtshilfe durchgeführt. 107 Frauen mit vorzeitigem Blasensprung zwischen 18^{+0} und 27^{+6} Schwangerschaftswochen wurden in die Studie eingeschlossen. Die entwicklungsdiagnostische Untersuchung von 46 der 82 überlebenden Kinder, welche die Einschlusskriterien erfüllten, erfolgte mit korrigierten 2 Jahren, an der Entwicklungsambulanz der Pädiatrischen Abteilung des Landeskrankenhaus-Graz, mit Hilfe des Bayley Scales of infant Development.

Resultate

Die durchschnittliche Latenz von Blasensprung bis Geburt betrug 13 Tage. Die Überlebensrate betrug 70% (82 von 117), 17 Kinder verstarben bereits intrauterin und weitere 18 im ersten Lebensmonat. Umso höher das Gestationsalter bei Geburt und das Geburtsgewicht, desto geringer war das Auftreten von Komplikationen. Zu diesen sekundären Erkrankungen die die Kinder entwickelten zählten: Bronchopulmonale Dysplasie in 13 Fällen, intraventrikuläre Hämorrhagie unterschiedlichen Grades in 30 Fällen, periventrikuläre Leukomalazie verschiedenen Grades in 7 Fällen, ein posthämorrhagischer Hydrocephalus in 4 Fällen, Mikrocephalus in 2 Fällen, Ileus in 4 Fällen, nekrotisierende Enterokolitis in 2 Fällen, eine Darmperforation in 6 Fällen, Sepsis in 43 Fällen eine Retinopathie in 8 Fällen. 60% der Kinder die mit 2 Jahren getestet werden konnten zeigten eine unauffällige mentale sowie motorische Entwicklung.

Schlussfolgerung

Gestationsalter bei Geburt, Geburtsgewicht und akute Komplikationen wie z.B. Sepsis oder IVH sind von prognostischer Relevanz für Frühgeborene, da Kinder mit höherem Gestationsalter bei Geburt, höherem Geburtsgewicht und dem Fehlen von Komplikationen ein besseres Outcome erzielten. 60% der Kinder zeigten eine normale kognitive und motorische Entwicklung mit einem Alter von 2 Jahren korrigiert. Es ist möglich dass, das 2 Jahres Outcome durch die hohe Ausfallsrate (alle Kinder mit einem Geburtsgewicht über 1500g werden nicht an der Entwicklungsambulanz vorgestellt; einige der Kinder werden erst im Sommer 2012 getestet werden;) verfälscht wurde.

Abstract

Introduction

Preterm premature Rupture of the membranes is classified as one of the main reasons of extreme preterm birth. This complication of pregnancy is steadily increasing in the western world. It was the aim of this study, to consider the short- and long-term impacts that preterm premature rupture of the membranes between 18^{+0} to 27^{+6} weeks of gestation has on infants and to analyse and examine the cognitive and locomotor development of the affected infants at the age of 2 years corrected for prematurity.

Materials and Methods

A retrospective analysis composed of obstetric and neonatal data from the clinical Databases PIA and Medocs was carried out at the Division of Obstetrics and Maternal Fetal Medicine from cases in the years 2003 through 2010. 107 women with pPROM within 18^{+0} to 27^{+6} weeks of gestation were included to the study. 82 infants survived until discharge from hospital. The examination of the developmental outcome of 46 children, of a total of 82 infants who survived until discharge from hospital, took place at the age of 2 years corrected for prematurity at the Neurodevelopmental outpatient clinic, Medical University Graz with the help of the Bayley Scales of Infant Development.

Results

The mean latency between preterm premature rupture of the membranes and delivery was 13 days. The overall survival rate was 70% (82 of 117). 17 fetuses died in utero and another 18 preterm infants died within a maximum of 31 days post partum. The higher the gestational age at delivery and birth weight the lower was the rate of complications. The complications that the infants developed are: Bronchopulmonary dysplasia in 13 cases, different grades of intraventricular haemorrhage in 30 cases, different grades of periventricular leukomalacia in 7 cases, posthaemorrhagic hydrocephalus in 4 cases, microccephalus in 2 cases, ileus in 4 cases, necrotising enterocolitis in 2 cases, perforation of the bowels in 6 cases, sepsis in 43 cases, retinopathy of prematurity in 8 cases. 60% of the

children that could be tested with 2 years showed a normal mental and locomotor development.

Conclusion

Gestational age at birth, birth weight and acute complications such as sepsis, or intraventricular haemorrhage have prognostic importance for preterm infants, as infants with higher gestational age and birth weight as well as the absence of complications showed a better outcome. 60% of the infants showed a normal cognitive and locomotor development at the age of 2 years corrected for prematurity. It is possible that, the 2-year follow-up was squewed due to the high dropout rate (no infants with a birth weight above 1500g visited the Neurodevelopmental outpatient clinic and some of the infants will not be tested until summer 2012)

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Abbreviations

BMI	Body mass index
BPD	Bronchopulmonary dysplasia
BSID	Bayleys Scales of Infant Development
CLD	Chronic lung disease
CNS	Central nervous system
CP	Cerebral palsy
e.g.	For example
ELBW	Extremly low birth weight
GA	Gestational age
i.e.	That is
IPH	Intraparenchymal haemorrhage
IRDS	Infant respiratory distress syndrome
IUFD	Intrauterine fetal death
IVH	Intraventricular haemorrhage
LBW	Low birth weight
MR	Magnetic resonance
NEC	Necrotizing enterocolitis
pPROM	Preterm premature rupture of membranes
PVL	Periventricular leukomalacia
PVH	Periventricular haemorrhage
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
RR	Relative risk
SGA	Small for gestational age
TTTS	Twin to twin transfusion syndrome
VLBW	Very low birth weight
WHO	World Health Organisation

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1 Introduction

Preterm premature rupture of membranes (pPROM) is a main risk factor of adverse neonatal outcome, especially when leading to infection and preterm birth. However, due to improvements in obstetric and neonatal management the mortality of infants after extreme preterm birth is steadily decreasing.[1]

Counselling of patients with extreme pPROM is complex and burdensome both for the medical personal as well as for the families affected, since a high proportion of unknown variables are involved. The aim of this study was to evaluate the short- and long-term effects on infants born preterm due to pPROM. Furthermore we wanted to analyse the mental and locomotor development of these children at the age of 2 years corrected for prematurity. With the analysis of the gathered and evaluated data we can get valuable information regarding morbidity and mortality of the involved patients. The outcome of this study can later be integrated in the counselling of all the persons concerned.

1.1 Definition of preterm birth

Delivery before 37^{+0} weeks of gestation has been defined as preterm birth by the World Health Organization (WHO).[1]

Over the last two decades, the percentage of preterm deliveries has risen steadily. The preterm delivery rate in Europe and other developed countries is about 5-9% and is rising steadily, as for example in the USA from 9,5% in 1981 to 12,7% in 2005.[2] Only in the last few years can we see a slight drop in the rates of prematurity in some of the developed countries world wide.[1]

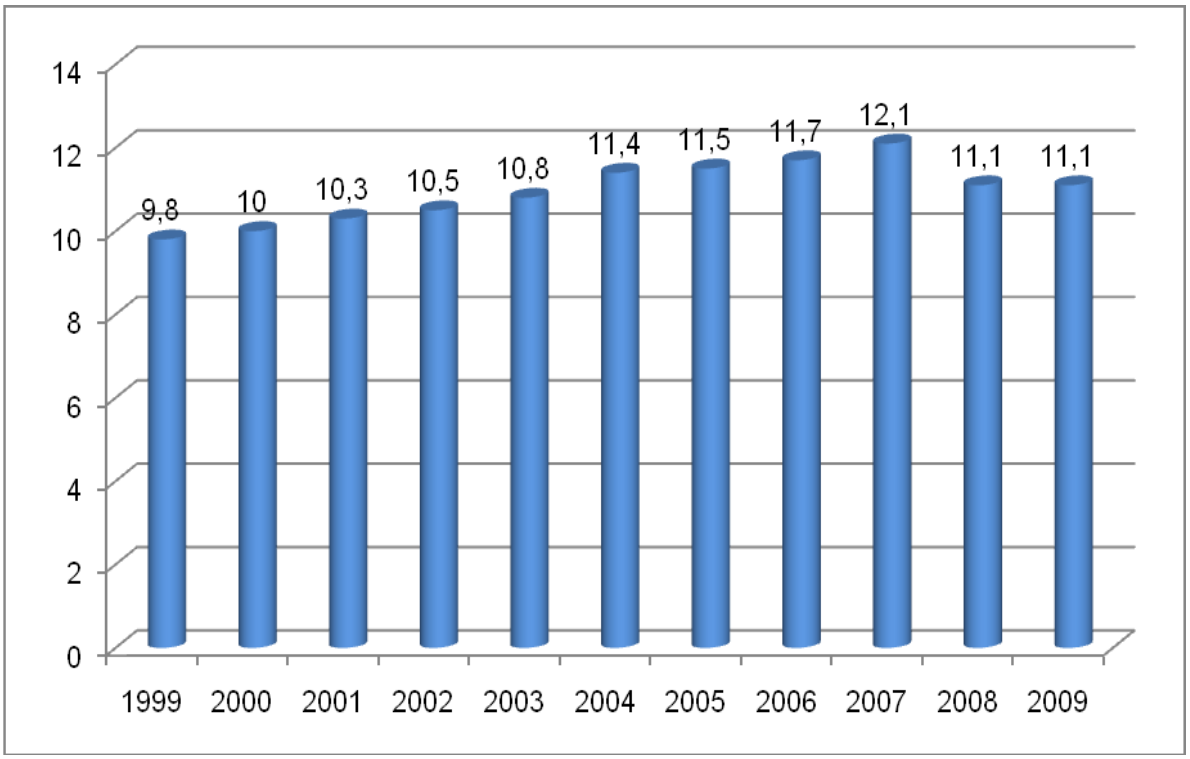

Figure 1: Preterm births as a percentage of live births in Austria, 1999 to 2009
Sources: Statistik Austria "Frühgeburten"
http://www.statistik.at/web_de/statistiken/bevoelkerung/geburten/022899.html
Date: 08.04.2011

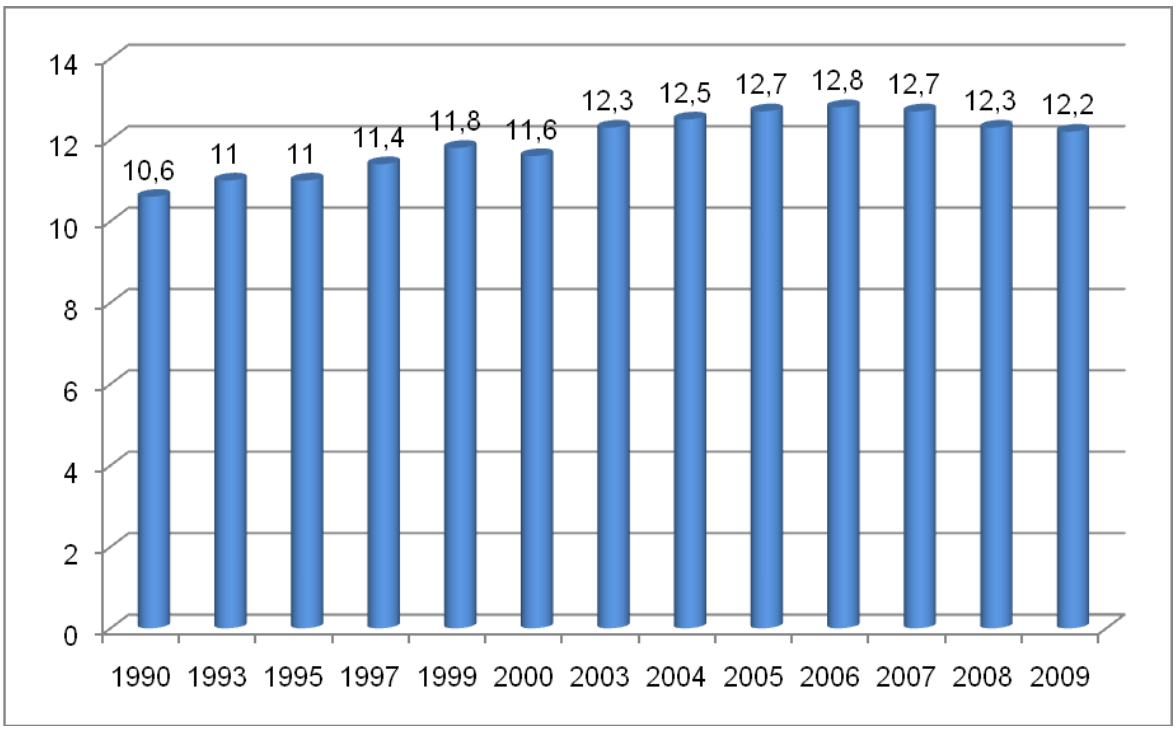

Figure 2: Preterm births as a percentage of live births in the US, 1990 to 2009
Sources: CDC (2001, 2002a, 2004a, 2005a, 2009).[1]

The *perinatal period* is defined as the period between 29^{+0} completed gestational weeks and the first 7 completed days of life; the *neonatal period* spans the time from delivery to 28 completed days of life.[11,12] Due to improvement in medical technology and perinatal care preterm infants show an increasing rate of survival which also includes those infants born between 23 and 24 weeks of gestation. Nevertheless, despite these improvements, preterm infants still have a far higher risk of morbidity and mortality due to their low gestational age (GA) at delivery and low birth weight than infants delivered at term. Prematurity is what makes these infants more vulnerable to complications than infants born later in pregnancy.[1] Extreme low birth weight [ELBW] is defined as a birth weight of <1000 grams, very low birth weight [VLBW] is defined as a birth weight of <1500 grams and low birth weight [LBW] is defined as a birth weight of <2500 grams.[12] Preterm infants also demonstrate a wide range of neurodevelopmental disabilities. Major disabilities include cerebral palsy, mental retardation, and sensory impairments. More subtle disorders can include language and learning problems, attention deficit hyperactivity disorder, and behavioural and social-emotional difficulties. Furthermore, preterm infants are more frequently affected by dystrophy and other health problems, such as asthma or reactive airway disease.[1]

Prematurity not only has consequences regarding the health of an infant, but also has an impact on the social-, and work-related - and for this reason financial situation - of the afflicted parents. As a result, opportunities are taken from the parents in different spheres of their lives. Starting with the delivery of a preterm infant near the limit of viability inevitably leads to an increased length of stay in hospital, which in turn may lead to maternal misery and later on to depressive symptoms. Preterm birth does not only have acute ramifications on families, but does also lead to long-term effects. Observations showed that school children who have been delivered with very low birth weight cause more stress in their family surrounding, as they need more support than children born at term. Studies also show that a less intensive parental relationship and a lower parental social affinity in certain issues, results from an early confrontation of the parents with the eventual loss of their child. All members of families of preterm infants face problems, as there are the possibility of a *poor family outcome* and *restricted social life*. Furthermore, parents sometimes even have to consider the probability that they will have no further children.

Another difficulty that may develop in a family with an infant born preterm is the fact that it may become hard for the parents to keep their jobs. Out of this results a financial burden that may weigh heavily on them.
On the other hand, giving birth to preterm infants may also have positive effects on the lives of the family members. It has been found that many people who care for a preterm infant develop a strong family connection, as they experience stronger personal feelings and marital closeness. The annual economic burden associated with preterm birth that weighs on the society in the United States was at least $26,2 billion in 2005, or $51,600 per infant born preterm.[1]

1.2 Epidemiology of preterm birth

One possible categorisation of preterm birth is spontaneous preterm birth versus induced. There are several diagnoses that are connected with preterm birth as for example hypertensive disorders, haemorrhage, and acute or chronic fetal affections which can either be intrauterine fetal distress, or intrauterine growth restriction. Spontaneous preterm delivery occurs in about two-thirds of the cases listed above. This includes spontaneous preterm labour and pPROM, or other diagnoses as for example cervical insufficiency. It is crucial that preterm birth is to be taken as a syndrome with several different conditions, which initiate and lead to the progression of preterm delivery.[10]
Preterm delivery, either for maternal or fetal reasons, which includes deliveries with induced labour or prelabour caesarean section, or spontaneous preterm labour with intact membranes and pPROM, is a symptom that leads to preterm birth regardless of the delivery mode which can be vaginal or by caesarean section.[2]

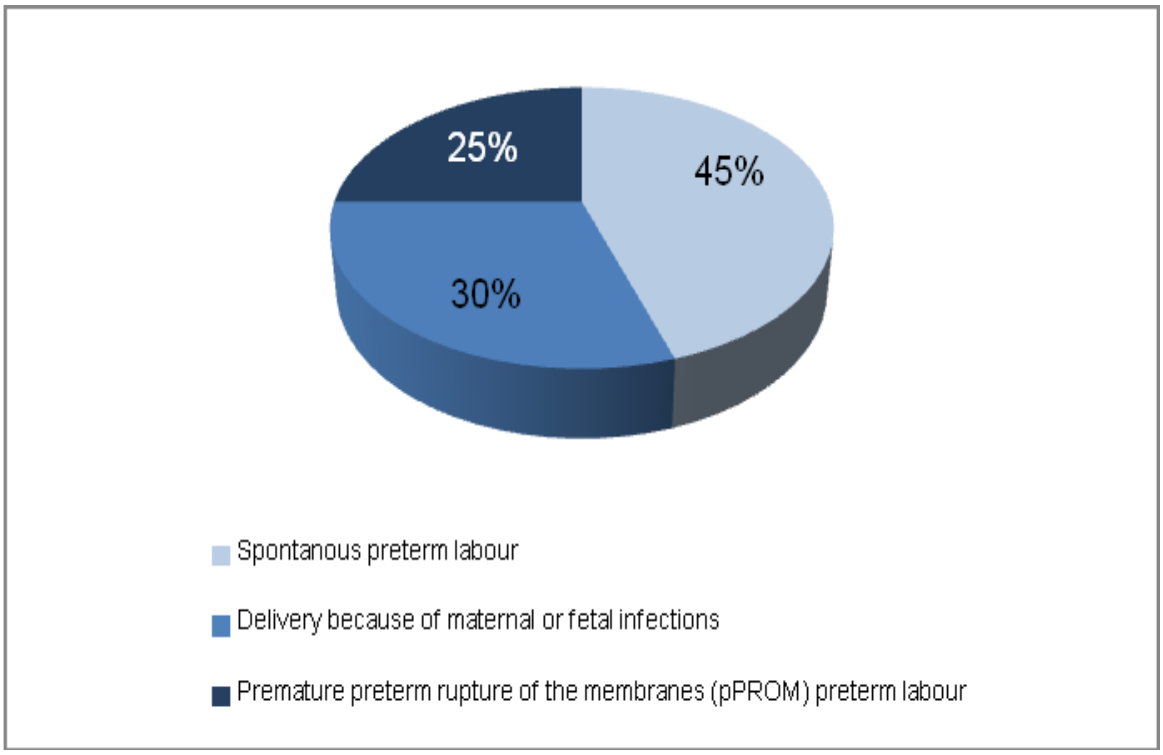

Figure 3: Obstetric precursers of preterm birth [2]

It is also possible to subdivide preterm births according to gestational age: Extreme prematurity (<28 weeks of gestation) represents the smallest group of preterm births, but the number is increasing. According to the grade of prematurity, infants born near term (34-36 weeks of gestation) represent the largest group.[2]

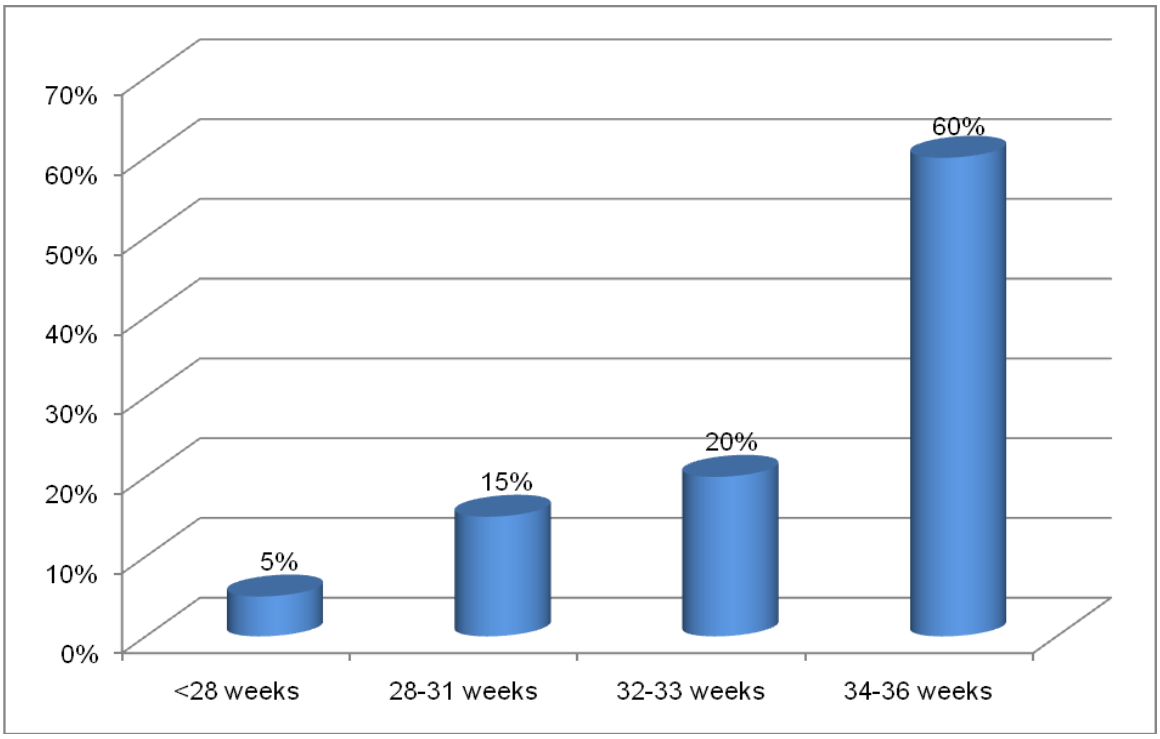

Figure 4: Preterm birth according to gestational age [2]

1.3 Causes of preterm birth

1.3.1 Demographic characteristics

Preterm birth can be associated with many maternal or fetal characteristics (maternal and fetal demographic data). As an example women of african-american or afro-caribbean origin are reported to have an increased risk of preterm delivery. The preterm birth rates of black women range from 16-18%, compared to 5-9% in white women. Further maternal demographic characteristics that may lead to preterm delivery involve low socioeconomic and educational status, low and high maternal ages, and single marital status.[2]

1.3.2 Period of time between two pregnancies

There is also a higher risk of preterm birth, if there is just a short time period between two pregnancies. A possible, however somewhat vague explanation for this may be, that the uterus needs time to return to its normal state after a pregnancy.[2]

1.3.3 Anatomical description of the uterus of adult women and its changes during pregnancy

The uterus of an adult woman is generally described as pear-shaped and lies between the urinary bladder and the rectum.[6,7,14] The stem of the pear is directed caudal and pulls into the upper part of the vagina. The systematic anatomy distinguishes 4 segments of the uterus: Fundus, corpus, isthmus and cervix. The fundus lies above the merging point of the tubes. The corpus uteri is the main body of the uterus and narrows at its inferior end. It is followed by the isthmus uteri which merges into the cervix uteri without any visible border on its surface.[6] The median length of the uterus of nulliparus women is 7,5cm, the width is about 4cm and the thickness is 2,5cm. The cervix uteri and corpus uteri have approximately the same size. After a pregnancy, the uterus grows 1-1,5cm in all of its dimensions and the corpus uteri is now 1-2cm larger than the cervix uteri.[7] The uterus of an adolescent woman weighs approximately 40-60g, the uterus of an adult woman weighs about 80-120g.[13] During pregnancy, the muscular mass of the corpus uteri increases through a combination of both hyperplasia and hypertrophy of the

muscular cells to approximately 1000-1500g which is about 20-30 times more than its usual mass.[8]

1.3.4 Infections

A frequent and important mechanism that leads to preterm delivery is infection, which is applicable to about 25-40% of all preterm births. Intrauterine or intra-amniotic infections are commonly associated with the onset of spontaneous preterm labour or pPROM and may lead to fetal injury and long-term handicaps such as periventricular leukomalacia (PVL), cerebral palsy (CP), and chronic lung disease. There are also different non-genital tract infections, including pyelonephritis, (asymptomatic) bacteriuria, pneumonia and appendicitis that are connected with, and therefore may lead to preterm delivery.[2] The most common microorganisms causing infections are those that are found in the vaginal tract and ascend through the vagina and the cervix. These include group B streptococcus, staphylococcus, enterococcus, E. coli, and anaerobe.[14]

However, the scientific evidence for prophylactic antibiotic therapy in the pregnancy without pPROM for the prevention of prematurity is rather controversial.[24]

There is however only little evidence, that viral infections are precursors for preterm delivery in comparison with bacterial infections.[24]

