Diploma Thesis

Neurological long-term outcome of premature infants after tocolysis between the 24th and 32nd week of gestation

Comparison between standard- versus maintenance tocolysis with Atosiban and Hexoprenalin

submitted by

Karla Tschabuschnig

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under the supervision of

Ass. Prof. PD Dr.med.univ. Daniela Ulrich

Assoz. Prof. PD Dr.med.univ. Gerhard Pichler

Graz, 2.2.2017

Affidavit

Hereby I declare that I have written this diploma thesis fully on my own without assistance of third parties. Furthermore I declare that I haven´t used any other sources than those cited and that all explanations copied directly or in their sense are marked as such.

Graz, 2.2.2017 *Karla Tschabuschnig eh*

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Zusammenfassung

Einleitung

Weltweit ist Frühgeburtlichkeit ein großes Gesundheitsproblem, da sie die Haupttodesursache von Neugeborenen darstellt. Die Rate an Frühgeburten steigt seit Jahren an, ebenso die Überlebensrate der Kinder aufgrund von Verbesserungen in der neonatalen Versorgung. Da immer mehr frühgeborene Kinder überleben, spielen die Auswirkungen auf die kindliche Entwicklung eine immer bedeutendere Rolle.

Wehenhemmer werden schon lange zur Verlängerung der Schwangerschaft eingesetzt, trotzdem gibt es wenige Studien, die sich mit ihrer Wirkung auf die neurologische Entwicklung der Kinder beschäftigen.

Material und Methoden

Mit einer retrospektiven Datenanalyse haben wir den Einfluss von zwei wehenhemmenden Mittel auf die Langzeitentwicklung der frühgeborenen Kinder analysiert. Zusätzlich haben wir die Entwicklung der Kinder verglichen, deren Mütter entweder Standard- oder Erhaltungstokolyse erhalten haben. Die mütterlichen und kindlichen Daten wurden aus den Krankenakten des LKH Graz erhoben. Unsere Hypothese war, dass es keinen Unterschied zwischen den Wehenhemmern oder der Art der Tokolyse hinsichtlich der Entwicklung der Kinder gibt. Die Langzeitentwicklung der Kinder wurde anhand der mit 2 Jahren durchgeführten Bayleys Entwicklungstestung (BSID-II) erhobenen Daten analysiert.

Resultate

Die statistischen Tests zeigten keinen signifikanten Unterschied in den Ergebnissen der Kinder, die intrauterin Hexoprenalin oder Atosiban ausgesetzt waren. Auch ob die Mütter Standard- oder Erhaltungstokolyse erhielten, zeigte keinen Einfluss auf die kindliche Entwicklung. Die Gültigkeit der statistischen Tests wurde leider durch die kleine Anzahl der untersuchten Kinder beeinträchtigt.

Fazit

Tokolyse wird häufig eingesetzt, um eine Schwangerschaft zu verlängern, jedoch kann die Behandlung potentiell Mutter und Kind schädigen. Keines der in unserer Studie verwendeten Tokolytika scheint vorteilhaft in Bezug auf die kindliche Entwicklung. Um die Effekte der Tokolyse auf die kindliche Langzeitentwicklung zu demonstrieren, werden weitere Studien mit einer größeren Studienpopulation benötigt.

Abstract

Introduction

Worldwide preterm birth is a major health problem. It is one main factor for neonatal deaths whereby premature delivery rates are rising. Fortunately medical support has made a lot of progress in neonatal care over the past decades and therefore also the numbers of survivors are rising. At the same time the effects on long-term outcome of infants has an increasing impact. Tocolytics have been used for a long time to prolong pregnancy but still there are few studies on the drug's effect on the neonatal long term neurodevelopment.

At the moment in Austria two medications are used for tocolysis: Hexoprenalin and Atosiban. Studies have shown that both are effective in delaying birth but Atosiban showed fewer side effects. There are few studies on the long-term neurodevelopmental outcome in regard to medication in premature infants.

Material and methods

In this retrospective study we analyzed the impact of the two tocolytics on the long-term neurodevelopment of preterm infants. Furthermore we compared the neurodevelopmental outcome of neonates whose mothers received standard or maintenance tocolysis. Maternal and neonatal data were retrieved from medical records of the University Hospital of Graz. We hypothesized that there is no difference in the outcome of neonates dependant on the tocolytic drug or type. The BSID-II was used to define neurodevelopmental outcome of infants at the age of 2 years.

Results

The statistical tests did not show any significant difference in the outcome of infants who were exposed to Hexoprenalin or Atosiban in utero. No effect on the neonatal long term development was seen between maintenance or standard tocolysis. It has to be noted that the validity of the test was impacted by the small number of infants included.

Conclusion

Tocolysis is frequently used to prolong pregnancy until the 34th week of gestation but could potentially harm mother and child. None of the used tocolytic agents or administration protocol used in our study was proven to be superior in regard to infantile neurodevelopmental outcome. Further trials with larger study population would be needed to evaluate the effects of tocolysis on the infantile long-term neurodevelopment.

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Abbreviation

ADHD	Attention deficit hyperactivity disorder
BPD	Bronchopulmonary dysplasia
BSID	Bayley Scales of Infant Development
Ca^{2+}	Calcium
cAMP	cyclic adenosine monophosphate
CCB	Calcium channel blockers
cGMP	cyclic guanosine monophosphate
CLD	Chronic lung disorder
CNS	Central nervous system
COX	Cyclooxygenase
CP	Cerebral palsy
DQ	Development quotient
ELBW	Extremely low birth weigth
i.v.	intravenous
IQ	Intelligence quotient
IRDS	Infant respiratory distress syndrome
IVH	Intra ventricular hemorrhage
LBW	Low birth weight
MDI	Mental development index
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
p.o.	per os
PDI	Psychomotor development index
PPROM	Preterm premature rupture of the membranes
PVL	Periventricular leucomalacia
ROP	Retinopathia of prematurity
SIP	Spontanous intestinal perforation
VLBW	Very low birth weight
WM	White matter

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1 Introduction

Worldwide preterm deliveries are a main health issue and cause millions of child deaths every year. Furthermore the numbers of premature births are increasing in the last years. Internationally the numbers of preterm delivery range from 5 to 15%. Fortunately the chance of survival of premature infants is rising but that goes along with rising numbers of morbidity. Premature neonates face a higher risk of diseases in the first months after their birth because their organs are more vulnerable to injury or infection. In the past few years also more and more effects of premature births on the long-term development can be observed. Several studies found higher risks of neurodevelopmental impairments in all age groups and behavioural and social issues at adolescence. Birth can be delayed by different tocolytics to allow the infants' organs to mature. The main aim of the application of tocolytics should be the best infantile outcome with few maternal side effects.

The aim of this study was to compare two different tocolytics and standard versus maintenance application to investigate, if there are any differences in the long-term outcome of child development. The results were measured at the corrected age of 2 by using the Bayley Scales of Infant Development. With this retrospective data analysis we received valuable information on the impact of tocolytics on the long-term development of infants.(1)

1.1 Preterm birth

1.1.1 Definition

The WHO defines preterm birth as every live delivery before the 37th gestational week. Premature delivery can be further split up into moderate - late preterm from the 32nd until the 37th week, very preterm from the 28th until the 32nd and extremely preterm before the 28th week of gestation. (1)

Neonates can also be classified by birth weight:

- low birth weight (LBW) < 2500g
- very low birth weight (VLBW) < 1500g
- extremely low birth weight (ELBW) < 1000g

It is also possible to make a relation between weight and gestational age. There are population based foetal growth charts, which show the average weight range for gestational age. Neonates which are smaller than the 10th percentile are called small for gestational age and above the 90th percentile they are called large for gestational age. Birth weight is an

important factor for neonatal mortality and morbidity. This is the reason that a lot of trials are based on weight rather than on gestational week. (2)

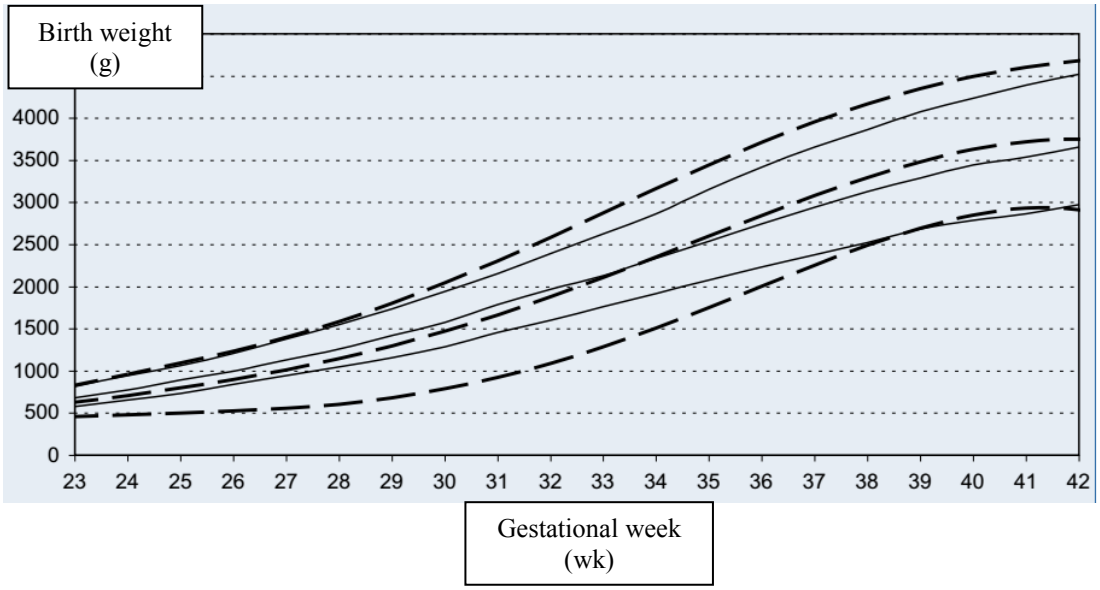

Figure 1: Comparison of intrauterine (continuous line) and extrauterine (discontinuous line) growth per gestational week. (3)

1.1.2 Neonatal deaths

The three leading causes for infant mortality are infections, complications of preterm birth, and intrapartum-related neonatal deaths. Worldwide preterm labour is the leading cause of newborn deaths and for infants under the age of 5 it is the second-leading cause of death after pneumonia. (1). Furthermore preterm birth adds up with other risk factors (for example infections) contributing to even more deaths. In numbers every year approximately around 1 million infants die due to preterm birth complications. (3)

In the USA preterm birth rates are around 12-13%, in Europe the numbers differ between 5-9%. Austria has one of the highest premature delivery rates in Europe. The numbers are steadily rising since 1991 and in the year 2014 they were at 7, 9%. (3), (4)

The problem also causes a lot of stress on the health care system, as especially very preterm born infants need much more care and are longer hospitalized. The economic consequences are enormous. For example the medical costs for extremely preterm birth make up more than 33%, while they represent only 5% of premature deliveries.

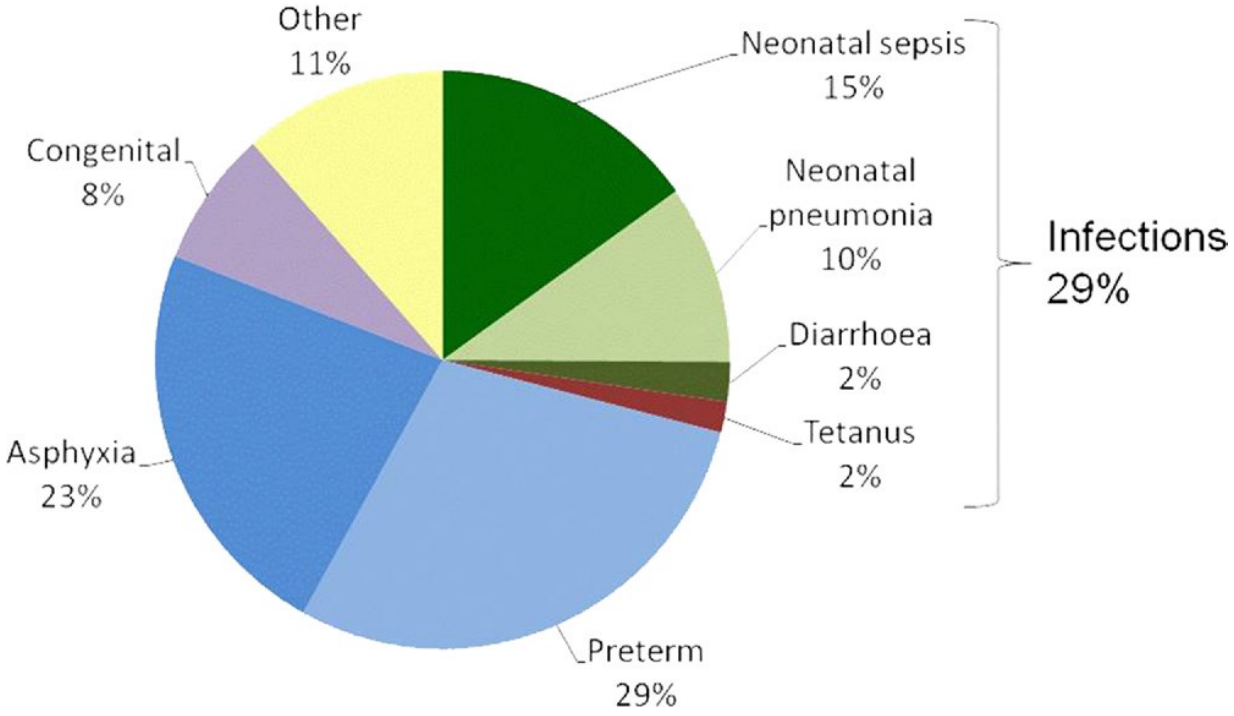

Figure 2: Causes of neonatal deaths (4)

80% of preterm deliveries occur between the 34th and 37th gestational week. During this time span survival rates are around 99%. Very preterm births make up 15% and extremely preterm birth just 5% of all preterm births, but these two groups are the reason for most neonatal deaths. (3)

While preterm birth rates are rising neonatal deaths are declining dramatically because of the effort put into antenatal, perinatal and postnatal care of the mother and baby. (1)

1.1.3 Risk factors of preterm birth

There are 3 main reasons of preterm delivery: maternal or foetal indications (30-35%), spontaneous preterm labour (40-45%) and preterm premature rupture (PPROM) of the membranes (25-30%). Preterm premature rupture of the membranes is defined as the rupture of the amniotic sac before the 37th week of gestation and must occur at least 1 hour before birth.

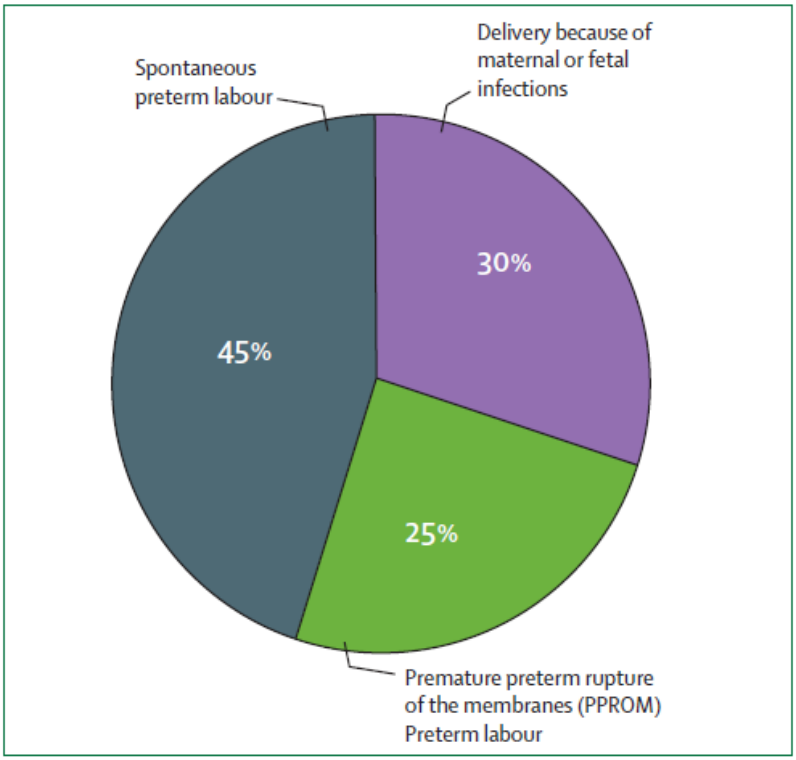

Figure 3: Precursors of preterm delivery (6)

The beginning of preterm labour is defined as the onset of regular contractions before the 37th gestational week accompanied by changes in cervical length.

