Medizinische Universität Graz

# Diplomarbeit

## Neurodevelopmental outcome at the age of two years in case of severe maternal preeclampsia

eingereicht von

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**OA. Dr. Manfred Mörtl und OA. Dr. Christa Rotky - Fast**

Graz, 10. Mai 2010 .....

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- Never, never, never quit -

'Winston Churchill'

# Zusammenfassung


## Ziel der Studie:

Im Rahmen der Präeklampsie wird das kindliche Outcome durch 3 Faktoren determiniert: die iatrogen bedingte Frühgeburtlichkeit, die in einem Prozentsatz von 12,5% bis 40% simultan vorkommende intrauterine Wachstumsretardierung und die mütterliche Erkrankung per se.
In dieser retrospektiven Untersuchung gilt es diese drei Outcome determinierenden Faktoren 2 Jahre post partum zu quantifizieren und deren Einfluss auf die neurologische Entwicklung von Kindern zu beurteilen.
Diese Fragestellung ist von außerordentlicher Bedeutung, da bis dato kaum Untersuchungen in Bezug auf das neurologische Langzeitoutcome durchgeführt wurden. Dieses Wissen ermöglicht jedoch eine Optimierung des präpartalenen Managements der Mutter, sowie eine Verbesserung der medizinischen Langzeitversorgung des Kindes, mit dem Fokus auf die Früherkennung von Entwicklungsverzögerungen und präventiver Frühförderung.

## Methodik

Im Zeitraum 1999 bis 200 5, wurde eine retrospektive Studie am Univ.-Klinikum Graz sowie dem LKH Klagenfurt durchgeführt, bei der alle Frühgeburten (<37 SSW) mit einem Gestationsgewicht unter 1500 Gramm, sowie reif geborene, aber dystrophe Kinder eingeschlossen wurden. Bei 29 dieser Kinder wurde mit einem korrigierten Alter von 24 Monaten ein Bayley's Test durchgeführt, anhand welchem die mentale und psychomotorische Entwicklung, mittels Einzeltests in den Subkategorien Sprache, Motorik (unterteilt in Fein- und Grobmotorik), Ausführung von Anweisungen sowie sozialem Verhalten beurteilt werden kann. Entwicklungsverzögerungen wurden mit leicht, mittel, schwer oder keine angegeben.
Diese Auswertungen wurden mit der Kontrollgruppe (Kinder gleichen Gestationsalters, aber Ausschluss mütterlicher Hochdruckerkrankungen während der Schwangerschaft) verglichen, um den Einfluss der Präeklampsie auf die neurologische Entwicklung beurteilen zu können.

Alle retrospektiv erhobenen Daten wurden mittels Microsoft Office Ecxel 2003 verwaltet. Als statistische Angaben wurden Häufigkeiten, Prozentwerte, Mittelwertsberechnungen, Standardabweichungen, Varianzen sowie Signifikanzen angeführt. Zur Prüfung statistisch signifikanter Unterschiede beider Gruppen wurde der T-Test für unverbundene beziehungsweise für verbundene Stichproben durchgeführt, ohne das Signifikanzniveau von 95% zu unterschreiten. Nur ein p-Wert unter 0,05 wurde somit als signifikant angesehen.

## Ergebnisse

Aufgrund der geringen Anzahl von 29 Kindern pro Gruppe konnte nur im Bezug auf das deutlich niedrigere Geburtsgewicht der präeklamptischen Gruppe (p=0,01) ein signifikanter Unterschied zur Kontrollgruppe aufgezeigt werden (mit einem Plus von 19,1 Prozent).

Auffallend war auch, die steigende Dystrophierate beider Gruppen im Rahmen des Krankenhausaufenthalts. Innerhalb der Kohorte kam es zu einem Anstieg von 31,6 Prozent bei Geburt auf 69 Prozent zum Zeitpunkt der Entlassung, in der Kontrollgruppe war sogar ein Anstieg von 5,3 auf 53,8% zu verzeichnen. Dieses Ereignis ist am wahrscheinlichsten auf das, in der Literatur beschriebene, verzögerte Aufholwachstum im Rahmen der Frühgeburtlichkeit, zurückzuführen. Das mittlere Entlassungsalter beider Gruppen betrug korrigierte 270 Gestationstage (38+4 SSW).

Bezüglich des neurologischen Langzeitoutcomes konnten keine signifikanten Unterschiede beider Gruppen aufgezeigt werden. In beiden Gruppen auffällig hoch war jedoch die Anzahl jener Kinder die keine Entwicklungsverzögerungen auswiesen(Kohorte 72,4% versus Kontrollgruppe mit 65,5%).
Im Falle einer Beeinträchtigung war diese mehrheitlich im sozialen Bereich (58,6% und 41,4%), gefolgt vom Sprach- (27,6% zu 34,5%) und Aufgabenbereich (24,1% zu 31%) zu beobachten. Die wenigsten Auffälligkeiten wurden im Bereich der Fein- und Grobmotorik diagnostiziert (10,3% zu 24,1%).

## Zusammenfassung

Aufgrund der zu geringen Fallzahl konnte mittels dieser Studie keine signifikante Auswirkung einer schweren mütterlichen Preeklampsie auf das entwicklungsneurologische Langzeitoutcome der Kinder nachgewiesen werden. Von umso größerer Bedeutung ist es, weiterführende Studien mit einer größeren Anzahl an Kindern durchzuführen, um einen eventuell bestehenden Einfluss signifikant nachweisen zu können.

# Abstract

## Aim of this study

The aim of this retrospective study was to evaluate the neurodevelopmental outcome on corrected 2-year infants after severe hypertensive disorders in pregnancy and to analyse the influence of severe pre-eclampsia on a long-term developmental outcome.

This question is of extraordinary significance because most studies concerning severe hypertensive disorders in pregnancy focus on maternal and fetal/neonatal short term outcome only, without paying attention to their long-term outcome. The knowledge of the long-term neurological outcome contributes both, to an optimization of the antepartum management of the mother, as well as improved medical care for the child by allowing special attention to long-term care, early detection of disabilities and initiation of early intervention.

## Methods

This is a retrospective study with a study group of 29 preterm and/or small for gestational aged infants (<37-weeks and <1,500 g or >37-weeks and gestational weight <10 percentile) born alive at the LKH Graz or the LKH Klagenfurt, after maternal severe preeclampsia between the years of 1999 and 2005. At a corrected age of 24 months, a neurological examination, according to Bayley was performed to assess the mental and psychomotor development of the child. The adverse neurodevelopmental infant outcome has been defined as no, low, medium or severe neurodevelopment delay and subdivided into delays, concerning motor function, language skills, social behaviour or mental function.

To prove significant differences statistically, a T - test was conducted for independent or related samples. Implications were based on a significance level of 95%; hence a p-value below 0.05 was considered significant. Frequencies, percentages, means, standard deviations and variances were used as statistical procedures.

## Results

Within the perinatal, postnatal, discharge periods and neurological outcome at the corrected age of 2 years, the only significant difference ($p = 0.01$) could be proven within the gestational weight. With an average gestational weight of 1,081 grams in the study group and 1288 grams in the control group, a plus of 19.1 percent could be registered.

As described in other studies, the process of delayed growth in the context of prematurity could be shown in both groups. At the time of birth 31.6 percent of the children within the study group and 5.3 percent within the control group had been dystrophic; at the time of discharge the percentage of dystrophies increased 69 percent in the study group and 53.8 percent in the control group. The mean corrected age at discharge was

38 + 4 weeks of gestation, the same in both the study group and the control group, without correlation to gestational periods of the infants.

It is significant to say however, that 72.4 percent within the study group and 65.5 percent of the control group passed the Bayley's Test without any disabilities at all.
Most abnormalities were observed in the 'social skills' (58.6 and 41.4 percent), followed by disabilities in 'language skills' (27.6 to 34.5 percent), 'task performance' (24.1 to 31 percent). The fewest disabilities occurred within the 'gross and fine motor skills' (10.3 to 24.1 percent).

## Conclusion

Neonatal care has changed over the passage of time, resulting in improved survival rates, which eventually results in delays of neurodevelopmental long-term effects in cases of children after severe maternal preeclampsia; as we assumed.
In this study, neurodevelopmental outcome did not differ between the study group, including children with severe maternal preeclampsia only, and the control group, with infants, of the same gestational age but without any form of hypertensive disorders of pregnancy. Hence, a significant correlation between severe maternal preeclampsia and a neurological developmental delay could not be revealed.
Therefore, future studies with correspondingly larger sample sizes are necessary to confirm the influence of preeclampsia on the infants' neurodevelopmental long-term outcome, to improve quality of perinatal care, for early detection of disabilities and initiation of early intervention, which would lead to a better quality of life for the child as well as for the mother/parents.

# Index

# I. Introduction

## 1. Purpose of the study

The aim of this retrospective study was to evaluate the neurodevelopmental outcome on corrected 2-year infants after severe hypertensive disorders in pregnancy and to analyse the influence of severe pre-eclampsia on a long-term developmental outcome.

This question is of extraordinary significance because most studies concerning severe hypertensive disorders in pregnancy focus on maternal and fetal/neonatal short term outcome only, without paying attention to their long-term outcome.
Severe hypertensive disorders in pregnancy are associated with fetal growth restrictions, iatrogenic preterm delivery, and not yet proven but hypothetically-assumed burden of trans-placental factors through maternal disease itself. Adverse neurodevelopmental outcome poses a serious threat to the newborn and the relation to preterm birth and small-for-gestational-age (SGA) status has been shown in many studies, but no study to date has focused on neurodevelopmental long-term outcome related to maternal pre-eclampsia.

The knowledge of the long-term neurological outcome contributes both, to an optimization of the antepartum management of the mother, as well as improved medical care for the child by allowing special attention to long-term care, with the focus on early interventions.

## 2. Objectives and limitations

Our primary aim has been the analysis of the influence of severe preeclampsia on a long-term basis by comparing two groups: all infants, born after 37 weeks of gestation with severe hypertensive disorders of pregnancy versus the control group, which included children of the same gestational age, but without maternal hypertensive disorders. Due to capacity reasons, only children born either before the completed 37 weeks of gestation with a weight of 1,500 grams or less, or infants with a gestational age over 37 weeks with signs of dystrophy (weight or size below the 10 percentile) could be followed up regularly at the University Hospital in Graz.
Infants not meeting these criteria were referred to an established pediatrician for further care. Hence, it was not possible to record these children's data for our retrospective study.

Therefore, the primary issue has been revised and adapted to these conditions, by including the criteria described above. Hence, only infants either born before completed 37 weeks of gestation with a weight of 1,500 grams or less, or infants with a gestational age above 37 weeks but with signs of dystrophy, with regular clinical follow ups at the LKH Graz or the LKH Klagenfurt have been used for study results. The conception of a control group has resulted, based on these criteria, with the same gestational periods as the study group and under the exclusion of any maternal pregnancy indicated hypertension.

In both groups, the following data interpretation has transpired:

- *perinatal period*: mode of delivery, gestational weight, length and head circumference, incidence of dystrophy, acid-base metabolism, adaption ability using the Apgar score one, five and ten minutes after birth, gestational weight, length and head circumference

- *hospitalization*: duration of in-patient stay, incidence of neurological/cerebral complications including cerebral complications such as intraventricular hemorrhage (IVH), perivenricular leukomalacia (PVL), periventriculat hemorrhage (PVH), and hydrocephalus, gestational age at time of discharge, weight, length and head circumference at time of discharge

- *at the age of two years*: assessment of neurodevelopmental outcome with differentiation of motor function, language or mental delay using the Bayley Test,

# 3. Working hypothesis

We hypothesised that next to gestational age and the rate of growth restriction, the severe maternal pre-eclampsia itself, is a risk factor for an adverse neurodevelopmental outcome.

# 4. Definitions of basic termini

## 4.1. Terms of preeclampsia

Preeclampsia is one of the most common medical disorders affecting pregnancy, with significant maternal and fetal morbidity and mortality. [1]

### 4.1.1. Definition and clinical manifestation

Preelampsia refers to the new onset of hypertension and proteinuria after 20 weeks of gestation in a previously normotensive women. [5] Additional signs and symptoms that can occur include visual disturbances, headache, epigastric pain, thrombozytopenia, and abnormal liver function. [2]

The clinical manifestations of preeclampsia generally appear anytime between the second trimester and the first few days post partum; however the initial pathogenetic findings of the disease arise much earlier in pregnancy. [5]

### 4.1.2. Pathogenesis

All of the clinical features of preeclampsia upon may be explained as maternal responses to generalized endothelial dysfunction. Disturbed endothelial control of vascular tone causes hypertension, increased vascular permeability results in edema and proteinuria, and abnormal endothelial expression of procoagulants leads to coagulopathy. These changes also cause ischemia of target organs, such as the liver, kidney, and placenta, sometimes with life-threatening results. The cerebrovascular manifestations of preeclampsia are poorly understood, but may represent a form of reversible posterior Encephalopathy, with loss of cerebrovascular autoregulation, and cerebral edema. [3]

4.1.3. Complications

The most serious maternal complications of preeclampsia include intracerebral hemorrhage, eclampsia, and renal failure, as well as hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome and posterior reversible encephalopathy syndrome (PRES). [1]

The fetal/neonatal burden of disease results from placental hypoperfusion and the frequent need for preterm delivery. [4]

4.1.4. Treatment

The definitive treatment of preeclampsia is delivery to prevent development of maternal or fetal complications from disease progression. Depending of the fetal gestational age, maternal and fetal condition, and the severity of preeclampsia, a decision must be taken in the best interest of the mother as well as the fetus. [5]

4.1.5. Classification

Preeclampsia is divided into following subtypes: mild, moderate, severe pre-eclampsia and eclampsia, which describes the presence of preeclampsia with additional convulsions.

To classify severe preeclampsia the following criteria established by the American College of Obstetricians and Gynecologists are recommended. [6, 7]

New onset proteinuric hypertension and at least one of the following:

- Symptoms of liver capsule distention such as right upper quadrant or epigastric pain, nausea, vomiting
- Hepatocellular injury: when serum transaminase concentration is at least twice normal
- Severe blood pressure elevation: either systolic blood pressure ≥160 mm Hg or diastolic ≥110 mm Hg on two occasions at least six hours apart
- Thrombocytopenia: with less than 100,000 platelets per cubic millimetres
- Proteinuria: 5 or more grams in 24 hours
- Oliguria <500 mL in 24 hours
- Fetal growth restriction
- Pulmonary edema or cyanosis
- Symptoms of central nervous system dysfunction such as: blurred vision, scotomata, altered mental status, severe headache (ie, incapacitating, "the worst headache I've ever had") or headache that persists and progresses despite analgesic therapy, cerebrovascular hemorrhage in worst case

## 4.2. Impairments of infants after severe hypertensive disorders of pregnancy

The fetal/neonatal burden of preeclampsia results from placental hypoperfusion and its fetal growth restriction and oligohydramnios as well as the frequent need for preterm delivery. [4]

The fetal consequences of chronic placental hypoperfusion are. Severe preeclampsia result in the greatest decrements in birth weight low weight compared to normotensive pregnancies.