1.3.5 Cervical shortening

It has been demonstrated that cervical length may act as a predictor of preterm delivery since the risk for preterm birth increases exponentially with decreasing cervical length. Goldenberg et al. showed that a cervical length of less than 25mm at 24 weeks gestation represents an increased risk for preterm birth in asymptomatic women.[2]

As reported by Iams et al[9]: Women with a cervical length measured less than 25mm showed a notable distinction according to the continuance of their pregnancy in comparison to women with a cervical length of more than 25mm and this discrepancy grew larger with the progression of the pregnancy. Furthermore, the researchers stated that a shorter cervix stands in direct correlation with preterm delivery, and is therefore an important risk factor that can shorten a

pregnancy significantly. In comparison to women with a cervical length longer than the 75th percentile, women with short cervixes at 24 completed gestational weeks have a relative risk (RR) of preterm birth in the following way: RR=2,35 for lengths at or below the 50th percentile (35mm), and RR=6,19 for lengths at or below the 10th percentile (26mm).[9] Furthermore, it has been postulated that funneling also correlates with an increased risk of preterm delivery.[9]

Tsoi et al.[25] reported that cervical length is a significant parameter in women with threatening preterm delivery due to preterm labour. They examined preterm delivery within 48h, 7 days and before 35 completed gestational weeks after the occurrence of preterm labour in women between 24 and 33^{+6} weeks of gestation and intact membranes. No woman who presented with a cervical length of 15mm or more did deliver her child within 48h and only 0,7% within 7 days. Therefore, the workgroup of King's College Hospital (Professor Nicolaides) recommends that a cervical length of <15mm should be regarded as an essential predictor for preterm delivery.[25]

1.3.6 History of former pregnancies

The risk of recurrent preterm delivery in women with previous preterm births ranges from 15-50% depending on gestational age and the number of previous deliveries. Pregnancy characteristics, such as multiple gestations have a considerable risk of preterm birth (15-20% of all preterm deliveries).[2]

1.3.7 Vaginal bleeding

Vaginal bleeding caused by placenta praevia, or placental abruption, but also without any of these reasons, also extremes in amniotic fluid (polyhydramnios or oligohydramnios) are associated with preterm labour and pPROM, and therefore with preterm birth.[2]

1.3.8 Maternal state of health

Moreover, abdominal surgery during the second and third trimester, maternal conditions such as asthma, thyroid disease, diabetes and hypertension, or a

history of cervical coninzation have been associated with an increase in the rate of spontaneous preterm birth.[2]

An increased risk of preterm delivery can be found in mothers who have to deal with high levels of psychological or social stress, as for example housing instability and severe material hardship. Another psychological factor related to preterm birth is depression, although data regarding this condition are inconsistent. Women who tend to suffer from depressions also show increased adverse behavioural patterns as smoking, drug, and alcohol abuse. Surveys show that 20-25% of women living in the USA smoke, and 12-15% of these continue throughout their pregnancy, which can lead to fetal growth restriction and indicated preterm birth. Unlike heavy alcohol consumption, which is known to be a risk factor for preterm birth, mild or moderate alcohol consumption has no effect on preterm delivery rates. Different studies have shown that drug abuse such as for example cocaine or heroin show a high risk of preterm birth.[2]

1.3.9 Maternal depletion

Another factor might be maternal depletion, as a pregnancy consumes maternal vitamins, minerals and amino acids, these may become scarce, if there is just a short interval between two pregnancies. Depending on diet, it can be difficult to restore these nutrients.[2]

1.3.10 Nutritional status of women

A further reason that increases the risk of preterm birth is the nutritional status of women, as i.e. a low pregnancy body mass index (BMI) shows a high risk of spontaneous preterm birth, as maternal thinness is associated with a lower blood volume and a reduced uterine blood flow. Obesity can be protective, compared to the risks of thin women, but leads to other complications during pregnancy, as obese women are more likely to develop diabetes or pre-eclampsia, which may lead to indicated preterm births.[2]

1.3.11 Gene defects

Ultimately, there can always be a genetic component such as single-nucleotide polymorphisms, which might be responsible for a higher risk in developing preterm labour or pPROM and therefore preterm delivery.[2]

1.4 Complications of preterm birth

Developmental immaturity can affect several organ systems and may lead to severe complications with lifelong adverse effects for health, growth and development of infants born preterm. Organ systems included are lungs and respiratory system, gastrointestinal-, cardiovascular-, central nervous-, immune-, and ophthalmic-system, as well as the hematologic system.[1]

1.4.1 Respiratory system

The most common complications regarding the lung and respiratory system are infant respiratory distress syndrome (RDS), bronchopulmonary dysplasia (BPD)/chronic lung disease (CLD) and apnea.[1]

About 80% of infants born in the US at an age of less than 27 completed gestational weeks will evolve a respiratory distress syndrome, which is highly related with a lack of surfactant. Infant type RDS (IRDS) is characterised as an increasingly insufficient gas exchange with the clinical presentation of dyspnoea due to primary surfactant deficiency.[12] There is an increasing rate of RDS with smaller gestational age (GA). RDS can be grave as it shows a mortality rate of 5%, although it is less common in infants born at 33-36 completed weeks of gestation and barely occurs in infants born at term. The incidence and severity as well as the frequency of mortality can be decreased by the antenatal administration of corticosteroids to mothers at risk of preterm delivery.[1]

"RDS is an acute illness treated with respiratory support (oxygen-, positive airway pressure, ventilator, or surfactant) as needed and improves in 2 to 4 days and resolves in 7 to 14 days" [1].

BPD/CLD, which is defined as a chronic lung-disease of premature babies or newborns, is associated with characteristic radiologic changes and that requires artificial ventilation and oxygen therapy beyond 28 days of life, or 36 completed gestational weeks, respectively.[12]

It is caused by injury, scarring of the airways and the alveoli, positive pressure ventilation, high oxygen concentrations, infections and other inflammatory triggers. BPD is a chronic disorder that above all, is induced by lung immaturity. Neonates who suffered from BPD have a higher probability to develop lasting respiratory problems during their infancy, than those who did not suffer from BPD. Furthermore children with BPD are associated with other health problems (they are more vulnerable to the effects of passive smoking and have higher rates of asthma), persistent growth problems and neurodevelopmental disabilities.[1]
A pneumothorax, defined as an accumulation of air in the pleural cavitiy, - the lung is collapsed to a greater or lesser extent - represents another important complication of the respiratory system.[12]

1.4.2 Gastrointestinal system

A severe complication of the gastrointestinal system of preterm infants is necrotizing enterocolitis (NEC), which is an acute injury of the small or the large intestines that causes inflammation, and injury to the bowel lining. It is defined as the transmural necrotizing inflammation of the intestinal wall of an infant.[12] The development of NEC is normally observed in the first 2 weeks after birth. Typical difficulties of this condition are: feeding problems, abdominal swelling, hypotension and further symptoms of sepsis. The acute complications that infants with NEC suffer from are: perforation of the intestines, which leads to peritonitis and sepsis.[1] *"Long-term morbidities can include ileostomy, colostomy, repeated surgical procedures, prolonged parenteral nutrition, liver failure, poor nutrition, malabsorption syndromes, failure to thrive, and multiple hospitalisations"* [1]. The reason why infants receive only a parenteral diet during an acute illness is due to the potential fatal character of NEC.[1]

1.4.3 Central nervous system (CNS)

Infants that are born preterm are extremely vulnerable to CNS injury - which may occur during pregnancy, labour, delivery, or due to an illness or exposure in extrauterine life - as the formation of their central nervous system has not been completed. The most vulnerable regions in the brain are the white matter around the ventricles and high germinal matrix eminence. The explanation of the problem is, that preterm infants have only limited abilities for the auto regulation of cerebral

blood flow. Intraventricular haemorrhage (IVH), intraparenchymal haemorrhage (IPH), and white matter injury (including periventricular leukomalacia [PVL]) are the most common complications of CNS injury. It is possible to visualise brain injuries in preterm infants with transcranial ultrasound, which is cost efficient and easily available, as it can be performed at the bedside. Other screening possibilities include computerised tomography, and magnetic resonance (MR) imaging. MR imaging is increasingly used due to the better visualisation of the brain parenchyma. However, the costs are considerably higher and often additional sedation of the preterm infant is necessary.[1]

A serious complication of preterm birth is injury of the periventricular white matter, which includes a series of CNS injuries that can range from focal cystic necrotic lesions (also known as PVL), to ventricular dilation with irregular ventricular edges or cerebral atrophy, and lead to the development of extensive and bilateral white matter lesions.[1]

It is much harder to image white matter injury, than IVH or IPH and therefore ultrasound examinations should be performed repeatedly at 3 to 4 weeks after birth and at 34-36 weeks of postmenstrual age in order to detect possible signs of white matter injury, which evolve over time. An uneven density of white matter that resolves or that evolves into cystic lesions may be the first sign of a white matter injury. In order to identify white matter injuries properly, it is very important to take care of the timing and the quality of the performance of ultrasound examinations, as cystic lesions are likely to collapse with time.[1]

The most severe long-term neurodevelopmental impairment is CP, which develops 60-100% of infants with PVL. Two events have been linked to the onset of PVL in premature infants: intrauterine infection and hypoxemia.[3] The causes of PVL are a compound of several different factors that occur not only in the prenatal, but also in the perinatal period.[5] The development of PVL in preterm infants is connected to pPROM and prolonged rupture of membranes.[3,5] It has also been proven in a meta-analysis of 30 studies that chorioamnionitis is a risk factor for PVL (risk increased to 60-70%) and CP.[3,5]

Furthermore, birth asphyxia, recurrent apnea, patent ductus arteriosus, sepsis, seizures, duration of medical ventilation and hypocarbia are highly associated with PVL.[5]

It was reported that in preterm infants delivered before 32 weeks of gestation, vaginal delivery increased the risk of PVL, while there was a decrease in the incidence of PVL and CP in infants delivered by caesarean section.[3,20]

Baud et al. stated that the mode of delivery is the strongest independent risk factor for developing PVL and that the implementation of a lower segment caesarean section is associated with a lower incidence of PVL. In a study population of 99 infants, 20 developed PVL. Of 44 infants born vaginally, 17 suffered from PVL, compared to 3 infants out of 45 that have been delivered by lower segment caesarean section.[20]

As well O'Shea et al. as Murphy et al. claim that delivery without labour is related with a decreased risk of CP.[21,22]

As shown in other studies male gender has a higher risk of developing PVL.[3,5] It has been found that preeclampsia is associated with PVL, although the role of preeclampsia according to the outcome of preterm infants is very controversial in literature.[5] Neonates suffering from IVH were also reported to have a higher risk for PVL. It was also shown that infants who suffered from PVL were more immature, and their perinatal period was more troublesome than that of controls.[5]

Furthermore it was demonstrated that the duration of labour does not increase the risk to develop injuries of the white matter.[3]

As a last point it is poorly understood, if there is a connection between cerebral injuries and pre-eclampsia or small-for-gestational age (SGA).[4]

1.4.4 Immune system

The immune system of preterm infants is immature and therefore ineffective in fighting off bacteria viruses and other harmful organisms that can cause infections. The most common and serious manifestations of infections seen in preterm infants include pneumonia, meningitis, urinary tract infections and ultimately sepsis.[1]

An early onset sepsis is defined as the development of an infection within the first 3 days after delivery opposed to a late onset sepsis defined as the evolvement of an infection after the first 3 days of life.[12]

1.4.5 Cardiovascular system

Problems regarding the cardiovascular system of preterm infants can range from major morphological defects to dysfunctional auto-regulation of blood vessels (hypotension). One of the most common disorders that infants born preterm have to face is a patent ductus arteriosus, which can lead to heart failure and a diminished blood flow to other organs. In many cases it shows no symptoms and closes spontaneously during the first week of life. On the other hand a patent ductus arteriosus can increase the risks of developing an IVH, NEC, BPD, and can even lead to death.[1]

Another common complication concerning the cardiovascular system is hypotension. It is treated by the administration of boluses of saline and vasopressors.[1]

1.4.6 Hematologic system

Anaemia in prematurity is the most frequent complication regarding the hematologic system in preterm infants. It can result from several factors, as for example blood loss from continual blood sampling, a shorter survival of red blood cells, a subpar reaction to anaemia, and an increased need for red blood cells with advancing growth. Red blood cell transfusions are often used in preterm infants.[1]

1.4.7 Auditory and ophthalmic system

Congenital and perinatally acquired hearing disorders occur in 1-2 of 1000 newborns. Infants born preterm have a 10 to 50 times higher risk to suffer from this disease. The largest group of hearing disorders is hereditary, but it can also occur due to a number of pre- and postnatal complications, e.g. asphyxia, ototoxic medications, infections, immaturity, and hyperbilirubinemia. Infants delivered at less than 25 to 26 weeks of gestation, have a 1 to 5% higher risk to develop a significant hearing impairment which requires hearing aids. Preterm infants who have to be ventilated have also an increased risk to evolve otitis media and concurrent hearing loss.[1]

A common ophthalmologic disorder in preterm infants is retinopathy of prematurity (ROP), which is a neovascular retinal disorder. The incidence of this disease increases with decreasing gestational age and birth weight. There are also

environmental factors, which contribute to the development of ROP, as for example hypoxia, hyperoxia, variations in blood pressure, sepsis, and acidosis, which need to be avoided. Therefore it has been suggested to prevent drastic changes in blood pressure, blood oxygen and carbon dioxide levels, and acidosis.[1] Further complications regarding the eyes are: refractive disorders, strabismus, amblyopia, optic nerve atrophy, cataracts, and cortical visual impairment.[1]

1.5 Interventions to reduce morbidity and mortality of preterm birth

There are primary, secondary, or tertiary interventions to reduce the morbidity and mortality in preterm birth.[10]

1.5.1 Primary prevention

Primary prevention addresses women before or during pregnancy and is an increasingly luring strategy to prevent and reduce risk factors. It includes treatment (as for example nutritional supplementation, reducing or giving up smoking, periodontal- and prenatal care) and screening in order to choose the most suitable therapy.[10]

1.5.2 Secondary prevention

Secondary prevention includes all women with an increased risk of preterm birth based on obstetric history (e.g., previous preterm delivery uterine malformation) or current conditions like multiple gestation or vaginal bleeding.[10]

There is the possibility of preconceptional interventions, which involve women with an evident history of preterm birth (which includes both spontaneous and induced preterm births).[10]

It has been reported that there is a higher risk for preterm birth in a consecutive pregnancy as the gestational age at the time of delivery of the previous preterm birth decreases.[10]

Postconceptional interventions include modifications of maternal activity, nutritional supplements, closer surveillance, antibiotic treatment, progesterone, and cervical cerclage.[10]

Bed rest, limited work, and reduced sexual activity are often recommended to decrease the probability of preterm birth in pregnancies with history of indicated or threatened spontaneous preterm births, although it is not proven that these recommendations have any significant benefit on pregnancy outcome.[10]

A decrease in the production of inflammatory mediators was shown in studies that added omega-3-polyunsatturated fatty acids supplementary to a balanced diet in pregnant women Furthermore it has been proven that the rate of preterm deliveries in women with an increased risk of preterm birth was decreased about 50% if they received omega-3-supplements.[10]

A Cochrane systematic analysis showed no advantage in increased prenatal care, as it showed no decrease in rates of preterm birth in women with higher risk to develop a preterm delivery.[10] Another Cochrane review including 5,888 women concluded that the application of antibiotics had no significant effect on the prolongation of pregnancies or the prevention of pPROM in all study participants, although bacterial vaginosis could be eradicated. The risk of preterm birth might be decreased if antimicrobial treatment is administered before 20 weeks of gestation as resumed by Lamont. Further possibilities for the failure of antibiotics may be that they do not prevent or treat chorioamnionitis effectively and that co-factors, as diet, smoking, and genetic variations in inflammatory response, may affect the risk of preterm birth despite the use of an antimicrobial therapy.[10]

The intramuscular injections of 17-α-hydroxyprogesterone caproate, or vaginal administration of progesterone have been reported to reduce preterm births. Furthermore the risk of recurrent preterm birth was decreased by 40-55% by the administration of progesterone.[10]

As mentioned above (in chapter 1.3.4.), cervical shortening is a significant risk factor for preterm delivery. It may be challenging to identify those women, who would benefit from a cervical cerclage, since prophylactic cerclage for every woman with a history of preterm birth, but without a short cervix in the present pregnancy does not seem to be beneficial. Women with a short cervix (defined as

<25 mm-screened by transvaginal ultrasonography in the second trimester) in the present pregnancy and a previous preterm birth do benefit from receiving cervical cerclage, reducing the risk of preterm delivery before 35 weeks' gestation. The treatment of women with a short cervix, but without a history of preterm birth had no positive effect on the prolongation of their present pregnancy.[10]
Furthermore, it was found that women with singleton pregnancies, a short cervix and lack of history of preterm delivery, did not benefit from a cerclage. In addition, in twin pregnancies with short cervix and uneventful obstetric history women underergoing cerclage showed an even higher incidence of preterm delivery.[10]

1.5.3 Tertiary prevention

Tertiary prevention has either the goal to prevent delivery in women whose parturition process has already begun, or to improve the outcome of preterm infants. Management options can be divided into diagnosing preterm labour as early as possible, treatment of women with acute risk of preterm birth with, tocolysis and, intensive care after pPROM. The latter includes treatment for preterm labour and the delivery of preterm infants.[10]

Several randomised trials failed to demonstrate a decrease in the rate of preterm birth in women at risk who were trained to recognise early signs and symptoms of labour. It was also shown that the rate of preterm birth was not reduced, despite women at risk, participating in educational programmes to be sensitised regarding the possible complications of their pregnancy. These women had additional weekly or daily nursing contact, or even daily nursing contact plus uterine contraction monitoring.
Treatment to avert preterm labour in women with threatening symptoms of a cervical dilation or pPROM is not suitable to prolong a pregnancy in an extent that further intrauterine growth and maturation could be warranted. Nevertheless it is possible to delay preterm delivery so actions to be taken to reduce the neonatal morbidity and mortality. A main objective of these measures is to enable a fast transport of the (intrauterine transport) to a hospital that holds appropriate equipment for infants born preterm, particularly if these infants are expected to be delivered before 32 completed gestational weeks.[10]

Patients benefit from this strategy and therefore preterm infants are associated with an improved outcome.[10]

Furthermore, it is suggested that all women with threatened preterm labour should receive antibiotic treatment in order to avert preterm infants getting infected with group B streptococcus, as they have a higher risk to develop this complication. In the USA it was shown that since the acceptance of this treatment, the neonatal infection and corresponding mortality rates have decreased. However, the data on this issue is not strong and therefore there are no recommendations in Europe for a standardised screening for group B streptococcus in pregnancy[10]

The neonatal morbidity and mortality on the part of respiratory distress, IVH, NEC and patent ductus arteriosus, can be diminished by the antenatal administration of corticosteroids to the mother.[10]
In order to promote maturation over growth in fetuses that face preterm delivery, glucocorticoids are applied, as they induce the production of surfactant produced by type 2 pneumocytes, decrease vascular permeability and enhance the compliance of the lung. Furthermore it was reported that an improved reaction is attained if infants that received a corticosteroid application antenatal, are treated with glucocorticoids after delivery. Corticosteroids are administered intramuscularly either, as two doses of 12mg bethamethasone 24 hours apart, or in four doses of 6mg dexamethasone every 12 hours.[10]
The advantageous effects of the antenatal application of glucocorticoids, including reduced emergence of RDS, IVH, NEC, bronchopulmonary dysplasia and neonatal death, has been demonstrated in randomised, placebo-controlled trials and meta-analyses, although it is unsure how long fetal benefit maintains. When risk of preterm birth is initially perceived after 24 weeks of gestation, the current strategy is to limit the administration of antenatal corticosteroids to a single course with the option of a repeated course some four to six weeks later if the risk of severe preterm delivery persists.[10]

For the purpose of prolongation of a pregnancy in women with acute risk to develop preterm birth, which is predominantly due to active preterm labour and, less frequently due to pPROM, tocolytic drugs are utilised. The prime reason for

the application of these drugs is to delay birth by at least 48 hours. This is important in order to transfer a woman and her fetus at risk to a specialist unit. Furthermore, tocolytic drugs help to reduce the morbidity and mortality of the fetus, as they help prolong pregnancies long enough to induce fetal lung maturation. The number of preterm deliveries cannot be decreased with the administration of any tocolytic drug, as reported in al studies that deal with this topic.[10]

Cochrane meta-analyses indicate that calcium-channel blockers and an oxytocin antagonist (atosiban) can defer preterm delivery by 2-7 days with an optimum risk-benefit ratio. Furthermore it was argued that delivery could be postponed by 48h, by β_2-agonist drugs, as for instance ritodrine and terbutaline, yet they bring greater side effects than other agents. Another point concluded by the Cochrane analysts was that magnesium sulphate alone is ineffective in preventing preterm birth.[10]

In developed countries, 30% of preterm births result from pPROM. The current management includes surveillance for labour, infection and abruption, and administration of glucocorticoids or antibiotics. Two clinical trials justified the advantage of the administration of antibiotics, as the prophylactic treatment with ampicillin plus erythromycin and erythromycin or amoxicillin/clavulanic acid was related with prolongationof pregnancy, a lower rate of maternal chorioamnionitis, and a lower prevalence of neonatal morbidity, measured as compound neonatal outcome.[10]

Continuous use of tocolytics of more than 48 hours did not decrease the number of preterm births. Furthermore it was found that there is neither an effect on the rate of infants born preterm, their low-birth weight nor their gestational age at birth, if the mother received supervision through outpatient monitoring regarding uterine contractions, after a stay in hospital.[10]

The benefit of routine caesarean delivery for preterm or very low-birth weight infants remains to be matter of debate. However it was reported that intracranial haemorrhage occurs most likely before and after labour and not during labour and delivery. Although there is no evidence supporting the general use of caesarean section, it may prevent trapping of the head and other manipulations that might lead to trauma or hypoxia in infants in breech presentation. Caesarean section without labour is probably the best way to deliver VLB infants, as complications

like pPROM, cord prolapse, bleeding, or expected problems due to vaginal breech delivery may occur with expectant management.[10]

Eventually it can be said that the number of infants born preterm, was not reduced, but the rate of viability of these neonates has risen steadily. This is mainly due to the improved treatment modalities in neonatal care as well as due to obstetric interventions like antenatal glucocorticoid treatment, screening for asymptomatic bacteriuria, and prophylaxis for group B streptococcal disease.[10]

2 Materials and methods

In this retrospective data analysis the clinical records of all identifiable patients with pPROM between 18^{+0} and 27^{+6} weeks of gestation at the Division of Obstetrics and Maternal Fetal Medicine, Medical University Graz between January 2003 and December 2010, were reviewed. Data were retrieved from the local clinical electronic databases, and were collected in Microsoft Excel. Information about the course of pregnancy and delivery of the infants were extracted from PIA Fetal Database, which is used at the Division of Obstetrics and Maternal Fetal Medicine since June 2003, while therapies and examinations were obtained from medical reports of the Department of Paediatrics that are stored in open Medocs.
Main parameters of interest were GA at pPROM, GA at birth, latency period between these two events, fetal gender and neonatal outcome.

2.1.1 Inclusion criteria

All women treated for pPROM between 18^{+0} and 27^{+6} weeks of gestation between July 2003 and October 2010 were included to the study.

2.1.2 Exclusion criteria

Women with pPROM before 18^{+0} and after 27^{+6} weeks of gestation and all women without pPROM were excluded from the study.

2.1.3 Management

We did not examine the management of the infants, as there were no standardised measures. We wanted to give an overview regarding the complications infants born preterm have to face and the different treatments that they received.

2.2 Bayleys Scales of Infant Development

In order to define neurodevelopmental outcome at the age of two years children were tested for their mental and locomotor abilities by using the Bayleys Scales of Infant Development-2nd Edition (BSID-II) at the Neurodevelopmental outpatient clinic at the Department of Paediatrics of the Medical University Graz.

The BSID is an individual test to examine the level of development of children between 1 and 42 months. It has proved itself preferable to diagnose development delay and to plan early intervention.

The method is comprised of three parts: a Cognitive Scale, a Locomotor Scale and a Behaviour Rating Scale. With the help of the Cognitive Scale and the Locomotor Scale it is possible to evaluate the current functional level regarding the cognitive-, linguistic-, social-, as well as the fine- and gross-motor skills of a child. By means of the Behaviour Rating Scale it is possible to appraise the childlike performance during the test-situation, which simplifies the interpretation of the results concerning the Cognitive- and Locomotor Scale.

The three components of the examination complement each other in the entire assessment of the early childhood development. The tasks regarding the Cognitive Scale acquire early cognitive performances, habituation, problem-solving competence, early number sense, classification and categorisation skills, vocalisation and language competence together with social-communicative skills. The chores of the Locomotor Scale gather the increasing posture control right up to rising as well as the fine- and gross motor coordination. This involves movement control when rolling, crawling, sitting, standing, walking, running and jumping. The Locomotor Scale contains the fine motor manipulation when grasping, the use of pens appropriate to the children's age and the imitation of gesticulations.