There are a couple of risk factors for premature delivery and at the moment it looks like it is a mix of multiple mechanisms for example inflammation, uteroplacental haemorrhage or ischemia, uterine over distension, stress and immune responses. In most cases it is not possible to identify one single reason for the onset of preterm birth.

Women of African-American and African-Caribbean heritage have a higher risk of preterm delivery than white women. Asian women have a higher risk of small for gestational age deliveries without higher rates of preterm birth. Another interesting factor is that women with higher income usually deliver more likely on term. The reasons behind these demographical and social differences are not well understood and there is no clear conclusion on the reasons for these risk factors yet. (3)

Several studies have shown that women who become pregnant within 6 months of the last delivery are two times more likely to deliver preterm. A possible explanation is that the uterus is not back in its normal state again and might still be inflamed. In addition the mother has not yet achieved normal levels of vitamins, minerals and amino acids. Women who have already had a preterm birth also often deliver earlier the second time. (5), (6) A low BMI and low levels of zinc, iron and folate are also risk factors. (7) Statistically 60% of twins and almost all higher multiple gestation are born too early. A very important factor is intrauterine infection being the estimated reason for premature labour in 25-40%. (5) If preterm delivery occurs between the 21st and 24th week of gestation almost all histological examinations confirm a chorionamnitis, while between the 35th-36th gestational week only in 10% these

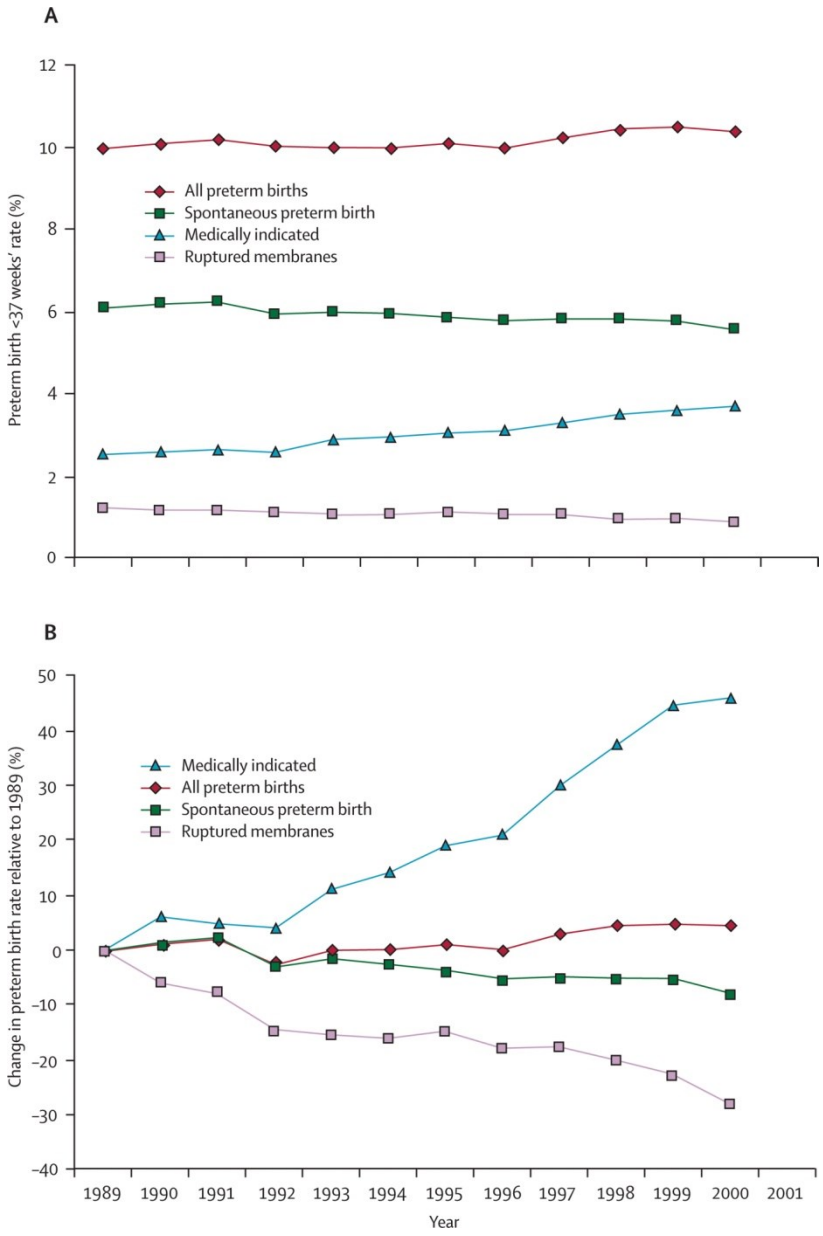

Figure 4: Trend of spontaneous and indicated premature labour rates over 10 years. (6)

results can be found. Women with bacterial vaginosis deliver 1.5 to 3 times more often early, another interesting aspect is that in African-American women in the USA bacterial vaginosis occurs 3 times more often and this could be a possible explanation for the higher premature birth rates in black women. Shortening of the cervix under 25 mm imply an increased risk of preterm labour. More risk factors include: vaginal bleeding, oligo- and polyhydramnions, maternal abdominal surgery, maternal medical disorders like thyroid dysfunction or high blood pressure, previous procedures on the cervix like cone biopsy, abnormalities of the uterus, stress, smoking, cocaine, heroin, cervical insufficiency, trichomoniasis and a higher frequency of contractions. (3)

1.2 Treatment of causes leading to preterm birth

There are several different guidelines for diagnosis and treatment of preterm labour and there is no first line drug for tocolysis. In this chapter I will discuss tocolysis and the most common treatments.

1.2.1 Prevention and diagnosis

The best option to prevent premature labour is to eliminate the risk factors described in the chapter before, especially the ones which can be easily changed by lifestyle modification.
Before any kind of treatment is given, the diagnosis of preterm labour has to be confirmed. After the 18th gestational week all abdominal and pelvic symptoms should be handled as warning signs. Regular contractions, changes in cervical length or dilatation and a foetal fibronectin test lead to the diagnosis. Uterine contractions occur also in women who are not going into labour and therefore premature delivery is often over diagnosed. After preterm labour is confirmed it should be investigated if there are any contraindications for prolonging pregnancy, for example infections or inflammations. The main aim of tocolysis is to minimise child mortality and morbidity. Still there is limited evidence that prolonging pregnancy has any benefits on the infant's outcome. It is possible to prolong pregnancy for 48 hours and if needed even longer. (8), (9)

1.2.2 Non-medical treatment

One of the essential things to do is to minimize physical activity. If the contractions are secondary due to another cause, the primary ones should be treated first. There are several possibilities for primary causes such as uterine infection, systemic medical conditions like thyroid dysfunctions or physiological problems like cervix insufficiency. In case of cervix insufficiency it is possible to do a cervix cerclage or to insert a cerclage pessary. (8), (9)

1.2.3 Medical therapy for inhibiting labour

There are several different drugs available to inhibit labour and they also vary from country to country. In every case there a personal decision has to be made to fit patient's needs. The primary aim of tocolysis to delay preterm birth for more than 48 hours so that glucocorticoids can be applied which significantly reduce respiratory distress syndrome in infants. Furthermore, it is important to allowfurther growth and maturity of the foetuses organs. The second aim is to transfer the mother to a hospital with a special care unit for neonates.

1.2.4 Cellular pathway to uterine contraction

Cells of the myometrial tissue regulate contractions by changing the intracellular Ca2+ concentration. Tocolytic drugs can influence Ca2+ channels, cyclic adenosinmonophosphate or cyclic guaninmonophosphate. (8), (10)

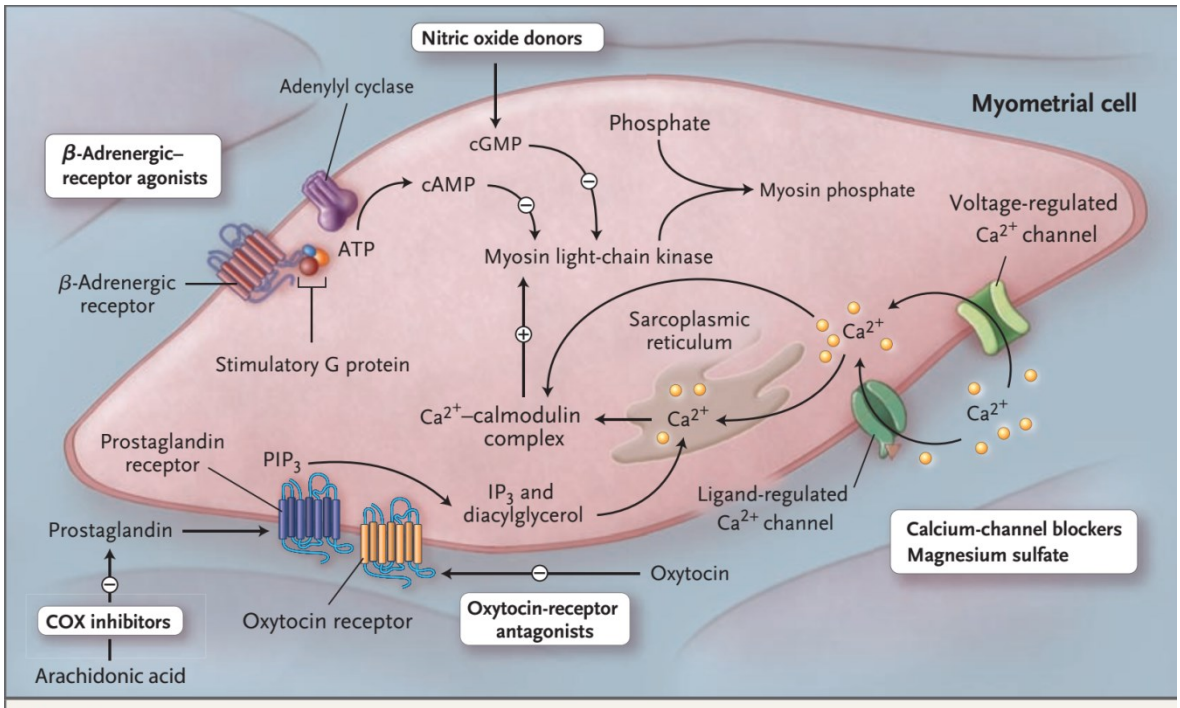

Figure 1. Sites of Action of Commonly Used Tocolytic Drugs.
COX denotes cyclooxygenase, PIP_3 phosphatidylinositol triphosphate, IP_3 inositol triphosphate, cAMP cyclic AMP, and cGMP cyclic guanosine monophosphate.

Figure 5: Mode of action of different tocolytics (12)

1.2.5 Beta2-adrenergic agonists

Since about 40 years beta2-adrenergic agonists have been used to arrest preterm delivery. Beta2-adrenergic agonist receptors can be found mainly in peripheral smooth muscle tissue, like the uterus, bronchia, blood vessels and the intestines. In these tissues beta2-adrenergic agonists increase cyclic Adenosinmonophosphate (cAMP) and thereby increase intracellular calcium and phosphorylation of myosin light chain kinase, which inhibits contractions. The

most common adverse effects are tachycardia, hypokalaemia, hypoglycaemia, shivering and dyspnoea. Usually beta2-adrenergic agonists are applied for 48 hours but it is possible to administer them longer, though there are no studies confirming any benefits in regard to the maternal or foetal side. There are many different beta2-adrenergic agonists used worldwide, for example ritodrine, salbutamol, fenoterol, hexoprenalin and terbutaline. In our study Hexoprenalin (Hexoprenalin) was applied intravenously (i.v.). Hexoprenalin has shown fewer side effects than other beta2-adrenergic agonists. (11), (12), (13)

1.2.6 Oxytocin receptor antagonists

Oxytocin receptor antagonists were one of the few drugs specially developed to prevent preterm labour. Oxytocin receptors can be found in the mammary gland, the myometrium and the endometrium. These tocolytics block oxytocin receptors and thereby prevent a rise in intracellular calcium, which prevents uterine contractions. The most common side effects are nausea, vomiting, chest pain, headache and hypotension. There were two drugs created: Atosiban and barusiban, but barusiban failed to show significant effects in clinical trials. Atosiban (Atosiban) was the second tocolytic drug given i.v. to patients in this study. Atosiban has shown similar effectiveness on prolonging pregnancy as beta2-adrenergic agonists with fewer maternal side effects. (14), (15)

1.2.7 Nitrovasodilator

Nitrovasodilators have been used for delaying labour since more than 100 years. The most commonly used for delaying labour is called glyceryl trinitrate. The data is limited and conflicting, hence glyceril trinitrate is not commonly used for the prevention of preterm labour. (16), (17)

1.2.8 Calcium channel blocker (CCB)

The most frequently used tocolytics are CCB but they are not officially licensed for this purpose yet. They reduce the intracellular calcium concentration and thereby relax the muscle tissue of the uterus. Clinical trials have reported equivalent efficacy of nifedipine to traditional tocolytics. Furthermore patients treated with nifedipine have shown fewer side effects than beta2-adrenergic agonists. Most frequent side effects are hypotension, headache, tachycardia, anxiety, vomiting, palpitation and flushing. (18)

1.2.9 Cyclo-oxygenase (COX) inhibitors

COX inhibitors decrease prostaglandin production, which usually enhances the number of gap junctions in myometrial tissue and also increases intracellular Ca2+ concentration. Indomethacin is a nonspecific COX inhibitor and the most commonly used one as a tocolytic.

In some clinical trials a significant delay in delivery could be displayed and COX inhibitors have shown fewer maternal side effects than other tocolytics. COX inhibitors should never be applied after the 32nd week of gestation to prevent closure of the ductus arteriosus. There have been reports of neonatal renal failure after exposure to COX inhibitors and this also needs to be inquired in a clinical trial. (19), (20), (21)

1.2.10 Magnesium sulphate

Magnesium has been described to have a tocolytic effect in two studies in the 1980s but the results could not be confirmed by a Cochrane systematic review later on. Further studies even described an increase of neonatal mortality. As there are no benefits and severe side effects magnesium should not be used as a single agent tocolytic therapy. It can be given as a neuroprotective agent in women with preeclampsia though. Magnesium sulphate can also be used to reduce the risk of cerebral palsy. (22,23)

1.2.11 Oxytocin receptor antagonists versus beta2-adrenergic agonists

In our following study Atosiban, an oxytocin receptor antagonist and Hexoprenalin, a beta2-adrenergic agonist were used and I will now focus on these two groups in comparison in clinical trials.

Both have shown their efficacy in delaying birth by 48 hours in several studies. None of the two tocolytics could display any benefit in comparison to placebo for infant mortality and respiratory distress syndrome.

Atosiban showed fewer maternal side effects, especially for the cardiovascular system. The trial "The Evidence Regarding Maintenance Tocolysis" has shown that subcutaneous infusion of Atosiban or Terbutaline (a beta2-adrenergic agonist) is beneficial to maintenance tocolysis. The study "A prospective randomised trial of Atosiban versus hexoprenaline for acute tocolysis and intrauterine resuscitation." pointed out that Atosiban and hexoprenalin were similar in efficacy for tocolysis. Atosiban had fewer side effects but uterine contraction sustained faster. (24), (25), (26), (27), (28)

1.2.12 Standard versus long-term tocolysis

Usually tocolysis is given for 48 hours but treatment can be prolonged if further uterine quiescence is needed.