Preeclampsia does not appear to accelerate fetal maturation, as once believed. The frequency of neonatal morbidities such as respiratory distress, intraventricular hemorrhage, and necrotizing enterocolitis are similar in infants of preeclamptic women and age-matched nonhypertensive controls. [8]

| Outcome measure | Normal blood pressure, (percent) | Mild preeclampsia (percent) | Severe preeclampsia (percent) |
|---|---|---|---|
| **Maternal** | | | |
| Liver dysfunction | 0.2 | 3,2 | 20,2 |
| Kidney dysfunction | 0.3 | 5,1 | 12,8 |
| Placental abruption | 0.7 | 0.5 | 3,7 |
| Induced labor | 12,1 | 41.5 | 58.7 |
| Cesarean delivery | 13,3 | 30,9 | 34.9 |
| Delivery <34 weeks | 3,2 | 1,9 | 18,5 |
| **Fetal or neonatal** | | | |
| Growth restriction | 4,2 | 10,2 | 18,5 |
| Admission to NICU | 12,7 | 27,3 | 42.6 |
| Respiratory difficulty | 3,8 | 3,2 | 15,7 |
| Brain hemorrhage | 0.2 | 0.5 | 0,0 |
| Fetal death | 0.9 | 0.5 | 0.9 |
| Neonatal death | 0.5 | 0.5 | 0.9 |

Table 1: Fetal and neonatal complications of pre-eclampsia

### 4.2.1. Preterm delivery

#### 4.2.1.1. Definition [9]

Prematurity is defined as a birth that occurs before 37 completed weeks (less than 259 days) of gestation. Different degrees of prematurity are defined by gestational age (GA), which is calculated from the first day of the mother's last period, or birthweight (BW).

The classification based upon gestational age is as follows:

- Late preterm birth: gestational age between 34 and less than 37 weeks
- Very preterm birth: gestational age less than 32 weeks
- Extremely preterm birth: gestational age at or below 25 weeks

Premature infants are also classified by birth weight (BW):

- Low birth weight (LBW): birth weight less than 2500 g
- Very low birth weight (VLBW): birth weight less than 1500 g
- Extremely low birth weight (ELBW): birth weight less than 1000 g

#### 4.2.1.2. Morbidity

Complications of prematurity are the underlying reasons for the higher rate of infant mortality and morbidity in preterm infants compared to full term infants. The risk of complications increases with increasing immaturity. Thus, infants who are extremely premature, born at or before 25 weeks of gestation, have the highest mortality rate (about 50 percent) and if they survive, are at the greatest risk for severe impairment.

Complications of the premature infant are divided into short-term complications, which occur in the neonatal period, and long-term sequelae in patients who survive and are discharged from the neonatal intensive care unit (NICU). Short-term complications increase the risk of long-term sequelae. [10]

##### 4.2.1.2.1 Short term complications

Premature infants are at risk for developing short-term complications that result from anatomic or functional immaturity during the neonatal period. The risk of developing complications increases with decreasing gestational age and birth weight. [11]

*Hypothermia*

Rapid heat loss occurs in premature infants because of their relatively large body surface area and inability to produce enough heat. Heat is lost by conduction, convection, radiation, and evaporation. Hypothermia may contribute to metabolic disorders such as hypoglycemia or acidosis.

In extremely premature infants of less than 26 weeks gestation, hypothermia is associated with increased mortality and, in survivors, pulmonary insufficiency. [12]

*Respiratory distress syndrome (RDS)*

RDS is defined as a syndrome of acute and persistent lung inflammation with increased vascular permeability, caused by surfactant deficiency. It is characterized by four clinical features:

- Acute onset
- Bilateral infiltrates consistent with pulmonary edema
- A ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen ($PaO_2/FiO_2$) ≤200 mmHg, regardless of the level of positive end-expiratory pressure (PEEP). The $PaO_2$ is measured in mmHg and the $FiO_2$ is expressed as a decimal between 0.21 and 1.00.
- No clinical evidence for an elevated left atrial pressure. If measured, the pulmonary capillary wedge pressure is 18 mmHg or less. [13]

*Cardiovascular abnormalities*

Symptomatic patent ductus arteriosus is common in premature neonates, occurring in about 30 percent of VLBW infants [11]. The PDA shunts blood flow from left-to-right resulting in increased flow through the pulmonary circulation and decreased perfusion of the systemic circulation. The physiologic consequences of the PDA depend upon the size of the shunt and the response of the heart and lungs to the shunt. Significant shunting may present with a variety of symptoms including apnea, respiratory distress, or heart failure.

*Systemic hypotension*

Systemic hypotension in the immediate postnatal period is associated with significant morbidity (eg, intraventricular hemorrhage [IVH]) and mortality in preterm infants and may result in neurodevelopmental impairment [4]. Contributing factors to hypotension may include perinatal asphyxia, hemodynamically significant PDA, infection, hypoxia, immaturity of the receptors and systems that regulate blood pressure, and relative adrenal insufficiency [15].

*Intraventricular hemorrhage (IVH)*

Intraventricular hemorrhage, also known as subependymal/intraventricular hemorrhage, usually occurs in the fragile germinal matrix and occurs most frequently in infants born before 32 weeks gestation or less than 1500 g birth weight. The incidence of severe IVH (Grades III and IV) is about 12 percent in VLBW [11].

| Grade | Description on parasagittal view |
|---|---|
| I | Germinal matrix hemorrhage only or germinal matrix hemorrhage plus intraventricular hemorrhage less than 10 percent of ventricular area |
| II | Intraventricular hemorrhage, 10 to 50 percent of ventricular area |
| III | Intraventricular hemorrhage involving more than 50 percent of ventricular area; lateral ventricles are usually distended |
| IV | Parenchymal hemorrhage in any location with or without intraventricular hemorrhage, also referred to as periventricular hemorrhage |
| Associated lesions | Periventricular echodensities, cystic lesions |

Table 2: Severity of intraventricular hemorrhage on cranial ultrasonography

Very low birth weight infants who are small for gestational age (SGA) have a lower risk of IVH than do infants who are appropriate for gestational age (AGA) [16]. This difference may influence the prevalence of IVH reported in series that are based upon birth weight rather than gestational age.

Virtually all IVH in premature infants occurs within the first five postnatal days, with 50, 25, and 15 percent on the first, second, and third day, respectively, and 10 percent on the fourth day or after [17].

Common risk factors for IVH in premature infants are hemodynamic instability, abrupt changes in systemic blood pressure, pressure-passive cerebral circulation, deficient structural support of the germinal matrix vasculature, coagulation disturbances, thrombocytopenia, coagulation defects, medications like bicarbonate

therapy, maternal anticoagulation therapy, chorioamnionitis and inflammation mediated by cytokine production and release. [18]

*Periventricular leukomalacia (PVL)*

Periventricular leukomalacia (PVL) refers to injury of cerebral white matter that occurs in a characteristic distribution and consists of periventricular focal necrosis, with subsequent cystic formation, and more diffuse cerebral white matter injury. [19] Lesions may become cystic or hemorrhagic, with reduced white matter volume and ventricuIomegaly. [20,21]

PVL with focal necrosis (PVL I) as well as PVL with necrosis and in addition cyst formation (PVL II-IV) in deep white matter is more common in premature infants with gestational age between 24 to 32 weeks at birth, and is associated with the subsequent development of cerebral palsy (CP), intellectual impairment, and visual disturbances.. [19, 22]

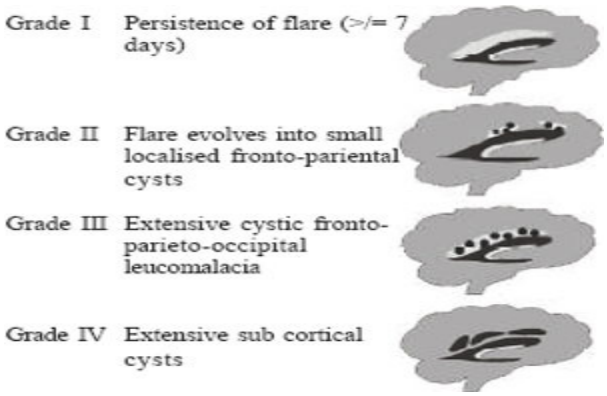


Figure 1: Classification of PVL

*Cerebral palsy (CP)*

Cerebral palsy consists of a heterogeneous group of nonprogressive clinical syndromes that are characterized by motor and postural dysfunction. These conditions, which range in severity, are due to abnormalities of the developing brain resulting from a variety of causes, such as perinatal asphyxia, neonatal encephalopathy, brain malformations, multiple births, stroke in the perinatal period, intracranial hemorrhage (ICH), intrauterine infection, posthemorrhagic hydrocephalus as a complication of IVH, e.g..

Although the disorder itself is not progressive, the appearance of neuropathologic lesions and their clinical expression may change over time as the brain matures.. [23]

CP is divided into four major classifications to describe different movement impairments, which reflect the areas of the brain that are damaged. [24]

- Spastic cerebral palsy caused by damage to the corticospinal tract or the motor cortex
- Ataxia type caused by damage to the cerebellum
- Athetoid or dyskinetic is mixed muscle tone caused by damage to the extrapyramidal motor system and/or pyramidal tract and to the basal ganglia
- Hypotonic CP appears limp with hardly or no movement

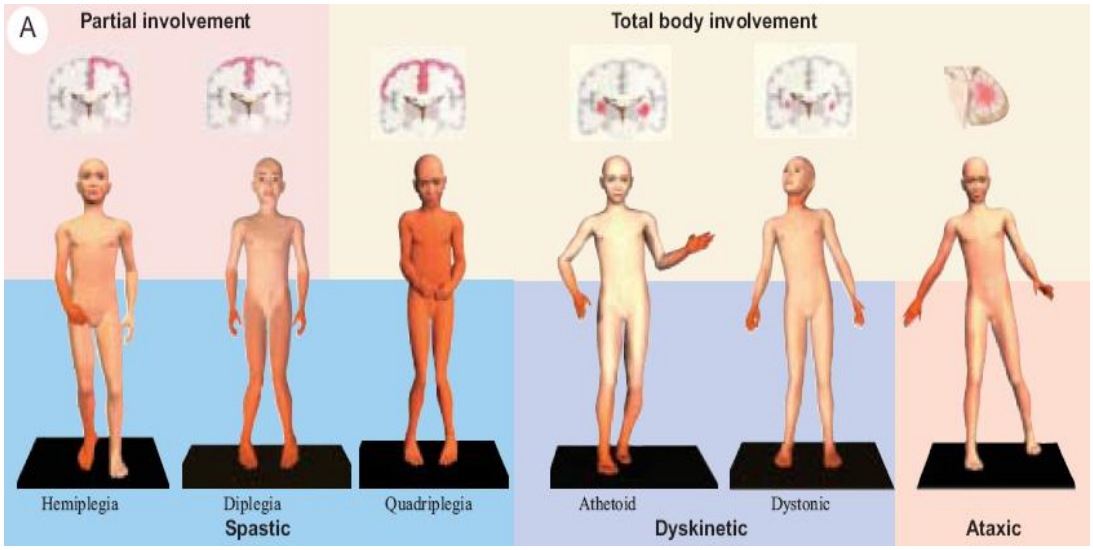


Figure 2: major classifications in CP to describe different movement impairments

*Glucose abnormalities*

Disorders in glucose supply or metabolism can result in hypoglycemia or hyperglycemia

N*ecrotizing enterocolitis (NEC)*

Necrotizing enterocolitis occurs in 2 to 10 percent of VLBW infants and is associated with an increase in mortality. Survivors are at increased risk for growth delay and neurodevelopmental disabilities. In addition, 10 percent of preterm infants with NEC will have long-term gastrointestinal difficulties with persistent loose stools or frequent bowel movements. [18]

*Infection*

Late-onset sepsis, defined as occurring after three days of age, is a common complication among premature infants. As an example, in a study from the NICHD Neonatal Research Network, one or more episodes of sepsis (defined as a positive blood culture associated with clinical signs suggestive of infection) occurred in 21 percent of VLBW infants who survived more than three days. Gram-positive organisms caused infection in 70 percent of cases, and coagulase-negative staphylococcus accounted for 48 percent.

Patients who developed late-onset sepsis were more likely to die than those who were uninfected, and survivors had longer hospital stays (79 versus 60 days). Other complications associated with an increased risk of infection included prolonged intubation, bronchopulmonary dysplasia, prolonged intravascular access, PDA, and NEC. [25]

Also, neonatal sepsis is associated with increased likelihood of poor neurodevelopmental outcome and growth impairment. In another report from the NICHD Neonatal Research Network, ELBW survivors who had one episode of neonatal infection compared to those who were uninfected were more likely to have adverse neurodevelopmental outcome and poor growth. [26]

*Retinopathy of prematurity (ROP)*

Retinopathy of prematurity is a developmental vascular proliferative disorder that occurs in the incompletely vascularized retina of premature infants. The incidence and severity of ROP increases with decreasing gestational age or birth weight. The condition typically begins about 34 weeks postmenstrual age (PMA), although it may be seen as early as 30 to 32 weeks. ROP advances irregularly until 40 to 45 weeks PMA and resolves spontaneously in the majority of infants. However, patients with severe untreated ROP are at increased risk for poor ocular outcome with vision impairment. [18]

4.2.1.2.2 Long term complications

Impaired neurodevelopmental outcome is a major long-term complication of surviving premature infants, especially extremely premature infants who are born at or below 25 weeks gestation.

Outcome studies primarily from North America and Western Europe have demonstrated increased prevalence of the following neurodevelopment disabilities in survivors of premature birth compared to individuals who were born fullterm (FT) [27]:

- Impaired cognitive skills
- Motor deficits including mild fine or gross motor delay, and cerebral palsy
- Sensory impairment including vision and hearing losses
- Behavioural and psychological problems

Preterm survivors with severe neonatal brain injury (IVH grade III or IV, periventricular leukomalacia (PVL), or severe ventriculomegaly) have the most severe neurodevelopment impairment and are the most likely to use school services, need additional support in reading, writing, and mathematics. [28]

ELBW and VLBW children are more likely than children born with normal birth weight (NBW) to have specific behavioural problems and psychological problems. These include attention deficit hyperactivity disorder, general anxiety, depression, and poor social interaction. Premature adolescent and young adult survivors tend to engage in less-risky behaviour and be shyer than those born full-term [29].

In contrast, some studies suggest that despite their increased risk of neurodevelopmental disability, patients who are preterm survivors may overcome these difficulties and become functional young adults at a comparable rate to those who were born fullterm. Summarizing can be said that although infants of any gestational age may have a neurodevelopmental deficit, the rates of neurodevelopmental disabilities increase with decreasing birth weight and gestational age.

4.2.1.3. Mortality

Prematurity and its complications cause almost 30 percent of neonatal deaths. The earlier a baby is born, the more likely it is to die. [30, 31] Infants born at or before 25 weeks of gestation have the highest mortality rate (about 50 percent) and if they survive, are at the greatest risk for severe impairment [8], while about 50

to 70 percent of babies born at 24 to 25 weeks, and more than 90 percent born at 26 to 27 weeks, survive. [30,31]

### 4.2.2. Dystrophy

#### 4.2.2.1. Definitions [52]

*Small for gestational age (SGA)*

The most common definition of small for gestational age (SGA) refers to a weight below the 10th percentile for gestational age. However, this definition does not make a distinction among infants who are constitutionally small, growth-restricted and small, and not small but growth-restricted relative to their potential.