The tasks and test situations of the BSID have been designed in a way that easily arouses the interest of the children, so they can show observable behavioural reactions. These behavioural reactions are the foundation for a clinical examiner to estimate the appropriateness of the performance and the functional level that the child renders. Nancy Bayley stressed that particular approaches are necessary in the examination of infants that differ considerably from inquiries regarding older children, or adults. In this context Bayley emphasised that the development of abilities in the first two years of life *"does not follow a neatly arrayed factor pattern*

of "mental" or "motor" abilities" (Bayley,1993, S.2). Actually many skills and characteristics of an early stage of life differentiate in the course of time *"and thus any classification of abilities into parallel arrays measuring different factors is artificial and serves no useful purpose"(Bayley, 1993, S.2).*

The perception of Bayley in terms of structure and progression of childhood development lead to the progression of a particular kind of infant examination. The BSID combines a flexible implementation with a standardised approach, i.e. the test contains precise instructions for the accomplishment of the tasks, however it is possible to adjust the pace and sequence of the performance of the assignment to various factors as for example the age, temper and the success quotient of the child.

Despite its flexible performance the Bayleys Scales of Infant Development can be described as "Power Test". The chores in a Power Test are organised according to their degree of difficulty. The tasks of the BSID are presented in an adapted Power-Sequence, even though the instructions are not implemented in the accurate sequence of their complexity. It is for instance not expected that a child is able to name pictures before it knows specific words.[15]

2.2.1 Inclusion criteria for the Bayleys-test

All children at the corrected age of 2 years according to prematurity, born preterm and with a birth weight under 1500g are included to the study.

2.2.2 Exclusion criteria for the Bayleys-test

Out of 100 infants born alive, 82 were discharged from hospital. A total of 36 children have been excluded from the study: 9 children with a birth weight above 1500g, because these children are not routinely included in long-term neurodevelopmental assessment. 13 children that have been delivered in the year 2010, as they have not yet reached the corrected age of 2 years according to prematurity. 14 children were lost due to follow up or were excluded due to incomplete data, leaving 46 children for further analysis.

3 Results

3.1 General results

From a total of 19523 deliveries between January 1st 2003 and December 31st 2010, 107 women met the inclusion criteria (representing a frequency of 0,5%). There were 97 (91%) with singleton pregnancies, 9 (8%) with twins, and 1 (1%) with triplets, giving a total of 117 fetuses who were managed expectantly for spontaneous pPROM between 18^{+0} and 27^{+6} weeks of gestation. Maternal age ranged from 17 years to 44 years, (mean: 32 years). Intrauterine death occurred in the triplets and in one of nine twins pregnancies, however in this case death was due to twin-to-twin transfusion syndrome (TTTS). In two of nine twin pregnancies neither infants survived, in one case, one infant died after delivery, and 12 (10%) of a total of 117 infants survived until discharge from hospital.

14 (12%) of the 97 singleton infants died in utero, 13 (11%) postpartally within 31 days. Seventy singleton newborns (60%) of a total of 117 infants born preterm survived until discharge from hospital.

Overall 17 (15%) infants died in utero, 18 (15%) postpartally within 31 days, and 82 (70%) infants of a total of 117 infants (70 from singleton pregnancies and 12 from twin pregnancies) survived until discharge from hospital.

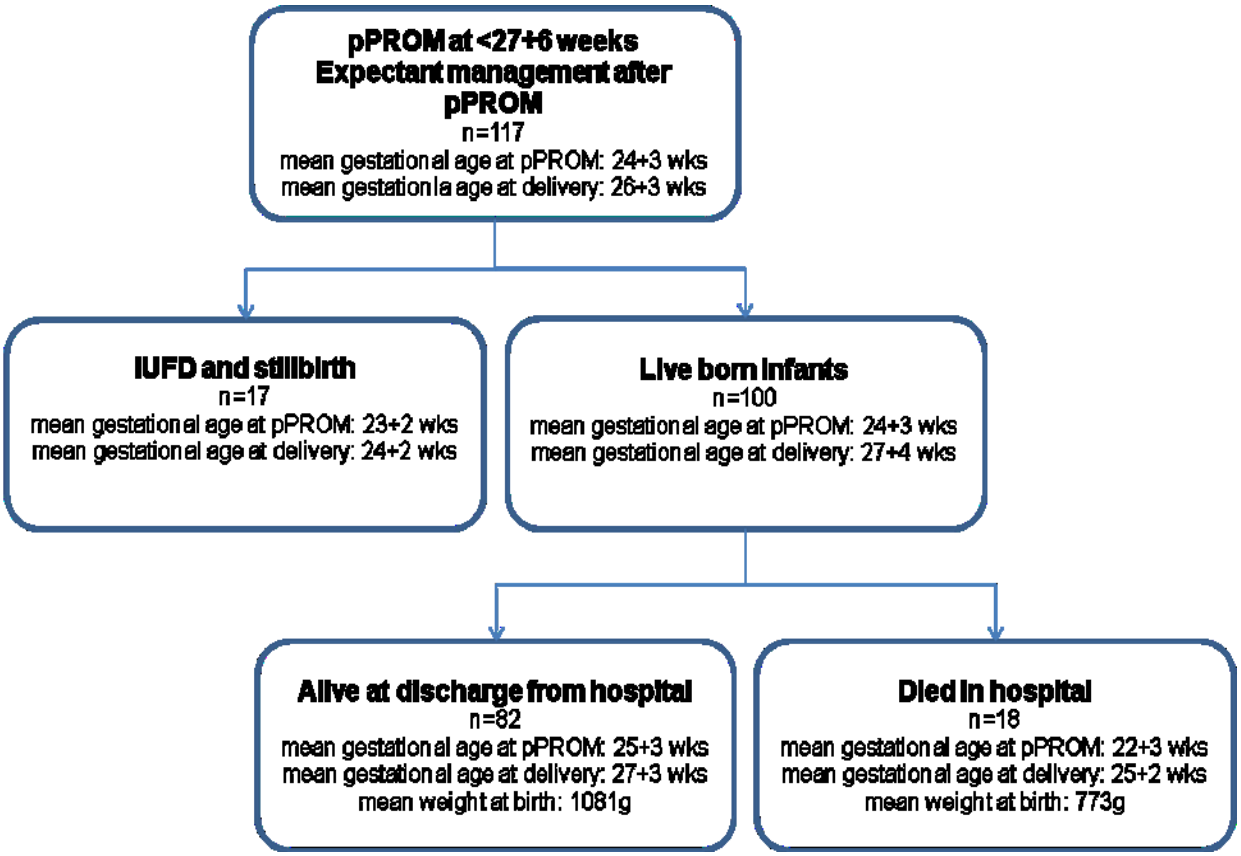

Figure 5: Study protocol based on Figure 1 in Pristauz et al. [16]

100 (85%) of 117 fetuses, were born alive, from these, 18 (15%) died within a few days after delivery and 17 (15%) died in utero.

From 117 infants included in the study 72 (62%) were male and 45 (38%) female. From the 72 male infants, 52 (72%) survived until discharge from hospital, 12 (17%) died postpartally, and 8 (11%) died in utero. 30 (67%) of 45 female infants survived until discharge from hospital, 6 (13%) died after delivery and 9 (20%) suffered IUFD.

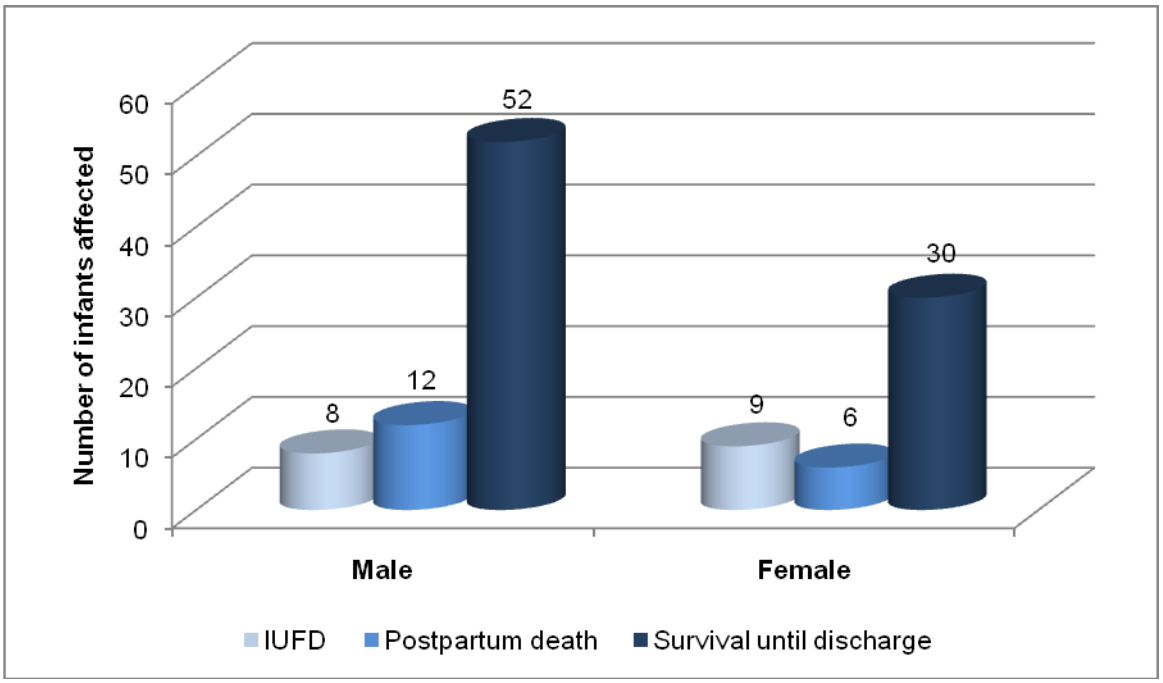

Figure 6: Infant mortality dependent on gender

The mean birth weight of the 117 fetuses was 968g, 627g of the infants who died in utero, 773g of the infants who died postnatally, and 1081g of the infants that survived until discharge from hospital. The highest birth weight of the surviving infants was 2362g and the lowest birth weight was 471g.

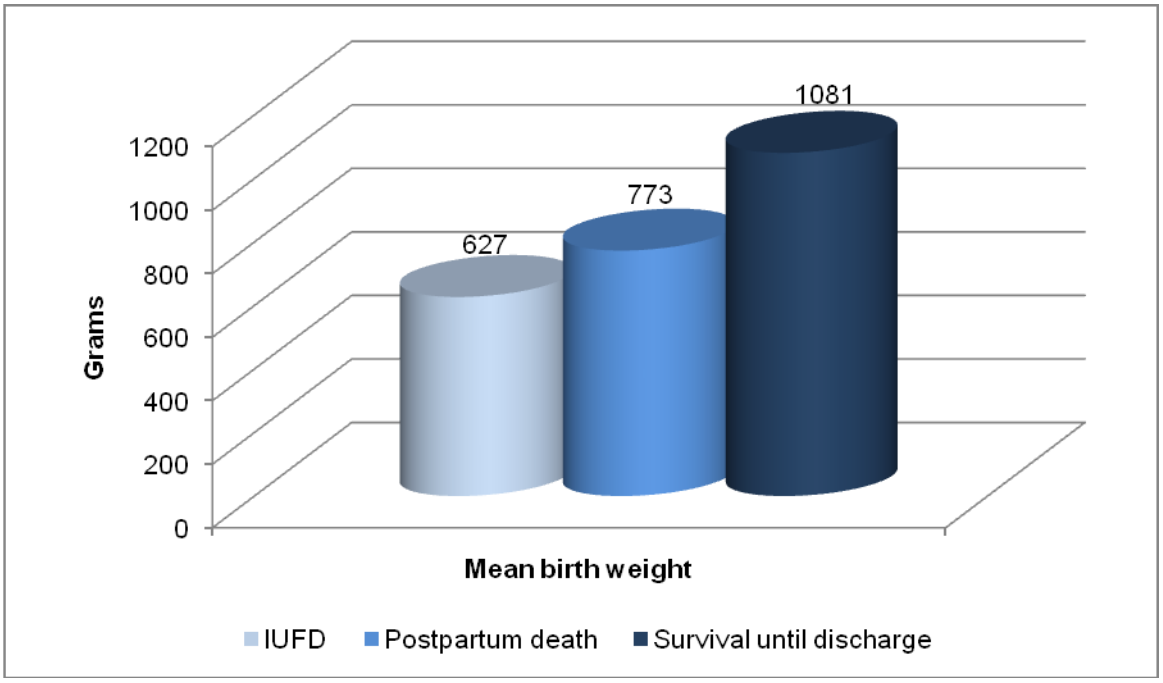

Figure 7: Infant mortality dependent on birth weight

The latency period between pPROM and delivery lasts from 0 days to 69 days (mean 13 days). 76% of the 117 infants were delivered between 0-20 days, 21% at 0 days, 18% at 1-2 days, 23% at 3-10 days, and 14% at 11-20 days.

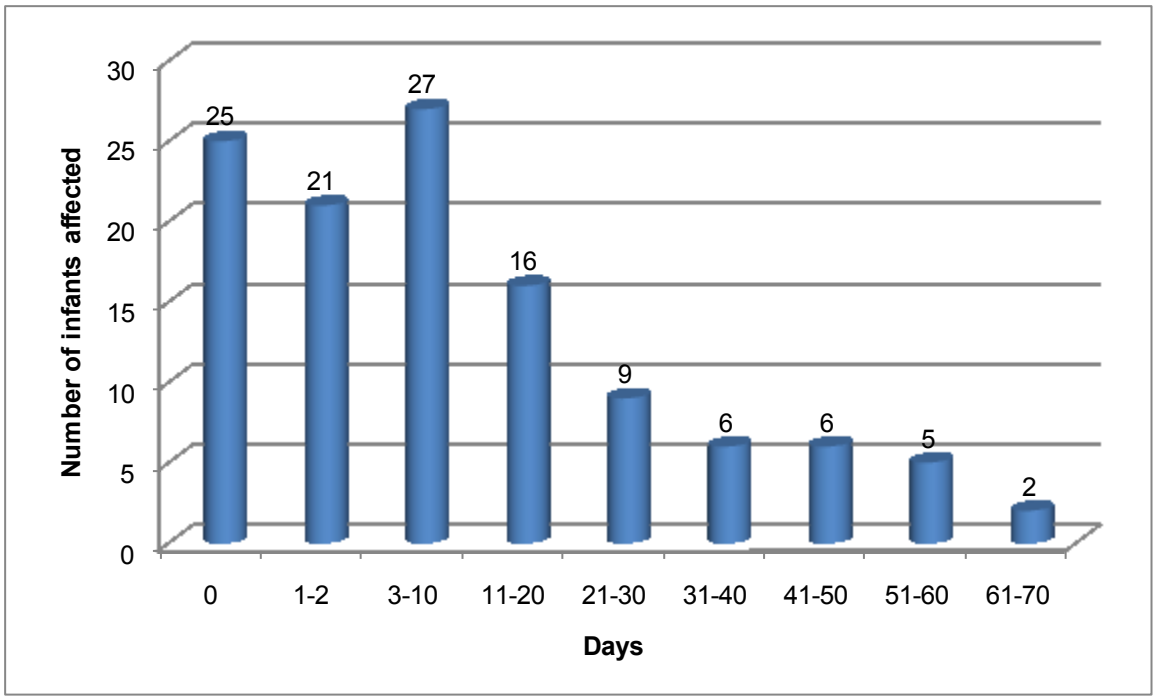

Figure 8: Latency between pPROM and delivery

GA at pPROM ranged from 18^{+2} to 27^{+6} weeks. There were 41 cases with pPROM $<24^{+0}$ weeks from which 41% were born alive and discharged from hospital, 32% died postpartally and 27% died in utero. At the GA of 24^{+0} to 25^{+6} weeks there were 38 cases with pPROM. 76% of these were live births, 13% died after delivery and in 11% intrauterine fetal death occurred. In the group of $26+^{0}$ to $27+^{6}$ weeks, there were 38 cases of pPROM from which 95% were born alive and only 5% died in utero.

GA at pPROM		**IUFD**	**Postpartum death**	**Survival until discharge**
$<24^{+0}$	n=41	11	13	17
24^{+} to 25^{+6}	n=38	4	5	29
26^{+0} to 27^{+6}	n=38	2	0	36

Table 1: Survival rates of 117 fetuses by gestational age at pPROM

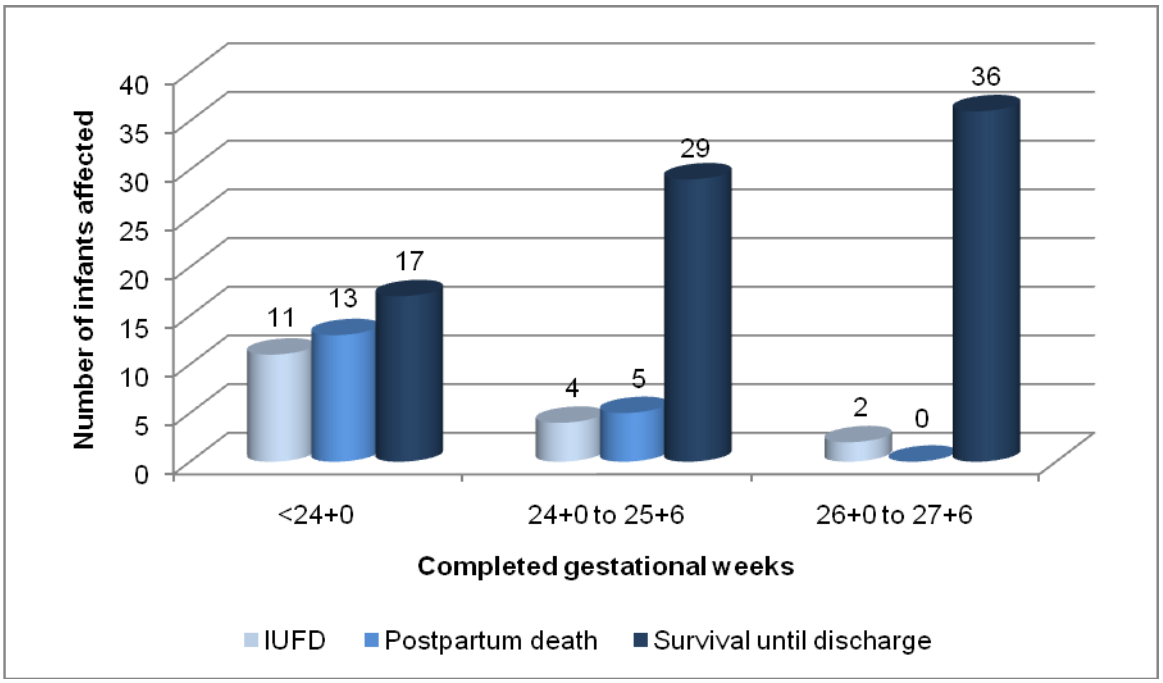

Figure 9: Infant mortality dependent on gestational age at pPROM

GA at delivery varied from 23^{+1} to 33^{+6} weeks. There were 15 deliveries $<24^{+0}$ weeks from which 13 % were born alive and discharged from hospital, 20 % died postpartally and 67% died in utero. At the age of 24^{+0} to 25^{+6} there were a total of 35 deliveries of which 60%, were live births, 26%, died after delivery and there were 14% of intrauterine fetal deaths. At the GA of 26^{+0} to 27^{+6} completed weeks there was a total of 42 deliveries, from which 81%,of the infants were born alive, 14%, died postpartally and 5% died in utero. In the groups from 28^{+0} to 33^{+6} completed weeks there was a total of 25 deliveries from which 100% of the infants were born alive.

GA at delivery		**IUFD**	**Postpartum death**	**Survival until discharge**
$<24^{+0}$	n=15	10	3	2
24^{+0} to $25^{+}+^{6}$	n=35	5	9	21
26^{+0} to 27^{+6}	n=42	2	6	34
28^{+0} to 29^{+6}	n=13	0	0	13
30^{+0} to 31^{+6}	n=10	0	0	10
$32+^{0}$ to 33^{+6}	n=2	0	0	2

Table 2: Survival rates of 117 fetuses by gestational age at delivery

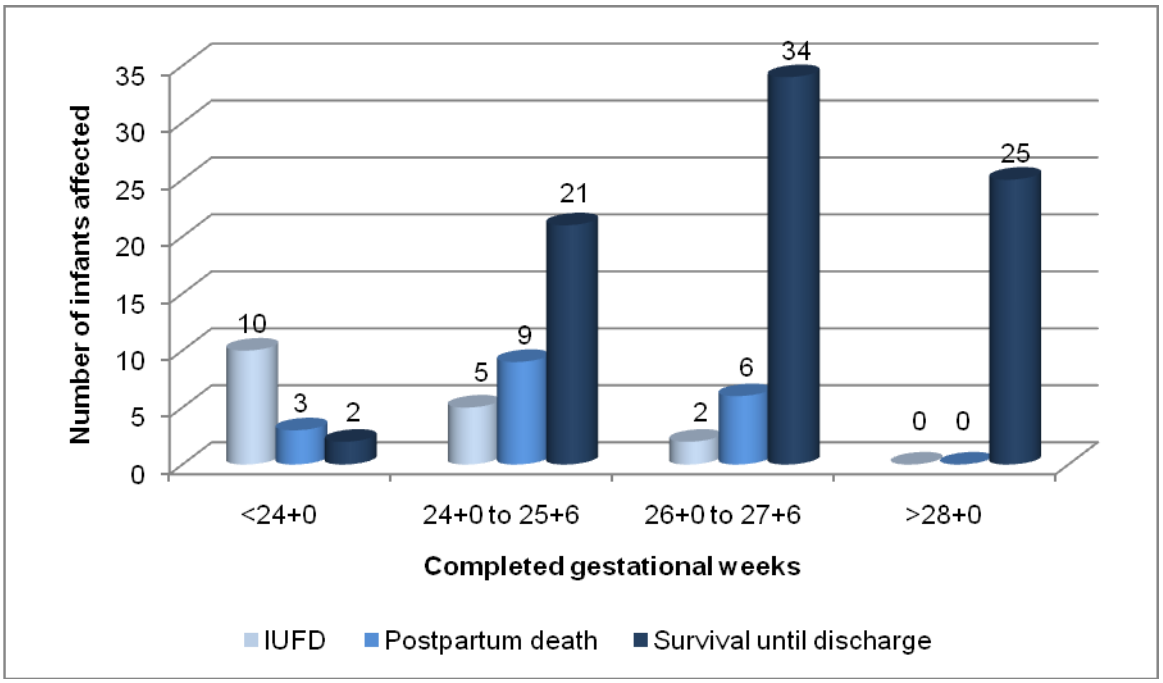

Figure 10: Infant mortality dependent on gestational age at delivery

In table 3 one can see general obstetric measures and information regarding the infants that could be discharged from hospital in relation to their GA at delivery.

	Weeks								
	23 n=2	**24 n=11**	**25 n=10**	**26 n=12**	**27 n=22**	**28 n=7**	**29 n=6**	**30 n=7**	**31-33 n=5**
Gender (m)	1/2	6/11	6/10	8/12	15/22	2/7	4/6	6/7	5/5
Multiple pregnancy	0/2	2/11	1/10	0/12	2/22	2/7	0/6	0/7	0/5
Delivery mode (sectio)	2/2	9/11	7/10	11/12	19/22	5/7	6/6	6/7	2/5
Median birth weight (g)	600	714	921	912	1021	1204	1530	1440	1866
Antibiotic administration	2/2	11/11	10/10	12/12	21/22	6/7	4/6	7/7	5/5
Tocolytic administration	2/2	10/11	8/10	10/12	19/22	6/7	1/6	6/7	4/5
Corticosteroid administration	2/2	11/11	7/10	11/12	18/22	7/7	5/6	7/7	3/3

Table 3: Obstetric measures and general information of surviving infants regarding their GA; 23, 24, 25, etc. = completed gestational weeks; n=number of infants

GA at the time of pPROM of 18 infants that died postpartally, varied from 18^{+5} to 25^{+5} weeks. The time between pPROM and delivery lasts from 0 to 53 days. The age of the infants at their death varies from 0-31 days.