There are some main problems with evaluating the effects of tocolysis:

- diagnosis of preterm labour
- gestational age play an important role in delaying labour

- benefit/harm ratio might depend on gestational age
- cause of preterm labour are important for the infantile outcome

There is not enough evidence to support maintenance tocolysis at this point. Trials haven't shown any benefits of the neonatal outcome by prolonging pregnancy for more than 48 hours. Every case of preterm labour is unique though and in selected cases maintenance tocolysis could be beneficial. Further trials would be needed and should be prospective and include neonatal outcomes depending on gestational age. (25)

1.3 Complications following premature birth

There are many perinatal and postnatal complications affecting preterm infants. Here I will only discuss a selection of the most important conditions, which we also investigated in the course of this study. With higher survival rates of premature infants also more postnatal complications have to be expected. Neonatal intensive care units (NICUs) have a significant effect on infant survival rates but it is hard to find these care facilities in rural areas. One of the most important factors is the early identification of high-risk pregnancies and the referral of these women to a specialised centre.

1.3.1 Mortality

As mentioned before child mortality is much higher in preterm infants. With every gestational week the survival rate increases. Survival rates differ from country to country,

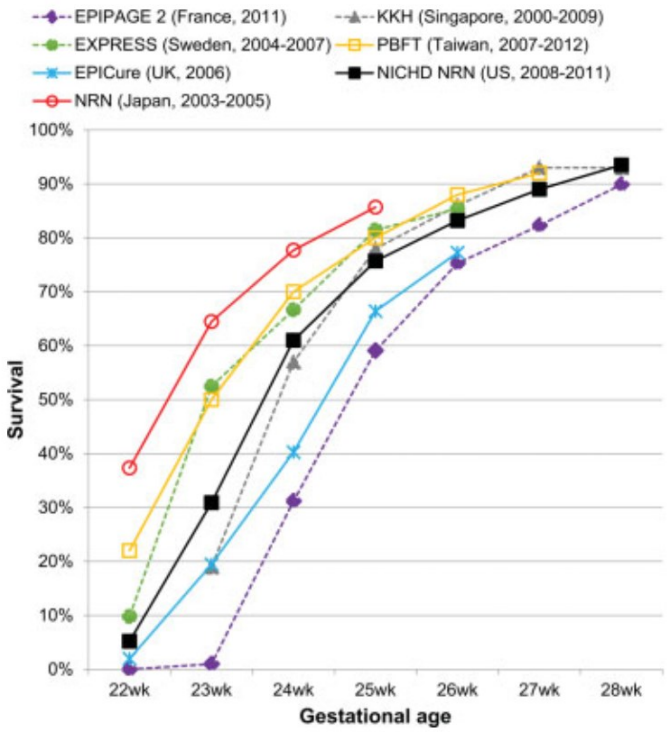

Figure 6: Survival rates per gestational week in various countries (31)

mainly because of different definitions of life birth, collection of data, ascertainment of death and selection of which infants will be included. A very important factor for the differences in mortality rates internationally is that there are many different standards on active treatment versus comfort treatment, especially for the youngest infants born before the 24th gestational week. A study, which included only infants receiving active treatment found, that at the 22nd gestational week 23% and at the 23rd week already 33% survived.(29)

1.3.2 Lungs and respiratory system

Normally foetuses start breathing movements where they in-and exhale amniotic fluid at the 10^{th} gestational week. Between the 30^{th} – 32^{nd} gestational weeks the foetal lungs start to produce surfactant factor, which is a lipoprotein and reduces surface tension in the alveoli and helps to keep them open. (30)

1.3.3 Infant respiratory distress syndrome

Infant respiratory distress syndrome IRDS is common (around 80%) in infants born before the 27^{th} gestational week and develops because of lack of surfactant. Symptoms are rapid breathing, grunting, poor colour, crackling, diminished breathing sounds, retractions of muscles under the thorax and flared nostrils. IRDS can lead to respiratory failure because of fatigue, apnoea and hypoxia. It is treated with respiratory support depending on severity and surfactant can be applied through an endotracheal tube. It reduces mortality by 40%, air leak by 40-65% and chronic lung disease but has not shown any effect on long term outcomes.(30)

1.3.4 Bronchopulmonary dysplasia (BPD) and chronic lung disease (CLD)

The terms chronic lung disease and bronchopulmonary dysplasia are used synonymously. There are different definitions of BPD, the most common one is the need of respiratory oxygen support after the 36th gestational week. It is a chronic disorder which results from injuries of the fragile lungs of preterm infants. Positive-pressure ventilation, high oxygen concentrations and infections injure the immature lungs easily. The lungs of infants, who suffer from BPD, fill easier with mucus and other fluids, tend to trap air and collapse easier. All of these factors contribute to less lung growth and development.

For treatment of BPD bronchodilators and diuretics are commonly used. There are also studies on intramuscular injections of vitamin A, which show modest improvement of survival rates. Systemic corticosteroids were used before but several studies have shown severe long-term impacts on infants. (30)

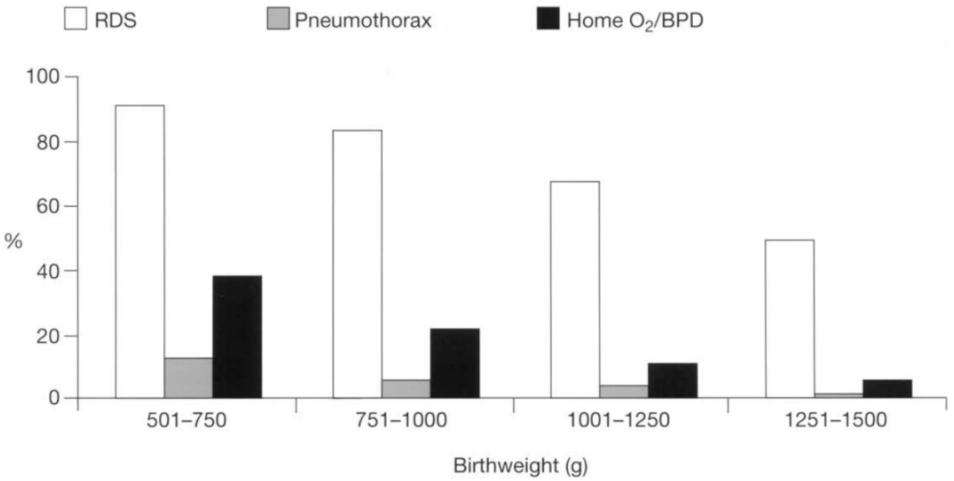

Figure 7: Percentage of neonates in need of oxygen, with BPD, Pneumothorax and IRDS in relation to birth weight registered in the Vermont-Oxford Neonatal Network Database in 2000 (33)

1.3.5 Necrotizing enterocolitis (NEC)

NEC is the injury and inflammation of small or large bowels followed by necrosis. The condition is the second most common cause of death in neonates. 7% percent of low-birth weight infants and 3% of infants born before the 33rd gestational week suffer from NEC.

Symptoms include abdominal distension, feeding difficulties, arterial hypotension and signs of sepsis.

The most important factor for a good outcome is the early detection of NEC. In the beginning it is sufficient to treat infants with intravenous nutrition and fluid, antibiotics, nasogastric suction and physical monitoring, while more severe cases need surgery ranging from peritoneal drainage to laparotomy with resection of the infected bowel segment. After a large resection of bowels it could be that intestinal transplantation might be needed later in life. (30), (31)

1.3.6 Spontaneous Intestinal Perforation (SIP)

SIP is the term for perforation of the intestines without any demonstrable cause. It is a frequent problem in preterm infants while there are only few cases of term babies affected by it.

Theories about the pathogenesis include hypo-perfusion due to hypoxia or stress. Abdominal swelling and vomiting are the symptoms a newborn with SIP presents.

Peritoneal drainage can be used as single therapy or to stabilize patients for laparoscopy. Infants with SIP have better outcomes than those suffering from intestinal perforation following NEC. (32)

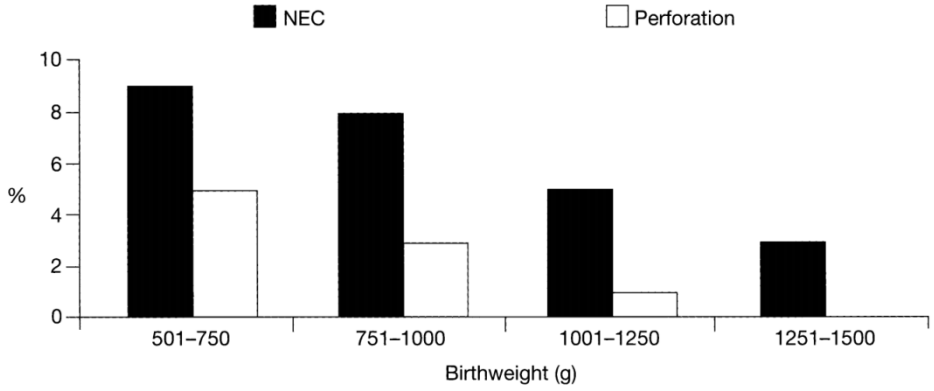

Figure 8: Percentage of neonates with NEC and intestinal perforation in relation to birth weight registered in the Vermont-Oxford Neonatal Network Database in 2000 (33)

1.3.7 Intraventricular haemorrhage (IVH)

IVH is the bleeding into the cerebral ventricular system. In neonates born with less than 1500g IVH occurs in around 20% and in those with a weight between 500 and 750 g the percentage is even higher with 45%.

Typically it starts in the periventricular germinal matrix below the lateral ventricles and then proceeds to bleed into the ventricles. In severe cases the bleeding can dilate the ventricles and increase intracranial pressure.

Most infants are asymptomatic and the diagnosis is found during routine ultrasound screening. In severe cases infants present with abnormalities in tone, movement, consciousness, eye movement and respiration. The condition can take on a dramatic dimension with coma, seizures, quadriparesis and stupor.

IVH is staged into 4 grades:

- 1-2 mild IVH – higher risk of developmental disabilities
- 3-4 moderate to severe IVH - higher risk of post-haemorrhagic hydrocephalus, cerebral palsy and cognitive impairments

Out of the infants suffering from IVH grade 3-4 45-85% will develop mental deficiencies and 75% of them will depend on special education in school. (33)

1.3.8 Periventricular Leukomalacia (PVL)

PVL is an injury affecting the tissue of the cerebral white matter, which causes necrosis or coagulation close to the lateral ventricles. Around 5% of premature infants with a birth weight below 1500g develop PVL.

The condition is built by two components: the diffuse and the focal injury of white matter (WM). The focal one consists of localized necrosis deep in the WM and builds cysts while the diffuse one only affects oligodendroglia.

Focal aspects can be discovered by ultrasound while the diffuse one can't be detected by it.

The clinical symptoms of PVL include spastic diplegia, cognitive and behavioural deficits.

The main factors which cause PVL are the immaturity of the vascular supply of the WM, impairment of cerebrovascular regulation, low blood pressure, the vulnerability of preoligodendrocytes, excitatory neurotransmitters and substances build because of inflammatory responses.

90% of premature infants with PVL survive the first 28th days but of these 20-25% develop cognitive or behavioural deficiencies later on in life and 10% will suffer from cerebral palsy. (30), (34)

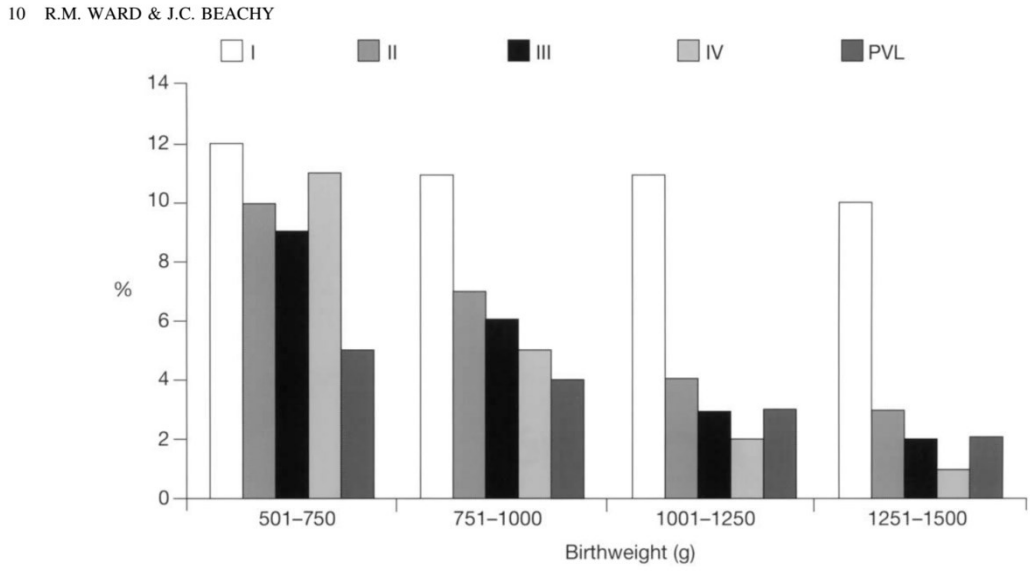

Figure 9: Percentage of neonates with IVH grades I-IV and PVL in relation to birth weight registered in the Vermont-Oxford Neonatal Network Database in 2000 (33)

1.3.9 Retinopathy of prematurity (ROP)

ROP is a neovascular retinal disorder and the most common disease of the eye in premature infants. It occurs in 90% of neonates with a birth weight less than 750g and in 42-45% of infants with a birth weight below 1500g.

Risk factors for ROP are oxygen therapy, variations in blood pressure, sepsis, and acidosis, low vitamin E levels and light exposure.

The pathological pathway of ROP consists of two phases: first the retina suffers from a loss of blood vessels and second they proliferate. Normally retinal blood vessels start growing around the 8th week but they only reach retinal periphery shortly before birth. Because of

the sudden higher oxygen amount in the blood when infants are born premature, the vessels stop growing and around the 30th – 32nd week starts a hypoxia –induced neovascularization which can cause scarring of the retina.

Fortunately in 80% of the cases ROP resolves without any impairment of the infants's eyes. (30,35)

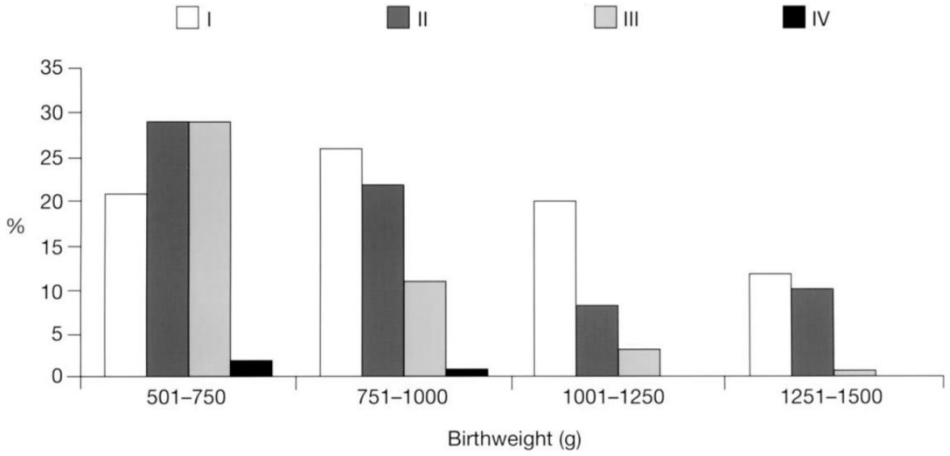

Figure 10: Percentage of neonates with ROP grade I-IV in relation to birth weight registered in the Vermont-Oxford Neonatal Network Database in 2000 (33)

1.4 Child development

As the numbers of preterm born infants and their survival rates are rising, also the long-term complications of these infants are increasing. The main focus has always been the short-term impairment of the infants but as there is a growing number of infants getting to adulthood the focus switches to long-term consequences. Premature birth is not like a disease with certain symptoms but rather increases the risk of certain adverse outcomes. There are also a lot of other societal, biological and environmental factors which contribute to the infant's development and should be taken into consideration.