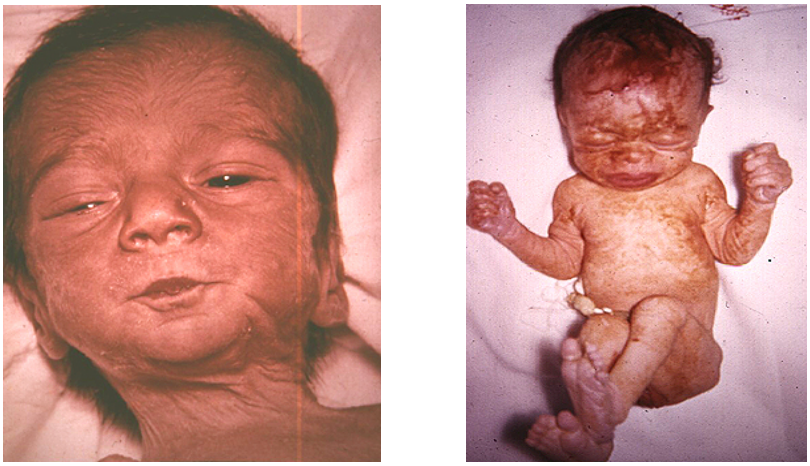

Figure 3: Clinical manifestation of small for gestational age infants

SGA infants appear thin with loose, peeling skin and decreased skeletal muscle mass and subcutaneous fat tissue. The face has a typical shrunken or "wizened" appearance, and the umbilical cord often is thin.

*Appropriate/large for gestational age (AGA/LGA)*

If the newborns birth weight lies above the 10th percentile and below the 90th percentile for that gestational age, it's defined as appropriate for gestational age (AGA). Infants are classified as large for gestational age (LGA) if their birth weight lies above the 90th percentile for that gestational age.

*Low, very low and extremely low birth weight (LBW, VLBW, ELBW)*

Low birth weight (LBW) is defined as a fetus that weighs less than 2500 g regardless of gestational age. Other definitions include Very Low Birth Weight (VLBW) which is less than 1500 g, and Extremely Low Birth Weight (ELBW) which is less than 1000 g. Normal Weight at term delivery is 2500 g - 4200 g

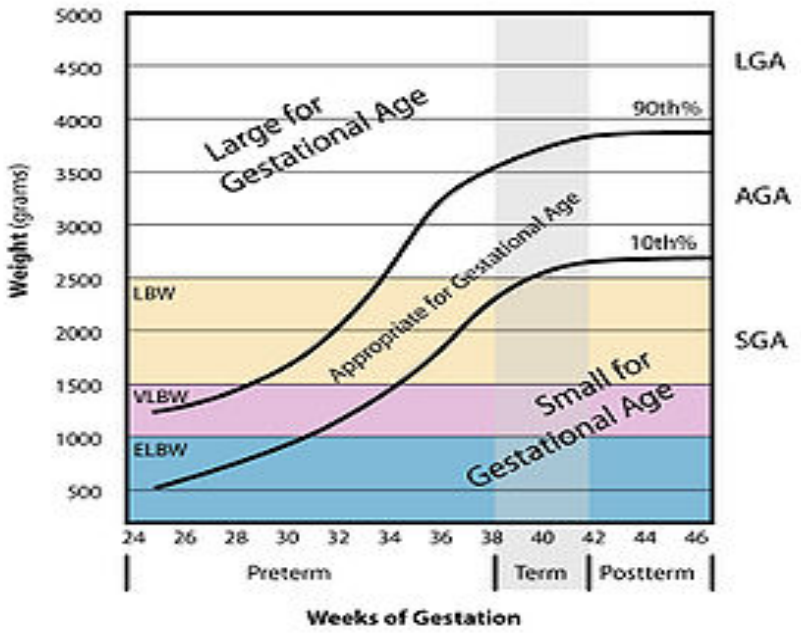


Figure 4: Picturing of LGA, AGA, SGA

| *Gestational age, weeks* | *Male* | *female* |
|---|---|---|
| *20* | 270 | 256 |
| *21* | 328 | 310 |
| *22* | 388 | 368 |
| *23* | 446 | 426 |
| *24* | 504 | 480 |
| *25* | 570 | 535 |
| *26* | 644 | 592 |
| *27* | 728 | 662 |
| *28* | 828 | 760 |
| *29* | 956 | 889 |
| *30* | 1117 | 1047 |
| *31* | 1308 | 1234 |
| *32* | 1521 | 1447 |

| *Gestational age, weeks* | *Male* | *female* |
|---|---|---|
| *33* | 1751 | 1675 |
| *34* | 1985 | 1901 |
| *35* | 2205 | 2109 |
| *36* | 2407 | 2300 |
| *37* | 2596 | 2484 |
| *38* | 2769 | 2657 |
| *39* | 2908 | 2796 |
| *40* | 2986 | 2872 |
| *41* | 3007 | 2891 |
| *42* | 2998 | 2884 |
| *43* | 2977 | 2868 |
| *44* | 2963 | 2853 |

Table 3: Tenth percentile of birth weight (g) for gestational age by gender

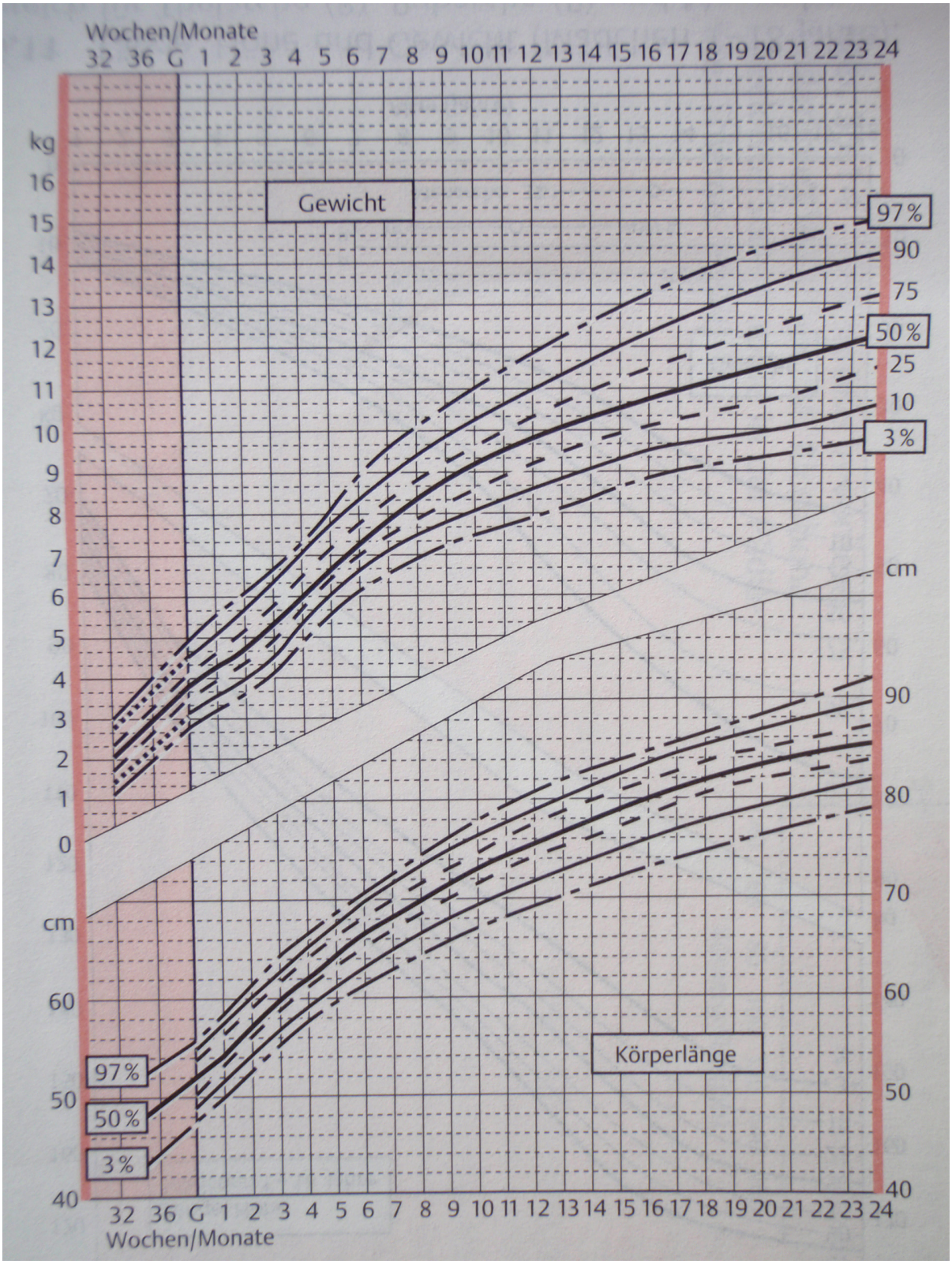


Figure 5: Somatogramm of birth weight and gestational body length (from 32 weeks of gestation to 24 month) for females

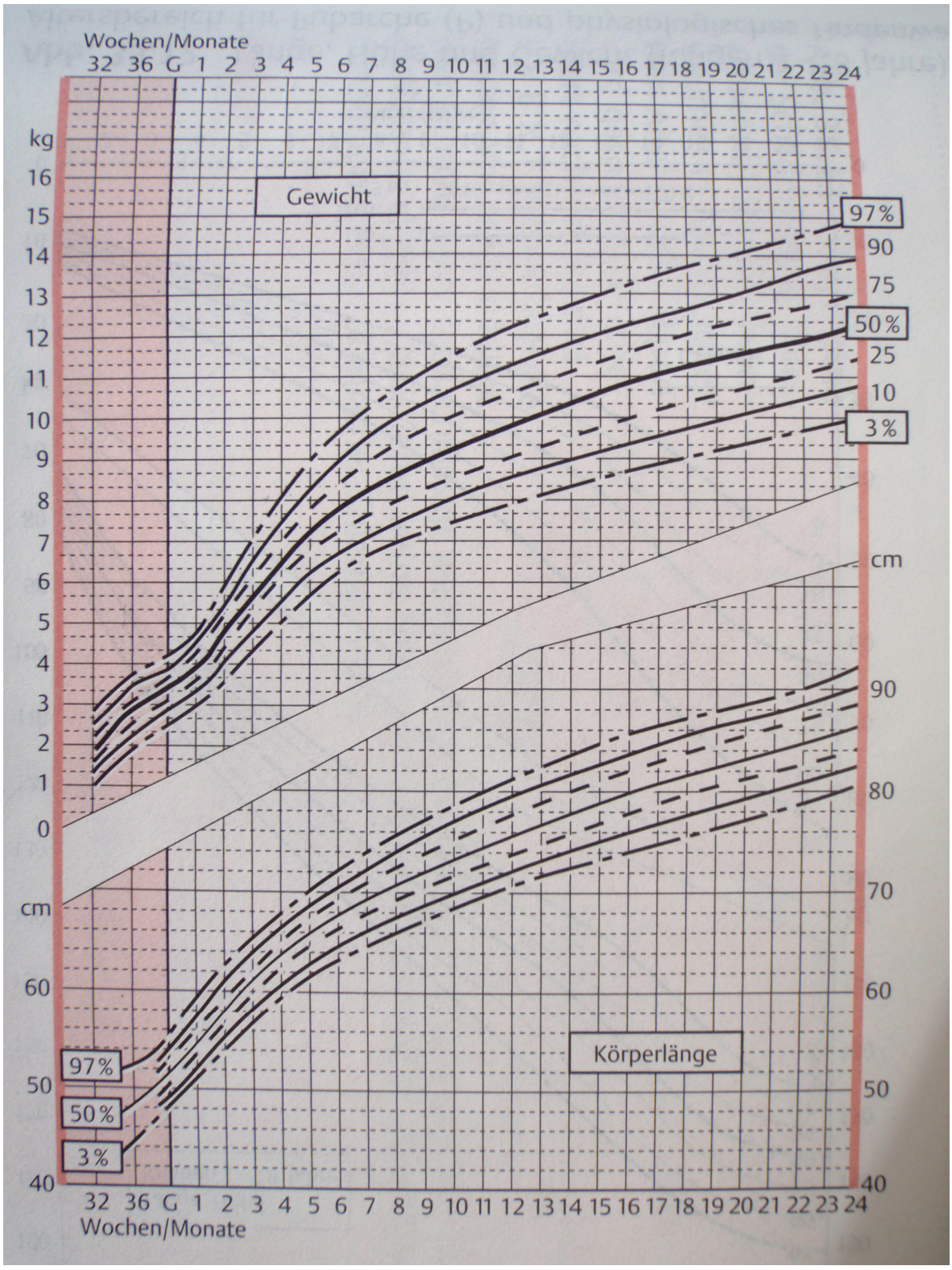


Figure 6: Somatogramm of birth weight and gestational body length (from 32 weeks of gestation to 24 month) for males

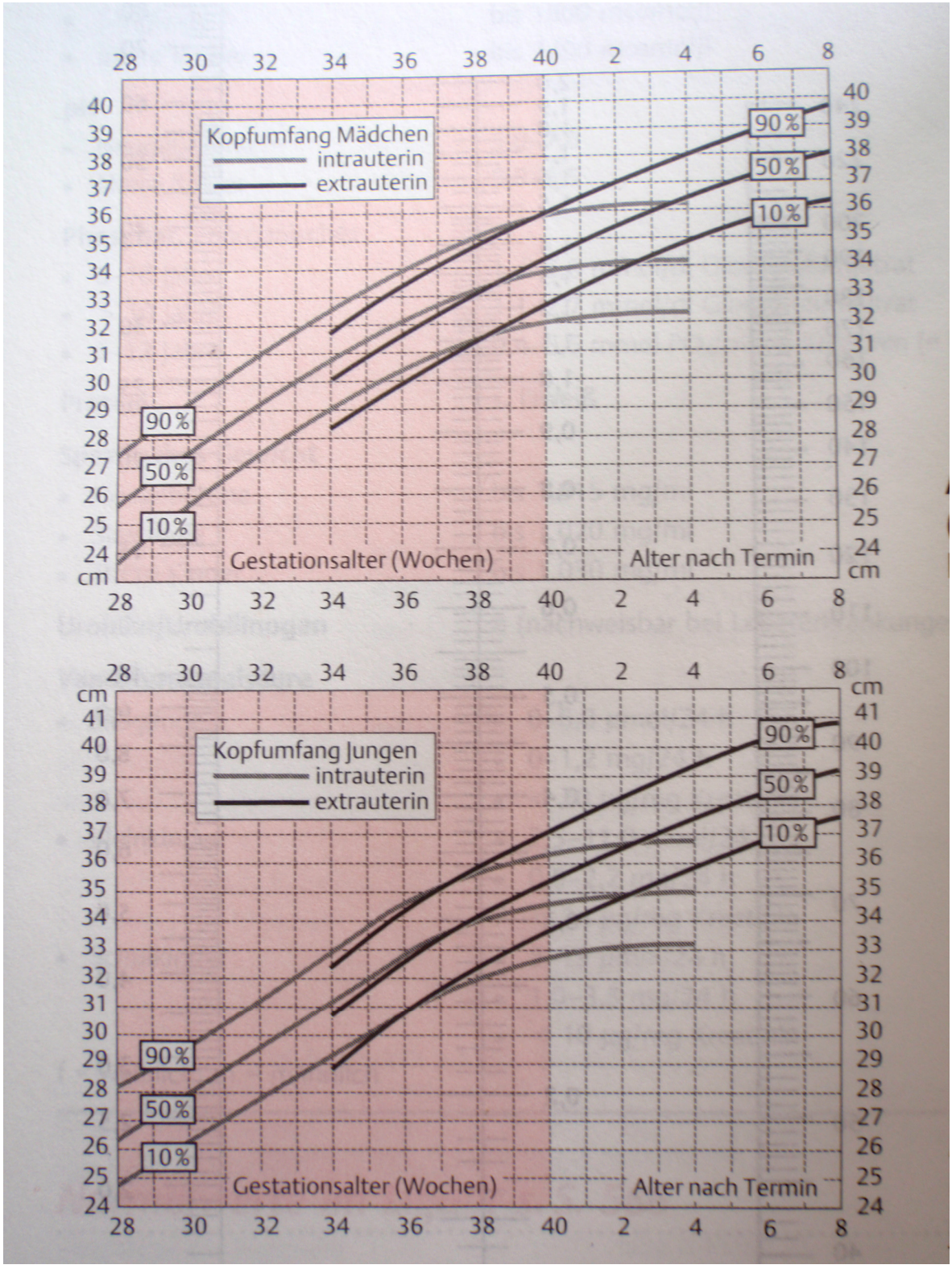


Figure 7: Somatogramm of gestational head circumferences (from 32 weeks of gestation to 24 month) for females and males

*Intrauterine growth restriction (IUGR)* [32]

Intrauterine growth restriction (IUGR), also called fetal growth restriction (FGR) is often used as synonym for small for gestational age (SGA), but SGA babies have usually been the subject of intrauterine growth restriction (IUGR) and its underlying disease. IUGR is the term used to designate a fetus that has not reached its growth potential because of genetic or environmental factors. This term should not be used to describe a constitutionally small, but otherwise healthy fetus.