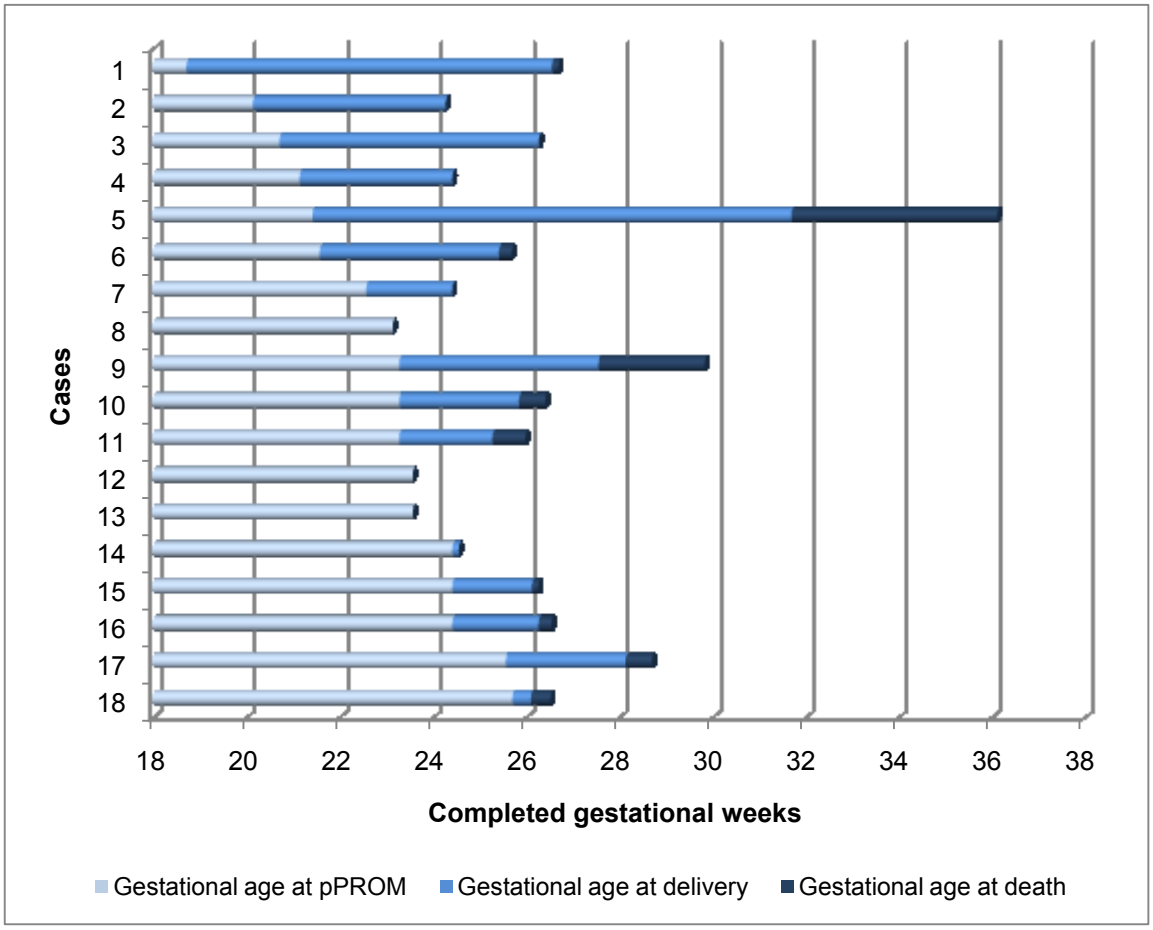

Figure 11: Gestational age at pPROM, delivery, and death of the infants that died postpartally

Of 92 women who gave birth to live infants, 85 (92%) received prenatal antibiotic treatment, 3 (3%) did not and in 4 (5%) cases there was no data available. 74 (80%) of these 92 women also received prenatal tocolytic treatment, 17 (19%) did not and in one case (1%) it was not recorded if tocolyisis was administered or not. A total of 81 (88%) out of 92 women received corticosteroids (for the maturation induction of the fetal lungs), 4 (5%) did not and in 7 (7%) cases it is not documented. 73 (68%) of 107 included women were delivered by caesarean section while 34 (32%) were delivered vaginally. Of 82 infants surviving until discharge from hospital, 67 (82%) were delivered by caesarean and 15 (18%) spontaneously, compared to a total of 18 who died in hospital, from whom 10 (56%) were delivered by caesarean section and only 8 (44%) spontaneously.

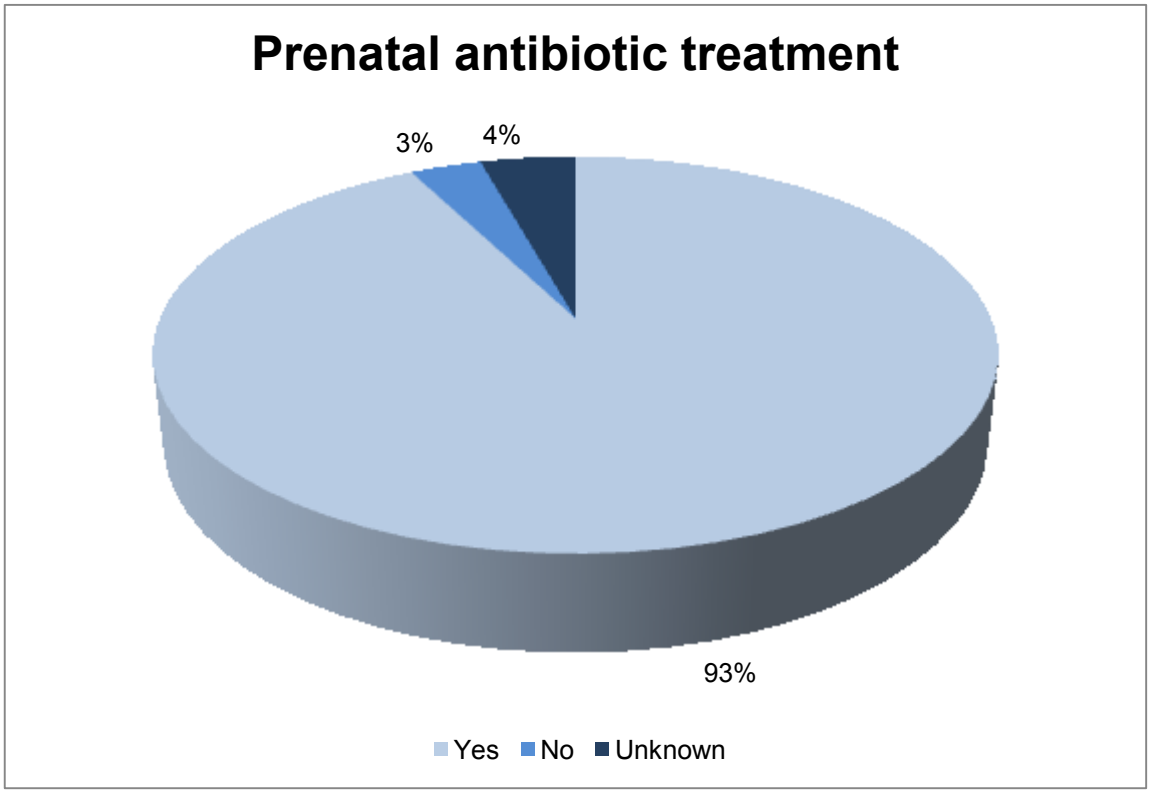

Figure 12: Prenatal antibiotic treatment

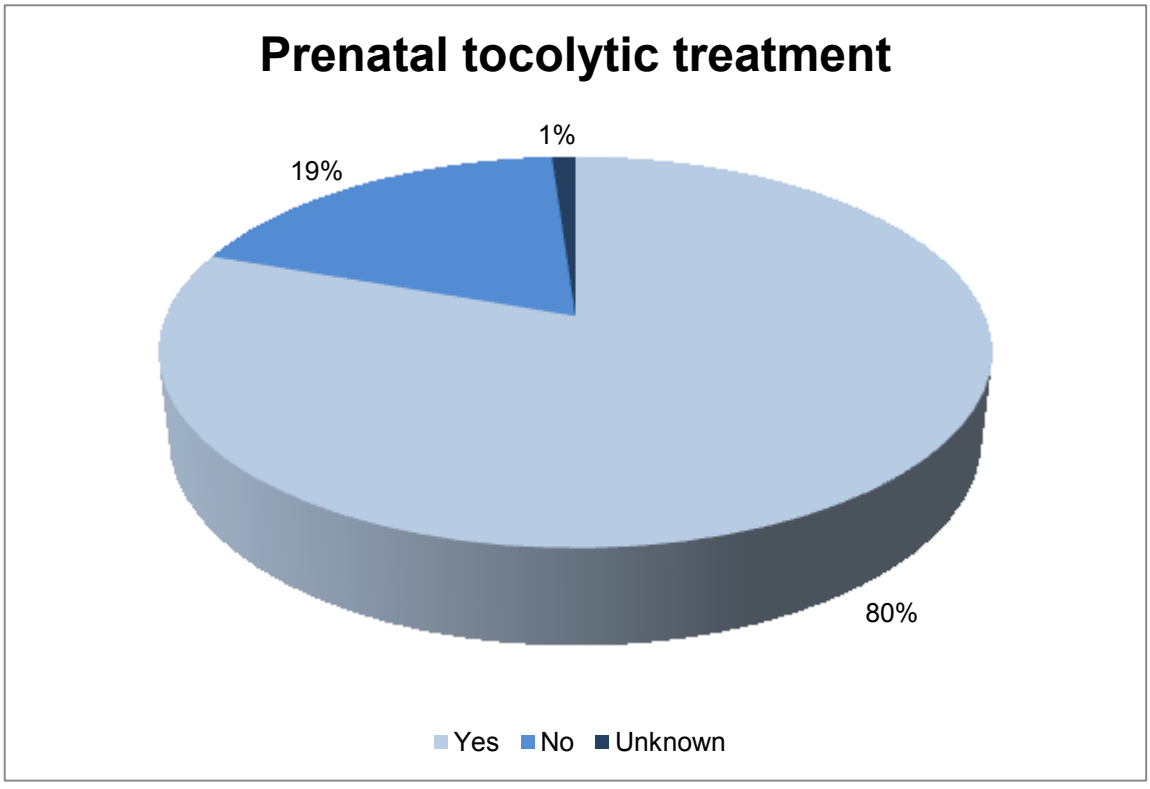

Figure 13: Prenatal tocolytic treatment

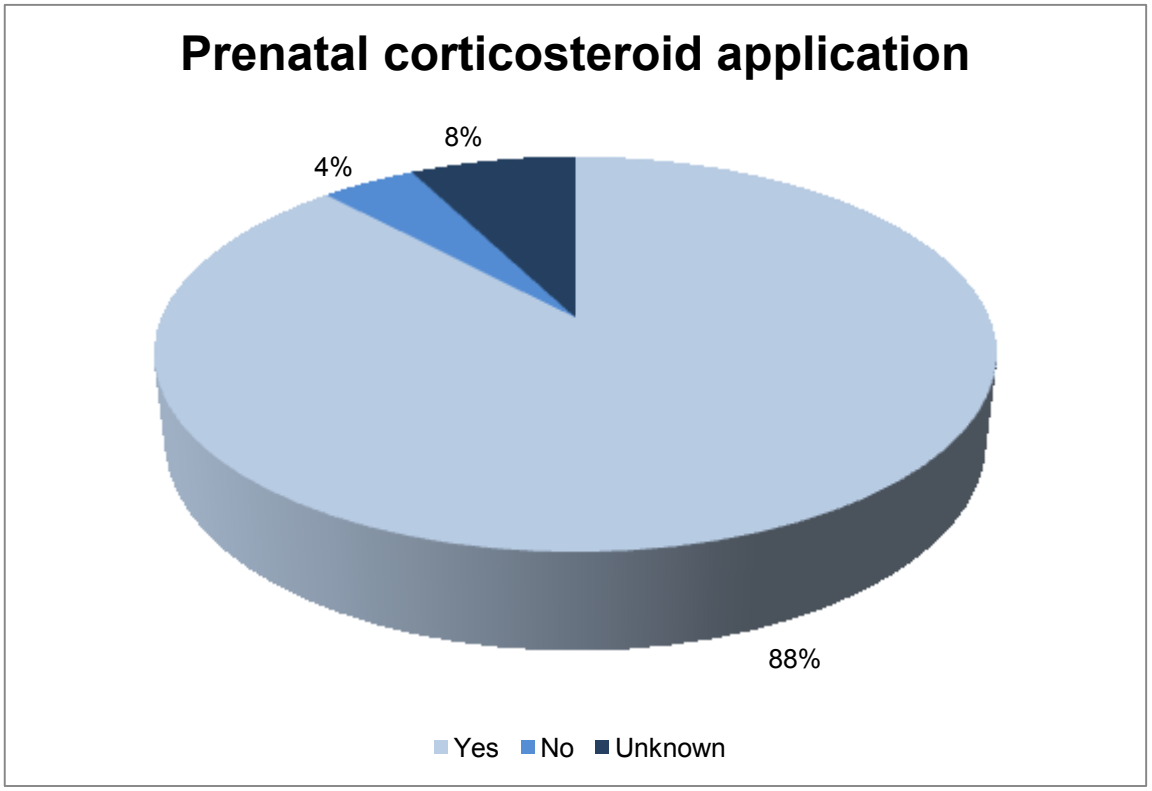

Figure 14: Prenatal corticosteroid application

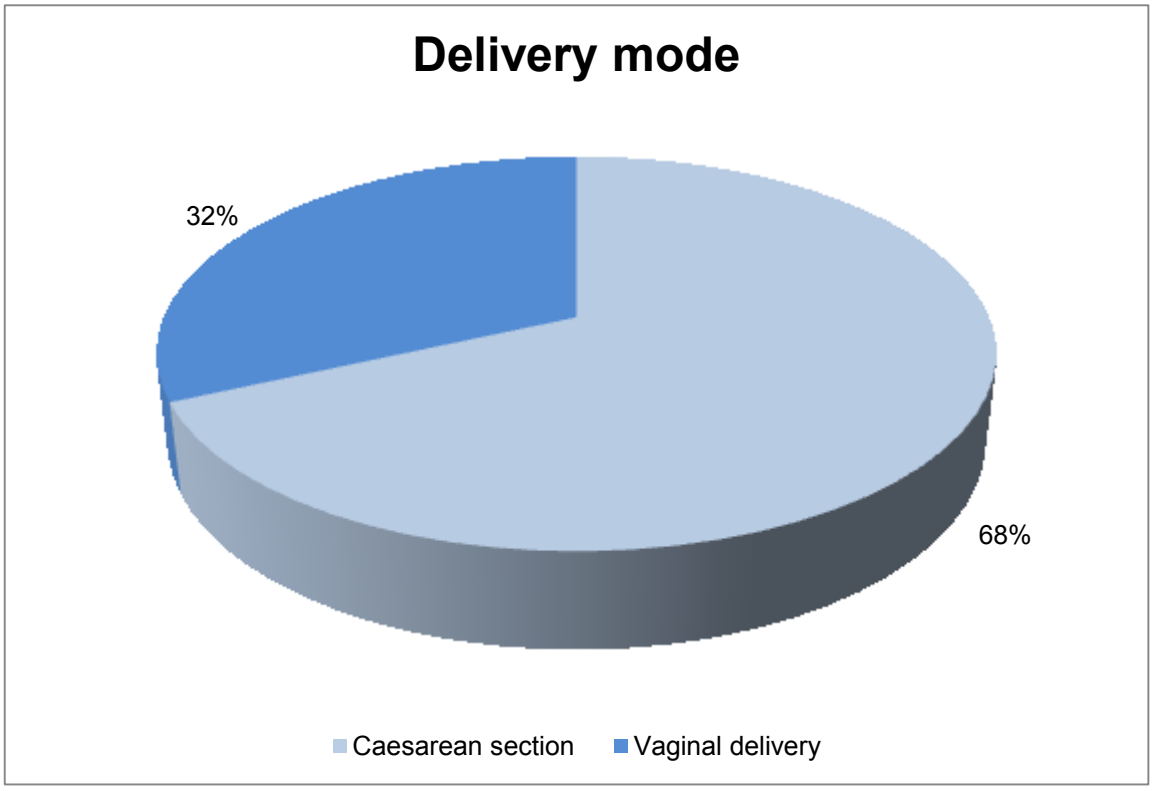

Figure 15: Delivery mode

3.2 Complications of the respiratory system

The infants suffered from several complications regarding the different organ systems as: respiratory-, circulatory-, gastro-intestinal-, and nervous-system.
The major complications regarding the respiratory system are listed in figure 10.

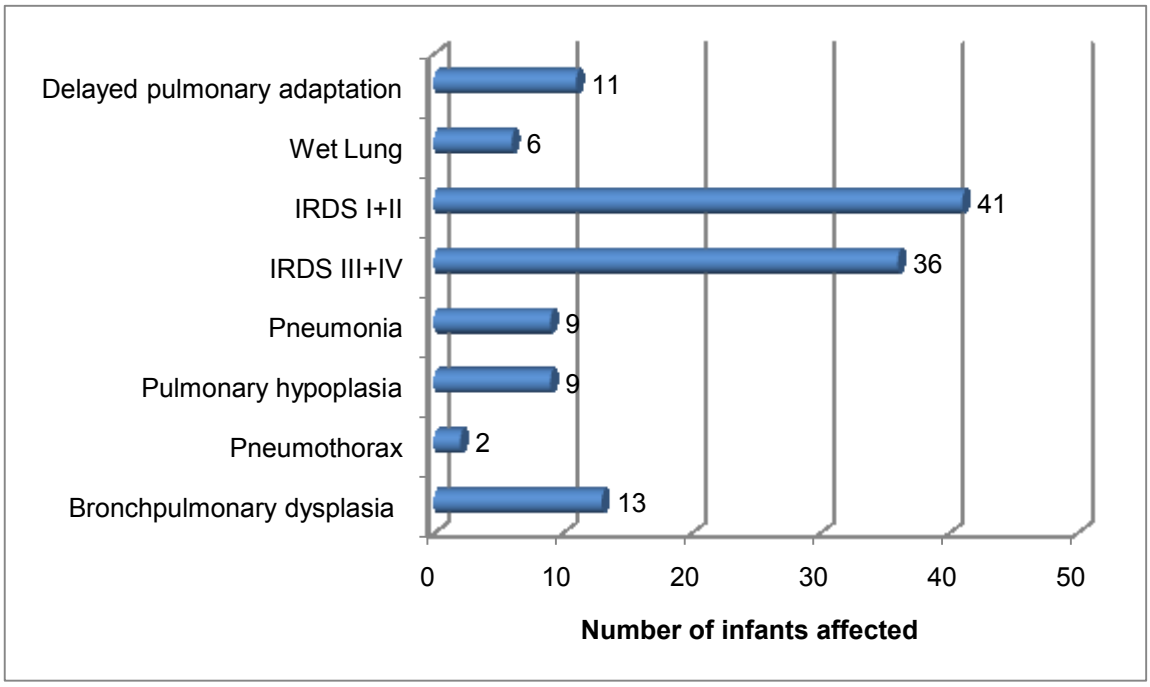

Figure 16: Respiratory complications

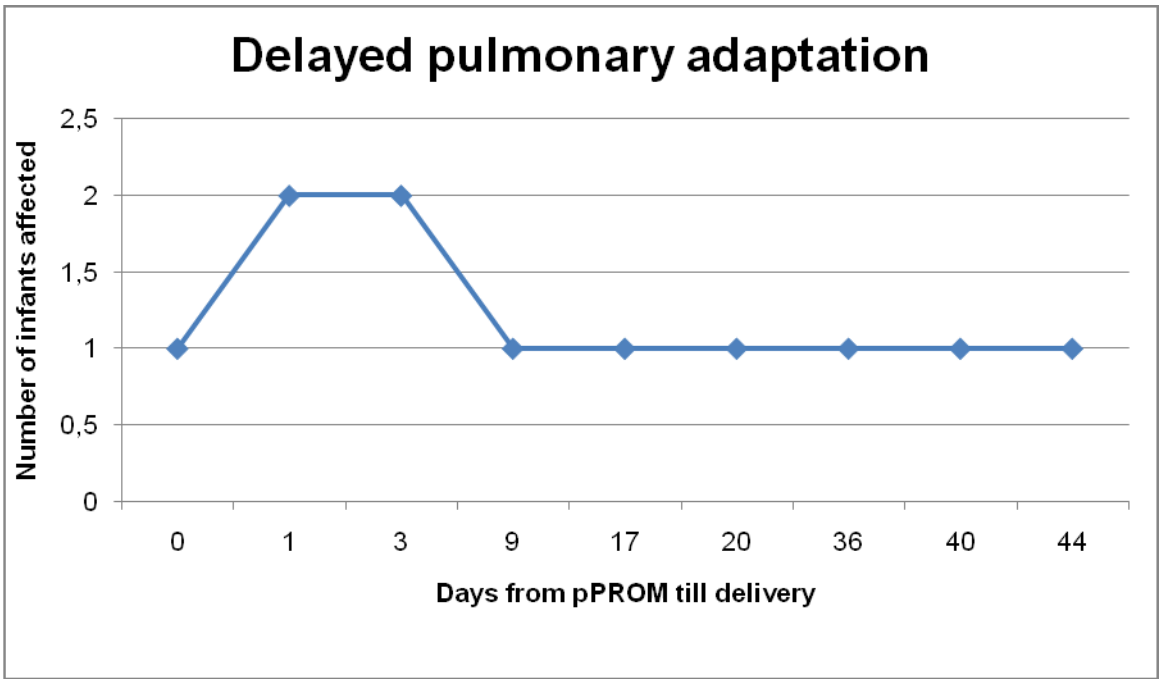

Figure 17: Latency period between pPROM and delivery, and distribution of delayed pulmonary adaptation during this period of time

11 (11%) of the 100 live born infants suffered from a delayed lung adaptation, but all of them survived. The mean latency period between pPROM and delivery was 16 days (range: 0-44 days). Mean GA at pPROM and delivery was 26^{+4} (range: 24^{+2} to 27^{+5} weeks) and 28^{+4} weeks (range: 25^{+4} to 32^{+1} weeks), respectively. 55% of the infants who developed this complication, were delivered within 9 days after pPROM.

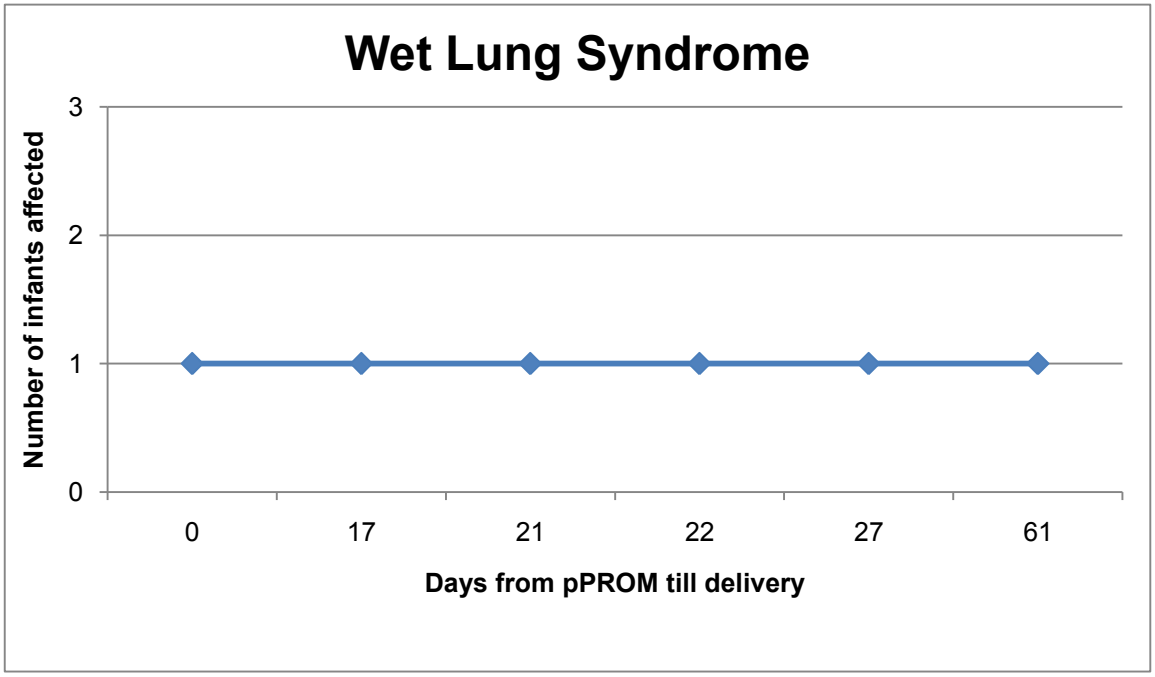

Figure 18: Latency period between pPROM and deliver, and distribution of wet lung syndrome during this period of time

All 6 of 100 live born infants developing a wet lung syndrome survived until discharge from hospital. The mean latency between pPROM and delivery was 25 days (range: 0-61 days). Mean GA at pPROM and at delivery in this subgroup was 26^{+4} (range: 22^{+6} to 27^{+3} weeks) and 29^{+3} weeks (range: 25^{+6} to 29^{+4} weeks), respectively. Only 1 infant was delivered within a latency period less than 11 days between pPROM and birth. 83% of the infants were given birth between 17 and 61 days latency from pPROM till delivery.