1.4.1 Bayley Scales of Infant Development (BSID)

The first edition of the BSID was published by Dr. Nancy Bayley in 1969. She was an American psychologist who collected data for several years on the normal development of infants to standardize a test for infants between the ages of 1 to 42 months. The second edition of the BSID was published in 1993 and the third one in 2006. (36) There is also a German version which was published in 2007 and is a revised and adapted version of the BSID II. For the evaluation of the infants in our study the BSID II in German was used. Today the BSID is the gold standard for the psychomotor and mental evaluation of infants. The test should only be used by professionals and includes the evaluation of the infants's language, cognitive, social, fine motor and gross motor skills. The test consists of three main

parts: the cognitive scale, the motor scale and the behavioural scale. The cognitive scale assesses early memory performance, habituation, problem solving techniques, number conception, classification- and categorisation techniques, language skills, social-communication techniques and vocalisation. The motor scale evaluates body posture, fine and gross motor skills, coordination and body control while rolling, crawling, sitting, walking, running and jumping. The fine motor skills include for example grabbing, use of pens and imitation of hand movements. The behavioural scale judges the infants's attention, arousal, task orientation, emotional regulation and quality of movements. The achievements in the cognitive and motor scale can be evaluated in standardized sheets, while the behavioural observation is an addition for the other two scales. Information is collected by observing the child before, during and after the test situation in their behaviour towards other infants, their parent/parental figure and test person. It can be grouped as: normal, moderately impaired and well below normal. This behavioural classification is also important for validation of the test situation.

The test situation is especially developed to awaken interest in the toddlers to promote compliance. Although the test is standardized it is possible to be flexible, for example can order and pace of the tasks be adapted to the child's age, temper and succession rate. It is a so called Power-Test, which means that the tasks are sorted by their level of difficulty and that there are some tasks which are extremely difficult to solve and are not expected to be solved by everyone. The BSID is based on results of years of infant and toddler research. The BSID was developed to describe a child's normal development in the first three years of life but traditionally was used a lot to identify infants at risk. Today it is very often used for this purpose in many psychological and paediatric settings. There are different methods to evaluate a child's development, the main ones are: development tests, parent questionnaires, anamneses, infant neurological examinations. Especially important are running investigations of toddler development to estimate global cognitive and motor therapy aims. Another side effect of the test is that the parents can get a good insight into their infants's strengths and weaknesses to support their infants depending on the findings. As mentioned before the BSID was developed to describe normal infants so it is not ideal to be used to identify special development disorders, these would need further investigation. Also the BSID can't be used to screen infants and toddlers with severe disabilities because these infants would experience disadvantages in the test situation. The test can be adapted to a child's needs but then it is not possible to evaluate it in a standardized manner, but it can be used to describe a child's behaviour, skills and to control therapy aims. The examiner has

to decide if the test can be evaluated by standard measurements. It is possible to use the BSID also for infants out of the age range but then again no standardized evaluation is possible, but it can be used for running investigation. The BSID can also be used to evaluate specific medical interventions. A doctor can compare a child's score with the norm data of coeval infants and allows detecting main development problems and investigating these further with different tests. Furthermore the BSID-II contains information about different clinical subgroups and their average achievements in the test. This allows the examiner to see if a child scores average in its subgroup.

For Austria and Germany there are few references for these special groups because these data is rarely collected systematically. For the German version the results of infants with medical risk factors from the Heidelberg University Hospital were compared to infants with the same condition in other countries with. There could be shown the results correlating and meeting the clinical expectations. This shows that the BSID-II German version is comparable with the English version.

A medical decision should never be based on solely one diagnostic test like the BSID.

Development tests were designed to document if a child has basic skills in a defined time span. Infant and toddler tests set milestones which should be achieved in an age group while intelligence tests are designed to predict the learning aptitude or mental disorders of infants. So intelligence tests correlate the results to forecast later abilities of infants while development tests just show the child's abilities at the moment.

Prediction based on tests performed on infants and toddlers is limited but it is of central interest. Early childhood examination can predict later intelligence if they are based on the same basic skills as the intelligence tests later on. One trial compared the performances at the BSID of infants with biological risk factors at the age of 12 months to verbal and motor performances at the age of 4 ½ years and another one used the BSID Mental Scale at the age of 6 month and compared it to the Stanford-Binet-IQ Test at the age of 24 and 48 months. Both of them confirmed a correlation between the outcomes if there was not any intervention. The performances of infants who received support almost scored the same as the average in their age group.

Factors which narrow the validity of the tests are:

- interaction with the parents and their educational background
- the infant's or toddler's temper
- the learning environment
- the child's motivation

- low test-retest-reliability

The examiner should have good knowledge of a child's development and a qualified job in the field. Very often interdisciplinary teams work together in groups and the test situation is filmed and documented for evaluation purposes. (36)

1.4.2 Execution and evaluation

The parent or guardian should be present all the time, because sometimes the examiner has problems to achieve the child's wanted reaction. The examiner has to instruct the parent or guardian clearly when they should be included at a special test.

The test order is flexible and can vary with the child's interest and temper. If the infant or toddler needs a brake the task can be resolved after a couple of minutes.

There are special observation of behaviour items in the test which can be observed before, during and after the test and mainly focus on social and interaction skills of the child.

The test should be minimized to be as short as possible and to vary with the child's attention span. Typically it shouldn't last longer than 35 minutes for an infant under the age of 15 months while older ones can take tests up to 60 minutes.

The examiner should take enough time to contact and interact with the child in consideration of the child's age before the beginning of the test to make sure test results are not impaired by communication problems. (36)

1.4.3 Examination of infants born preterm

Generally the tasks should correlate to the corrected age of the child, while the chronological age should only be noted on the test paper. If the infants are older than 24 months it is possible to add some chronological age tasks.

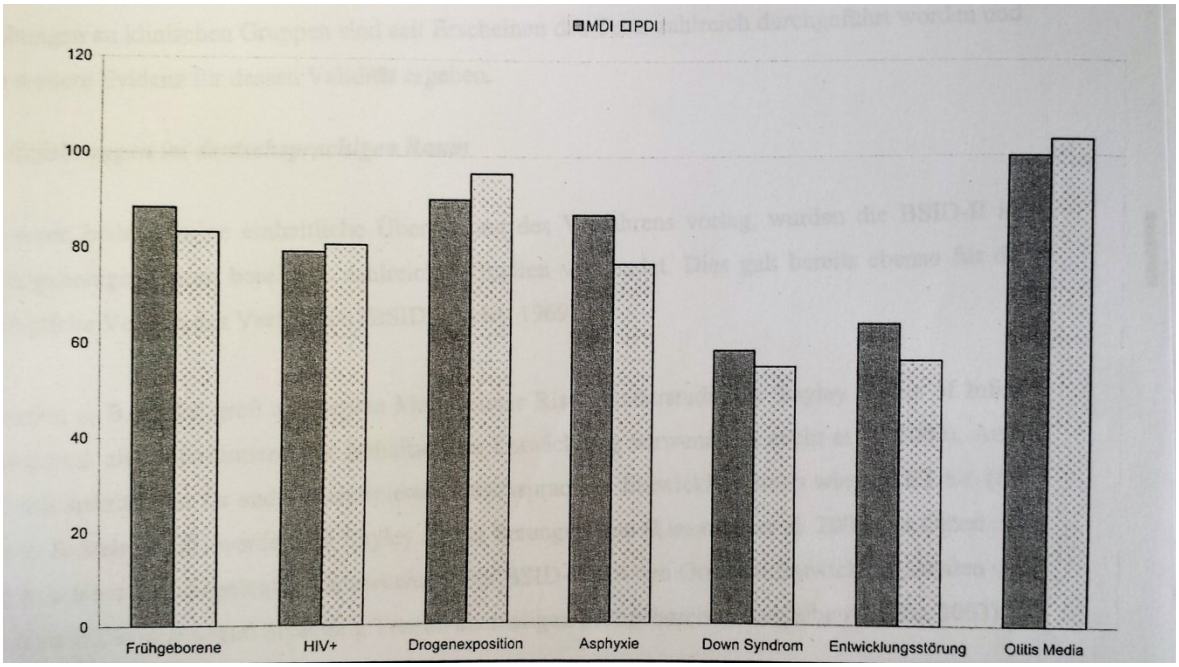

Figure 11: Different subgroups and their mean scores in the MDI and PDI (36)

The task areas were assorted by analysing the infants in the norm sample group and every item-set contains items which can be solved by 90% of the infants and some which can be solved by only 15%. Sometimes there is advanced information that an infant can't be categorised in their age group and then the one which is mostly similar to the child's developmental level should be chosen. It is also possible to start at one age group and to change it during the test situation if necessary. If a child has special skills in one field the examiner can choose a higher or lower level for different skills but then the evaluation should be interpreted with caution. (36)

1.4.4 Interpretation

It is the duty of the examiner to put the BSID outcomes into context with the clinical situation. The final diagnosis should be made in a synopsis of the patient's history, the BSID results, behavioural observation in different situations, impression of the test situation and social and cultural situation at home.

The test consists of two main parts, the Mental Development Index (MDI) and the Psychomotor Development Index (PDI). Both of them have a mean test score of 100 for a defined age group. It is expected that two thirds of all infants will achieve scores between

85 and 115, 95% of infants will score between 70 and 130 and almost all of them 99, 9% will have scores between 55 and 143. There is the alternative of using a nominal classification but examiners are very often not consistent in their language and use different terms synonymously and also these terms differ with every examiner. (36)

1.5 Neurodevelopmental disabilities

Neurodevelopment disabilities refer to a group of impairments affecting the central nervous system (CNS). These disorders are one of the main long-term concerns in premature infants. There are several disorders associated with malformation or injury of the child's brain. (36)

1.5.1 Cerebral Palsy (CP)

CP is a collective term for a group of chronic conditions which affect control of movement and posture. The symptoms result from malformation or injury of the motor locations in the CNS. The characteristics of the disease vary from person to person and can change over time. Typically CP becomes noticeable in early childhood and includes difficulty with walking, balance, fine motor skills and involuntary movements. In addition there can occur impairments of sensation, behaviour, cognition and communication. Furthermore the infants are more likely to develop epilepsy and secondary musculoskeletal problems. The diagnosis of CP should not be made before the age of 1 1/2 years because about 17-48% of preterm infants show signs of neuromotor disabilities during babyhood but most won't develop CP. Studies have shown that there is a correlation between transient neuromotor impairments and later on risk of behavioural and school problems. The impact of CP on the infants depends on which limb is affected and the severity of functional limitation. CP can be classified into a mild, moderate and severe form. Different longitudinal studies have shown that there is a steady correlation between the results of neuromotor tests at the age of 18-30 months and school age. In Sweden a study by Hagberg and associates in 1996 found almost stepwise increasing numbers of CP with gestational age:

- 1.4 per 1000 live births > 36^{th} week
- 8 per 1000 live births 32^{nd} - 36^{th} week
- 54 per 1000 live births 28^{th} – 31^{st} week
- 80 per 1000 live births < 28^{th} week

A trial carried out in Britain 1995 found that among the survivors of infants born before the 26th gestational week 20% were diagnosed with CP at the age of 6. Most other trials focused on birth weight; there the risk to develop CP was 10% for infants with ELBW and 7% for infants with VLBW. Circa 40 – 50% of infants diagnosed with CP were born preterm.

As mentioned before CP is an umbrella term and can be split in different subtypes. For premature infants the most frequent group is spastic diplegia. This type is defined by tense skeletal muscle tone, hyperreflexia and restricted movement around joints. Spastic diplegia affects both lower limbs and usually requires physiotherapy and medical interventions. Spastic hemiplegia is the term for spasticity on one side of the body and spastic quadriplegia affects all extremities.

The trial already mentioned before, which was set in Sweden and executed by Hagberg and associates in 1996 also divided the infants with CP in different subgroups:

- 60% of them had spastic diplegia
- 22% spastic hemiplegia
- 7% spastic quadriplegia

Furthermore they reported on additional impairments:

- 39% mental retardation
- 26% epilepsy
- 18% visual impairment
- 23% hydrocephalus

(8), (37), (38)

1.5.2 Coordination and planning impairments

Minor neuromotor dysfunction is an umbrella term for mild motor disabilities which are persistent but impact the infants only slightly. For example, if a child has slightly slower movements but still can walk by the age of 2 years and is generally mobile. The infants diagnosed with minor neuromotor dysfunction mostly only stand out while playing with other infants. These infants's main difficulties are in the fields of coordination, fine motor skills, motor planning and sensorimotor integration. A finish study published in 2005 examined infants born with ELBW at the age of 5 and reported following results:

- 51% coordination problems
- 18 – 20% abnormal reflexes or posture
- 17% involuntary movements

Other trials have shown that infants with VLBW (without CP and mental impairments) show significantly more problems with visual perceptual, visual motor, fine motor and visual spatial tasks than term infants. Also it could be demonstrated that the earlier infants were born the higher the percentage of impairments. It is important to detect neuromotor dysfunctions early to support the infants' development. (8), (39)

1.5.3 Cognitive impairment

Cognitive impairment can be measured by the Intelligence Quotient (IQ) or for younger infants by the Development Quotient (DQ). The IQ can't be used in early childhood because it demands visual-motor and perceptual abilities, which can only be evaluated in older infants. For the DQ and IQ test many aspects of a child's mental skills have to be considered. Intelligence is a composition of auditory and visual processing, abstract thinking, apprehending of syntax, complex language processing, visual perception and visual spatial processing. The IQ test is globally standardized and the mean score is 100. The IQ test gives an overview of a person's intelligence and can highlight areas where someone shows better or worse performances but it is not possible to make any exact conclusion about any specific disability. Usually for preterm infants for the DQ test the corrected age is used because neuromaturation outside the womb mainly follows the same timeline as in utero. The difference in IQ test scores between chronological and corrected age can be shown up to 8 years. Intellectual disability is defined as a mental disorder consisting of impairment of intellectual and adaptive functioning with IQ scores bellow 70.

A trial in Norway reported that they found an increased risk of 6, 9 times for intellectual disability in infants born before the 32nd gestational week and 1, 4 times in infants born between the 32nd and 36th gestational week compared to term infants. The risk of intellectual disability was also increased with less birth weight. Birth weights between

Table 1: Correlation between birth characteristics and intellectual disability (40)

Birth characteristics	*General population*[b]	*Study population (N=30 037)*		*OR*	*95% CI*	*P value*	*MR by aetiological groups*				
	%[c]	*Without MR N=29 859*	*With MR N=178*				*Prenatal N=105*	*Perinatal N=8*	*Postnatal N=5*	*Undetermined N=25*	*Unspecified N=35*
		N[d]	*N (%)*				*N*	*N*	*N*	*N*	*N*
Gestational age (w)											
<32	0.6	178	7 (3.9)	6.9	3.2, 15.0	<0.0001	0	5	0	2	0
32–36	3.8	1139	9 (5.1)	1.4	0.7, 2.7	0.5	7	0	1	1	0
>36	95.6	28 542	162 (91.0)	1.0	–	–	98	3	4	22	35
Birthweight (g)											
<1500	0.4	109	7 (3.9)	11.6	5.3, 25.4	<0.0001	1	5	0	1	0
1500–2499	3.1	926	12 (6.7)	2.3	1.3, 4.2	0.007	9	0	0	3	0
≥ 2500	96.5	28 824	159 (89.3)	1.0	–	–	95	3	5	21	35
Head circumference											
<3rd centile	2.7	785	13 (7.3)	2.9	1.7, 5.2	0.0003	13	0	0	0	0
≥ 3rd centile	97.3	29 074	165 (92.7)	1.0	–	–	92	8	5	25	35
Apgar at 1 min											
0–2	0.5	153	7 (3.9)	8.2	3.8, 17.9	<0.0001	1	6	0	0	0
3–6	4.1	1229	13 (7.3)	1.9	1.1, 3.4	0.03	8	1	1	1	2
>6	95.3	28 477	158 (88.8)	1.0	–	–	96	1	4	24	33
Apgar at 5 min											
0–2	0.1	20	4 (2.2)	35.4	12.0, 104.8	<0.0001	0	4	0	0	0
3–6	0.8	246	7 (3.9)	5.0	2.3, 10.9	<0.0001	1	4	0	2	0
>6	99.1	29 593	167 (93.8)	1.0	–	–	104	0	5	23	35

CI, confidence interval; OR, odds ratio; –, not calculated.