Moderate and severe IUGR are defined as birth weight in the 3rd to 10th percentile and less than 3rd percentile, respectively. Normal term infants typically weigh more than 2500 g by 37 weeks gestation

4.2.2.2. Morbidity

Fetal growth is important because there is an inverse relationship between the fetal/neonatal weight percentile and adverse perinatal outcome, with the greatest risk at weights below the third percentile for gestational age. [33]

4.2.2.2.1 Short term complications

SGA infants have a variety of associated clinical problems beginning at birth. Mildely affected preterm infants have increased risks of acidemia, respiratory distress, intraventricular hemorrhage, and necrotizing enterocolitis. Severely affected term newborns deprived of oxygen and nutrients may have a difficult cardiopulmonary transition with perinatal asphyxia, meconium aspiration, or persistent pulmonary hypertension. [34]

Both spontaneous and induced preterm births are more common in pregnancies complicated by FGR. Infants with IUGR who are delivered before term also may have complications of prematurity, including necrotizing enterocolitis, respiratory distress syndrome, impaired thermoregulation, hypoglycemia, polycythemia/hyperviscosity, impaired immune function, and neutropenia that may increase their risk of infection. [35]

4.2.2.2.2 Long term complications

SGA infants are at increased risk for impaired growth and neurodevelopment. They have different patterns of growth depending upon the etiology and the severity of growth restriction. In moderately affected infants, growth during the first 6 to 12 months after birth may be accelerated, resulting in attainment of normal size in most children. [36, 37] In comparison, severely affected SGA infants frequently weigh less and are shorter than AGA infants throughout childhood and adolescence. [38]

In addition, affected children with neonatal complications had significantly lower IQ scores and poorer neurodevelopmental outcome at three years than did those with uncomplicated courses [39].

IUGR appear to effect neurodevelopment and behavior in adolescents as well as young adults. According to the Barker hyptothesis, fetal growth restriction appears to be an antecedent to some cases of hypertension, hyperlipidemia, coronary heart disease, stroke and diabetes mellitus in the adult [40].

4.2.2.3. Mortality

Fetal, neonatal, and perinatal mortality are increased in small for gestational age (SGA) compared to appropriate for gestational age (AGA) infants. Mortality increases as growth restriction becomes more severe, rising abruptly when birth weight is less than or equal to the fifth percentile. [41].

# 5. Reason for the methodical approach

To improve the early identification of children with developmental disability, the American Academy of Pediatrics (AAP) recommends that all infants and young children be screened for developmental delays. They recommend performing developmental surveillance at every well-child visit and using formal, standardized screening tools at select age intervals (9, 18, and 24 or 30 months) and if developmental concerns are raised by the parent or provider during surveillance. [42]

There are different developmental screening tests listed below, and all are able to correctly identify 70 to 80 percent of children with and without developmental disabilities.

## 5.1. Developmental screening tests

### 5.1.1 Parent report screens

Screening tests that draw on information that is reported by the parents may be more suitable for primary care than those that require direct observation or elicitation of developmental skills. Such tests can be self-administered in waiting or examination rooms, attached to an appointment letter, administered online before an appointment, or delivered by interview in person or over the telephone. Such tests are usually less expensive, take only a few minutes of professional time to interpret, eliminate the challenge of directly eliciting skills from children who, for whatever reason (illness, sleepiness, anxiety, fear), may not demonstrate their best effort on the day of testing. [43, 44]

### 5.1.2. Direct elicitation screens

Screening tests that rely on direct observation or elicitation of skill typically are used by pediatric healthcare providers who have a particular interest in developmental problems [45]. There are three different, brief, general developmental screening tests that make use of direct observation and/or elicitation of skills and that correctly identify 70 to 80 percent of children with and without developmental disabilities.

5.1.2.1 Brigance Screens-II

The Brigance Screens-II can be used to screen development in children from 0 to 90 months. It consists of nine separate forms, one for each 12-month age range, each of which takes 10 to 15 minutes to administer.
It uses parent report (in the 0- to 24-month age range), direct observation, and elicitation to assess speech-language, motor skills, and general knowledge at younger ages and reading and math at older ages. The

scoring system provides cut-off quotients (which determine the need for further evaluation), percentiles, and age-equivalent scores in various domains and overall. The Brigance Screens-II identifies 70 to 82 percent of children with giftedness or developmental and academic problems, and correctly identifies 70 to 82 percent of children without such conditions. [46, 47]

#### 5.12.2 Bayley Infant Neurodevelopmental Screener (BINS)

The Bayley Infant Neurodevelopmental Screener (BINS) can be used to screen development in children 3 to 25 months. It uses 10 to 13 directly elicited items per three- to six-month age range to assess neurologic processes (reflexes and tone), neurodevelopmental skills (fine motor, language), and cognitive processes.
It categorizes performance into low, moderate, or high risk via cut scores and provides subtest cut scores for each domain. The BINS detects 75 to 86 percent of children with neurodevelopmental problems and correctly identifies 75 to 86 percent of children without such conditions. [46, 48]

#### 5.1.2.3. Denver Developmental Screening Test-II (DDST-II)

The DDST-II is a directly administered tool that is designed to screen expressive and receptive language, gross motor, fine motor, and personal-social skills in children zero to six years of age [49]. The results indicate a risk category (normal, questionable, abnormal). According to a study, the DDST-II detects 83 percent of children with neurodevelopmental problems, but sensitivity is limited at 43 percent [50].

## 5.2. Reason for selected Bayley Infant Neurodevelopmental Screening Test

In Klagenfurt, as well as at the Paediatric University Hospital in Graz the Bayley Infant Neurodevelopmental Screening Test is the standardized screening test for children, born before 37 completed weeks and a gestational weight ≤ 1,500 gram or in newborns which are small for gestational age.

At an age of 24 months, the BINS is a standardized, reliable and valid method to assess the neurologic development of the children in the following five categories: reflexes and tone, language skills, fine and gross motor development, and cognitive process. Neuropediatricians evaluate every single category and assess a score: a score lower than 65 points defines a severe developmental delay, 65 to 75 points moderate, 75 to 85 points mild and above 85 points no developmental delay. For the ultimate overall assessment only the terms are used, the scores are not mentioned in the final report.

# II Material und Methodical

## 1. Study design

This is a retrospective study with a study group of 29 preterm and/or small for gestational aged infants (<37-weeks and <1,500 g or >37-weeks and <10 percentile) born at the LKH Graz or the LKH Klagenfurt, alive after maternal severe preeclampsia between the years of 1999 and 2005. At a corrected age of 24 months, a neurological examination, according to Bayley was performed to assess the mental and psychomotor development of the child. The adverse neurodevelopmental infant outcome has been defined as no, low, medium or severe neurodevelopment delay and subdivided into delays, concerning motor function, language skills, social behaviour or mental function.

## 2. Retrospective maternal analysis

Between January 1999 and December 2005 a total of 18,034 infants were born in Graz and 10,230 infants in Klagenfurt.

Acquisition

The acquisition of the database resulted from using PIA, a "Patient-information-retrieval-program", and searching for the following terms: "oligohydramnion", "intrauterine Wachstumsretardierung", "intrauterine growth retardation" (IUGR), "small for gestational age" (SGA), "small for dateness" (SFD), "EPH-Gestose", "schwangerschaftsinduzierter Hochdruck" (SIH)," (Prä-)Eklampsie," and "(H)ELLP-Syndrom".
Additional registers of birth, midwifes' diaries and the pre-existing data record, containing all women suffering from hypertension or/and proteinuria during pregnancy and its respective perinatal information, has been used to collect as many data as possible.

The data from 297 women was collected using PIA, 8 by using the registers of birth, 99 by reading midwifes' diaries, and 194 by using the pre-existing data record.
In total, the number of women suffering from hypertensive disorders of pregnancy was 572 (99 from the LKH Klagenfurt and 473 from the LKH Graz), which resulted in an incidence of hypertensive disorders during pregnancy of 2.03 percent.

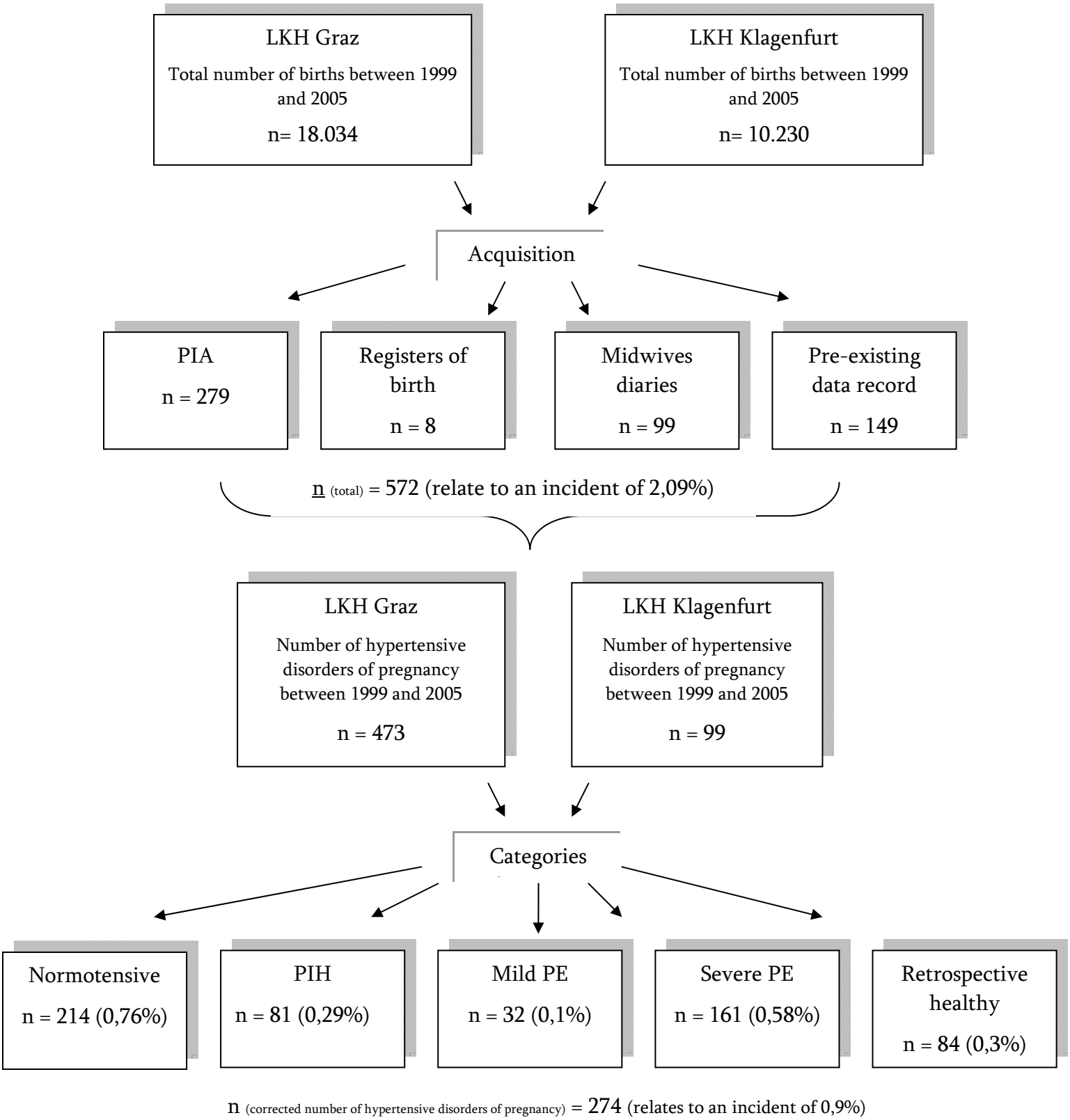


Figure 8: Retrospective maternal analysis

Selection and assignment to subcategories

These 572 women were divided into the following subcategories:

*1. Normotensive:*

214 women which neither fulfilled the criteria of hypertensive disorders in pregnancy nor were healthy

*2. Pregnancy indicated hypertension (PIH):*

81 women which retrospectively fulfilled the criteria of hypertensive disorders in pregnancy

*3. Mild preeclampsia (mild PE):*

32 women, fulfilling the criteria for mild preeclampsia

*4. Severe preeclampsia (severe PE):*

161 women, fulfilling the criteria for severe preeclampsia

*5. Healthy:* 84 women, retrospectively estimated as "healthy"

Finally, in Graz and Klagenfurt, the total number of women fulfilling either the criteria of PIH, mild or severe preeclampsia was 274, which relates to a corrected incidence in hypertensive disorders during pregnancy of 0.9 percent.

## 3. Retrospective analysis of infants

Acquisition

The data from the 161 women with severe preeclampsia have been used to search for appending newborns, again by using PIA, the registers of birth, midwifes' diaries, and the pre-existing data record.
In total, the number of infants born alive after severe preeclampsia during pregnancy was 167, 52 in Graz and 115 in Klagenfurt.