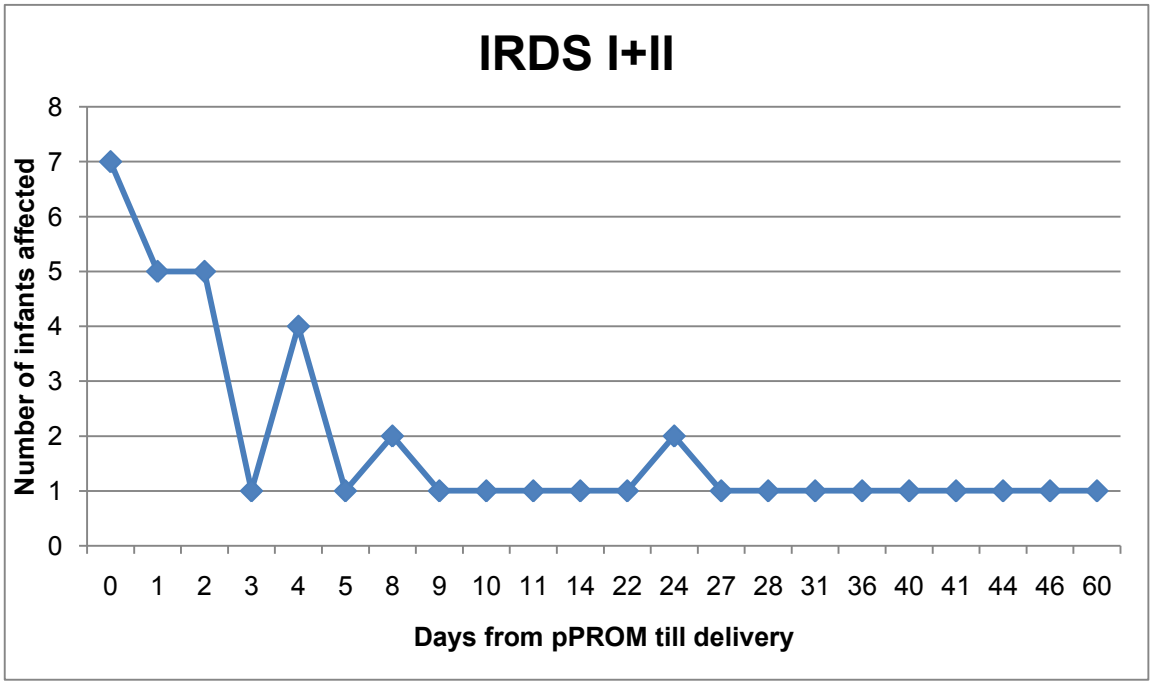

Figure 19: Latency period between pPROM and delivery, and distribution of IRDS I/II during this period of time

41 (41%) of 100 live born infants suffered from IRDS I+II. While 5 of the affected infants died postnatally, 37 survived until discharge from hospital. 4 of the infants died within the first 4 days after delivery and one after 31 days. The mean latency period between pPROM and delivery in these newborns was 14 days (range: 0-60 days). Mean GA at pPROM and delivery was 25^{+4} (range: 18^{+2} to 27^{+6} weeks) and 27^{+3} weeks (range: 24^{+2} to 32^{+1} weeks), respectively. From 41 infants who suffered from IRDS I+II, 68% have been delivered within 11 days after pPROM. Of 17 infants who were delivered within 2 days after pPROM, 2 did not receive lung maturation and in 3 cases this was not documented. In 4 infants the lung maturation was not be completed. One of the infants who did not receive corticosteroids, died postnatally.

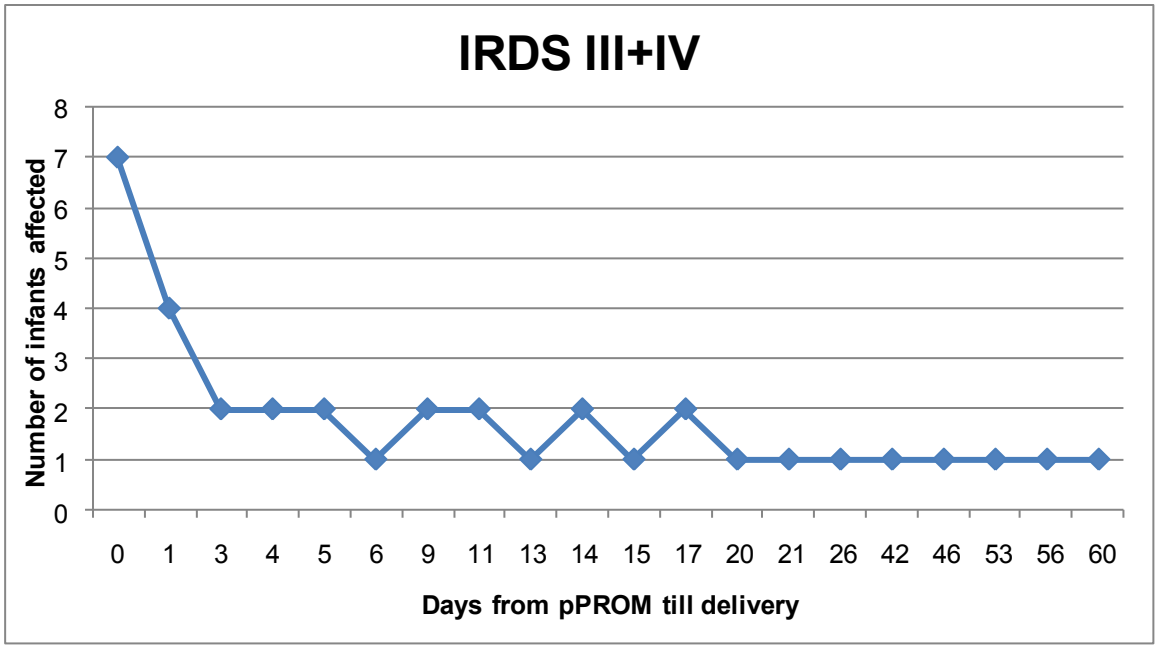

Figure 20: Latency period between pPROM and delivery, and distribution of IRDS III/IV during this period of time

36 (36%) of the 100 live born infants developed IRDS III+IV. 9 (25%) of these died postnatally while 27 (75%) survived until discharge from hospital. Of the 9 infants who died, 8 deceased within 5 days after birth and 1 at the age of 16 days. The mean latency period between pPROM and delivery in these newborns was 14 days (range: 0-60 days). The mean GA at pPROM and delivery was 24^{+3} (range: 18^{+5} to 27^{+6} weeks) and 26^{+3} weeks (range: 23^{+1} to 30^{+6} weeks), respectively. From 36 infants who suffered from IRDS III+IV, 61% have been delivered within 11 days after pPROM. Out of 11 infants who were delivered within 1 day after pPROM, all children received corticosteroids for lung maturation, but in 4 cases this could only be applied once before the delivery of the infants. 2 of the 4 infants who did not receive a complete lung maturation induction, died postnatally.

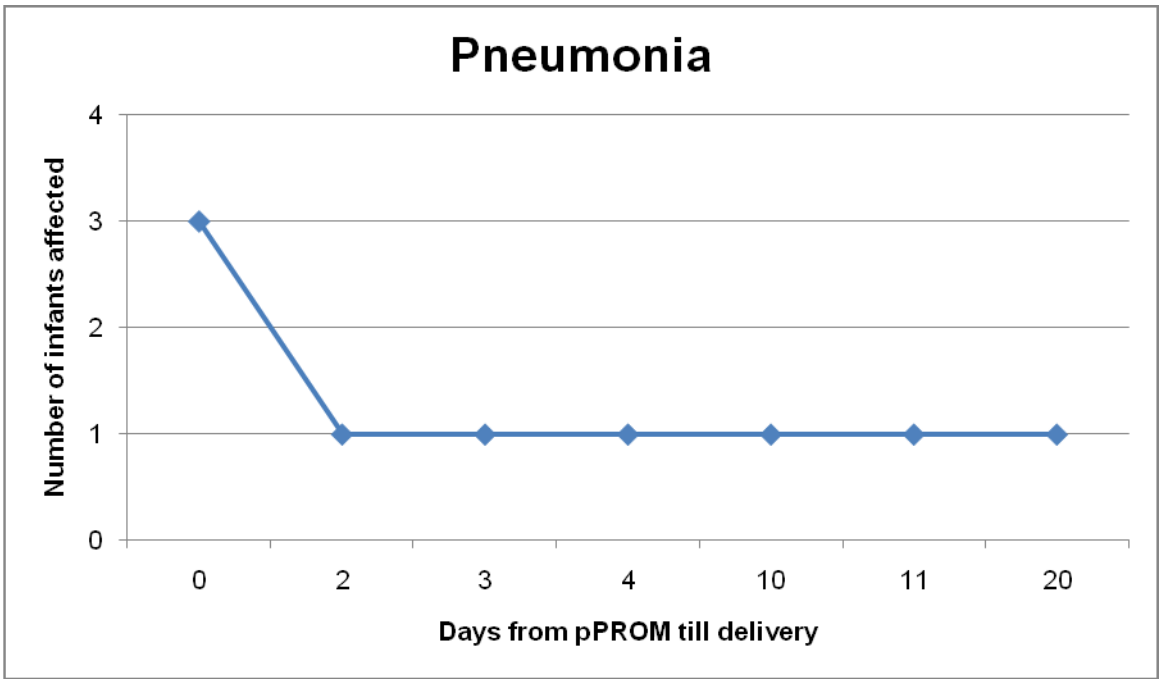

Figure 21: Latency period between pPROM and delivery, and distribution of penumonia during this period of time

9 (9%) of 100 live born infants developed pneumonia and all could subsequently be discharged from hospital. The mean latency period between pPROM and delivery was 6 days (range: 0-20 days). Mean GA at pPROM and delivery was 24^{+3} (range: 23^{+1} to 25^{+6} weeks) and 25^{+3} weeks (range: 24^{+0} to 28^{+3} weeks), respectively. 89% of the infants developed this ailment within 11 days after pPROM.

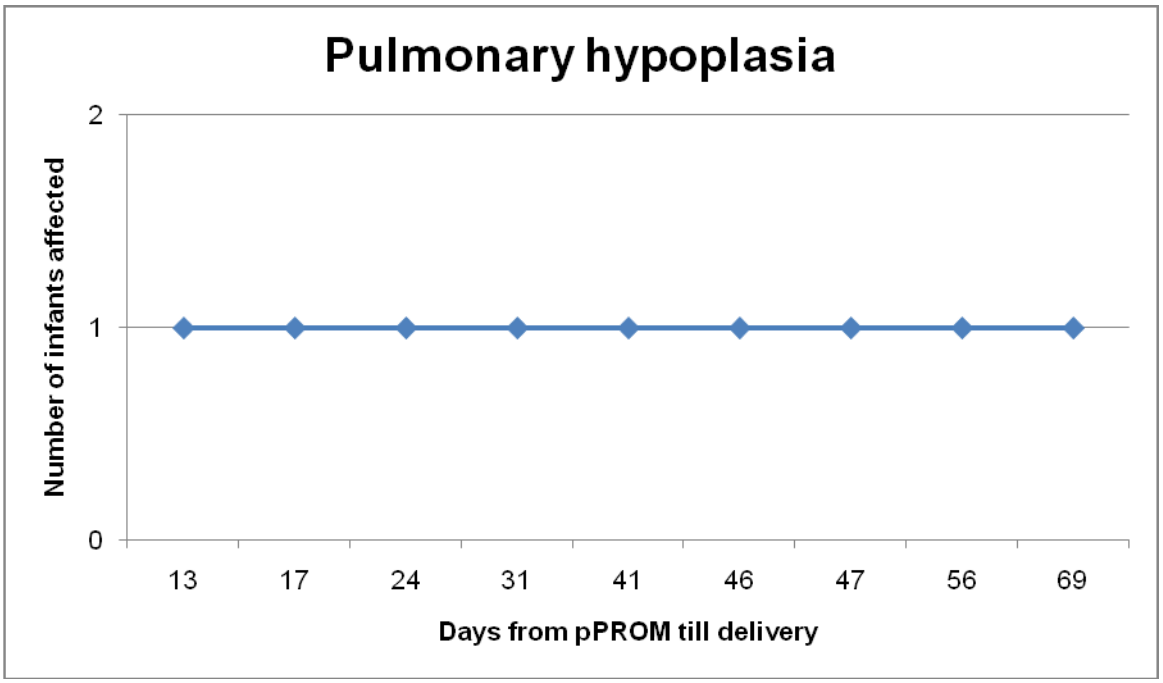

Figure 22: Latency period between pPROM and delivery, and distribution of pulmonary hypoplasia during this period of time

9 (9%) of 100 live born infants developed pulmonary hypoplasia. 5 of these could subsequently be discharged from hospital while 4 died. 3 of the latter infants died within 2 days after delivery and one at the age of 31 days. The mean latency from pPROM till delivery was 38 days (range: 13-69 days). The mean GA of the fetuses at pPROM and delivery was 21^{+3} (range: 19^{+2} to 23^{+6} weeks) and 27^{+2} weeks (range: 24^{+2} to 31^{+3} weeks), respectively. None of the infants was delivered before 13 days latency period between pPROM and birth.

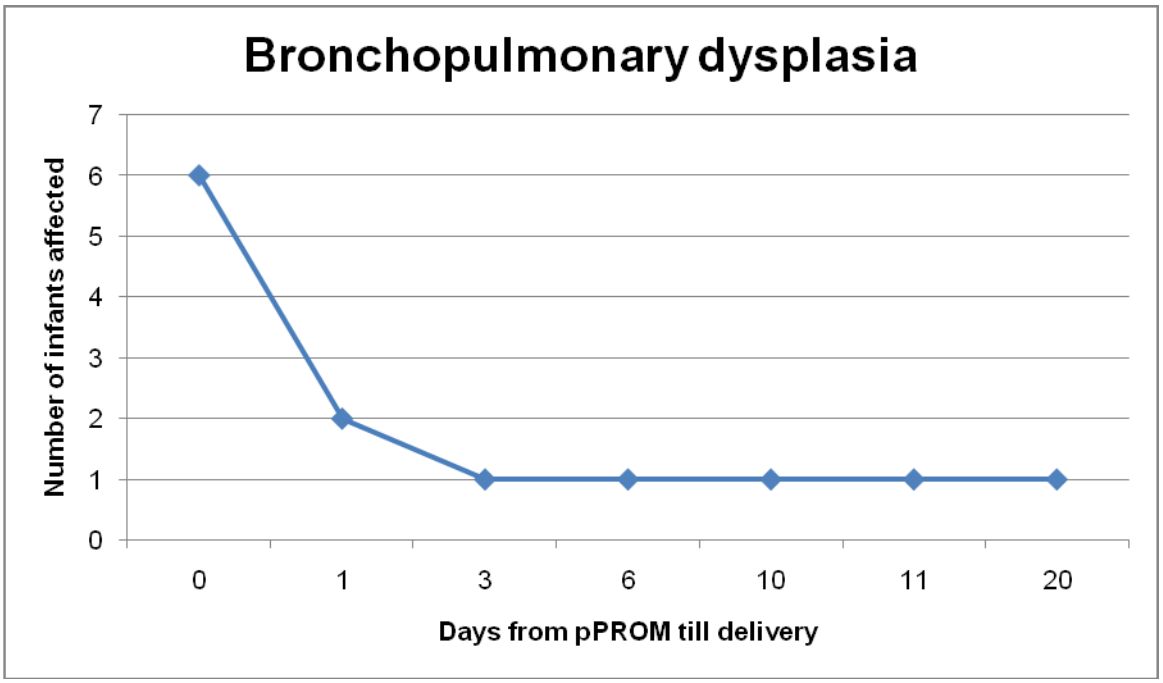

Figure 23: Latency period between pPROM and delivery, and distribution of BPD during this period of time

As a consequence of the diagnoses mentioned above, the infants developed further complications. 2 (2%) infants were affected by pneumothorax and one of these died 31 days postnatally. The GA of the infant that died was 21^{+3} weeks at pPROM and 27^{+2} weeks at delivery. The latency between pPROM and delivery was 41 days. The initial diagnoses of this infant concerning the respiratory system were the development of a pulmonary hypoplasia and an IRDS I/II.

The GA of the infant that was discharged from hospital was 24^{+4} weeks at pPROM and 26^{+5} weeks at delivery. The latency period between pPROM and birth was 15 days. The diagnosis regarding the respiratory system that the infant evolved initially was an IRDS III/IV.

13(13%) of 100 live born infants developed BPD. All of the infants could be discharged from hospital. Mean GA at pPROM and delivery was 24^{+3} (range: 23^{+1} to 27^{+6} weeks) and 25^{+2} weeks (range: 24^{+0} to 28^{+3} weeks), respectively. The mean latency between pPROM and birth was 4 days (range: 0-20 days). 92% of the infants that evolved this malady were born within a latency of 11 days from pPROM till birth. The respiratory conditions that the infants who developed a BPD suffered from primarily were IRDS I/II, IRDS III/IV and pneumonia. The distribution of the particular diagnoses reads as follows: 2 infants developed IRDS I/II, 2 IRDS

I/II+ pneumonia, 5 IRDS III/IV, 2 IRDS III/IV+ pneumonia, and 2 infants suffered from pneumonia without IRDS I-IV.

3.3 Complications of the cardiovascular system

In figure 15 one can see some of the complications concerning the circulatory system, that infants that were born alive, suffered from.

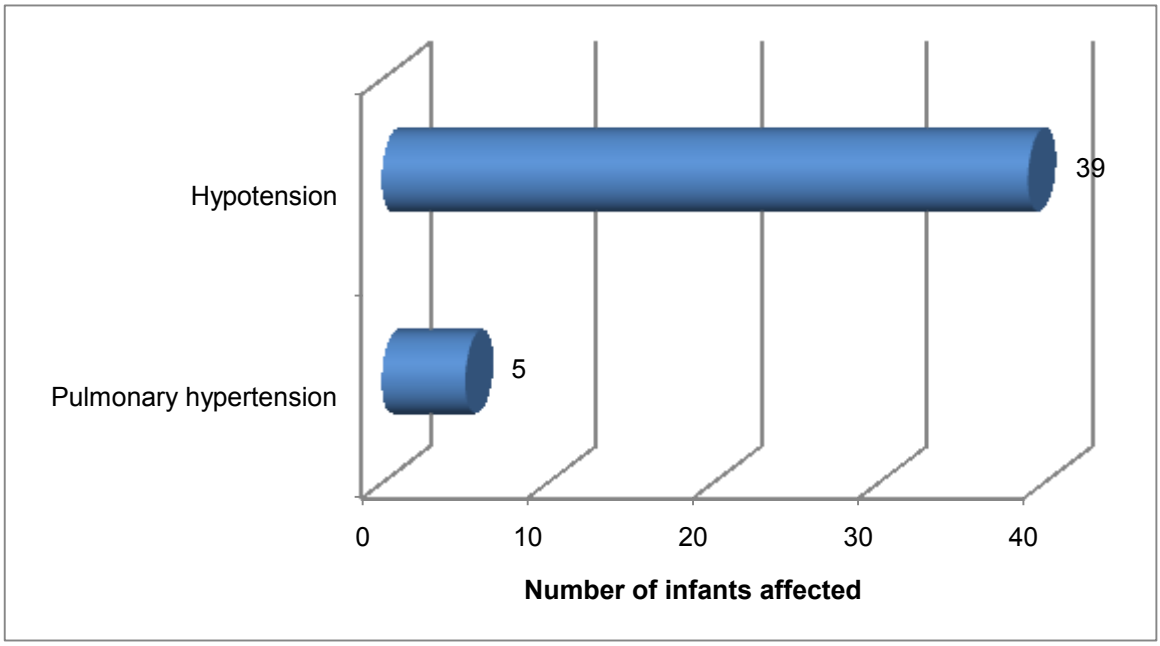

Figure 24: Cardiovascular complications

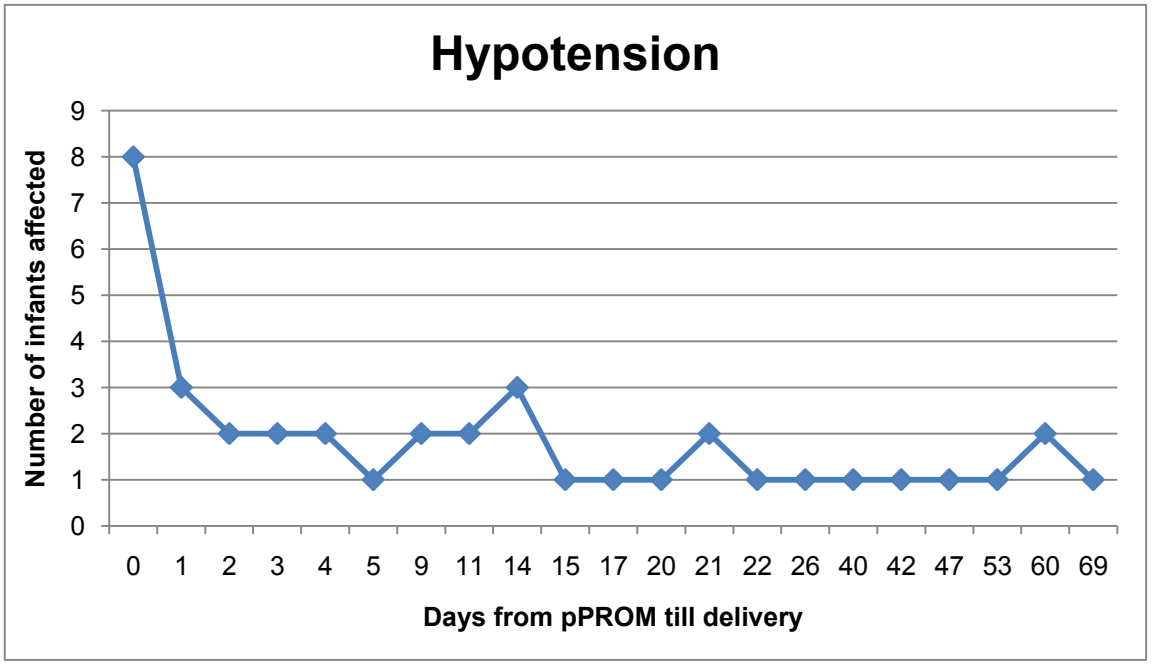

Figure 25: Latency period between pPROM and delivery, and distribution of hypotension during this period of time

39 (39%) of 100 live born infants developed hypotension. 31 of these could subsequently be discharged from hospital while 8 died postnatally. 5 of the latter died within the first 5 days of their life and one at the age of 16 days. 59% were delivered within 11 days after pPROM. The median latency between pPROM and delivery was 16 days (range: 0-69 days). Mean GA at pPROM and delivery was 24^{+4} (range: 18^{+2} to 27^{+6} weeks) and 26^{+3} weeks (range: 23^{+2} to 31^{+3} weeks), respectively. 1 of these 39 infants also developed a delayed pulmonary adaptation, 3 suffered from pulmonary hypoplasia, 2 from wet lung syndrome, 13 from IRDS I+II, 23 from IRDS III+IV, and 5 neonates developed pneumonia. As a long-term complication 7 infants evolved BPD.

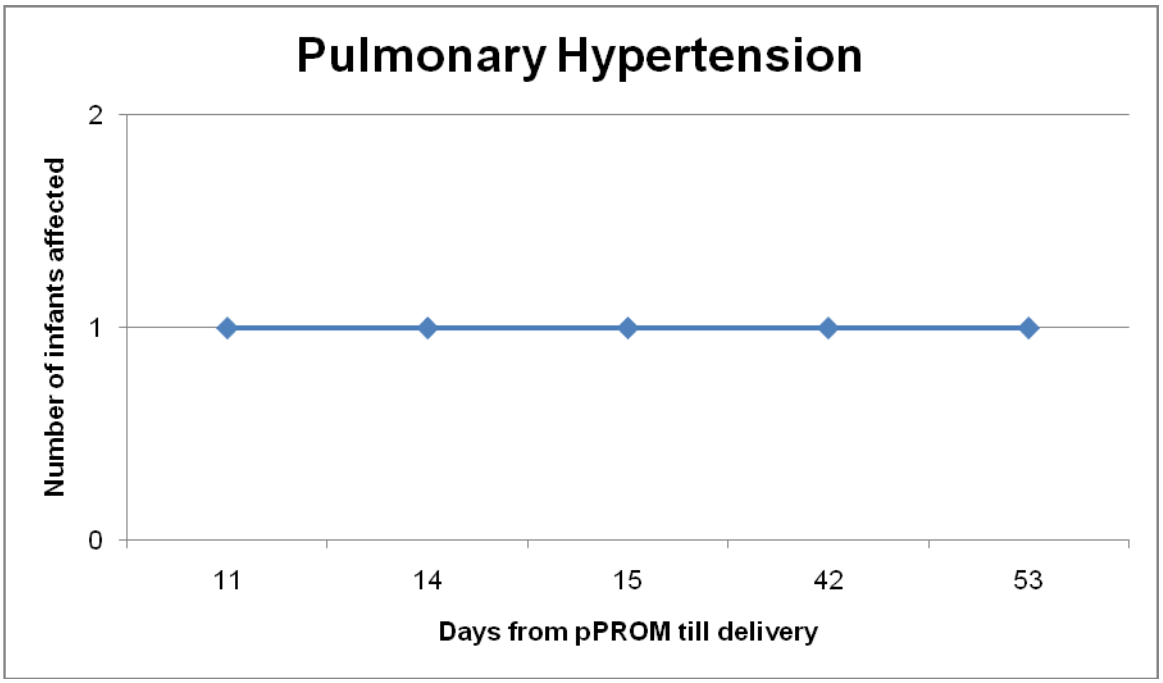

Figure 26: Latency period between pPROM and delivery, and distribution of pulmonary hypertension during this period of time

5 (5%) of the 100 live born infants developed pulmonary hypertension. While 3 infants died, 2 could subsequently be discharged from hospital. All 3 infants died within the first 4 days of their lives (2 at the age of one day and 1 at the age of four days). Mean GA at pPROM and delivery was 22^{+4} (range: 18^{+5} to 25^{+4} weeks) and 26^{+3} weeks (range: 26^{+0} to 27^{+4} weeks), respectively. The mean latency period between pPROM and birth was 27 days (range: 11-53 days). 80% of the infants were born after 11 days latency between pPROM and delivery. Additionally all 5 infants suffered from hypotension. 1 infant evolved IRDS I+II, 4 IRDS III+IV, 1 IVH I, 3 IVH II/III+ PVH, 1 ventricular dilatation/megaly, 2 seizures, 1 microcephalus, 3 meconium obstruction, 1 ileus, 3 early onset sepsis, 1 late onset sepsis and 2 infants developed ROP.