[a] The few missing values in children with MR in Figure 1 have been considered normal.

[b] All children (*N*=26 310) born between 1980 and 1985 in Akershus County alive at 1 year of age.

[c] Medical Birth Registry of Norway.

[d] Numbers estimated according to frequency in general population.

2500 g and 1500 g increase the risk by 2,3 times, between 1500 g and 1000 g by 12 times, between 1000 g and 750 g by 15 times and under 750 g by 22 times. (40)
Preterm infants only make up 4% of Infants with intellectual disability. Many other studies have also shown that the lower the gestational week the higher the risk for mental retardation. Recent studies reported that infants with VLBW have mean IQ scores one standard deviation below the average.
Two studies of the connection between test scores in early child hood and at school age showed a significant improvement of the infants. It is hard to tell if these advancements can be attributed to improvement of the infants or because different tests were used at different ages. IQ–tests performed by young adults who had at least VLBW showed significant lower IQ scores than the control group with normal birth weight. Even if the IQ-scores were average, there were still more young adults with cognitive processing problems in the VLBW group. (8), (40), (41), (42)

1.5.4 Visual impairment

Preterm infants are at higher risk to develop ophthalmic morbidities. Rates of myopia increase with decreasing gestational age and severity of ROP and can be found in 20 – 22% of infants with VLBW. Hyperopia was reported in 12% and astigmatism in 29% of infants born before the 29th gestational week. Another trial revealed that 13% of very preterm infants used glasses while only 4% of term infants needed them. A correlation could be found between strabismus, IVH, PVL and severity of ROP. Infants born before the 26th gestational week had strabismus in 24%, the ones born before the 32nd gestational week had it in 19%, while only 3% of the control group had strabismus. The sequelae of ROP include cataract, glaucoma and retinal detachment. Furthermore visual acuity can be affected by optic nerve atrophy and amblyopia. As visual impairments are very common in premature infants there should be a regular ophthalmic follow-up on them to detect any impairment as early as possible. (43), (44), (45), (46)

1.5.5 Hearing impairment

All different grades of severity of hearing impairments occur in premature infants more often than in the general population. According to a British study of 6-year-olds auditory acuity was severely damaged in 3% of infants born before the 26th gestational week and could not be corrected with hearing aids, another 3% could be corrected and 4% had mild hearing impairment. In the control group consisting of term infants only 1% showed sever damage of the auditory acuity and it could be corrected with hearing aids and also only 1% showed

mild impairment of the sense of hearing. Another trial indicated that infants born with VLBW had hearing impairment in 7%. Moreover premature infants seem to have problems with auditory processing and discrimination. Again one very important factor is the early detection of the hearing impairment to improve long-term outcomes. (43), (47), (48)

1.5.6 School complications

Many different impairments, like speech and language disabilities, learning impediments and lack of attention contribute to problems in school. Three trials reported about primary school problems, infants examined were between the ages of 8 and 10 and born with ELBW. Out of these infants 13 – 33% had to repeat a class, 15 – 47% needed special aid and 2 - 20% were placed in special education. Studies carried out in early adolescence reported that ELBW infants were 3 to 5 times more likely to repeat a class and were 3 – 10 times more often supported by special education assistance than the control group. It could also be shown that the lighter the birth weight the higher the risk of complications in school. At the age of 18 only 36% of ELBW infants were in regular classrooms without any special education.

The main problems premature infants have to face in school are learning disabilities. The underlying causes are difficulties in understanding and using written and spoken language. The diagnosis of a learning disability can be made through different tests, but there is no internationally standardized test or definition. Generally studies suggest that around 10% of infants are affected. In preterm infants with average IQ scores learning disabilities are 3 to 10 times more likely to occur. The more complex school tasks get the more problems occur for preterm infants. The main difficulties for them are arithmetics and reading. (8)

1.5.7 Behavioural and social problems

It is hard to define behavioural and social problems and the most diagnosis just come from surveys of parents and teachers. Diagnosed attention deficit/hyperactivity disorder (ADHD) rates are 9 – 15% higher in premature infants compared to only 2% in the control group. Another study found a significant difference for attention, processing speed and working memory between infants born before the 28th gestational week and term born infants. Parents and teachers described that ELBW infants lack social competence, have a higher risk for hyperactivity, are less competent in athletics, show less adaptability and develop fewer social and leadership skills. Trials on the connection between preterm birth and autism were inconclusive.

By meta-analysing 16 studies it could be shown that 81% of them found a higher risk of behavioural problems in premature infants. Also most of them found a higher risk of ADHD and externalizing and internalizing symptoms in preterm infants.
In adolescence and young adulthood preterm born people tend to take fewer risks, which shows as lesser drug use, less violent behaviour and lose their virginity later than the general population. The premature infants also have shown fewer relationships with friends and family. (8)

1.6 Tocolysis and long-term outcome of premature infants

Here I will describe 3 different trials on the connection between long-term outcome of premature infants and tocolytic agents received antenatal. Unfortunately there are few studies on this subject and so only some tocolytic agents and their effects on long-term outcome are discussed here.

1.6.1 Beta2-adrenergic agonists and neurodevelopmental long-term outcomes

The trial "In utero beta 2 adrenergic agonist exposure and adverse neurophysiologic and behavioural outcomes" took place in America and was published in 2009. Overstimulation of beta2-adrenergic receptors in utero can influence the equilibrium of sympathetic-to-parasympathetic tone and thereby increase the number of infants with autism spectrum disorders and other behavioural disorders. (49) In humans the use of terbutaline during pregnancy was associated with difficulties with expressive language. Several studies have shown that the treatment with terbutaline or albuterol of the mother, whether per inhalationem for asthma or i.v. for tocolysis, was connected with autism spectrum disorders in the infants. (50) Another trial performed with fenoterol for tocolysis and later on beta2-adrenergic agonists p.o. reported on a higher number of psychiatric disorders and cognitive and motor impairments. An increased risk of poorer school performances without any other impairment could be shown in the group of infants whose mothers got ritodrine during pregnancy. Premature infants exposed to ritodrine in utero could also be associated with higher heart rates and blood pressure in adolescence. (49) There were also studies which could not make a correlation between ritodrine and adverse long-term outcomes though. A possible explanation for this would be that ritodrine was not given in the same amounts as in the studies listed above. Because of these findings asthma therapy with beta beta2-adrenergic agonists during pregnancy should only be inhaled, for quick relief and if possible other substances should be used for severe asthma. (49) The study "Child Development After Maternal Tocolysis with Beta-Sympathomimetic Drugs" reported a negative impact of

beta2-adrenergic agonists in term infants in the term infants while in premature infants no adverse effects could be found. (51) Because the duration and dose of applied beta2-adrenergic agonists seems to be the most important factor for adverse long-term outcome of infants, the drugs shouldn't be given any longer than indicated. (49), (51)

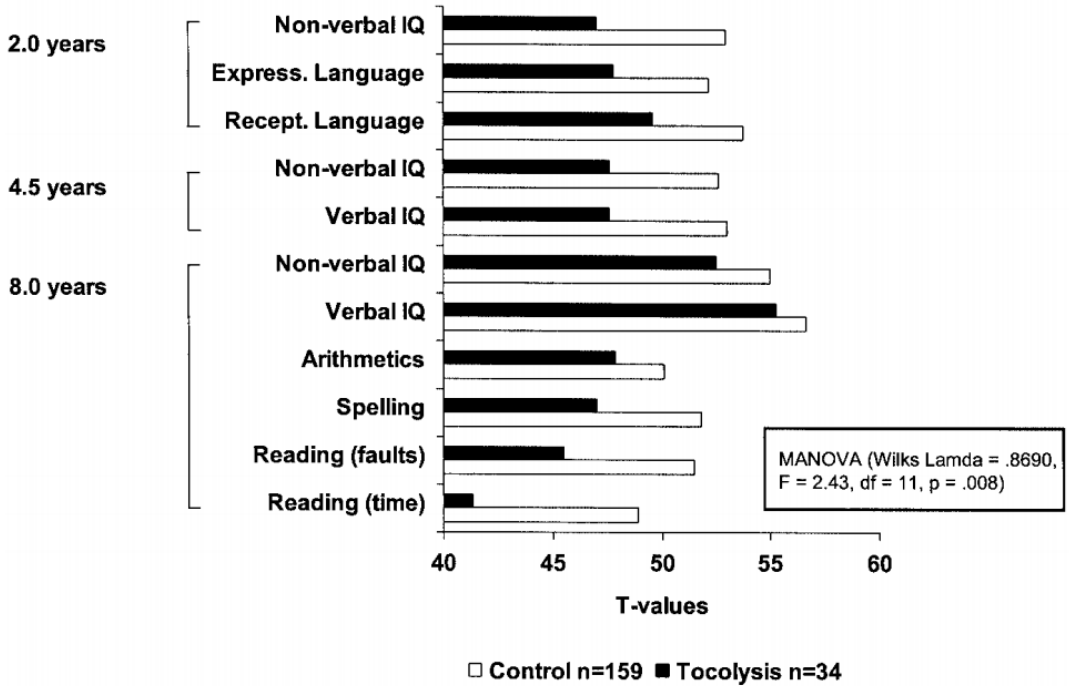

Figure 12: Cognitive development in term infants exposed to tocolysis with beta2-adrenergic agonists compared to unexposed infants (54)

1.6.2 Nitrodilators and tocolysis

The study "Neonatal neurodevelopmental outcomes following tocolysis with glycerol trinitrate patches" published in 2005 by Gill et al compared long-term effects of infants at the age of 18 months, whose mothers received glycerol trinitrate patches or beta2-adrenergic agonists. The trial took place in Australia, Hong-Kong and Singapore and included 156 infants. The conclusion of the trial was that there were more preterm infants with development delays than in the general population. There was no significant difference between the two tocolytic agents in rates of cognitive or neuromotor disabilities. (52)

Table 2: Comparison between infants exposed to beta2-adrenergic agonists and glycerol trinitrate patches (52)

	β2 agonist	GTN	
n	54	58	*P*
Median corrected age, months	18	18	.208
(I-Q range)	(18-19)	(18-19)	
Median locomotor	100	102	.686
(I-Q range)	(84.5-107)	(90-112)	
Median personal social	98	94	.301
(I-Q range)	(89-110)	(84.5-102)	
Median hearing and language	95	95	.645
(I-Q range)	(84-104.5)	(84.5-110)	
Median eye hand coordination	100	103	.397
(I-Q range)	(91.75-108)	(93-112)	
Median performance	102	102	.902
(I-Q range)	(90-110)	(90-108)	
Median total	98	97	.873
(I-Q range)	(91.5-103)	(89.5-107.2)	

P, Mann-Whitney *U*.

1.6.3 COX-inhibitors and tocolysis

The trial "Neurodevelopmental outcome of premature infants after exposure to antenatal indomethacin" by Sanjiv et al published in 2008 reports on the long-term outcome of preterm infants who were exposed to Indomethacin antenatal. The retrospective cohort study examined 87 premature infants at the age of 16 – 42 month. The infants exposed to Indomethacin did not show any more neurodevelopment impairments than the ones unexposed.

1.6.4 Influences on long-term outcome

A lot of different factors contribute to a child's development and a lot of other causes influence the neurodevelopment of premature infants. We have to keep in mind that the

impairments and outcomes described before can be influenced by social and biological factors too. Worldwide risks to affect an infant's development are:

- Inadequate cognitive stimulation
- Iodine deficiency
- Iron-deficiency
- Intrauterine growth restriction
- Malaria
- Intra uterine growth restriction
- Maternal depressive symptoms
- Exposure to violence
- Institutionalization
- Male gender

The main protective factors are:

- Breastfeeding
- Maternal education

There is strong evidence that these risk and protective factors play a very important role in a child's development. Environmental and social factors very often are able to level out other impairments. Especially social and economic factors can be changed and therefore a main focus should also be on decreasing the risk factors and increasing the protective factors. (53), (54), (55)

2 Material and methods

2.1 Methods

In this retrospective data analysis we collected data of infants whose mothers were treated with tocolytics between the 24th and the 32nd gestational week and their mothers. The ethic committee at the Medical University of Graz approved the trial. The mothers were mainly treated at the Department of Obstetrics and Gynaecology, Medical University Graz but some also were treated at another hospital first and then brought to Graz to deliver. All infants were born at the Division of Obstetrics and Maternal Foetal Medicine, Medical University Graz between 2004 and 2011. Information about the mothers was extracted from written health records stored at the Department of Obstetrics and Gynaecology. To collect the right data set first of all the patients had to be filtered in PIA to sort out only women who received tocolysis before the 32nd gestational week. The collected data was demographic and included information about pregnancy and delivery, laboratory values, ultrasound-findings, tocolytic

drugs and their side effects and short-term and long-term outcome of the infants. Data about the course of pregnancy and delivery was retrieved from PIA Fetal Database. The neurodevelopment of the infants was evaluated by using open Medocs and written clinical records which were stored at the Department of Paediatrics and Adolescent Medicine. Our primary aim was to classify infants in different levels of development by using results from the BSID-II. We analysed the MDI and PDI and arranged the outcome in 3 groups: general development, psychomotor development and mental development and within each group we classified the scores according to the BSID-II in normal, moderately impaired and well below normal development. Unfortunately only few infants were assessed with the BSID-II and some scores were not available. So we decided to also classify the infants by screening through the electronic health records and evaluate the neurodevelopmental outcomes by written diagnosis. Therefore we also made different groups: general neurodevelopmental outcome, motor development, language development and behavioural/social development. As mentioned in the chapter before several studies reported that the infants' results at such an early age are not really representative later in life and especially slight impairments very often level out, so we decided to split the neurodevelopmental outcome in normal and impaired and put all infants who had only shown slight-moderate impairments into the normal group.

Another problem we faced was that patients very often received not only 1 tocolytic but both of them. Hexoprenalin and Atosiban were switched various times because of side effects or ineffectiveness. The additional group is called "switch" and was included in most statistical analyses.

2.1.1 Statistical analyses

For the statistical analysis descriptive statistic was used to compare the effect of different groups on long-term outcome by using Fisher's exact test and/or Chi-squared test. Numerical data was evaluated by using standard deviation and t-test. Categorical data was assessed by using empirical probability.

2.1.2 Inclusion criteria

All infants whose mothers received tocolysis between the 24th and the 32nd gestational week at the Division of Obstetrics and Maternal Foetal Medicine, Medical University Graz between 2004 and 2011 were included. Only infants who were assessed at the corrected age of 2 at the University Hospital of Graz were included in the trial.

2.1.3 Exclusion criteria

Women with multiple pregnancies or with premature rupture of the membranes were excluded.

2.2 Material

As mentioned before the electronic health records were extracted from PIA and open Medocs. PIA foetal data base is a software to store medical pictures and information and focuses on obstetric and gynaecological ultrasound information. Open Medocs is a medical database which collects information about the patients and allows access for all authorized medical staff in hospitals connected by the program. The data was collected in Microsoft Office Excel and then statistically analysed in IBM SPSS Statistics 23.

3 Results

3.1 Study population

In the beginning 131 data sets were collected and the in- and exclusion criteria reviewed. Our study population is defined by infantile and maternal criteria, only singletons whose

Figure 13: Flow-chart of child eligibility

mothers received tocolysis before the 32nd gestational week and who were assessed at the age of 2 were included. Eight (7%) cases had to be excluded because of twin pregnancies. Unfortunately 3 (2%) neonates died within the first week in hospital. The main exclusion criterion was the presence at the two-year evaluation, where only 47 (41%) infants were examined (Fig.13).