For every single infant the following data had been gathered:

- Date of birth
- Mode of delivery
- Gestational age (in weeks and days)
- Gestational weight (in grams)
- Length at birth (in cm)
- Head circumference at birth (in cm)
- Apgar score (1,5, and 10 minutes after birth)
- Acid-base state (pH)
- Need of intensive care
- Cerebral complication during hospitalization such as intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), periventricular hemorrhage (PVH), and hydrocephalus

- Discharge state (including: duration of hospitalization, corrected age at discharge, weight, length and head circumference, any neurological abnormalities during hospitalization or/and at discharge, discharge diagnosis)
- Neurological assessment using the Bayley Test, at the age of two years

Selection

Six infants in Graz and 15 in Klagenfurt were excluded because they were multiples. Also, two infants per hospital died intrauterine or after birth and were excluded for this reason and, in Klagenfurt five and in Graz four children's data were not attainable. Hence, the total number of infants, born after severe preeclampsia during pregnancy had been 40 in Graz and 93 in Klagenfurt.

Out of these 40 infants in Graz, 17 were given regular medical check ups at the University Hospital Graz (criteria see above) and out of 93 newborn in Klagenfurt, 27 fulfilled the "follow up criteria" of the University Hospital in Graz.
From these children only 12 in Graz and 17 in Klagenfurt have actually been followed up. The other 15 children either did not avail to the opportunity of regular visits at the LKH until the age of 2 or had not planned any follow ups.

Finally, the total number of infants, alive, single birth, with regular medical check ups at the University Hospitals in Graz or Klagenfurt, and the ability to collect all necessary data, was 29.

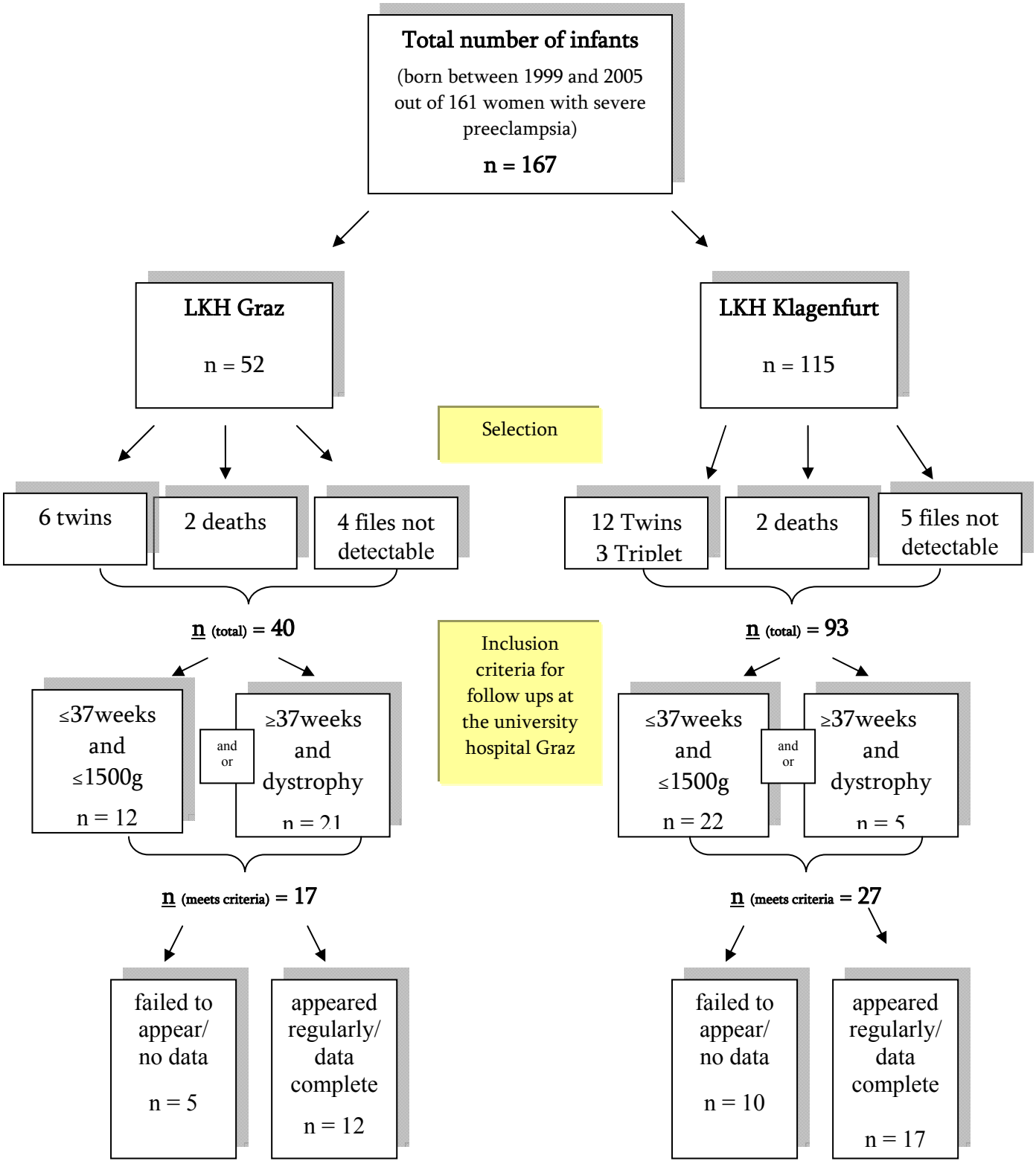


Figure 9: Retrospective analysis of infants

## 4. Statistics

All retrospective data have been acquired and subsequent managed using Microsoft Office Excel 2003. To prove significant differences statistically, a T - test was conducted for independent or related samples. Implications were based on a significance level of 95%; hence a p-value below 0.05 was considered significant. Frequencies, percentages, means, standard deviations and variances were used as statistical procedures.

# III Results

## 1. Birth statistics and hypertensive disorders of pregnancy

### 1.1. Birth statistics at the LKH Graz and Klagenfurt from 1999 until 2005

Between 1999 and 2005, 28,264 women gave birth at the LKH Graz or Klagenfurt, which correlates to an average of 4,037 infants per year.

During these six years, the rate of multiple births decreased per annum with an average of 103 twins and only 4 triplets but the preterm births slightly increased, by 268 preterm births below the completed 37 weeks of gestation in the LKH Graz. [51]

| demographic data: births | n total | mean value Graz (per annum) | mean value Klagenfurt (per annum) | total mean value (per annum) | Percent |
|---|---|---|---|---|---|
| births | 28264 | 2576 | 1461 | 4037 | 100 |
| twin - births | 715 | 69 | 34 | 103 | 2,6 |
| triplet - births | 25 | 2 | 2 | 4 | 0,09 |
| preterm births | 2.573 | 268 | not acquired | not acquired | 14,2 |

Table 4: Birth statistics at the LKH Graz and LKH Klagenfurt between 1999 and 2005

### 1.2. Incidence of hypertensive disorders of pregnancy

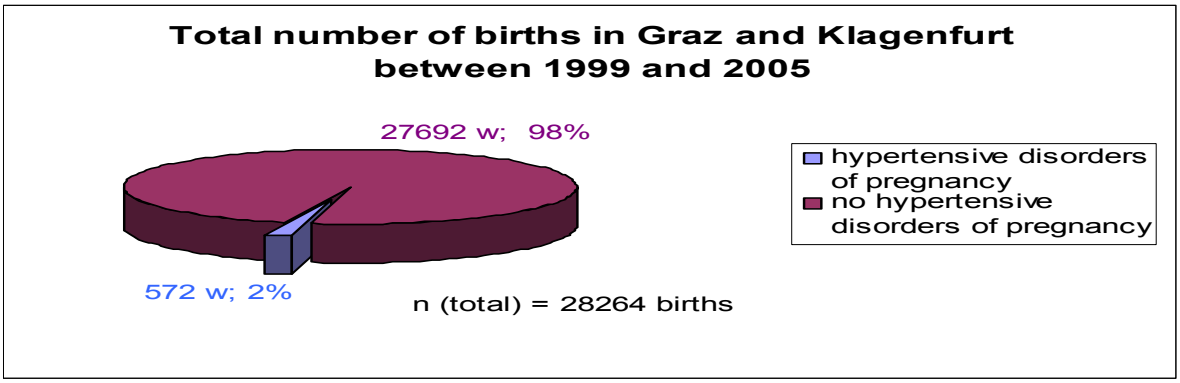


Figure 10: Incidence of hypertensive disorders of pregnancy

As demonstrated in the figure above, the actual number of women affected with mild or severe preeclampsia, amounted to 572 out of 28,264 women who delivered at the LKH Graz or Klagenfurt between the years 1999 and 2005. This retrospective result correlates to a total of 2.02 percent, well below current literature.

As described in the chapter "Material and Methodic", the data of 572 women with hypertensive disorders of pregnancy had been collected, resulting in 99 in LKH Klagenfurt or 17.3 percent and 473 in LKH Graz with a remaining 82.7 percent.

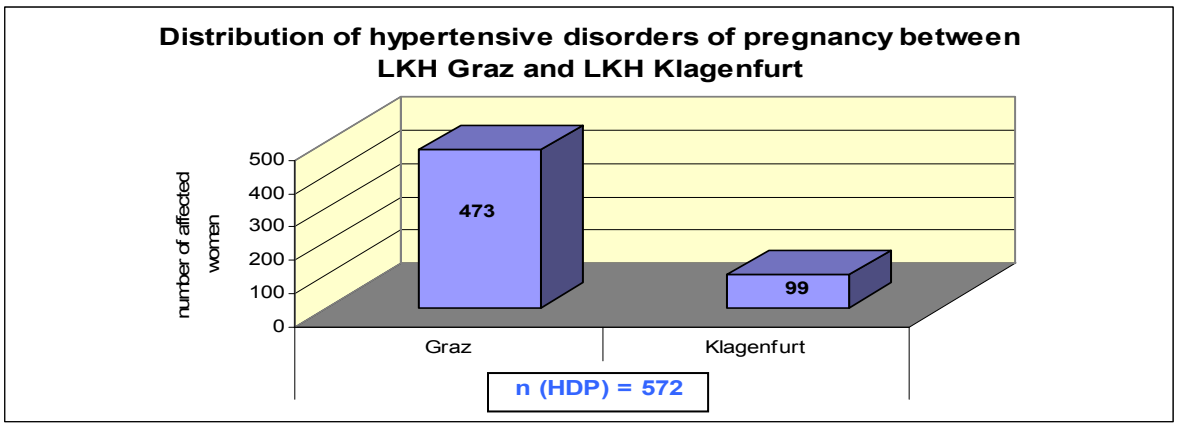


Figure 11: Distribution of hypertensive disorders of pregnancy at the LKH Graz and LKH Klagenfurt

Retrospectively, these 572 women had been assigned the following subcategories,:

- *Normotensive:* 214 women, which is equivalent to 0.81 percent out of a total of 26,284 women, giving birth either in the LKH Graz or Klagenfurt from 1999 until 2005
- *Pregnancy indicated hypertension (PIH):* 81 women, which is equivalent to 0.81 percent out of a total of 26,284 women
- *Mild preeclampsia (mild PE):* 32 women, which is equivalent to 0.12 percent out of a total of 26,284 women
- *Severe preeclampsia (severe PE):* 161 women, which is equivalent to 0.61 percent out of a total of 26,284 women
- *Healthy:* 84 women, which is equivalent to 0.32 percent out of a total of 26,284 women

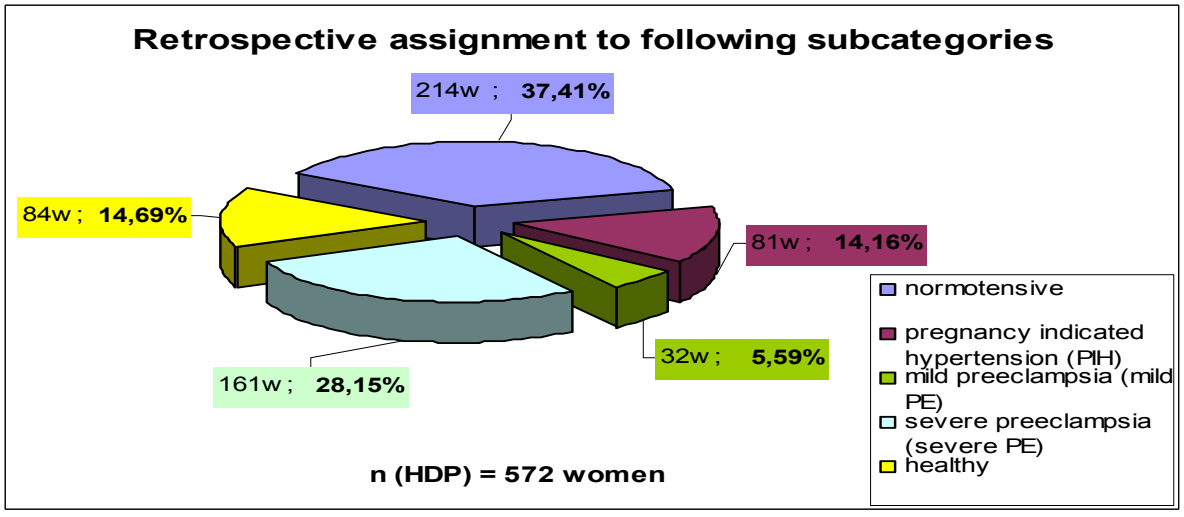


Figure 12: Allocation of 572 women, associated with hypertensive disorders of pregnancy, to 5 subcategories

## 1.3. Incidence of preterm birth in severe preeclamspia

Once the 161 women had been diagnosed with severe preeclampsia, they were assigned to one of the following categories, depending on the newborn's gestational age.

| demographic data: preterm birth in severe preeclampsia | n Graz | n Klagenf | n total (Klagenfurt and Graz) | n total (percent) | GW < 10 ptl (Graz) | GW < 10 ptl (Klagenf) | GW < 10 ptl (n=total) | GW < 10 ptl total (percent) |
|---|---|---|---|---|---|---|---|---|
| **term** (> 38+0 weeks of gestation) | 14 | 14 | 28 | 17,39 | 6 | 5 | 11 | 6,83 |
| **late preterm** (between 34+0 and 37+6 weeks of gestation) | 17 | 45 | 62 | 38,50 | 8 | 30 | 38 | 23,6 |
| **preterm** (between 32+0 and 33+6 weeks of gestation) | 7 | 28 | 35 | 21,74 | 4 | 16 | 20 | 12,42 |
| **very preterm** (between 25+1 and 31+6 weeks of gestation) | 10 | 25 | 35 | 21,74 | 4 | 5 | 9 | 5,6 |
| **extemely preterm** (<25+0 weeks of gestation) | 1 | 0 | 1 | 0,62 | 1 | 0 | 1 | 0,62 |

Table 5: Distribution of gestational age at birth and incidence of dystrophy, divided into gestational sections

Table 5 shows that only 28 out of 161 infants had been born to term (a percentage of 17.4) and the remaining 133 infants were premature, which shows that in cases of severe maternal preeclampsia, prematurity occurs in 82.6 percent of newborns.

At the LKH Klagenfurt and Graz, the average gestational age was 34 + 1 weeks of gestation (239.4 days of gestation), while the most preterm infant had been born after 24 + 5, the oldest infant after 41 + 4 weeks of gestation.