3.4 Complications of the central nervous system

The most important complications of infants born preterm, regarding the nervous system are listed in figure 21.

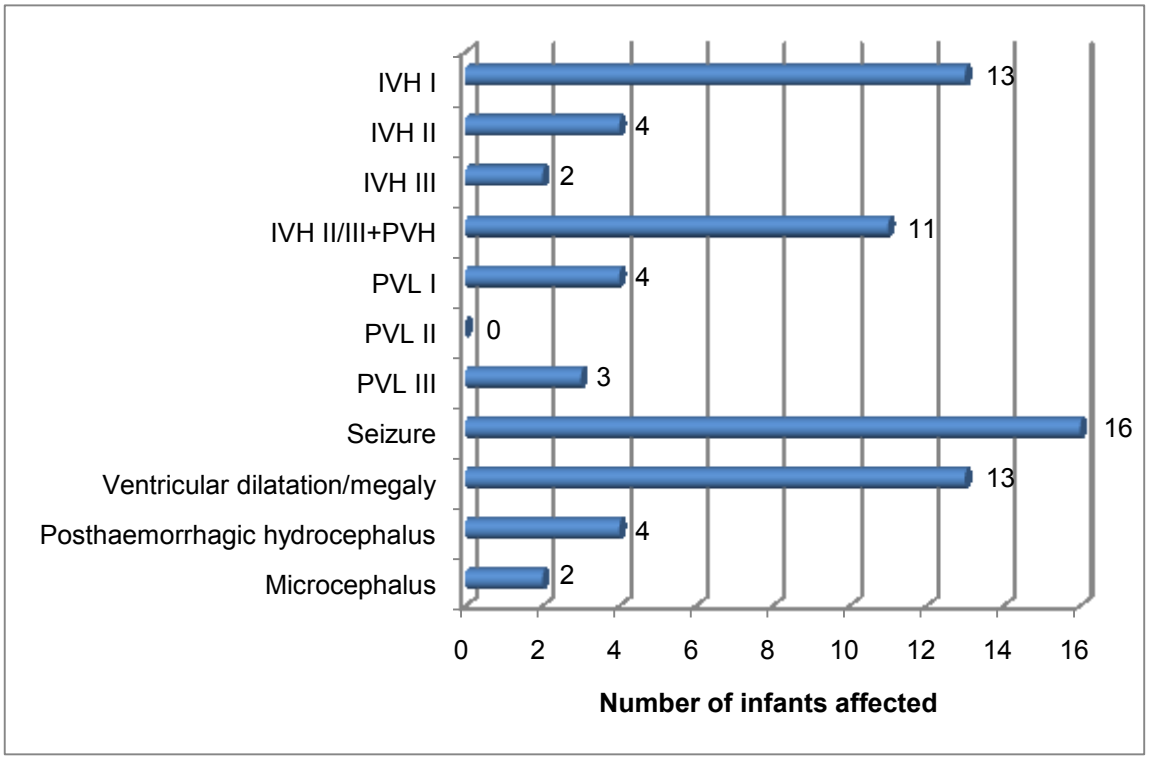

Figure 27: Cerebral complications

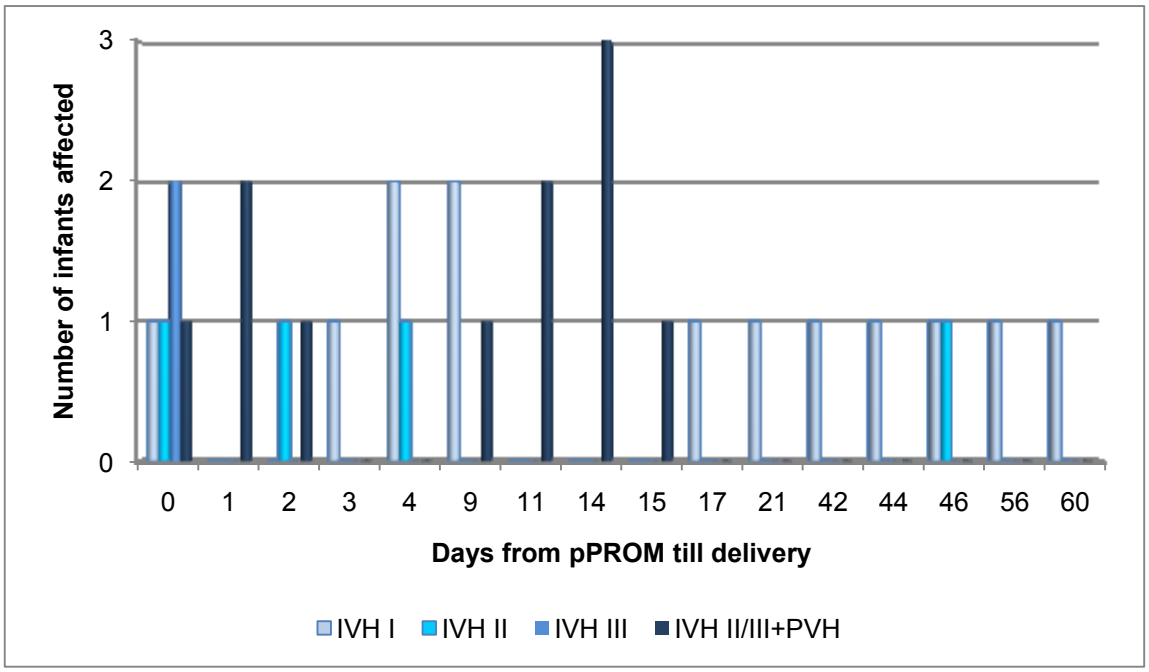

Figure 28: Latency period between pPROM and delivery, and distribution of IVH I, IVH II, IVH III, and IVH II/III+PVH during this period of time

30 (30%) of 100 live born infants developed IVH I-III+PVH within the first days of their lives.

13 infants suffered from IVH I. All could be discharged from hospital. Mean GA at pPROM and delivery was 24^{+4} (range: 20^{+3} to 27^{+6} weeks) and 28^{+3} weeks (range: 24^{+0} to 32^{+1} weeks), respectively. The mean latency between pPROM and birth was 24 days (range 0-60 days). 46% of the infants were born inside 11 days between pPROM and delivery.

4 (4%) of 100 live born infants developed IVH II. All of the infants could subsequently be discharged from hospital. The mean latency period between pPROM and delivery was 13 days (range: 0-46 days). Mean GA at pPROM and delivery was 25^{+4} (range: 21^{+6} to 27^{+4} weeks) and 27^{+3} weeks (range: 24^{+2} to 28^{+3} weeks), respectively. 75% of these were delivered within 11 days between pPROM and birth.

2 infants developed an IVH III. Both could be discharged from hospital. The latency between pPROM and delivery was 0 days in both cases. One infant was born with 25^{+1} weeks of gestation and the other one with 25^{+4} gestational weeks.

11 of 100 live born infants developed IVH II/III+PVH. While 7 of the infants died postnatally 4 could subsequently be discharged from hospital. 6 of the infants died within 5 days after birth and 1 at the age of 16 days. The mean latency period between pPROM and delivery was 8 days (range: 0-15 days). Mean GA at pPROM and delivery was 24^{+3} (range: 23^{+2} to 27^{+3} weeks) and 25^{+3} weeks (range: 24^{+1} to 27^{+5} weeks), respectively. 64% of the infants have been born within 11 days between pPROM and delivery. Additional ailments that these infants suffered from are: 2 evolved BPD, 3 pulmonary hypertension, 1 ventricular dilatation/megaly, 7 seizures, 1 posthaemorrhagic hydrocephalus, 1 ileus, 8 early onset sepsis, 2 late onset sepsis and 1 infant developed ROP.

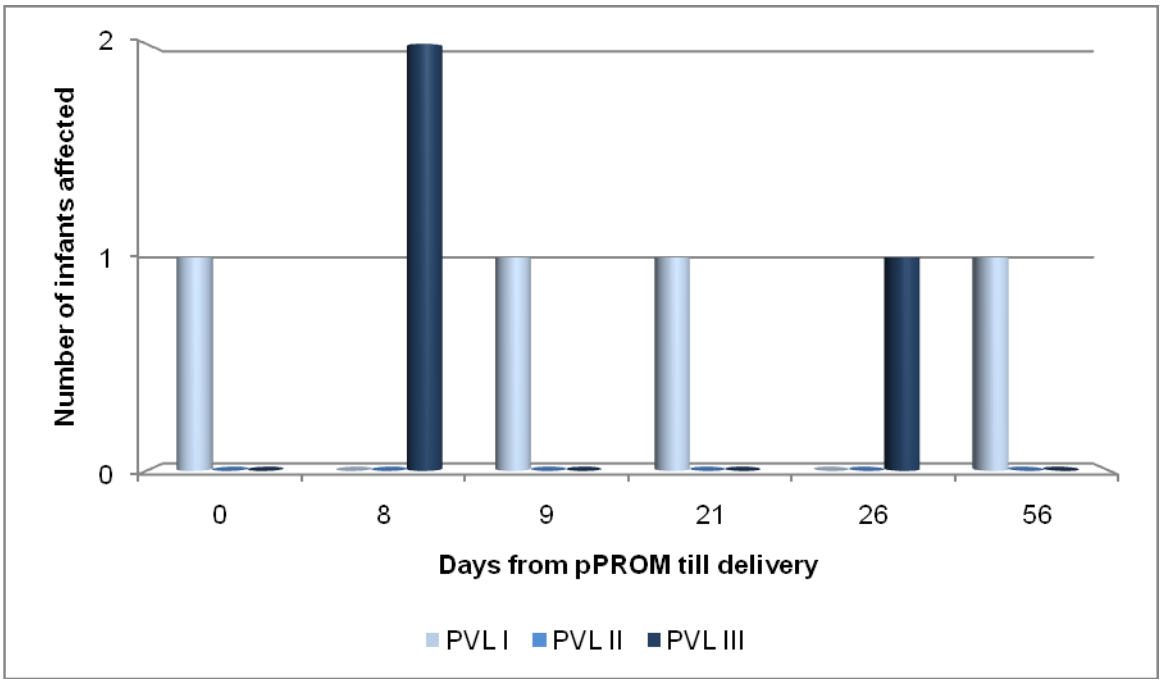

Figure 29: Latency period between pPROM and delivery, and distribution of PVL I, PVL II, and PVL III during this period of time

7 (7%) of 100 live born infants developed PVL I-III. All infants could be discharged from hospital.

4 (4%) infants evolved PVL I during the first days after their birth. Mean GA at pPROM and delivery was 24^{+2} (range: 21^{+0} to 27^{+1} weeks) and 27^{+3} weeks (range: 24^{+4} to 30^{+1} weeks), respectively. The mean latency period between pPROM and birth was 22 days (range: 0-56 days). 50% of the neonates were born within 11 days between pPROM and delivery. Further maladies that the infants developed were: 1 evolved pulmonary hypoplasia, 1 lung syndrome, 3 IRDS III/IV, 1 pneumonia, 1 BPD, 3 developed hypotension, 1 IVH I, 2 seizures, 2 ventricular dilatation/megaly, 2 meconium obstruction and 1 developed an early onset sepsis. In this study group, no infants developed PVL II.

3 (3%) of the 100 live born infants developed PVL III. The GA at pPROM was 22^{+6}, 25^{+3} and 27^{+1} weeks (mean: 25^{+3} weeks). The GA at delivery was two times 26^{+4} weeks and once 28^{+2} weeks (mean 27^{+3} weeks). The latency period between pPROM and delivery was 26 days, and twice 8 days (mean 14 days). Two of three infants were born within 11 days between pPROM and delivery. Additional diagnoses that the infants evolved are: 2 developed IRDS I/II, 1 IRDS III/IV, 1 hypotension, 1 ventricular dilatation/megaly and 1 evolved early onset sepsis.

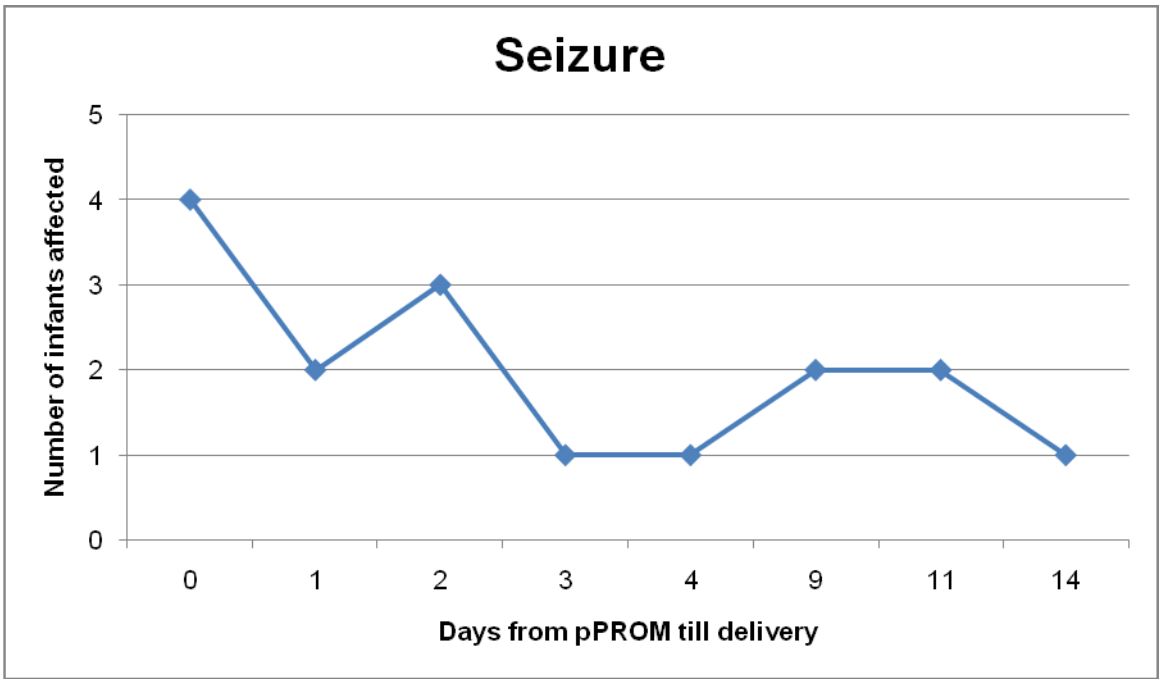

Figure 30: Latency period between pPROM and delivery, and distribution of seizures during this period of time

16 (16%) of 100 live born infants born preterm, 16 developed seizures. 11 infants survived until discharge from hospital while 5 infants died within 5 days after delivery. The mean GA at pPROM and delivery was 24^{+3} (range: 22^{+6} to 27^{+3} weeks) and 25^{+3} weeks (range: 23^{+2} to 27^{+5} weeks), respectively. The mean latency between pPROM and delivery was 4 days (range: 0-14 days). Of 16 infants born alive, 94% were delivered within 11 days between pPROM and birth.

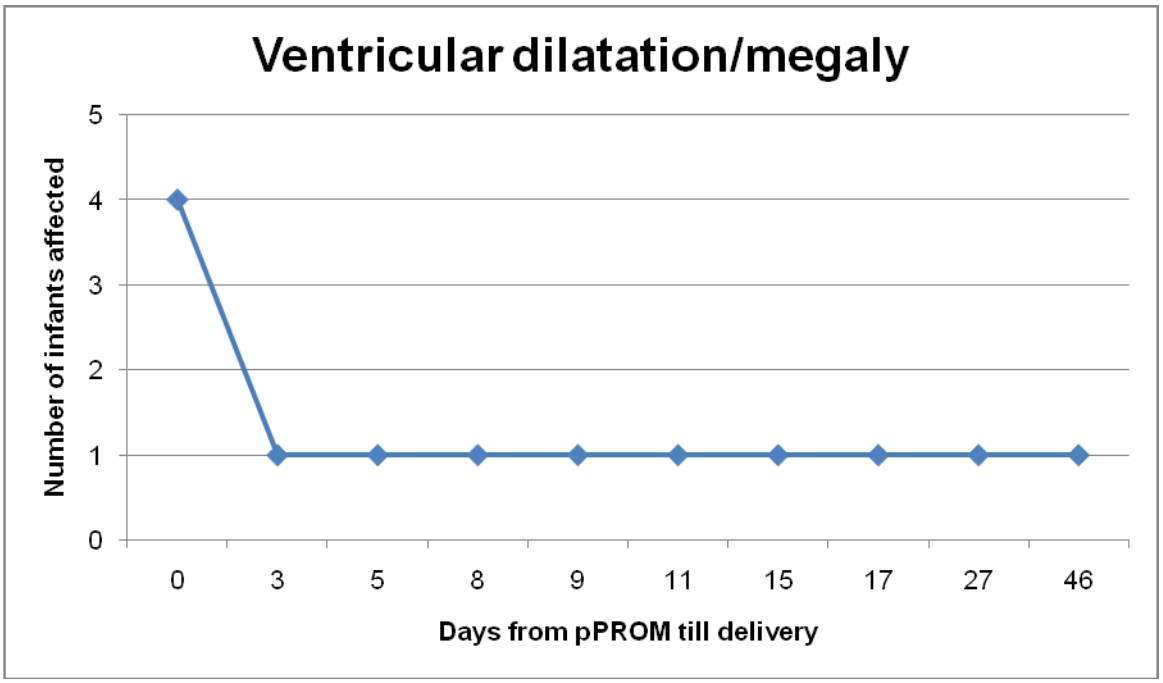

Figure 31: Latency period between pPROM and delivery, and distribution of ventricular dilatation/megaly during this period of time

13 (13%) of the 100 live born infants developed ventricular dilatation/megaly. All infants could be discharged from hospital. Mean GA at pPROM and delivery was 25^{+4} (range: 21^{+6} to 27^{+4} weeks) and 26^{+4} weeks (range: 23^{+2} to 30^{+2} weeks), respectively. The mean latency between pPROM and birth was 11 days (range: 0-46 days). 69% of the infants were born within 11 days between pPROM and delivery.

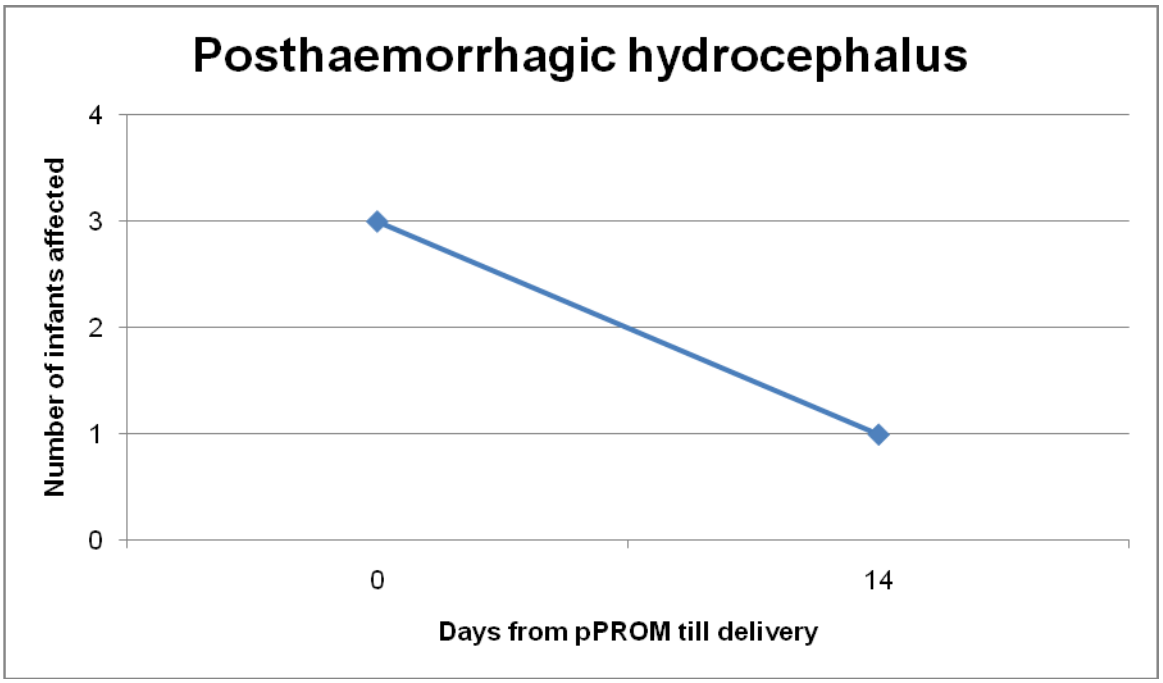

Figure 32: Latency period between pPROM and delivery, and distribution of posthaemorrhagic hydrocephalus during this period of time

As a consequence of the diagnoses regarding the nervous system which are expressed above, the infants developed further complications.

2 (2%) of 100 live born infants developed microcephalus. Both infants survived and could subsequently be discharged from hospital. The GA at pPROM was 20^{+6} weeks in one case and 21^{+6} weeks in the other. In one child, the GA at delivery was 26^{+6} weeks and in the other one it was 28^{+3} weeks. The latency period between pPROM and birth was once 42 days (delivery at 26^{+6} weeks) and the other time it was 46 days (delivery at 28^{+3} weeks). Infants who were affected by this complication, also suffered from other ailments, as there are: 1 infant evolved pulmonary hypoplasia, both IRDS III/IV, 1 suffered from hypotension, 1 from pulmonary hypertension, both developed IVH I, one suffered from meconium obstruction that advanced into a perforation of the bowels, both evolved early onset sepsis, and one of the infants had the diagnosis ROP.

4 (4%) of 100 live born infants developed posthaemorrhagic hydrocephalus. 3 infants could be discharged from hospital while 1 died at the age of 16 days. The mean GA at pPROM and delivery was 25^{+3} (range: 23^{+2} to 27^{+4} weeks) and 26^{+3} weeks (range: 25^{+1} to 27^{+4} weeks), respectively. The mean latency period between pPROM and birth was 4 days (3 infants [75%] were delivered within the same day of pPROM and delivery and 1 infant within 14 days). Additional diagnoses

regarding the nervous system, that have been made are as follows: 1 of the infants developed IVH II, 2 IVH III, 1 IVH II/III+PVH, 3 ventricular dilatation/megaly, and 2 infants developed seizures.

The infants evolved also maladies regarding other organ systems, which are listed below: 1 suffered from IRDS I/II, 3 from IRDS III/IV, 1 from BPD, 3 from hypotension, 2 from meconium obstruction, 3 from early onset sepsis, and 1 infant developed ROP.

3.5 Complications of the gastro-intestinal system

Figure 27 lists the most important complications of the gastrointestinal system of preterm infants.