3.2 Maternal demographic data

Table 4 displays a collection of maternal demographical data and is divided into 3 groups for women who were treated with Hexoprenalin, Atosiban and both of them. The mean pregnancy duration in days was 191 and was about the same in all groups. The youngest woman was 16 years old and the oldest one 40, the mean age was 28 years. None of the patients were obese but one was anorexic with a BMI < 17.5. In the categories height and weight no abnormal features could be found. One woman was pregnant the 7th time and had given birth 5 times before, while the average number of gravidity was 2.3 and of parity 1.6. There was no significant difference in any characteristic between the three groups (Table 3).

Table 3: One way analysis of variances to analyze the differences in maternal demographic data between the Atosiban, Hexoprenalin and combined group

	F-test	p-value
Gestational week	0,563	0,573
Age	0,95	0,395
Height	0,009	0,991
Weight	2,264	0,119
BMI	2,534	0,093
Gravidity	0,384	0,683
Parity	0,505	0,607

In this patient population the women were affected from various gestational disorders. One (2%) woman suffered from gestational diabetes and two (5%) from preeclampsia. Four (9%) women had a temperature above 37.5 °C, which can be a sign for amniotic infection syndrome, during their hospital stay. Two (5%) patients knew already beforehand that the foetus had intra uterine growth restriction. There was not any noteworthy difference between the treatment groups.

As mentioned in the chapter before uterine contractions, cervical length and fibronectin define the beginning of labour. In our study population 20 (56%) women had a cervical length less than 25 mm, while 16 (44%) were still over 25 mm when tocolysis started and in eleven cases the information was missing. At the Medical University Graz the routine testing of fibronectin started in 2007 and in this study 9 women were tested positive and 6 negative.

Table 4: Maternal demographic data

Tocolytic drug			Gestational week (wk)	Age (y)	Height (m)	Weight (kg)	BMI (kg/m^2)	Gravidity	Parity
Hexo-prenalin	N	Valid	27	26	22	21	21	27	27
		Missing	0	1	5	6	6	0	0
	Mean		28,037	29,308	1,6473	61,048	22,695	2,000	1,444
	Median		28,000	29,500	1,6750	61,000	22,152	1,000	1,000
	Std. Deviation		2,5643	6,7038	,07066	8,6745	3,2524	1,5191	,9740
	Minimum		25,0	19,0	1,51	52,0	17,6	1,0	1,0
	Maximum		33,0	41,0	1,80	82,0	29,5	7,0	5,0
Switch	N	Valid	12	11	12	11	11	12	12
		Missing	0	1	0	1	1	0	0
	Mean		29,000	30,091	1,6458	55,227	20,699	2,500	1,583
	Median		29,500	30,000	1,6550	54,000	20,200	1,500	1,000
	Std. Deviation		2,6285	6,4878	0,06626	6,4937	2,7204	1,9306	,9962
	Minimum		25,0	20,0	1,54	47,0	17,0	1,0	1,0
	Maximum		33,0	39,0	1,75	67,0	25,2	6,0	4,0
Atosiban	N	Valid	8	6	8	7	7	8	8
		Missing	0	2	0	1	1	0	0
	Mean		28,625	25,500	1,6438	57,143	20,363	2,250	1,875
	Median		27,500	24,500	1,6500	59,000	19,467	1,500	1,000
	Std. Deviation		3,2923	8,1179	0,05041	5,5205	2,2119	1,7525	1,4577
	Minimum		25,0	16,0	1,55	50,0	18,1	1,0	1,0
	Maximum		33,0	40,0	1,73	64,0	24,3	6,0	5,0

Figure 14 shows the modes of delivery; the most common mode of delivery was emergency caesarean section in 49% of the cases. The second most common was spontaneous vaginal delivery (30%), followed by elective caesarean sections (17%) and only 2 (4%) infants were delivered with forceps. There were no significant differences between women treated with Hexoprenalin and Atosiban.

The reasons for caesarean section included:

- Pathological cardiotocography
- Prolapse of the umbilical cord
- Breech presentation
- Placenta praevia
- Foetal abnormality
- Sections before
- Preeclampsia
- Pleural effusion

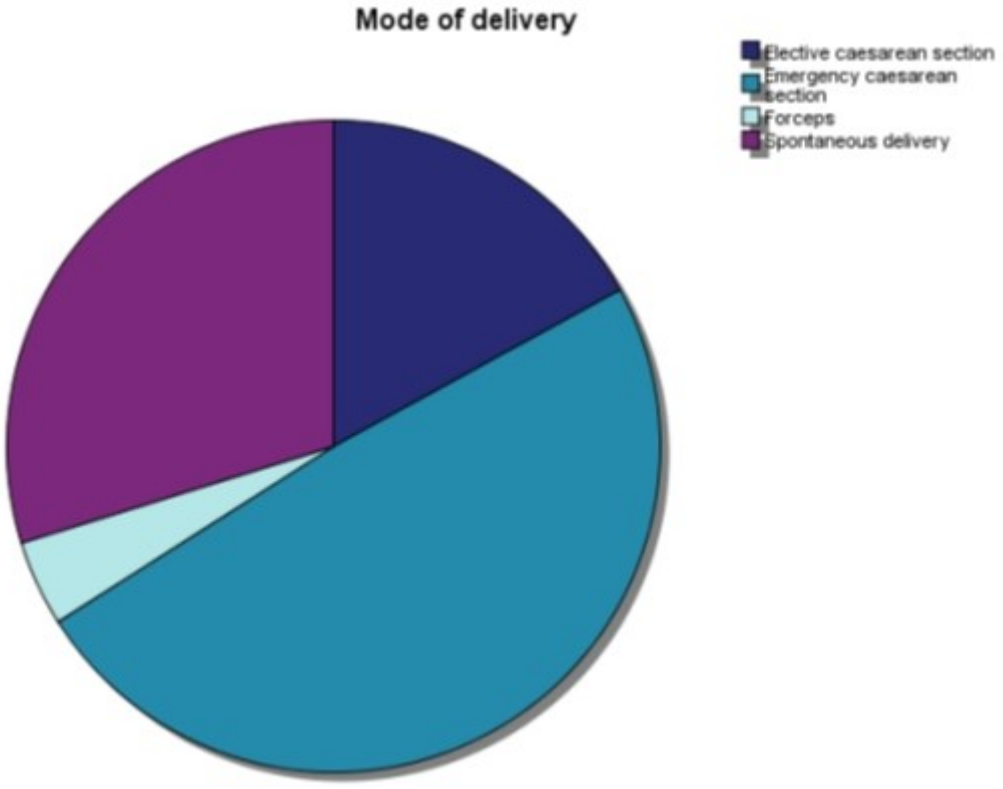

Figure 14: Mode of delivery

3.3 Tocolytics

Tocolysis was administered for an average of 5 days and started at the 26th gestational week without significant differences between the three groups.

Hexoprenalin was used in 27 (57%) cases, both medications were given to 12 (26%) patients and 8 (17%) were treated with Atosiban only.

Out of the 18 patients who received maintenance tocolysis, 8 (40%) were treated with Hexoprenalin, 4 (20%) with Atosiban and 8 (40%) with both. In the patient group who received standard tocolysis 14 (62%) were treated with Hexoprenalin, 4 (19%) with Atosiban and 4 (19%) times the tocolytic drug was switched.

Side effects occurred thrice; three patients had palpitations and one of them also reported nausea. One woman also had migraine after receiving Hexoprenalin. In all cases Hexoprenalin was used and exchanged to Atosiban and no more adverse effects occurred.

Table 5 shows how many women gave birth within 48 hours after starting tocolysis. In the Hexoprenalin group 13 women gave birth within 48 hours; in the group where both medications were applied 4 gave birth within 48 hours; in the Atosiban group 3 gave birth within 48 hours.

Table 5: Birth within 48 hours

Tocolytic drug			Frequency	Percent	Valid Percent	Cumulative Percent
Hexo prenalin	Valid	n	11	40,7	45,8	45,8
		y	13	48,1	54,2	100,0
		Total	24	88,9	100,0	
	Missing		3	11,1		
	Total		27	100,0		
Switch	Valid	n	8	66,7	66,7	66,7
		y	4	33,3	33,3	100,0
		Total	12	100,0	100,0	
Atosiban	Valid	n	5	62,5	62,5	62,5
		y	3	37,5	37,5	100,0
		Total	8	100,0	100,0	

3.4 Infantile demographic data and short-term outcome

Figure 15 shows the percentage of infants born per pregnancy week. 11 neonates were born in the 25th gestational week, with three of them born at the exact gestational age of 24+0. 21 (45%) were born extremely preterm and 22 (47%) very preterm and 3 (6%) preterm.

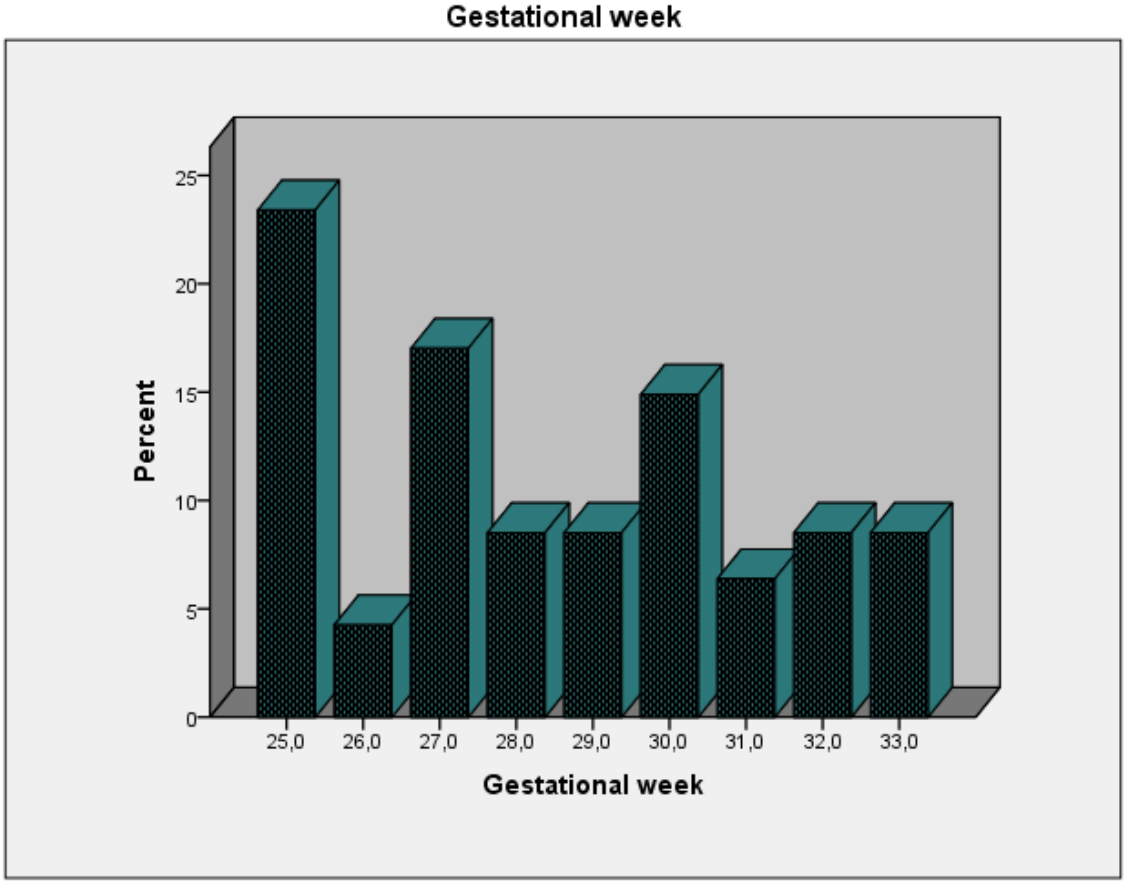

Figure 15: Percentage of infants born per gestational week

Table 6 represents the demographical data of the infants. Infants in the switch group were the heaviest and in the Atosiban group the lightest. Infants in the Hexoprenalin group were the shortest at birth but all of these differences were not statistically significant (Table 6). The mean weight was 1061g, max length was 37 cm, and the mean head circumference was 25, 6 cm. We also looked the APGAR score which is used to evaluate a child's adaption after birth. After 10 minutes only 3 infants had an APGAR score under 7. Five neonates had an umbilical cord pH under 7.2 which is an indication for hypoxia but should always be taken in consideration with the child's clinical appearance.

Table 6: Infantile demographic data

Tocolytic drug			Birth weight (g)	Length (cm)	Head circum-ference (cm)	APGAR 1 min	APGAR 5 min	APGAR 10 min	NA-pH	NV-pH	Base Excess
Hexo-prenalin	N	Valid	26	8	5	27	27	27	25	19	6
		Missing	1	19	22	0	0	0	2	8	21
	Mean		1127,346	37,250	40,700	5,630	7,852	8,296	7,2756	7,3505	-4,600
	Median		1060,000	37,500	27,500	6,000	8,000	9,000	7,3200	7,3500	-4,850
	Std. Deviation		424,8184	3,6154	32,6852	2,1865	1,7911	1,6128	0,13144	0,07677	3,1547
	Minimum		603,0	31,0	22,0	1,0	2,0	2,0	6,90	7,14	-8,3
	Maximum		2400,0	42,0	99,0	9,0	10,0	10,0	7,44	7,48	-1,3
Switch	N	Valid	12	4	3	11	11	11	10	8	2
		Missing	0	8	9	1	1	1	2	4	10
	Mean		1246,000	38,875	26,833	6,818	8,727	8,091	7,3080	7,3438	-3,700
	Median		1361,000	39,000	27,000	8,000	9,000	9,000	7,3100	7,3450	-3,700
	Std. Deviation		412,6932	3,8379	2,7538	2,0405	1,1909	2,8091	0,06339	0,07671	7,3539
	Minimum		710,0	34,5	24,0	4,0	6,0	0,0	7,24	7,25	-8,9
	Maximum		1960,0	43,0	29,5	9,0	10,0	10,0	7,40	7,47	1,5
Atosiban	N	Valid	8	3	3	8	8	8	5	6	5
		Missing	0	5	5	0	0	0	3	2	3
	Mean		1121,250	41,000	29,000	6,250	8,250	9,125	7,2740	7,3667	-3,780
	Median		1035,000	41,000	29,000	7,000	8,500	9,000	7,2400	7,3600	-3,100
	Std. Deviation		505,5248	5,0000	5,0000	2,1213	0,8864	0,3536	0,08081	0,09266	3,3907
	Minimum		590,0	36,0	24,0	2,0	7,0	9,0	7,19	7,25	-8,3
	Maximum		2210,0	46,0	34,0	8,0	9,0	10,0	7,37	7,48	0,2

Table 7 : One way analysis of variances to analyze the differences in infantile demographic data between the Atosiban, Hexoprenalin and combined group

	F-test	p-value
Birthweight	0,337	0,716
Length	1,026	0,388
Headcircumference	0,417	0,672
APGAR 1 min	1,257	0,295
APGAR 5 min	1,278	0,289
APGAR 10 min	0,808	0,452
NA-pH-Wert	0,311	0,735
NV pH	0,148	0,863
Base Excess	0,077	0,927

3.5 Neonatal short term outcome

In the Hexoprenalin group 84% suffered from IRDS, in the combined group 64% and in the Atosiban group 86%. Only 1 child developed NEC in the first week after birth. None of the neonates developed SIP.

Almost all neonates (93%) received oxygen after birth, only two did not and they were in the Hexoprenalin and switch group. Endotracheal surfactant was applied to 59% of neonates in the Hexoprenalin group, 67% in the switch group and 75% in the Atosiban group. In the Hexoprenalin group 85%, in the switch group 75% and in the Atosiban group 75% of infants were in need of invasive ventilation at some point.