In Klagenfurt, the mean gestational age was 33 + 6 weeks of gestation (237.2 days) while the most preterm newborn had been born after 26 + 2, the oldest infant after 41 + 1 weeks of gestation.

In Graz, the average gestational age had been 34 + 6 weeks of gestation (224.4 days), the most preterm infant was born after 24 + 5, the oldest infant after 41 + 4 weeks of gestation.

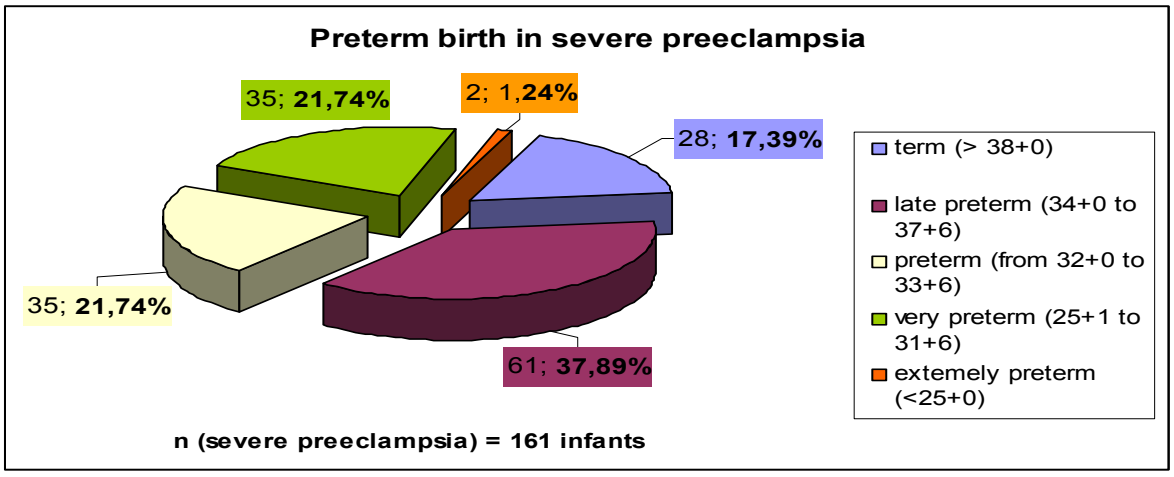


Figure 13: Distribution of gestational age at birth

## 1.4. Incidence of dystrophy in severe preeclamspia

Furthermore, Table 13 illustrates the incidence of dystrophy with gestational weights below the tenth percentile (GW < 10 ptl) at the LKH Graz and Klagenfurt, divided into gestational sections of prematurity. With 23.6 percent, most dystrophic infants had been between 34+0 and 37+6 weeks of gestational age, followed by 12.4 percent in the gestational section between 32+0 and 33+6 weeks. Newborns, older than the completed 38 weeks of gestation, with 6.83 percent, were close to the 5.6 percent, born after 25+1 and 31+6 weeks of gestation.

The explanation for the very low 0.62 percent for dystrophic infants born at a gestation period below the completed 25 weeks was the insufficient number of test persons in this gestational section. In this case, the random number was too small for a general statement.

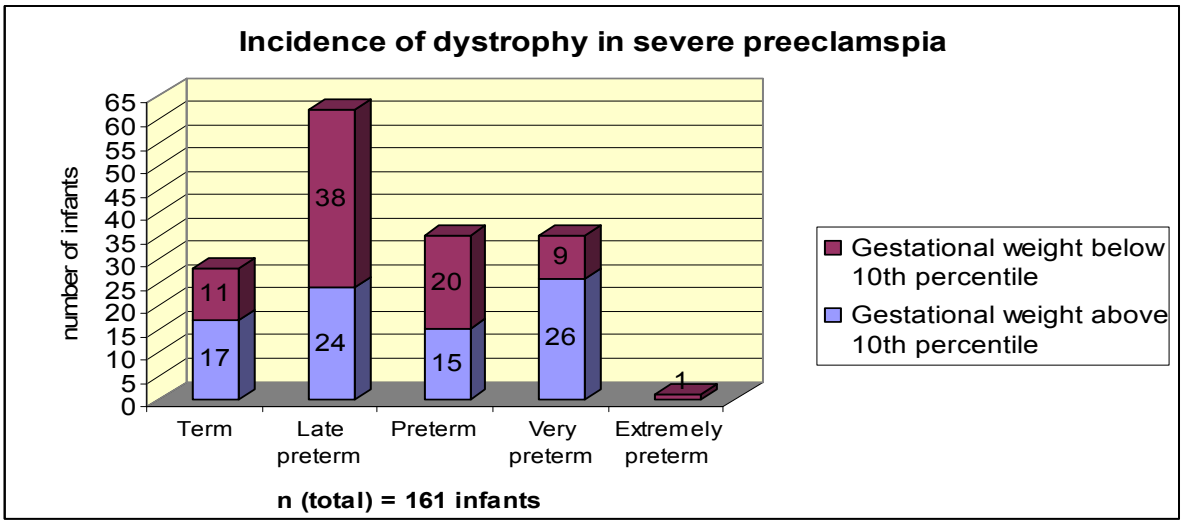


Figure 14: Number of premature infants, divided into terms of gestational age and weights

As shown in Figure 14, the gestational weights of 79 out of 161 infants were below the tenth percentile, which concludes that 49 percent of the newborns fulfilled the criteria of 'small for gestational age'. However, this definition does not make a distinction among infants who are constitutionally small, growth restricted and small, and not small but growth-restricted relative to their potential, as mentioned in chapter 4.2.

The gestational weights of the remaining 82 infants were above the tenth percentile, concluding that 51 percent of the newborns were either acceptable or even large for their gestational age.

## 2. Postnatal period

The necessary data acquisition was possible with 29 infants only, 18 females and 11 males with gestational ages between 24 + 5 and 34 + 3 weeks. We analysed the following periods: postnatal, hospitalization and discharge, as well as at the age of two years.

To create our control group, these 29 infants were matched with the same number of children with the same gestational terms, except for one late preterm instead of a preterm term infant due to the fact that no late preterm infant with neurological long term check ups could be found. The control group included 12 female and 17 male infants with gestational ages between 24 + 3 and 36 + 0 weeks.

During the postnatal period at the LKH Graz and LKH Klagenfurt, the following data was collected: term of birth, depending on the newborns gestational age (GA), mode of delivery (MOD), gestational weight in grams (GW (g)), gestational body seizure (GL (cm)) as well as head circumference at gestation (GHC (cm)), both in centimetres. Furthermore, clinical diagnosis "small for date" if made (CD), APGAR score one, five and ten minutes after birth (APGAR 1min/5min/10min) and the newborn's adaption ability, measured by gestational pH value (GpH) have been acquired.

| Term | GA | MOD | GW (g) | GL (cm) | GHC (cm) | CD | APGAR | G pH |
|---|---|---|---|---|---|---|---|---|
| Preterm | 32+2 | S | 1460 | 42,0 | 30,0 | | 8/9/9 | 7,15 |
| | 33+3 | S | 1300 | 40,0 | 29,0 | | 9/10/10 | 7,33 |
| Very Preterm | 29+2 | S | 1060 | 38,0 | 27,0 | | 7/9/9 | 7,27 |
| | 29+4 | S | 824 | 36,0 | 25,5 | + | 8/9/9 | 7,41 |
| | 25+6 | S | 600 | 33,0 | 22,5 | | 5/9/9 | 7,21 |
| | 27+1 | S | 820 | 35,0 | 24,5 | | 2/8/8 | 7,12 |
| | 28+4 | S | 1130 | 38,0 | 27,0 | + | 6/8/8 | 7,31 |
| | 28+4 | S | 760 | 35,0 | 25,0 | + | 6/9/9 | 7,28 |
| | 29+0 | S | 730 | 34,0 | 22,0 | + | 8/9/10 | 7,23 |
| | 27+2 | S | 930 | 37,0 | 25,0 | | 3/7/8 | 7,26 |
| | 31+4 | S | 1330 | 38,0 | 28,5 | | 6/9/9 | 7,29 |
| Extremely preterm | 24+5 | S | 425 | 29,0 | 20,5 | + | 7/9/9 | 7,28 |

Table 6: Postnatal data of the cohort at the LKH Graz

| Term | GA | MOD | GW (g) | GL (cm) | GHC (cm) | CD | APGAR | G pH |
|---|---|---|---|---|---|---|---|---|
| Late preterm | 34+1 | S | 1260 | 39,5 | 28,0 | + | 5/8/9 | 7,17 |
| | 34+3 | S | 1475 | 40,0 | 30,0 | + | 7/10/10 | 7,28 |
| Preterm | 33+0 | S | 1340 | 42,0 | 28,0 | | 8/10/10 | 7,16 |
| | 33+4 | S | 1450 | 42,5 | 28,5 | + | 5/10/10 | 7,36 |
| | 32+6 | S | 1305 | 41,0 | 28,0 | + | 8/9/10 | 7,39 |
| | 33+1 | S | 1480 | 42,0 | 29,3 | | 9/10/10 | 7,23 |
| | 32+0 | S | 1360 | 39,0 | 26,5 | | 9/9/10 | 7,33 |
| Very preterm | 31+6 | S | 1300 | 41,5 | 28,0 | | 9/10/10 | 7,25 |
| | 27+5 | S | 790 | 35,0 | 25,0 | + | 5/8/9 | 7,47 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 27+2 | S | 924 | 36,0 | 25,5 | | 6/9/9 | 7,30 |
| 27+3 | S | 760 | 37,0 | 23,0 | + | 5/10/10 | 7,22 |
| 31+4 | V | 1340 | 42,0 | 27,5 | | 8/10/10 | 7,17 |
| 28+5 | S | 970 | 36,5 | 25,3 | | 6/7/7 | 7,26 |
| 31+3 | S | 1495 | 43,0 | 31,0 | | 5/8/9 | 7,24 |
| 30+0 | S | 990 | 38,0 | 26,0 | + | 5/8/9 | 7,26 |
| 29+0 | S | 870 | 38,0 | 25,5 | | 8/10/10 | 7,27 |
| 28+5 | S | 882 | 36,0 | 24,3 | | 8/10/10 | 7,29 |

Table 7: Postnatal data of cohort at the LKH Klagenfurt

These data have been compared to data of the control group (see table below).

| Term | GA | MOD | GW (g) | GL (cm) | GHC (cm) | CD | APGAR | G pH |
|---|---|---|---|---|---|---|---|---|
| Late preterm | 34+6 | V | 2110 | 45 | 31 | | 8/9/9 | 7,14 |
| | 36+0 | S | 1410 | 41 | 29 | + | 9/10/10 | 7,3 |
| | 35+5 | S | 1250 | 49 | 28,5 | + | 9/10/10 | 7,28 |
| Preterm | 32+4 | S | 2280 | 47 | 33 | | 9/9/8 | 7,25 |
| | 32+1 | V | 1740 | 45 | 30 | | 8/8/9 | 7,37 |
| | 33+6 | S | 1170 | 38 | 27,5 | + | 9/10/10 | 7,26 |
| | 26+1 | S | 805 | 34 | 24 | | 2/8/9 | 7,13 |
| | 32+2 | S | 1230 | 39 | 27,5 | + | 9/10/10 | 7,29 |
| | 35+5 | S | 1250 | 49 | 28,5 | + | 9/10/10 | 7,28 |
| | 32+6 | S | 1490 | 47 | 28,5 | + | 7/8/9 | 7,27 |
| Very preterm | 31+0 | S | 1420 | 37 | 28 | + | 1/5/10 | 7,27 |
| | 29+2 | S | 1280 | 39 | 27 | | 6/8/9 | 7,25 |
| | 28+2 | S | 1070 | 37 | 24,9 | | 6/9/9 | 7,2 |
| | 31+4 | S | 1410 | 43 | 28,5 | | 8/9/9 | 7,3 |
| | 27+6 | S | 1200 | 36 | 27,5 | | 7/9/10 | 7,36 |
| | 27+3 | V | 1050 | 39 | 25,5 | | 9/9/10 | 7,31 |
| | 31+4 | S | 1080 | 39 | 28 | + | 8/9/10 | 7,35 |
| | 30+0 | S | 1220 | 38 | 28,5 | | 6/9/9 | 7,19 |
| | 31+4 | S | 1410 | 43 | 28,5 | | 8/9/9 | 7,25 |
| | 31+6 | S | 1290 | 40 | 26,5 | | 9/10/10 | 7,25 |
| | 26+0 | V | 1000 | 36 | 23,5 | | 1/7/9 | 7,11 |
| | 31+4 | S | 1332 | 40 | 29,4 | | 8/9/9 | 7,32 |
| | 29+0 | S | 1440 | 42 | 27,5 | | 6/8/8 | 7,33 |
| | 27+1 | V | 990 | 38 | 25,2 | | 8/9/8 | 7,22 |
| | 27+3 | V | 1080 | 39 | 25,6 | | 8/9/9 | 7,3 |
| | 28+2 | S | 1110 | 38 | 25,5 | | 9/9/10 | 7,15 |
| | 27+3 | S | 1018 | 37,5 | 25,9 | | 2/7/9 | 7,19 |
| | 28+4 | S | 1350 | 39 | 28 | | 5/9/9 | 7,4 |
| | 28+2 | S | 1360 | 38 | 23,6 | | 7/9/10 | 7,3 |
| Extremely preterm | 24+3 | S | 760 | 34 | 21 | | 8/10/10 | 7,35 |

Table 8: Postnatal data of the control group at the LKH Graz and Klagenfurt

## 2.1. Distribution of weight, seize and head circumference at birth

### 2.1.1. Gestational weight

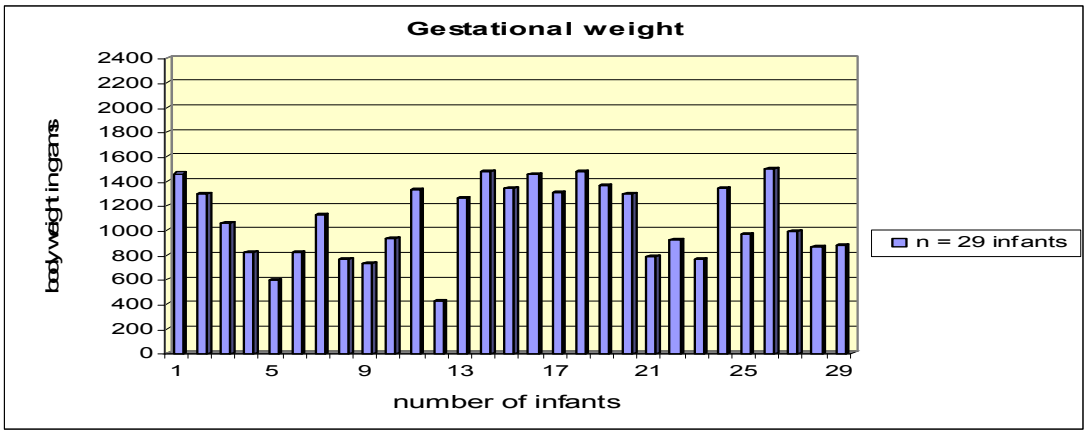


Figure 15: Distribution of gestational weights of the cohort at the LKH Graz and Klagenfurt

The mean gestational weight of all 29 infants within the study group was 1,081 grams. The gestational weight of 17 infants (58.6 percent) was below this average, while the remaining 12 newborns (41.4 percent) were above.