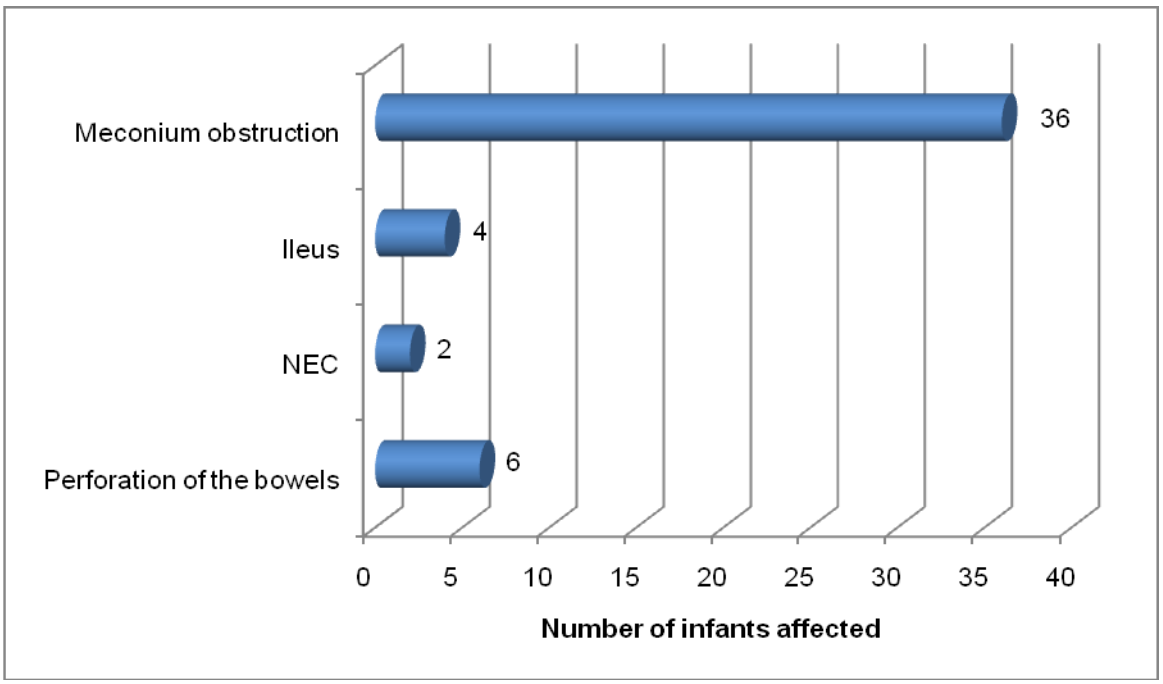

Figure 33: Gastro-intestinal complications

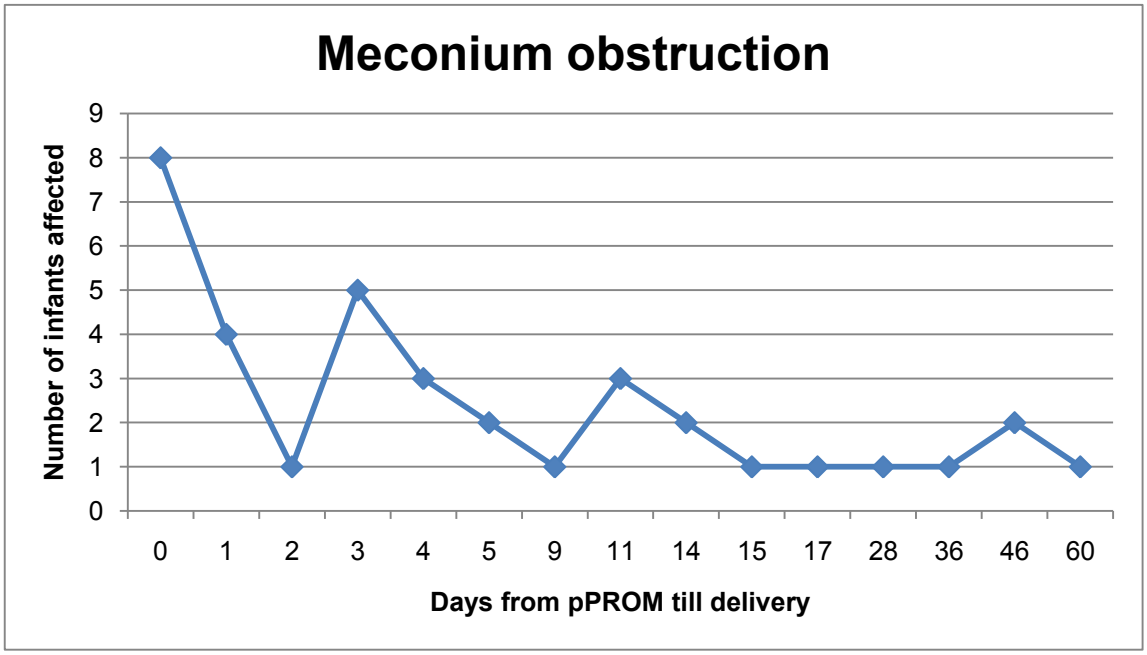

Figure 34: Latency period between pPROM and delivery, and distribution of meconium obstruction during this period of time

36 (36%) of 100 live born infants developed meconium obstruction. 31 could be discharged from hospital while 5 died. The latter died within 4 days after delivery. The mean GA at pPROM and delivery was 25^{+3} (range: 18^{+2} to 27^{+6} weeks) and 26^{+3} weeks (range: 23^{+2} to 30^{+0} weeks), respectively. The mean latency period between pPROM and delivery was 10 days (range: 0-60 days). 75% of the infants were born within 11 days between pPROM and delivery. Of these 36 infants, 3 developed ileus, 1 NEC and 4 suffered from perforation of the bowels.

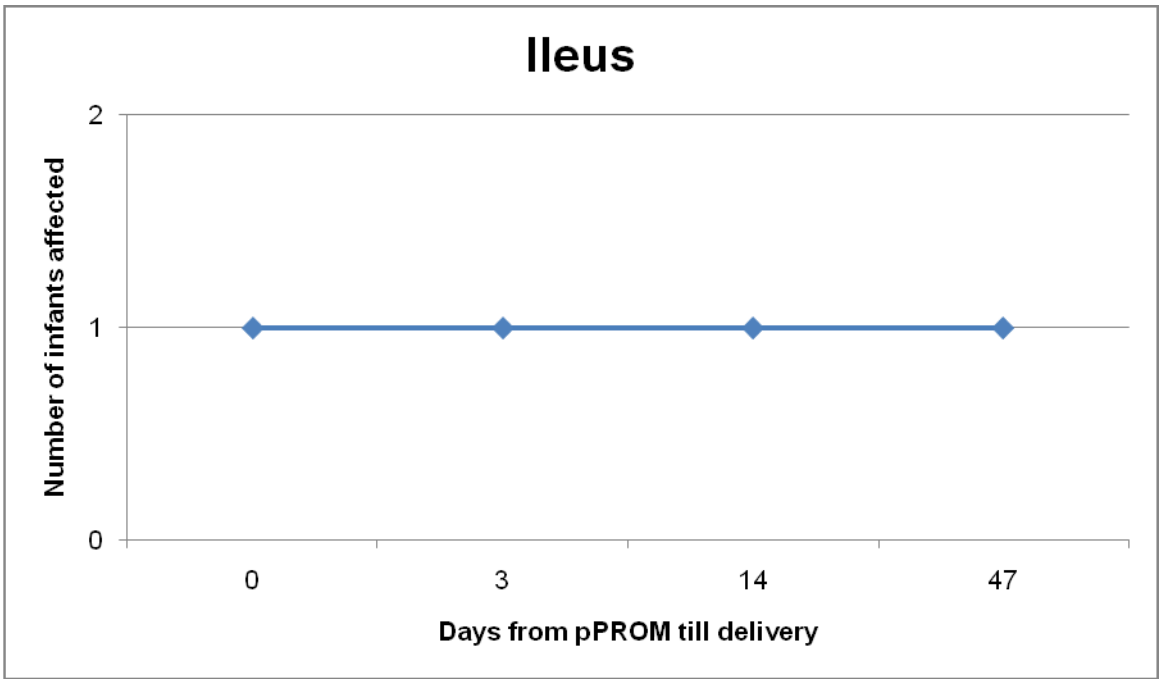

Figure 35: Latency period between pPROM and delivery, and distribution of ileus during this period of time

4 (4%) of 100 live born infants developed ileus which may be a complication that due to meconium obstruction. 3 of the infants could subsequently be discharged from hospital while 1 died at the age of 4 days. The mean GA at pPROM and delivery was 23^{+4} (range: 19^{+2} to 25^{+4} weeks) and 25^{+3} weeks (range: 23^{+2} to 27^{+4} weeks), respectively. The mean latency between pPROM and birth was 16 days (range: 0-47 days). 2 of the infants have been born within 11days between pPROM and delivery. As an aftermath 2 infants suffered from perforation of the bowels.

Another severe, sometimes fatal complication of meconium obstruction is NEC, which is not seldomly necessitating surgical treatment. 2 (2%) of 100 live born infants developed NEC. Both could subsequently be discharged from hospital. The GA at pPROM was 26^{+6} respectively 26^{+0} weeks. The GA at birth was 27^{+3} of one infant and 26^{+3} weeks of the other one. The latency period between pPROM and delivery was 4 days and 3 days. One of the infants had the primary diagnosis meconium obstruction. After the occurrence of ileus, a perforation of the bowels was diagnosed additionally. The same infant also suffered from an early onset sepsis in the beginning that turned into a late onset sepsis after the development of NEC and perforation of the bowels.

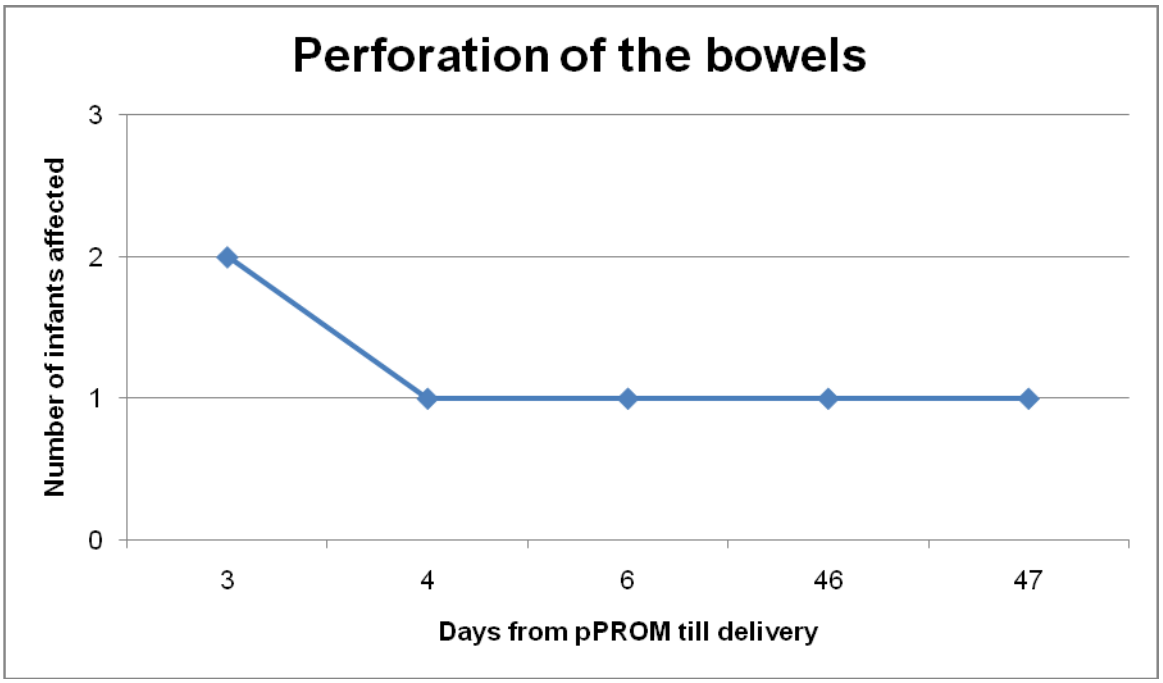

Figure 36: Latency period between pPROM and delivery, and distribution of perforation of the bowels during this period of time

6 (6%) of 100 live born infants developed perforation of the bowels. All infants could subsequently be discharged from hospital. Mean GA at pPROM and delivery was 23^{+3} (range: 19^{+2} to 27^{+1} weeks) and 26^{+3} weeks (range: 23^{+2} to 28^{+3} weeks), respectively. The mean latency between pPROM and birth was 18 days (range: 3-47 days). 67% of the infants were born within 11 days between pPROM and delivery. Regarding the gastrointestinal complications, 4 infants developed meconium obstruction as a primary diagnosis, 2 ileus and one suffered from NEC. Additional diagnoses concerning the other organ systems, that have been made, are listed below: 2 infants developed pulmonary hypoplasia, 1 suffered from IRDS I/II, 3 from IRDS III/IV, 2 from hypotension, 1 from IVH I, 1 from ventricular dilatation/megaly, 1 from seizures, 1 neonate developed a microcephalus, 4 early onset sepsis, 2 late onset sepsis and 2 infants developed ROP.

3.6 Further Complications

The infants born preterm suffered also from other diagnoses as for instance infections and long-term complications as ROP.

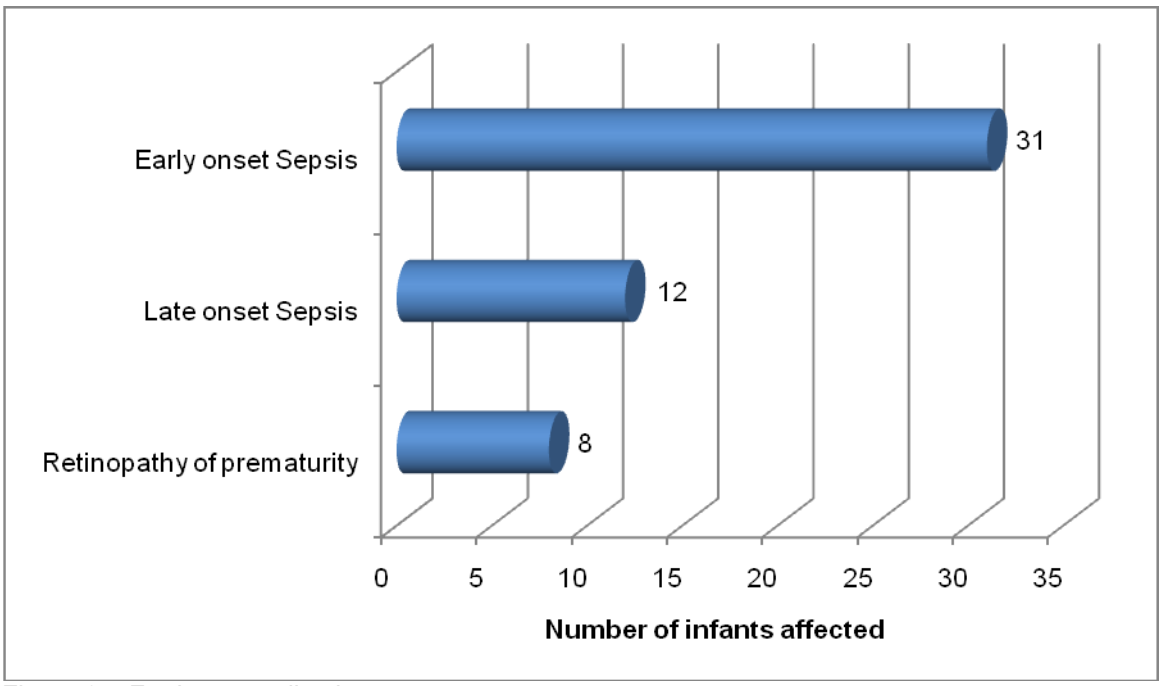

Figure 37: Further complications

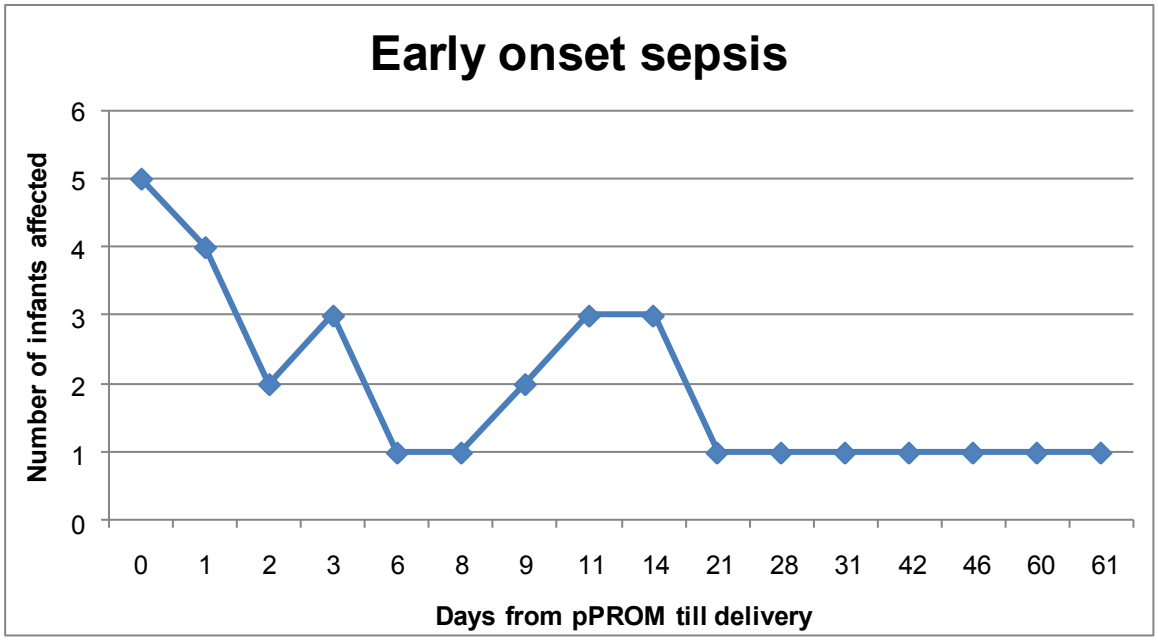

Figure 38: Latency period between pPROM and delivery, and distribution of early onset sepsis during this period of time

31 (31%) of 100 live born infants developed early onset sepsis. 22 infants survived until discharge from hospital while 9 died. 8 of the 9 deceased infants died within the first 5 days of their lives and 1 died at the age of 16 days. The mean GA at pPROM and delivery was 24^{+3} (range: 20^{+1} to 27^{+6} weeks) and 26^{+3} weeks (range: 23^{+1} to 30^{+6} weeks), respectively. The mean latency between pPROM and delivery was 13 days (range: 0-61 days). 68% of the infants who developed early onset sepsis were born within 11 days between pPROM and delivery. 3 of the infants developed late onset sepsis although their condition had become better in the mean time. Other maladies that the infants developed after birth were: 1 infant suffered from delayed pulmonary adaptation, 2 developed pulmonary hypoplasia, 1 wet lung syndrome, 12 IRDS I/II, 16 IRDS III/IV, 3 suffered from pneumonia, 4 from BPD, 14 from hypotension, 3 from pulmonary hypertension, 5 neonates developed IVH I, 2 IVH III, 8 IVH II/III+PVH, 5 ventricular dilatation/megaly, 1 PVL I, 1 PVL III, 10 seizures, 3 a posthaemorrhagic hydrocephalus, 2 a microcephalus, 14 meconium obstruction, 2 ileus, 1 NEC, 4 a perforation of the bowels, and 4 infants developed ROP.

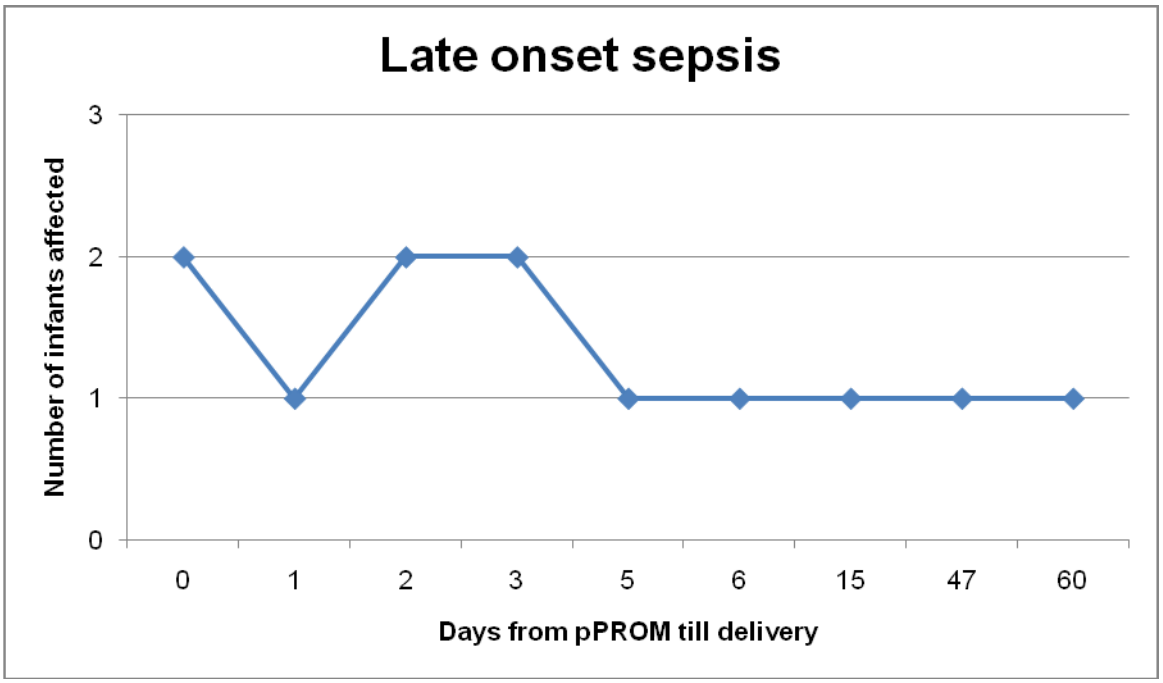

Figure 39: Latency period between pPROM and delivery, and distribution of late onset sepsis during this period of time

12 (12%) of 100 live born infants developed late onset sepsis. All children survived until discharge from hospital. The mean GA at pPROM and delivery was 24^{+2} (range: 18^{+2} to 27^{+4} weeks) and 26^{+3} weeks (range: 24^{+1} to 27^{+4} weeks), respectively. The mean latency period between pPROM and delivery was 12 days (range: 0-60 days), and 75% of the infants have been delivered within 11 days between pPROM and birth. The initial diagnoses regarding particular organ systems that the infants evolved are listed below: 1 of the infants developed pulmonary hypoplasia, 5 IRDS I/II, 5 IRDS III/IV, 2 pneumonia, 1 pneumothorax, 2 neonates suffered from BPD, 5 from hypotension, 1 from pulmonary hypertension, 2 from IVH II/III+PVH, 1 from ventricular dilatation, 1 from seizures, 6 from meconium obstruction, 1 from ileus, 1 from NEC, 2 from perforation of the bowels, and 2 infants developed ROP.

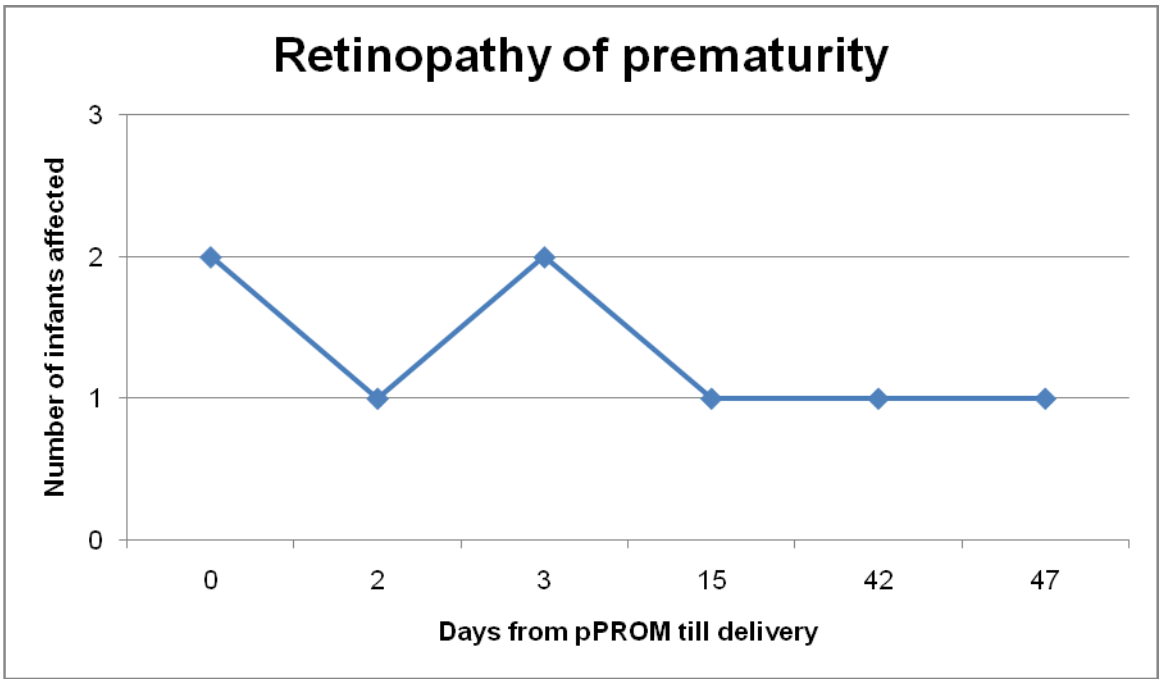

Figure 40: Latency period between pPROM and delivery, and distribution of ROP during this period of time

8 (8%) of 100 live born infants developed ROP. The mean GA at pPROM and delivery was 23^{+4} (range: 19^{+2} to 25^{+1} weeks) and 25^{+3} weeks (range: 23^{+2} to 26^{+6} weeks), respectively. The mean latency between pPROM and delivery was 14 days (range: 0-47 days). 63% of the infants were born within 11 days between pPROM and delivery. Other long-term complications that the infants suffered from are: 1 developed a pneumothorax, 3 BPD,1 developed a posthaemorrhagic hydrocephalus and 1 a microcephalus. Pertaining to the gastrointestinal system, 3 infants suffered from ileus and 2 of these developed a perforation of the bowels.