IVH was diagnosed in 15% in the Hexoprenalin group (1x grade 1, 2x grade 3), in the switch group 27% (grade 3) and in the Atosiban group in 17% (grade 3). Two infants with IVH grade 3 also developed PVH and another 6 developed PVL. In all groups infants were affected by BPD (15%) and ROP (9%). Out of the three neonates who died 2 had an IVH grade 3, PVH, arterial hypotension and were intubated from the beginning of their lives. One of them died after 4 and the other one after 5 days of neonatal care. The 3rd one was a special case because the mother had caesarean sections before in another country and in this pregnancy the uterus ruptured at the gestational age of 24+0. The infant survived for to 2 days with invasive ventilation in neonatal care. This neonate and one of the others also suffered from IRDS II.

The average duration of hospital admission was 66 days, with a minimum of 2 days and a maximum of 153 days.

3.6 Long-term outcome

As mentioned before only 47 infants underwent examination at the age of 2 years, because the main part 58% was lost to follow up. Out of these 18 (38%) were evaluated with the MDI

and 12 (26%) with the PDI and only 8 (17%) were evaluated by using both of them. The reason more infants were tested with the motor development scale is that they were not able to perform the cognitive test because of mental impairments. The other 62% of infants were also examined by a doctor, but not assessed with the BSID-II, but were still categorized into having a normal or impaired development. For these infants the doctor's diagnosis was used to classify infants into impaired or not.

Fisher's exact test was used to analyze the difference on development outcomes between infants whose mothers received Hexoprenalin or Atosiban; no significant ($p=1$) disparity could be found. Furthermore the influence of maintenance or standard tocolysis on the infantile development was explored, however no significant differences could be observed ($p=0.752$). The impact of birth weight and grade of prematurity on the infantile development could not be interpreted, because one of the assumptions of the Chi-squared test was violated, because of the small number of cases in the LBW group. Furthermore Fisher's exact test did not show a gender disparity ($p=0.114$).

In general 45.5% showed a normal motor, 25% a moderately impaired and 29.5% a well below normal motor development. 57% had normal, 18% moderately impaired and 25% well below normal language development. In behavioural and social development 75% had a normal, 16% moderately impaired and 9% well below normal development.

Figures 16, 17 and 18 show the numbers of infants affected by developmental impairments per tocolytic agent, maintenance versus standard tocolysis, gestational age and gender.

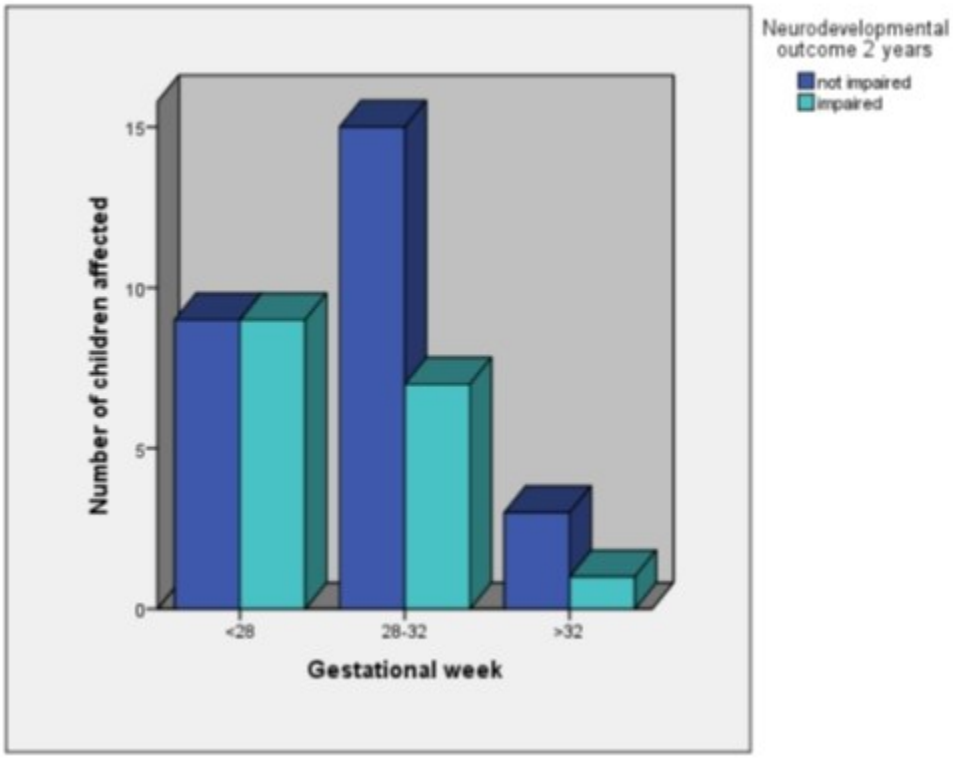

Figure 16: Number of infants with developmental impairments at the age of 2 per gestational week

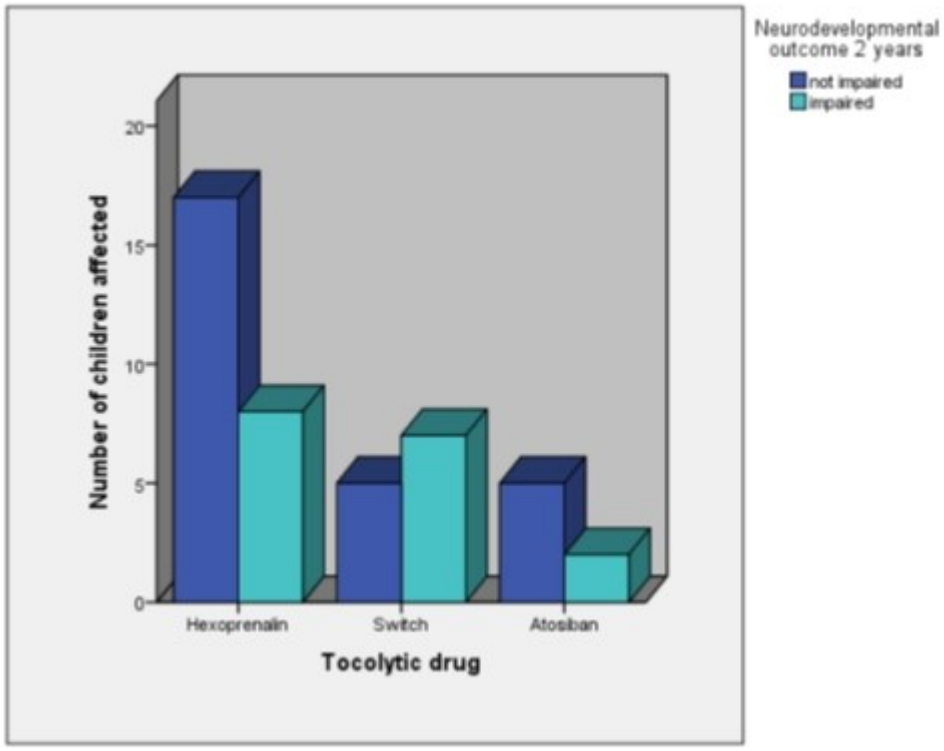

Figure 17: Number of infants with developmental impairments at the age of 2 per tocolytic drug

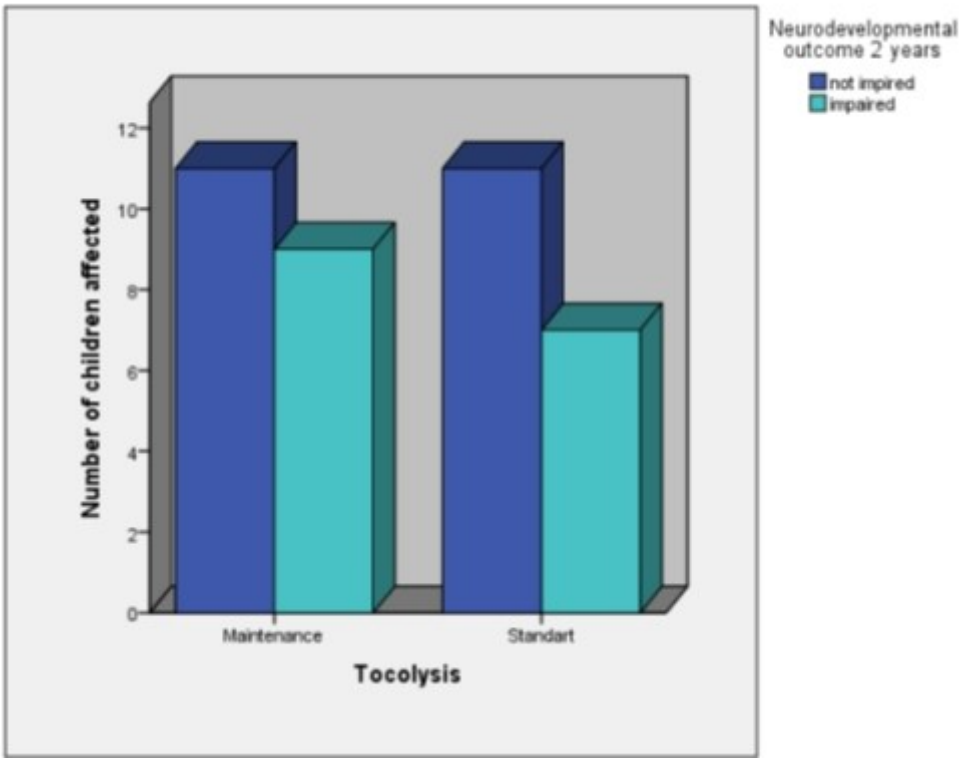

Figure 18: Number of infants with developmental impairments at the age of 2 per standard and maintenance tocolysis

3.7 BSID-II

According to the BSID-II 4 (50%) out of 8 infants who were tested with the PDI and MDI showed moderately impaired development at the age of two. These finding is heavily impacted by the fact that 7 infants could not take both tests because of disabilities or incompliance. In some cases data was missing and therefore was not included.

We compared the same factors as above with the combined results of the BSID-II and with the scores of the PDI and MDI, which we classified according to the BSID-II manual into normal, moderately impaired and well below normal development. Unfortunately due to the low number of cases only few tests were meaningful. The Fisher's exact test indicated that there is no impact on developmental outcomes due to tocolytic drug (p=0,429), length of tocolysis (p=1), VLBW and ELBW infants (p=1), gender (p=1) or gestational age (p=1). Figure 19 and 20 display how many infants were affected by developmental impairments within the three drug groups. Figure 21 and 22 show how many infants were affected by developmental impairments within the standard and the maintenance tocolysis groups.

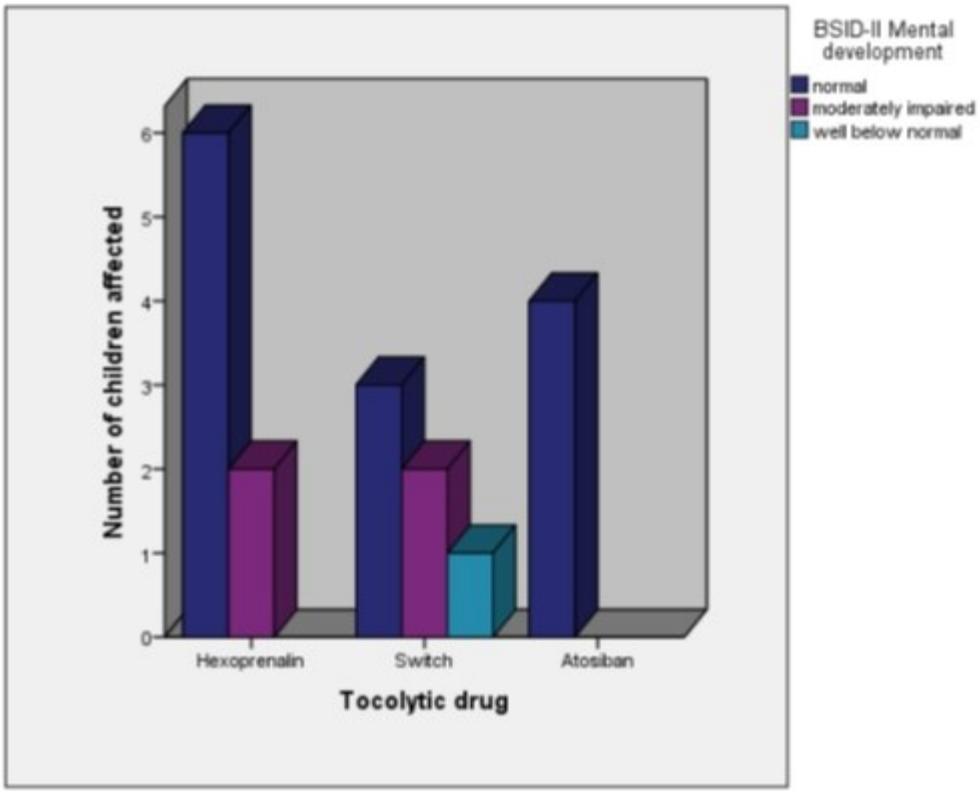

Figure 19: Number of infants affected by impairments in the BSID-II Mental development test per tocolytic drug

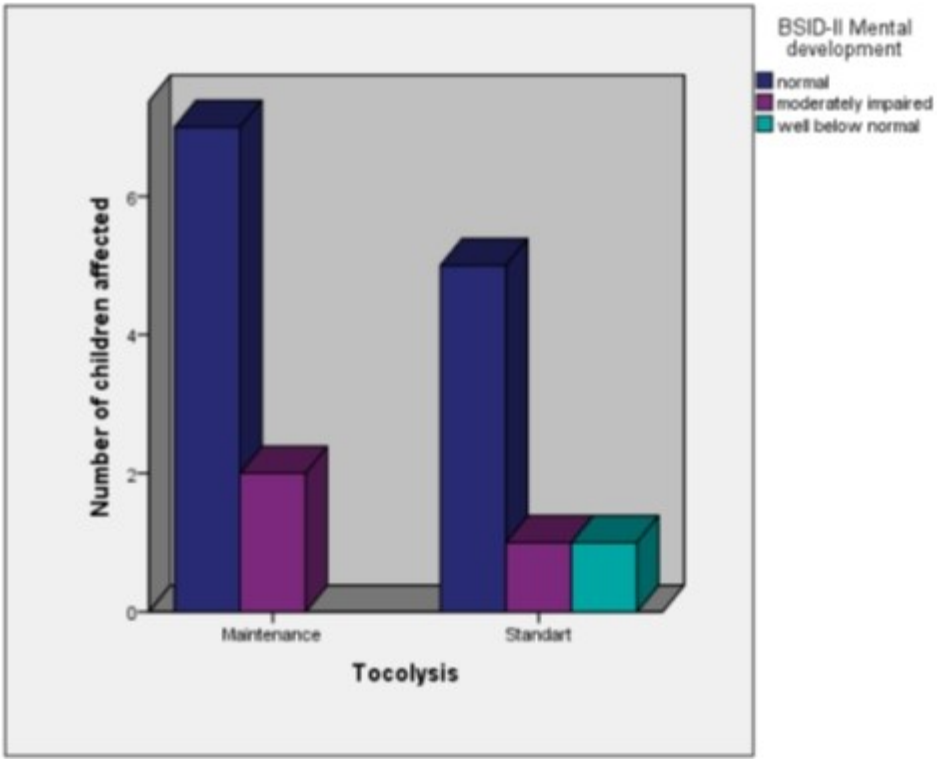

Figure 20: Number of infants affected by impairments in the BSID-II Psychomotor development test per tocolytic drug