The heaviest newborn reached a birth weight of 1,495 grams at a gestational age of 31 + 3 weeks, the lightest infant and also the youngest with an age of 24 + 5 weeks of gestation, weighed 425 grams.

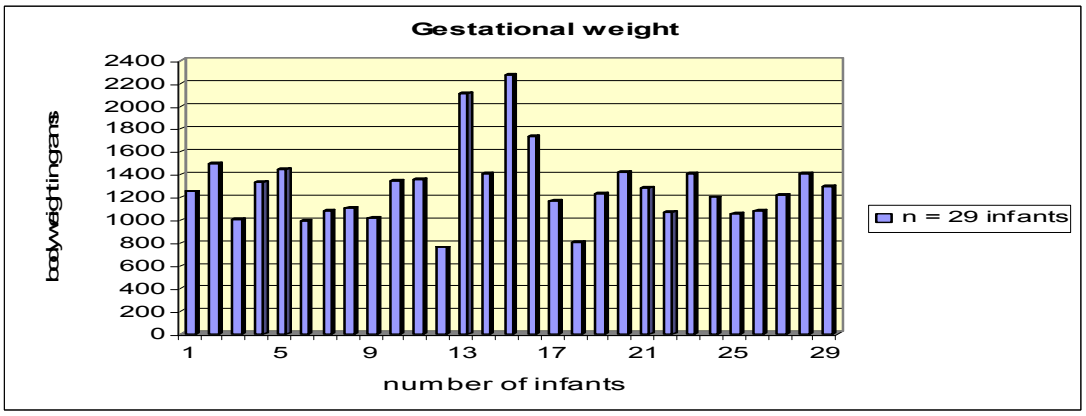


Figure 16: Distribution of gestational weights of the control group at the LKH Graz and Klagenfurt

In the control group, the mean gestational weight of all 29 infants was 1,288 grams. The gestational weight of 6 infants (20.7 percent) was below this average, while the remaining 23 newborns (79.3 percent) was above.

The heaviest newborn reached a birth weight of 2.280 grams at a gestational age of 31 +3 weeks, the lightest infant and also the youngest with an age of 24 + 3 weeks of gestation, weighed 760 grams.

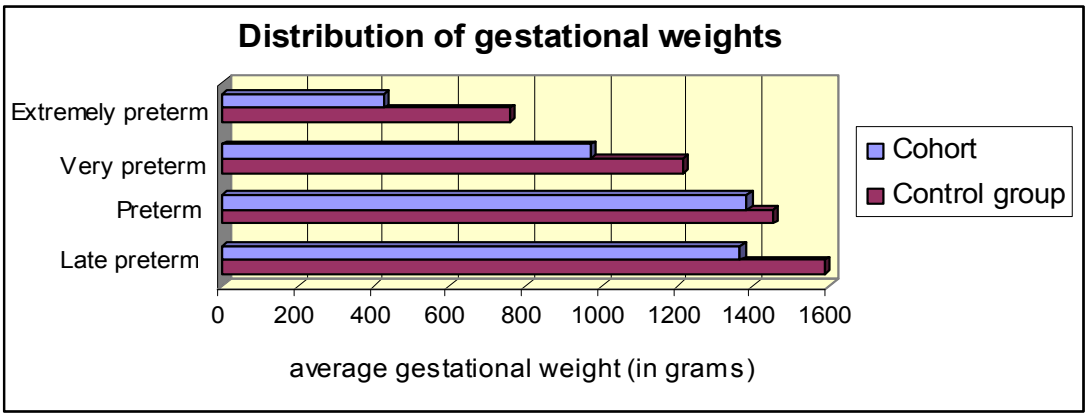


Figure 17: Comparison of gestational weights of cohort of control group

The mean gestational weight of the '*late preterm' period* (between a completed 34 and 37 + 6 weeks of gestation) was 1,367.5 grams in the study group and 1.590 grams in the control group.
Within this gestational period, the heaviest infant reached a weight of 1.475 grams in the study group and 2,110 grams in the control group and the lightest newborn was 1,260 grams in the study group and 1,419 grams in the control group.

The mean gestational weight of the '*preterm' section* (between completed 32 and 33 + 6 weeks of gestation) was 1,385 grams in the study group and 1,452 grams in the control group.
Within this gestational period, the heaviest infant reached a weight of 1,480 grams in the study group and 2,280 grams in the control group, and the lightest newborn was only 1,300 grams in the study group and 805 grams in the control group,

The mean gestational weight of the '*very preterm' section* (between 25 + 1 and 31+ 6 weeks of gestation) was 974 grams in the study group and 1,216 grams in the control group.
Within this gestational period, the heaviest infant reached a weight of 1,495 grams in the study group and 1,440 grams in the control group and the lightest newborn was only 600 grams in the study group and 990 grams in the control group,

A gestation period under the completed 25 weeks, in the '*extremely preterm' group*, the mean and only gestational weight was 425 grams in the cohort and 760 gram in the control group.

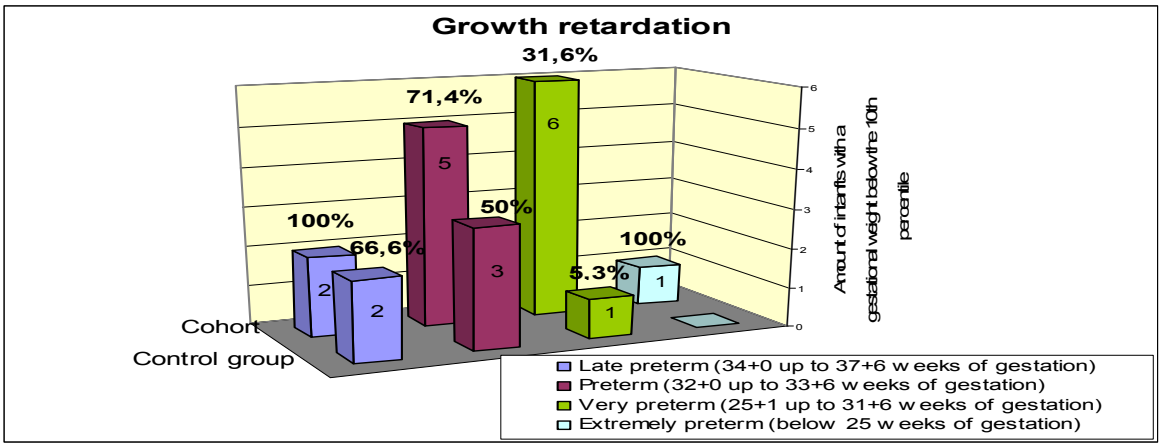


Figure 18: Incidence of growth retardation in severe maternal preeclampsia, depending on gestational age

In the late preterm period, in the study group as well as in the control group, two infants were each below the tenth percentile, equitable with an incidence of dystrophies of 100 percent in the study group and 66.6 percent in the control group.

Most growth retardations occurred within the preterm period, with five infants (71.4 percent) in the study group and three (50 percent) in the control group, followed by the very preterm period, with six infants (31.6 percent) in the study group and only one (5.3) in the control group.

The least number of dystrophic infants was in the under 25 weeks of gestation period, due to the low number of newborns in this gestational period. The study group, as well as the control group, consisted of only one infant each and are therefore, not significant.

### 2.1.2. Gestational seize

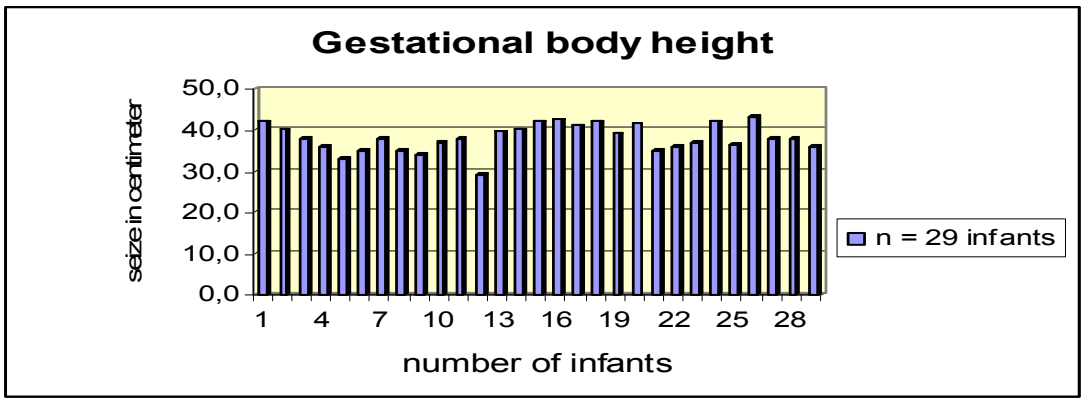


Figure 19: Distribution of gestational seize of the cohort at the LKH Graz and Klagenfurt

The mean gestational body size of all 29 infants within the cohort was 38.1 centimetres. The sizes of 17 infants (58.6 percent) were below this average, while the remaining 12 newborns (41.4 percent) were above. The largest newborn reached a body length of 43 centimetres at a gestational age of 31 + 4 weeks, the smallest and youngest at the same time, reached a size of only 29 centimetres at an age of 24 + 5 weeks of gestation.

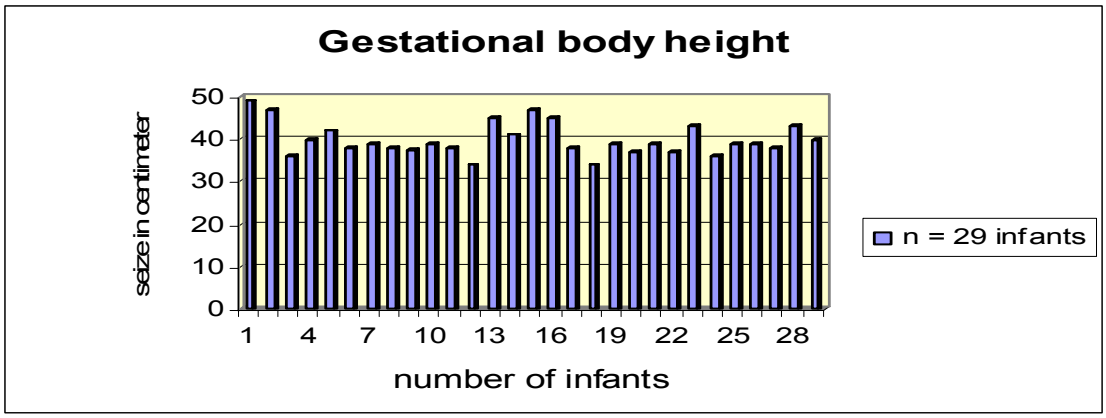


Figure 20: Distribution of gestational seizes of the control group at the LKH Graz and Klagenfurt

In the control group, the mean gestational size of all 29 infants was 39.9 centimetres. The gestational body lengths of 18 infants (62 percent) were below this average, while the remaining 11 newborns (38 percent) were above.

The largest newborn reached a size of 49 centimetres at a gestational age of 35 + 5 weeks, the smallest and also the most immature infant reached a body length of only 34 centimetres at a gestational age of 24 + 3 weeks.

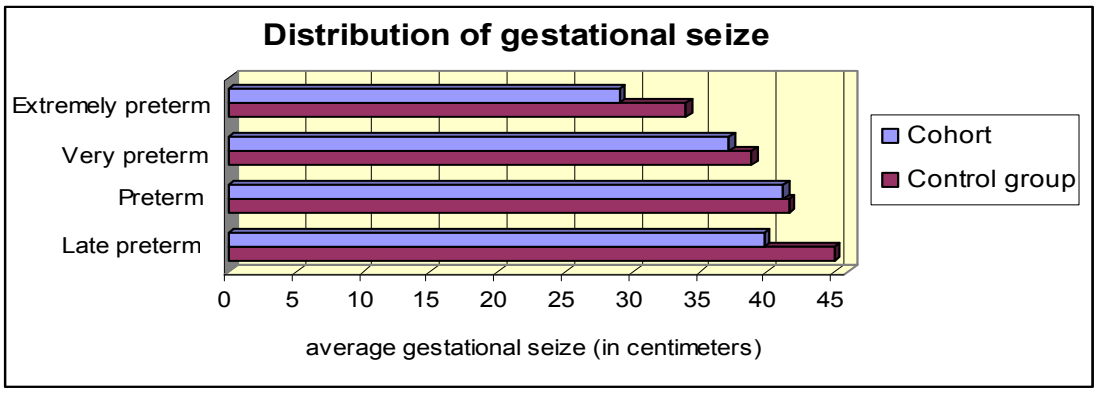


Figure 21: Comparison of gestational seizes of cohort and control group

The mean gestational size of the '*late preterm' period* (between completed 34 and 37 + 6 weeks of gestation) was 39.8 centimetres in the study group and 45 centimetres in the control group.

Within this gestational period, the largest infant reached a body length of 40 centimetres in the study group and 49 centimetres in the control group and the smallest newborn was 39.5 centimetres in the study group and 41 centimetres in the control group.

The mean gestational body length of the '*preterm' section* (between completed 32 and 33 + 6 weeks of gestation) was 41.2 centimetres in the study group and 41.6 centimetres in the control group.

Within this gestational period, the largest infant reached a size of 42.5 centimetres in the study group and 49 centimetres in the control group and the smallest newborn was 39 centimetres in the cohort and only 34 centimetres in the control group.

The mean gestational body size of the '*very preterm' section* (between 25 + 1 and 31+ 6 weeks of gestation) was very similar in both groups, with 37.2 centimetres in the study group and 38.9 centimetres in the control group.

Within this gestational period, the largest infant has reached a size of 43 centimetres in the study group as well as in the control group and the smallest newborn was 33 centimetres in the study group and 36 centimetres in the control group.

Under the completed 25 weeks of gestation, in the '*extremely preterm' group*, the mean and only gestational size was 29 centimetres in the study group and 34 centimetres in the control group.

### 2.1.3. Gestational head circumference

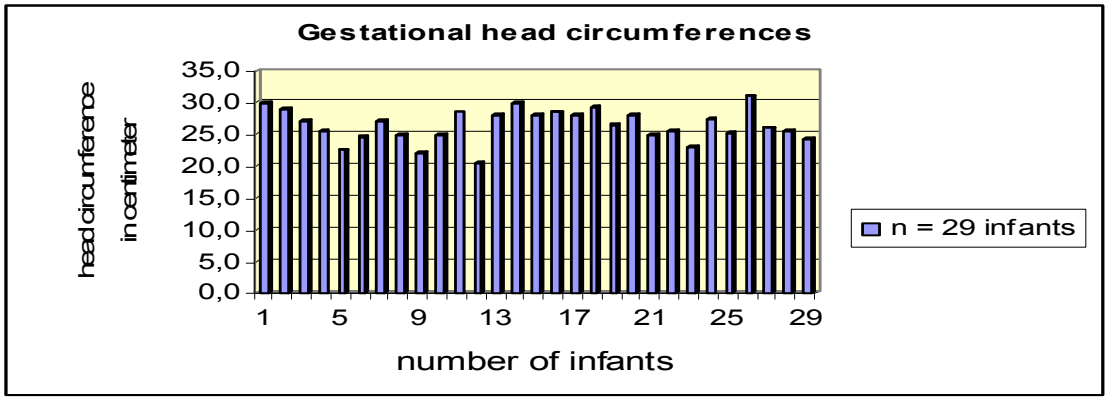


Figure 22: Distribution of gestational head circumferences of the cohort at the LKH Graz and Klagenfurt

The mean gestational head circumference of all 29 infants within the study group was 26.4 centimetres. The head circumference of 14 infants (48.3 percent) was below this average, while the remaining 15 newborns (51.7 percent) were above.