Table 4 shows the acute and long-term complications that the surviving infants developed dependent on their GA at delivery.

	Weeks								
	23 n=2	**24 n=11**	**25 n=10**	**26 n=12**	**27 n=22**	**28 n=7**	**29 n=6**	**30 n=7**	**31-33 n=5**
IRDS III/IV	2/2	5/11	3/10	6/12	5/22	2/7	3/6	1/7	0/5
BPD	0/2	6/11	3/10	0/12	3/22	1/7	0/6	0/7	0/5
IVH III	0/2	0/11	2/10	0/12	0/22	0/7	0/6	0/7	0/5
IVH II/III+PVH	0/2	2/11	0/10	1/12	1/22	0/7	0/6	0/7	0/5
PVL I-III	0/2	2/11	0/10	2/12	0/22	1/7	1/6	1/7	0/5
Posthaemorrhagic hydrocephalus	0/2	0/11	2/10	0/12	1/22	0/7	0/6	0/7	0/5
Sepsis	2/2	6/11	6/10	7/12	5/22	1/7	2/6	2/7	0/5
ROP	1/2	2/11	2/10	3/12	0/22	0/7	0/6	0/7	0/5
Ileus	1/2	1/11	0/10	1/12	0/22	0/7	0/6	0/7	0/5
NEC	0/2	0/11	0/10	1/12	1/11	0/7	0/6	0/7	0/5
Perforation of the bowels	1/2	0/11	1/10	2/12	1/22	1/7	0/6	0/7	0/5

Table 4: Acute and long-term complications of surviving infants regarding their GA;
23, 24, 25, etc. = completed gestational weeks; n=number of infants

3.7 Mental and locomotor outcome of the infants at the age of 2 years corrected according to the Bayleys-test

46 (56%) of the surviving 82 infants underwent neurodevelopmental assessment at the corrected age of 2 years while 36 (44%) were lost to follow-up. 9 children were not presented to the Neurodevelopmental outpatient clinic, as their birth weight was above 1500g. 13 children were lost due to their date of birth in the year 2010, as the Bayleys-test could not yet be performed. 14 children were lost due to follow-up, or were excluded due to incomplete data leaving 46 children who underwent the BSID.

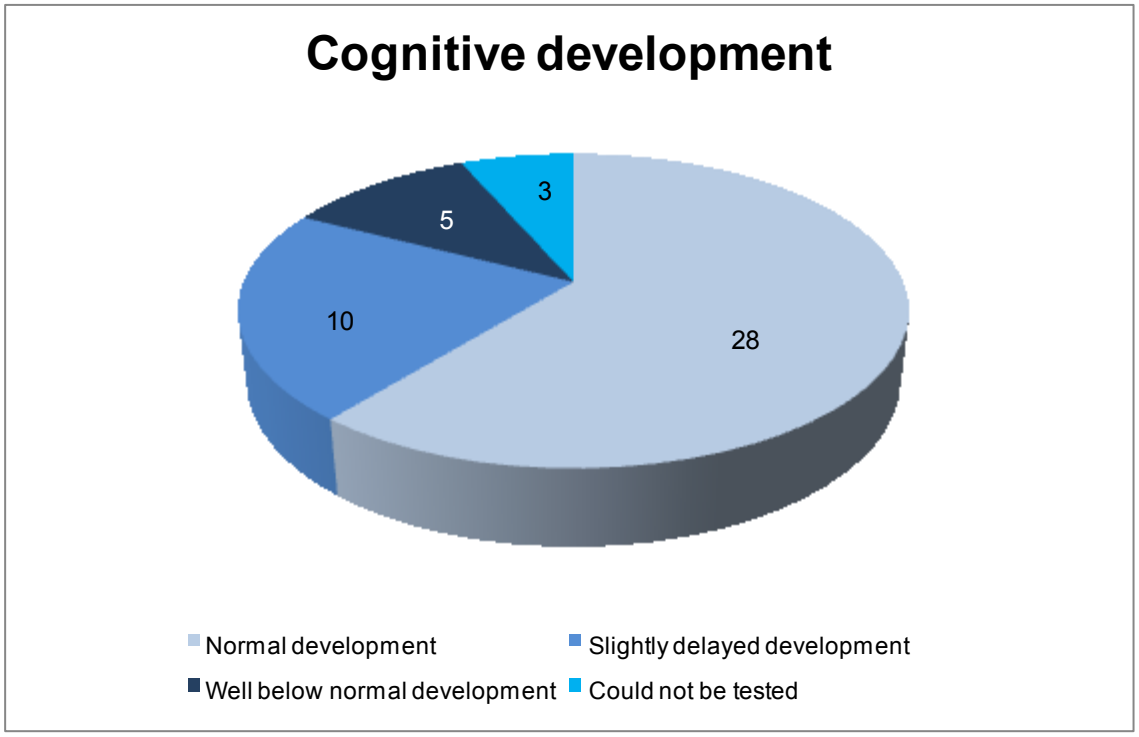

Figure 41: Cognitive development at the age of 2 years corrected, of the infants born preterm

28 (61%) showed normal cognitive development. Mean GA at pPROM and delivery was 25^{+3} (range: 19^{+2} to 27^{+6} weeks) and 27^{+3} weeks (range: 24^{+0} to 31^{+3} weeks), respectively. The mean latency between pPROM and birth was 12 (range: 0-69 days) days and the mean birth weight was 1033g (range: 471-1550 grams).
In 10 (22%) children, a slightly delayed development was diagnosed according to their age. Mean GA at pPROM and delivery was 25^{+3} (range: 21^{+6} to 27^{+4} weeks) and 26^{+3} weeks (range: 24^{+1} to 28^{+3} weeks), respectively. The mean latency

period between pPROM and delivery was 6 days (range: 0-46 days) and the mean birth weight was 961g (range: 620-1140 grams).

5 (11%) of the children born preterm had impaired cognitive development. Mean GA at pPROM and delivery was 22^{+4} (range: 18^{+2} to 26^{+4} weeks) and 26^{+5} weeks (range: 24^{+4} to 28^{+3} weeks), respectively. The mean latency between pPROM and birth was 30 days (2 infants were delivered within 0 days between pPROM and birth, 1 was born at 42 days after pPROM, 1 at 46 days and 1 at 60 days after pPROM). The mean birth weight was 866g (range: 640-1138 grams).

3 children could not be tested regarding their cognitive abilities. One child did not receive an adequate result due to its lacking cooperation during the test situation, 1 child was solely speaking Croatian, so the test could not be carried out appropriately and 1 child could not be tested due to its severe delayed locomotor development.

In table 5 one can see the mental development of the children included to the study at 2 years corrected for prematurity in relation to their GA at delivery.

	Weeks								
	23 n=2	**24 n=11**	**25 n=10**	**26 n=12**	**27 n=22**	**28 n=7**	**29 n=6**	**30 n=7**	**31-33 n=5**
Normal development	0/2	4/11	2/10	3/12	11/22	3/7	2/6	2/7	1/5
Slightly delayed development	0/2	2/11	0/10	2/12	5/22	1/7	0/6	0/7	0/5
Well below normal development	0/2	1/11	0/10	3/12	0/22	1/7	0/6	0/7	0/5
Could not be tested	0/2	2/11	0/10	0/12	1/22	0/7	0/6	0/7	0/5
Excluded	2/2	2/11	8/10	4/12	5/22	2/7	4/6	5/7	4/5

Table 5: Cognitive development at 2 years corrected for prematurity regarding the GA at delivery; 23, 24, 25, etc. = completed gestational weeks; n=number of infants

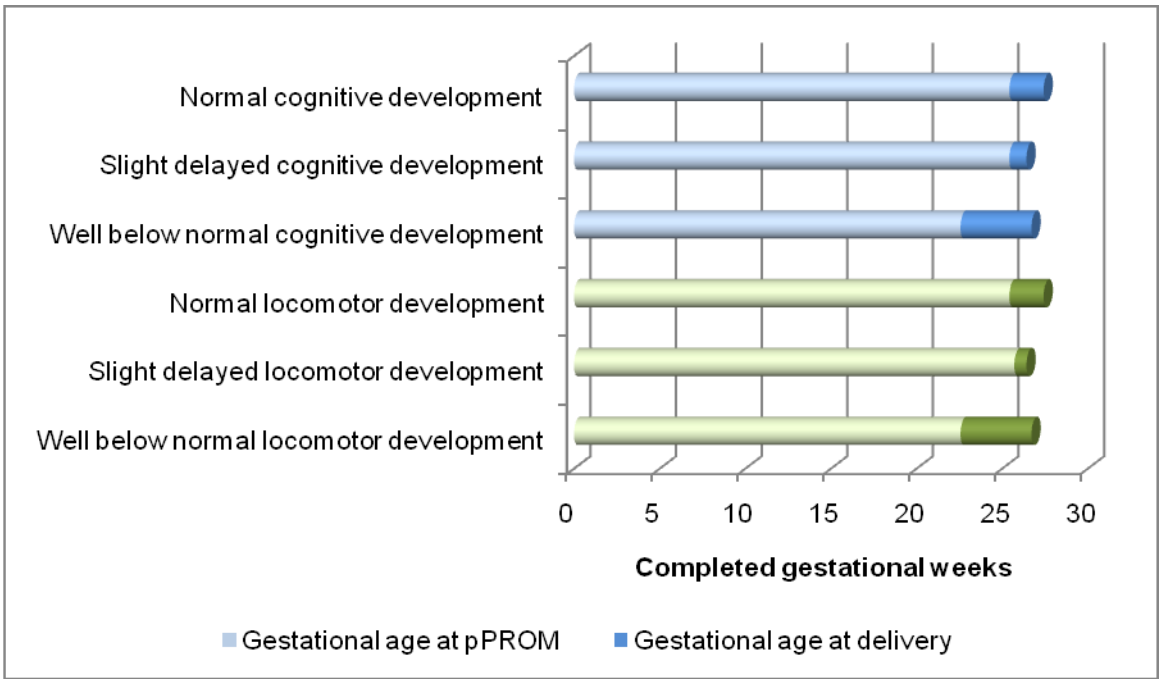

Figure 42: Distribution of gestational age at pPROM and delivery regarding the different cognitive and locomotor stages of development of the children at 2 years corrected to prematurity

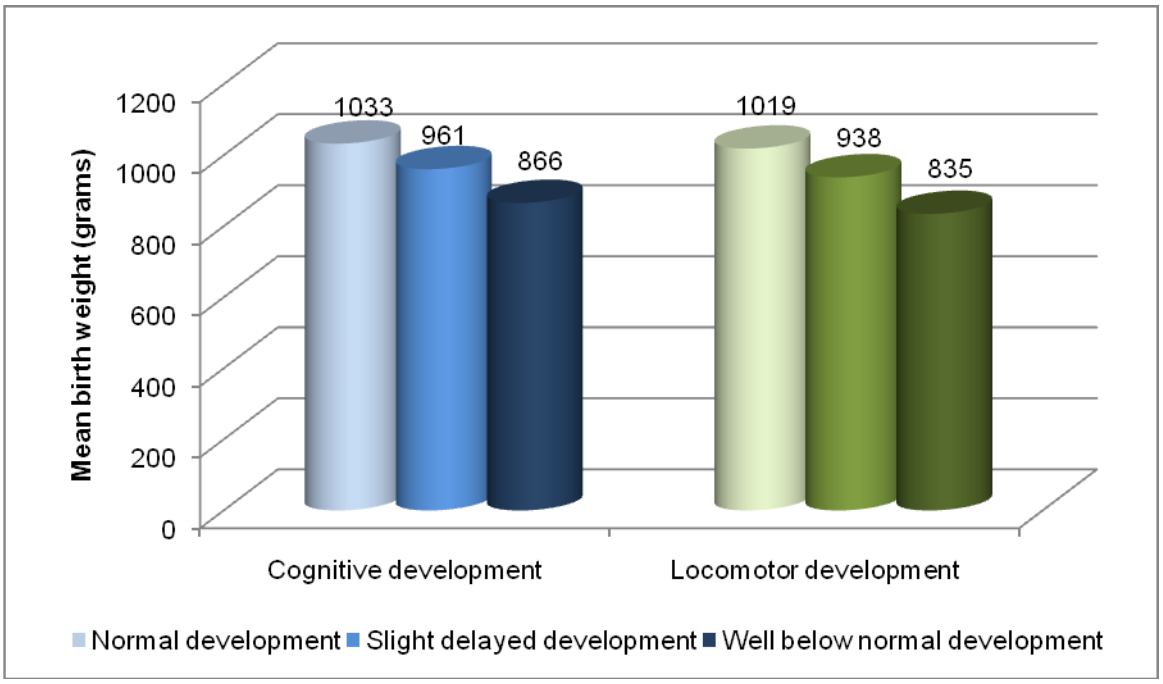

Figure 43: Distribution of birth weight regarding the different cognitive and locomotor stages of development of the children at 2 years corrected to prematurity

One can see the direct correlation of increasing GA at pPROM and delivery, as well as increasing birth weight, and a better cognitive and locomotor outcome of the children at 2 years corrected to prematurity.

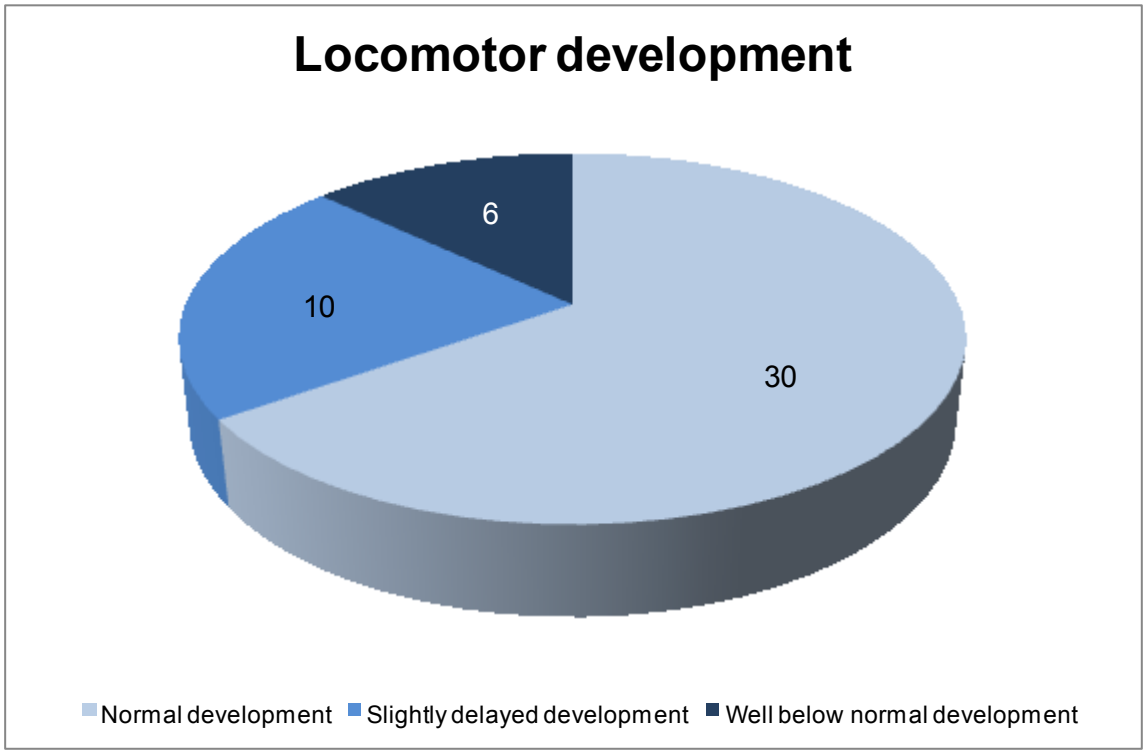

Figure 44: Locomotor development at the age of 2 years corrected of the infants born preterm

30 (65%) children who have been tested showed a normal locomotor development according to the state of their age. Mean GA at pPROM and delivery was 25^{+3} (range: 19^{+2} to 27^{+6} weeks) and 27^{+3} weeks (range: 24^{+0} to 31^{+3} weeks), respectively. The mean latency between pPROM and birth was 12 days (range: 0-69 days) and the mean birth weight 1019g (range: 471-1550 grams).

10 (22%) of the study participants showed a slightly delayed development regarding their age. The mean GA at pPROM and delivery was 25^{+5} (range: 21^{+6} to 27^{+4} weeks) and 26^{+3} weeks (range: 24^{+0} to 28^{+3} weeks), respectively. The mean latency period between pPROM and delivery was 6 days (range: 0-46 days) and the mean birth weight was 938g (range: 710-1140 grams).

6 (13%) of the infants born preterm turned out to have an impairment regarding their locomotor skills. The mean GA at pPROM and delivery was 22^{+4} (range: 18^{+2} to 26^{+4} weeks) and 26^{+5} weeks (range: 24^{+4} to 28^{+3} weeks), respectively. The mean latency between pPROM and birth was 25 days (3 children have been born within 0 days between pPROM and delivery, 1 at 42 days, 1 at 46 days and 1 at 60 days latency between pPROM and birth) and the mean birth weight was 835g (range: 640-1138 grams).

Table 6 shows the locomotor development of the children at an age of 2 years corrected in terms of their GA at delivery.

	Weeks								
	23 n=2	**24 n=11**	**25 n=10**	**26 n=12**	**27 n=22**	**28 n=7**	**29 n=6**	**30 n=7**	**31-33 n=5**
Normal development	0/2	4/11	2/10	4/12	12/22	3/7	2/6	2/7	1/5
Slightly delayed development	0/2	3/11	0/10	1/12	5/22	1/7	0/6	0/7	0/5
Well below normal development	0/2	2/11	0/10	3/12	0/22	1/7	0/6	0/7	0/5
Excluded	2/2	2/11	8/20	4/12	5/22	2/7	4/6	5/7	4/5

Table 6: Locomotory development at 2 years corrected for prematurity regarding the GA at delivery
23, 24, 25, etc. = completed gestational weeks; n=number of infants

Discussion

The main objective of this diploma thesis was the examination of the short- and long-term outcome of infants with extreme pPROM occurring at of 18^{+0} to 27^{+6} weeks of gestation. We decided to take 18^{+0} completed gestational weeks as bottom line of our inclusion criteria to the study, as we wanted to keep the failure rate low, due to the fact that the survival of infants who present with pPROM below 18 weeks of gestation is a rare event and only very few women decide to continue their pregnancy. Not all of the studies that deal with this topic are the same regarding their inclusion criteria, but are still valuable for comparison. One study that should be highlighted is that of Pristauz et al. which has an overlap concerning the inclusion criteria, and was also performed at our institution.

Overall, 70% (82) of included infants survived which is more than the 17% reported by Pristauz et al. and 56% reported by Manuck et al.[16,17] This discrepancy may result from slightly different inclusion criteria regarding the gestational age at pPROM. Both Pristauz et al. as in Manuck at al. the inclusion criteria for gestational age was very low (14^{+0} to 24^{+6} weeks).[16,17] A mere 13% of the neonates born in the group $<24^{+0}$ gestational weeks survived until discharge from hospital. There was a significant difference in the survival rate of infants born before 24^{+0} weeks and those born between 24^{+0} and 25^{+6} weeks, where 60% of the neonates survived. Mean gestational age at pPROM was 24^{+3} weeks and 26^{+3} weeks at delivery. The mean latency between pPROM and delivery was 13 days in this study, which is identical as in Pristauz et al, who report a mean of 13 days from pPROM till delivery, but lower GA both at pPROM (21^{+3} weeks) and delivery (23^{+2} weeks). This results from their inclusion criteria of a very low gestational age at pPROM (14^{+0} to 24^{+6} weeks).[16]

In contrary to Pristauz et al. who state that more female infants survived, our data show, that 52 (63%) male infants and 30 (37%) female neonates survived until discharge from hospital. 82% of the surviving infants in our study were delivered by caesarean section in comparison to 75% in the study of Pristauz et al. It is possible that this minor deviations result from the larger number of study cases. Another study of Zanardo et al. reported that there is a connection between pPROM lower GA at birth, and that women with pPROM had vaginal deliveries

more often. In contrast, our study showed that 67% (78 of 117 infants including IUFD and neonates that died posnatally) were delivered by caesarean section.[18]

Our study also revealed that the majority of women with infants that could subsequently be discharged from hospital did receive antibiotics (n=73, 95%), tocolytics (n=61, 79%) and induction of lung maturation (n=69, 90%)

Of 82 infants that were discharged from hospital, 50% (41) have been born with ELBW, 34% (28) have been delivered with VLBW and 16% (13) neonates had LBW at birth.

The frequency of certain complications was comparable to previous data by Pristauz et al. They reported BPD in 25% of infants compared to 16% in our study, IVH III-IV in 17% of infants compared to 7% in our study. This may result partly from improved neonatal care and partly due to the higher gestational age for inclusion in our study. PVL was diagnosed in 8% of infants by Pristauz et al. in comparison to 9% in our study. Furthermore Pristauz et al. reported sepsis in 33% of infants compared to 38% in our study. A last disease that we could compare with Pristauz et al. was ROP, which evolved in 25% of infants according to Pristauz et al. in comparison to 10% in our study.[16] This difference is also mostly due to the higher gestational age as inclusion criteria in our study. Regarding the development of NEC, Schmolzer et al. state in their study from 2006 that through a multimodal strategy to NEC prophylaxis (including feeding of donor human milk, and after one week breast milk of the preterm infants mother, the enteral administration of antibiotics, antifungal agents, and probiotics) the incidence of NEC is 0,7% in infants who are treated within the first 24 hours of their lives.[23] Our study showed an incidence of NEC of 2%. The slight difference may result from the fact, that Schmolzer et al. included all VLBW infants to their study, and we did include only the infants with pPROM. Our study shows that no infants who were delivered between $31+^{0}$ to $33+^{6}$ weeks, developed a severe acute or long-term complication.

It was difficult to compare the cognitive and locomotor development of the infants at 2 years corrected for prematurity, as the number of surviving infants that could be included to the developmental tests was different in our study and that of Pristauz et al.

The failure rate was 25% (3/12 children have been excluded from the test) in Pristauz et al. compared to 44% (36/82 children) in our study.

Regarding the cognitive development, Pristauz et al. reported that 67% (n=6) of children showed a normal outcome compared to 61% (n=28) in our study, 22% (n=2) showed a slightly delayed development which was identical with our observations of 22% (n=10) in our study. Finally Pristauz et al. stated that 11% (n=1) of children showed impaired cognitive development, which was seen similarly in 11% (n=5) in our study. Actually both studies showed the same results but there is a limitation as the children in Pristauz et al. were examined with help of the Griffiths test, and not with the Bayleys-test as it was not used at the Department of Paediatrics then.[16] Beaino et al. state that the mean prevalence of mild cognitive deficiency for children without moderate to severe neurosensorial disabilities was 21% and that of severe cognitive deficiency was 11%, which correlates well with the data from our study, but a limitation of this comparison is, that these children have been tested at the age of 5 years and not at the age of 2 years as in our study.[19]

Pristauz et al. state that 78% (n=7) of children showed a normal outcome regarding their locomotor abilities compared to 65% (n=30) in our study, 11% (n=1) showed a slightly delayed development compared to 22% (n=10) in our study and 11% (n=1) of children showed impaired locomotor development in comparison to 13% (n=6) in our study.[16] These differences can be due to the different type of test used in the two studies.

3.8 Limitations

As pPROM does not appear in great numbers, the main limitation of our study as well as in Pristauz et al. was the relatively low study population. Furthermore the retrospective analysis of our study turned out to be problematical, as we found that some cases were managed inconsistently

3.9 Conclusion

With the help of improved obstetric measures and intensive neonatal care, an increased number of infants survive after extreme pPROM and consecutive premature delivery, as also shown in this study. Gestational age, birth weight and absence of complications have prognostic importance for infants born preterm due

to pPROM. About 60% of the preterm infants that have been tested show a normal cognitive and locomotor development at the age of 2 years corrected for prematurity. It is expected that the number of infants with normal development is higher, as all children with a birth weight above 1500g have not been tested at the Neurodevelopmental outpatient clinic, as well as all the infants born in 2010, as they have not yet been examined.

Advances in the obstetric and neonatal management lead to decreased mortality and morbidity in preterm infants. Nevertheless, one has to critically question whether it is ethically correct to continuously to decrease the borders of viability, without questioning the potential morbidities and long-term complications including the neurodevelopmental impairment of affected infants. Furthermore one has to keep in mind the psychological and financial burden that may encumber on the parents of infants with severe disabilities due to very preterm birth.

Decisions concerning the management of extreme pPROM should be taken individually in a mutual agreement between the parents and the physicians. We have not yet found screening methods that allow precise predictions regarding the medical condition of fetuses after pPROM, and this uncertainty makes it complicated to decide how long a pregnancy should be prolonged over the immediate time of induction of lung maturation, without risking an intrauterine infection which in turn is likely to worsen the neonatal outcome. Therefore parents need to be extensively counselled about potential adverse long-term effects next to the data on mere survival.

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