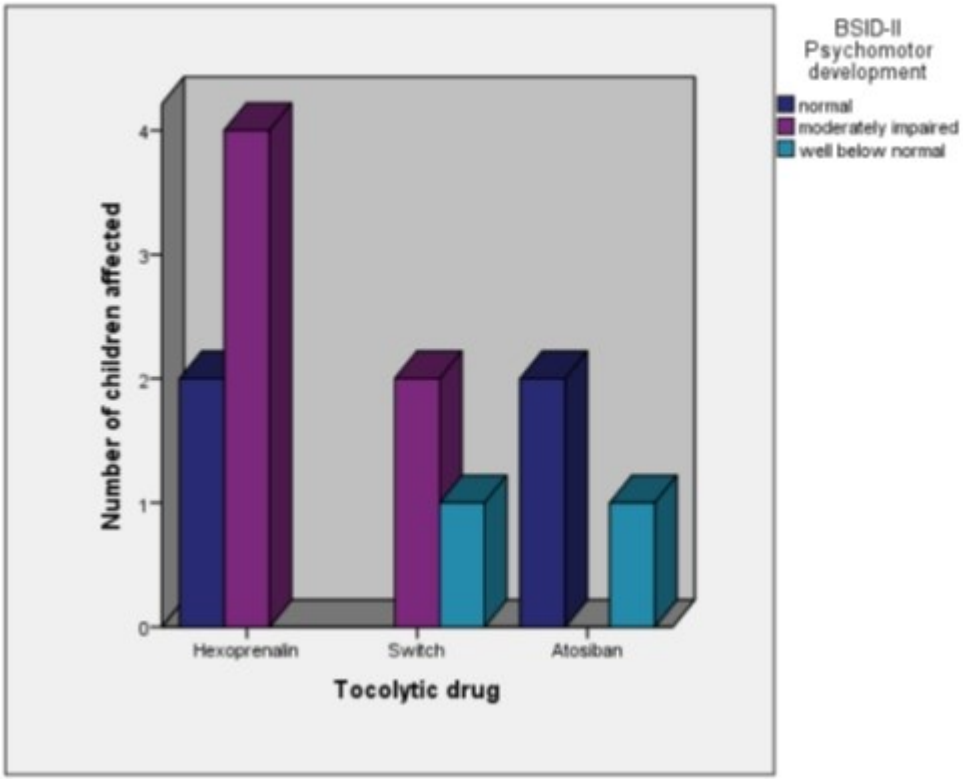

Figure 21: Number of infants affected by impairments in the BSID-II Mental development test per standard and maintenance tocolysis

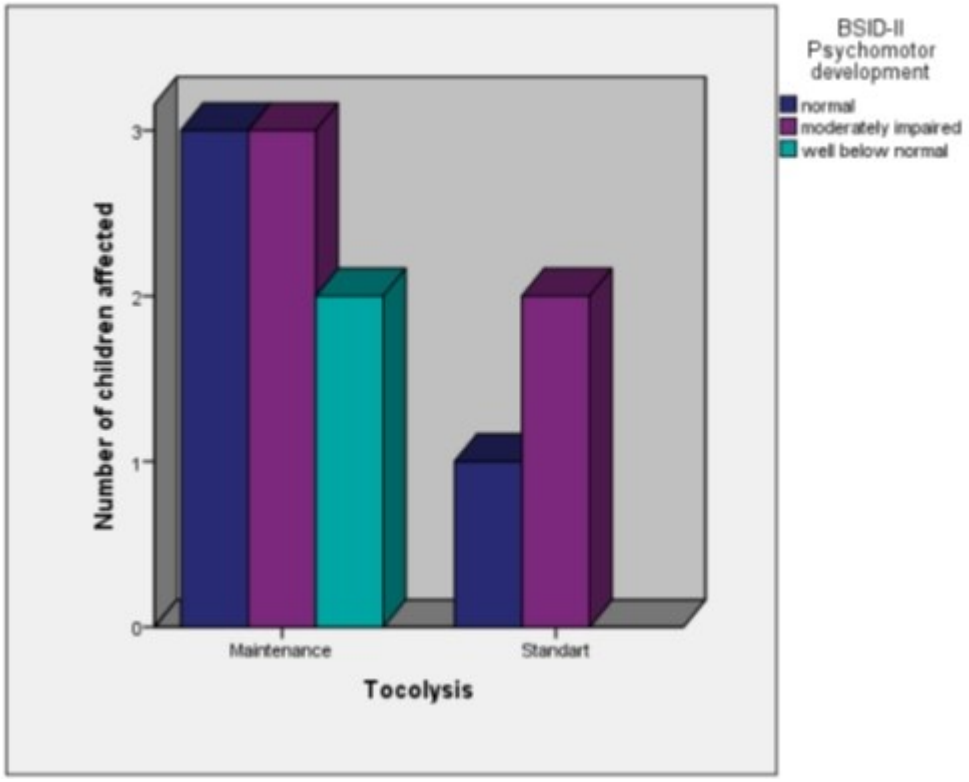

Figure 22: Number of infants affected by impairments in the BSID-II Psychomotor development test per tocolytic drug

The comparison of the PDI and MDI did not show any significant test results, due to the small sample size. Table 6 shows the mean scores of the MDI (93) and PDI (81). The lowest score was 64 and the highest 114 for the MDI, while in the MDI the lowest was 54 and the highest 107. In regard MDI the Atosiban group had the highest score with 103, followed by the Hexoprenalin group with a mean of 95; the switch group had the lowest average score (87). In regard the PDI, the switch group had the lowest mean score (70), followed by the Hexoprenalin group (83) and the Atosiban group (85). These findings are in line with the international scores displayed in the BSID-II, where the mean score in the MDI for preterm infants was 88.6 (SD 15.7) and in the PDI 83.5 (SD 21.6).

Table 8: Mean PDI and MDI scores

Statistics			
		MDI	PDI
N	Valid	18	12
	Missing	29	35
Mean		94,222	80,583
Median		96,000	80,000
Std. Deviation		16,0424	13,7739
Minimum		64,0	54,0
Maximum		114,0	107,0

3.8 Long-term outcome after the age of two years

37 infants were examined at the Department of Paediatrics and Adolescent Medicine in Graz after the age of two years. Any signs of impaired development were noted in the child's electronic health record. There was not anything like a standardized test or follow-up for all preterm infants after the age of 2 years and the examinations had various different reasons. The infants were between the age of 3 and 8 years and out of the 38 (81%) 18 (47%) had no impairment at all, 16 (42%) had a moderately impaired development and 4 (11%) were well below normal developed. In this statistical analysis we also had the problem that the motor, language and behavioural/social outcomes were split into 3 groups which left us with too little numbers to interpret the Chi-squared test.

The infants above the age of two years were diagnosed with the following problems: 4x microcephalus, 2x general motor impairment, 2x attention deficit hyperactivity disorder, 3x perceptual disturbance, 3x language impairment, 3x spastic diplegia, 2x dystrophy and 1x hemiparesis.

The cross tabulations 9, 10 and 11 display the number and percentages of infants with motor, language and behavioural/social development difficulties split into Hexoprenalin, switch and Atosiban group and into these groups into maintenance and standard tocolysis.

In the Hexoprenalin group two (22%) infants had moderate motor impairment; one (11%) of the mothers was treated with standard and one (11%) with maintenance tocolysis. In the switch group also two (33%) infants showed slight motor problems; again one (17%) mother received standard and one (17%) maintenance tocolysis. In the Atosiban group one (33%) infant had severely impairment in motor development in the standard tocolysis group.

Table 9: Motor development > 2 years

Tocolytic drug				Motor development > 2 years			Total
				normal	moderately impaired	well below normal	
Hexo prenalin	Tocolysis	Maintenance	Count	3	1		4
			% of Total	33,3%	11,1%		44,4%
		Standard	Count	4	1		5
			% of Total	44,4%	11,1%		55,6%
	Total		Count	7	2		9
			% of Total	77,8%	22,2%		100,0%
Switch	Tocolysis	Maintenance	Count	3	1		4
			% of Total	50,0%	16,7%		66,7%
		Standard	Count	1	1		2
			% of Total	16,7%	16,7%		33,3%
	Total		Count	4	2		6
			% of Total	66,7%	33,3%		100,0%
Atosiban	Tocolysis	Maintenance	Count	1		0	1
			% of Total	33,3%		0,0%	33,3%
		Standard	Count	1		1	2
			% of Total	33,3%		33,3%	66,7%
	Total		Count	2		1	3
			% of Total	66,7%		33,3%	100,0%

In the Hexoprenalin group two (22%) children had moderate motor impairment; one (11%) of the mothers was treated with standard and one (11%) with maintenance tocolysis. In the switch group also two (33%) children showed slight motor problems; again one (17%) mother received standard and one (17%) maintenance tocolysis. In the Atosiban group one (33%) infant had severely impairment in motor development in the standard tocolysis group.

Table 10: Language development > 2 years

Tocolytic drug				Language development > 2 years			Total
				normal	moderately impaired	well below normal	
Hexo-prenalin	Tocolysis	Maintenance	Count	3	1	0	4
			% of Total	33,3%	11,1%	0,0%	44,4%
		Standard	Count	4	0	1	5
			% of Total	44,4%	0,0%	11,1%	55,6%
	Total		Count	7	1	1	9
			% of Total	77,8%	11,1%	11,1%	100,0%
Switch	Tocolysis	Maintenance	Count	3	1		4
			% of Total	50,0%	16,7%		66,7%
		Standard	Count	2	0		2
			% of Total	33,3%	0,0%		33,3%
	Total		Count	5	1		6
			% of Total	83,3%	16,7%		100,0%
Atosiban	Tocolysis	Maintenance	Count	1			1
			% of Total	33,3%			33,3%
		Standard	Count	2			2
			% of Total	66,7%			66,7%
	Total		Count	3			3
			% of Total	100,0%			100,0%

Language development was moderately impaired in one (11%) child, whose mother received maintenance tocolysis with Hexoprenalin. Another one (11%) in the Hexoprenalin group was severely impaired but its mother had standard tocolysis during pregnancy. In the group where both medications were applied one (17%) child showed moderately impaired language development. None of the infants in the Atosiban group were affected by language impairments.

Table 11: Behavioural/social development > 2 yearss

Tocolytic drug				Behavioural/social development > 2 years		Total
				normal	moderately impaired	
Hexo-prenalin	Tocolysis	Maintenance	Count	3	1	4
			% of Total	33,3%	11,1%	44,4%
		Standard	Count	4	1	5
			% of Total	44,4%	11,1%	55,6%
	Total		Count	7	2	9
			% of Total	77,8%	22,2%	100,0%
Switch	Tocolysis	Maintenance	Count	3	1	4
			% of Total	50,0%	16,7%	66,7%
		Standard	Count	2	0	2
			% of Total	33,3%	0,0%	33,3%
	Total		Count	5	1	6
			% of Total	83,3%	16,7%	100,0%
Atosiban	Tocolysis	Maintenance	Count	1		1
			% of Total	33,3%		33,3%
		Standard	Count	2		2
			% of Total	66,7%		66,7%
	Total		Count	3		3
			% of Total	100,0%		100,0%

In the Hexoprenalin group two infants (22%) showed signs of behavioural/social problems; one (11%) where the mother received maintenance and one (11%) where the mother received standard tocolysis. In the switch group one (17%) child had social/behavioural difficulties. In the Atosiban group none of the infants showed signs of behavioural/social problems.

4 Discussion

The aim of this retrospective data analysis was to consider the 2 year neurodevelopmental outcome of infants whose mothers received tocolysis before the 32nd gestational week for preterm labour. Tocolysis is a common treatment all around the world and considered a standard therapy for women with premature uterine contractions. Although beta2-adrenergic agonists and oxytocin receptor antagonists have been used for a long time for this purpose there are few trials covering the long-term outcome.

The defining goal of tocolysis is to decrease the developing infant's mortality and morbidity. (9) In fact, trials on tocolysis shouldn't focus on the prolongation of pregnancy or only early neuromotor outcomes, but on the infants' long-term consequences caused by premature

birth. Of course the maternal adverse effects have to be taken into consideration and short-term consequences play a very important role as the majority of neonatal deaths occur in the first weeks after birth. Short-term outcomes are easier to measure and more often examined in studies, while the long-term outcomes are hard to obtain. (30)

The main focus of this study was on the neurodevelopmental consequences of intrauterine exposure to Atosiban and Hexoprenalin. The findings in our study suggest that there is no difference in long-term outcome between the group of infants, whose mothers were given Atosiba and the ones, whose mothers received Hexoprenalin. Several studies have covered the effects of $beta_2$-adrenergic agonists on the infants's mental, motor, behavioural and social development before with some of them providing a follow up into adolescence. Unfortunately oxytocin receptor antagonists haven't been well examined and we could not find any study on the long-term consequences. Trials before have implied that infants, whose mothers were treated with $beta_2$-adrenergic agonists prenatally, have to face more neurodevelopmental impairments in early childhood and also have more behavioural and social problems later on in life than control groups. (8)

The second focus was on infantile adverse outcomes of infants whose mothers received standard versus maintenance tocolysis during pregnancy. In our study we found no significant difference in the psychomotor or mental development of infants at the age of 2, whose mothers received maintenance tocoysis. Studies on the effect of tocolysis on infantile development have pointed out that one of the most important factors for poor infantile results is the duration of tocolysis, with some studies suggesting that anything over 72 hours impairs the child's development and others that more than two weeks go along with poorer outcomes. (49), (51)

4.1 Limitations

This study was affected by many major limitations. The main problem we faced was the limited number of infants, who were assessed at the age of 2 years. Only 43 (38%) of the premature born infants were examined while the rest was lost to follow up. With such limited numbers the validity of statistical tests is very low and in some cases the significance was not given any more because the numbers in the different groups were too small for statistical comparison.

One important factor which caused that problem was that very often not Atosiban or Hexoprenalin was applied but both of them were given to the mother, because of adverse effects or no impact on uterine contraction. That left us with a very big group of infants who were exposed to both medications antenatally. In this group the time tocolysis was given

varies and we do not know the exact amount of hours each medication was received by the mothers. Hexoprenalin represented the biggest group, the group where medication was switched was the second biggest and Atosiban was the smallest one. Especially the difference in these groups was a major problem for the statistical test situation.

The low number of infants also does not permit further investigation of possible factors affecting infantile outcomes. In our study population mothers were included who had known gestational diseases and some of them took medication during pregnancy which we did not consider. Also studies have shown that there are a lot of social and economic factors which contribute to a child´s development and can even level out impairments. (30)

The missing follow-up data also very likely influenced the outcome because many infants without any development problems are generally more likely not to attend the test at the age of 2. Furthermore infants with birth weights above 1500g were not always invited to be examined, but only if they showed any developmental impairments.

In this study we compared two groups of infants, whose mothers all received medication. To really tell the difference in adverse long-term outcomes a placebo-controlled trial with preterm infants would be needed.

Another problem in our study was the variety in hours tocolytics were given to compare standard and maintenance tocolysis. Maintenance tocolysis can mean anything from over 48 hours until our longest application of 40 days.

For the general neurodevelopmental outcomes we classified infants into groups based on the diagnoses of different doctors, which were not standardized and the terms used to describe the infants varied. The BSID-II was only evaluated in few cases although this test provides a good standardized test situation and evaluation, which also would allow international comparison.

The analysis of the BSID-II should be interpreted very carefully, because most infants with well below normal scores did not take part in both tests. The main reason was that they were not able to complete one or both tests, therefore no child is considered to have a well below normal development in both tests. The missing information may have an impact on the outcomes on the statistical analysis performed with this data.

The scores the infants achieved in the MDI and PDI were similar to international scores of preterm infants tested for the BSID-II, which suggests that tocolysis doesn’t affect neurodevelopmental outcomes.

4.2 Conclusion

Our study could not find any advantage of one of the tocolytic agents in terms of neurodevelopmental outcome for preterm born infants. Neonates in the maintenance tocolysis group and standard tocolysis group haven't shown any developmental differences at 2 years.

Tocolysis is frequently used to prolong pregnancy, but can potentially harm the mother and child. Furthermore the treatment could not demonstrate to improve the infantile long-term outcome. It is questionable whether it is necessary to use tocolysis in the dimension as it is in use today, especially if it´s given more than 48 hours and later on in pregnancy. For the future it should be a major aim of studies to focus on the pregnancy week neonates were born in, because the neonates born at low gestational age are more likely to profit from tocolysis and its prolonged use. (55), (56) Another important factor is to sensitise parents on the importance of follow-up because some impairments will not be detected before school age or adolescence and could cause problems. If these development issues were detected earlier, the infants could receive support and improve their outcome later in life.

In conclusion further studies with a larger study population on this topic are needed to evaluate the effect of tocolytics on the long-term outcome of preterm infants.

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