The largest head circumference was 30 centimetres at a gestational age of 34 + 3 and 34 + 6 weeks, the smallest was the extremely preterm infant with a size of 20.5 centimetres.

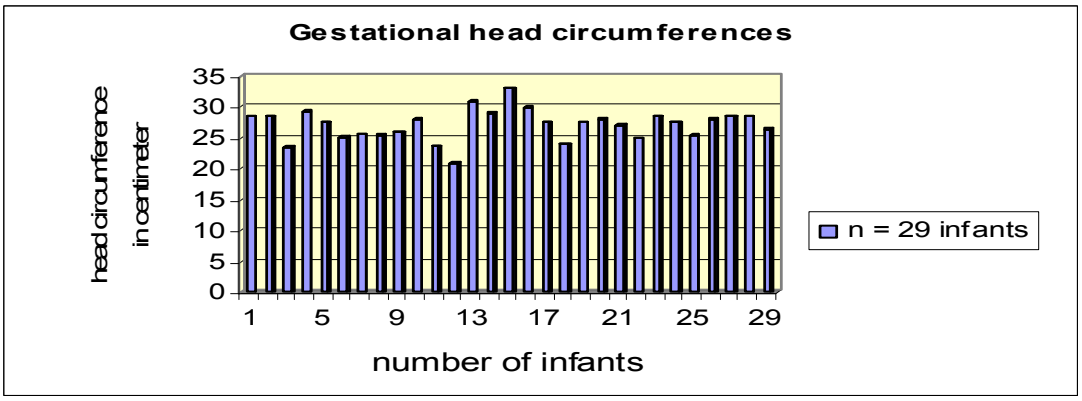


Figure 23: Distribution of gestational head circumference of the control group at the LKH Graz and Klagenfurt

In the control group, the mean gestational head circumference of all 29 infants was 27.1 centimetres; 11 infants (37.9 percent) were below this average, while the remaining 18 newborns (62.1 percent) were above. The largest newborn reached a head circumference of 33 centimetres at a gestational age of 32 + 4 weeks, the smallest and also the most immature infant reached a head circumference of only 21 centimetres at a gestational age of 24 + 3 weeks.

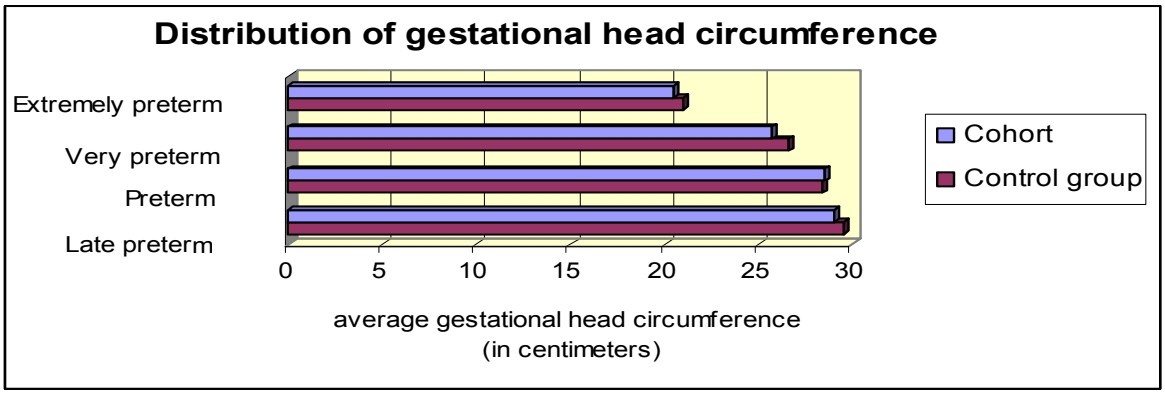


Figure 24: Comparison of gestational head circumferences of cohort and control group

The mean gestational head circumference of the '*late preterm' period* (between completed 34 and 37 + 6 weeks of gestation) was 29 centimetres in the study group and 29.5 centimetres in the control group.
Within this gestational period, the largest head circumference was 30 centimetres in the study group and 31 centimetres in the control group, and the smallest head size was 28 centimetres in the study group and 28.5 centimetres in the control group.

At time of birth, the average head circumference of the '*preterm' section* (between completed 32 and 33 + 6 weeks of gestation) was 28.5 centimetres in the study group and 28.4 centimetres in the control group.
Within this gestational period, the largest head reached a size of 30 centimetres in the study group and 33 centimetres in the control group, and the smallest head circumference was 26.5 centimetres in the cohort and only 24 centimetres in the control group,.

The mean gestational head circumference of the '*very preterm' section* (between 25 + 1 and 31+ 6 weeks of gestation) was 31 centimetres in the study group and 29.4 centimetres in the control group.
Within this gestational period, the largest infants head reached a circumference of 31 centimetres in the cohort and 29.4 centimetres in the control group, and the smallest newborn was 23 centimetres in the study group and 23.5 centimetres in the control group.

Below the completed 25 weeks of gestation, in the '*extremely preterm' group*, the mean and only head circumference was 20.5 centimetres in the study group and 21 centimetres in the control group.

## 2.2. Assessment of the infants' vitality

### 2.2.1. Acid base metabolism

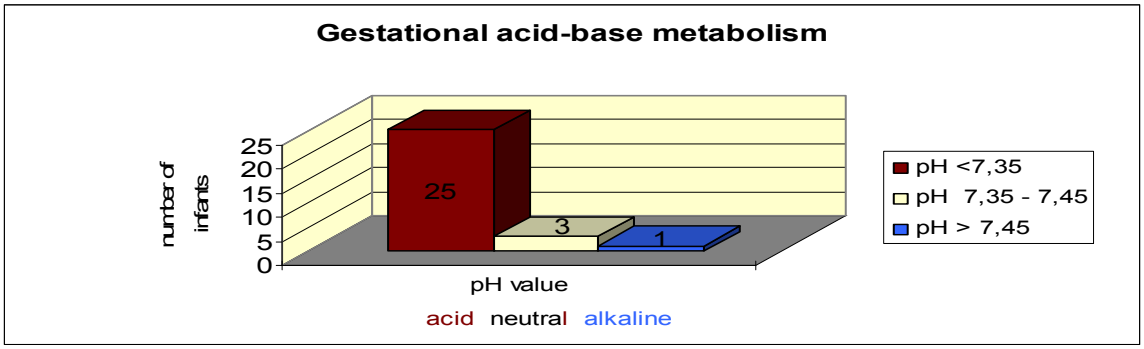


Figure 25: Acid base states at time of birth of cohort

In the study group, 25 infants (86.2 percent) were acid, with a pH value below 7.35 at the time of birth, three newborns (10.3 percent) were neutral, with a pH between 7.35 and 7.45, and only one was alkaline with a pH higher than 7.45 (3.4 percent).

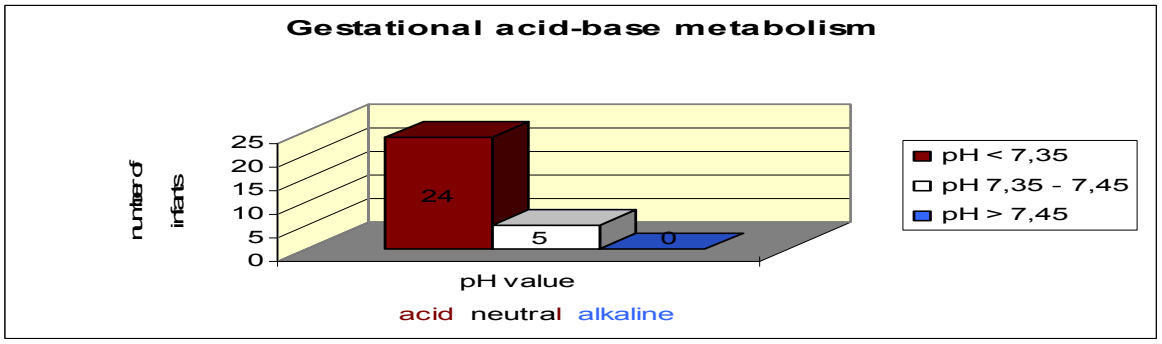


Figure 26: Distribution in the acid base states at time of birth – control group

In the control group 24 infants were acid (82.8 percent), with a pH value below 7.35 at the time of birth and five newborns were neutral (17.2 percent), with a pH between 7.35 and 7.45. No infants were alkaline within the control group.

### 2.2.2. Apgar index

The Apgar index is used to quantify the most important criteria for the assessment of the newborn. The determination of the score is performed one, five and ten minutes after the severing of the umbilical cord, the result is then taken from the total of the scores for an individual criteria.

| Score | 0 | 1 | 2 | Component of acronym |
|---|---|---|---|---|
| **Skin color** | blue, pale all over | trunk pink, extremities blue | body and extremities pink | **A**ppearance |
| **Heart rate** | no | < 100/min | ≥ 100/min | **P**ulse |
| **Reflex responsiveness** | no response | grimace when stimulated | cry, cough, sneeze when stimulated | **G**rimace |
| **Muscle tone** | none | flexed extremities | active movement | **A**ctivity |
| **Respiratory effort** | absent | slowly, irregular, gasping | strong, cry | **R**espiration |

Table 9: The five criteria of the Apgar score

The Apgar index provides only a very limited prognostic significance but it should be used as criteria for intervention in impaired adaptation of the newborn. An Apgar score of 9 to 10 is ideal, 7 to 8 is within normal range, from 4 to 6 moderate distress, but a score of 0 to 3 indicates severe distress which requires immediate resuscitation of the infant.

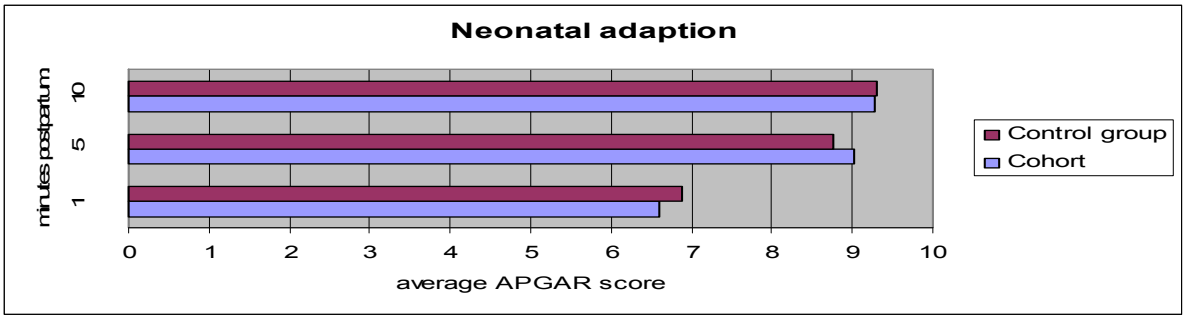


Figure 27: Mean Apgar scores of the cohort and control group after 1, 5 and 10 minutes

Figure 27 represents the adaptation of the newborns one, 5 and 10 minutes after birth. It shows that the mean Apgar score amounts to 6.6 in the first minute, 9 after 5 minutes and 9.3 after 10 minutes of birth in the study group. The average Apgar scores within the control group hardly differ with 6.87, 8.8 and 9 after one, five and 10 minutes.

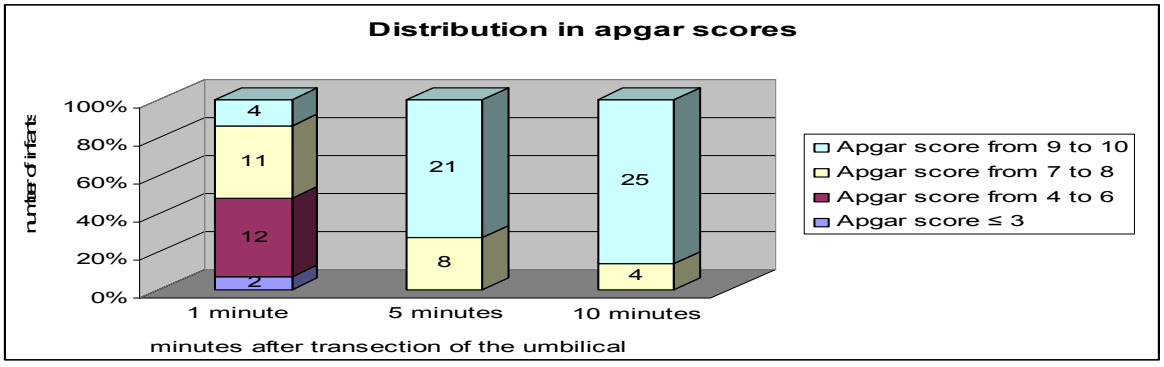


Figure 28: Apgar scores of the cohort (1, 5 and 10 minutes after birth)

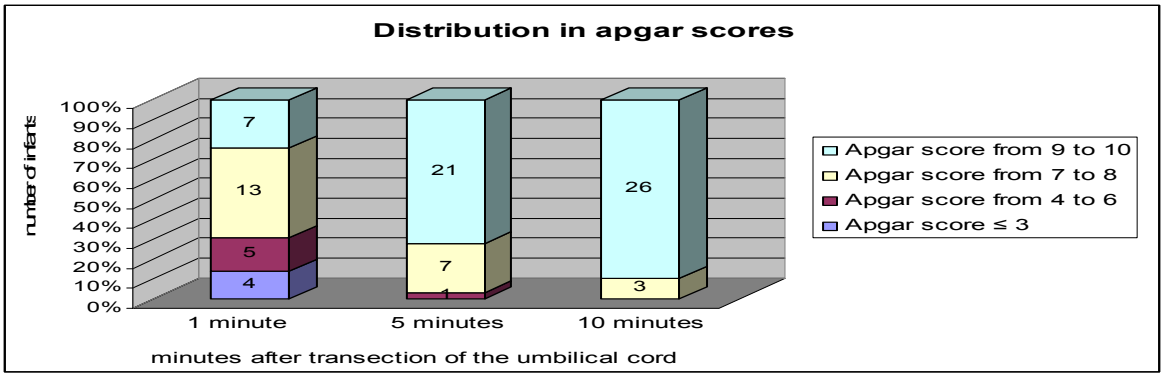


Figure 29: Apgar scores of the control group (1, 5 and 10 minutes after birth)

Figures 28 and 29 indicate the Apgar scores of all 29 infants in the study group as well as in the control group, depending on the time of measurement.
In the study group, within the first minute, two infants (6.9 percent) suffered from severe scores, 12 infants (41.4 percent) from moderate distress, 11 newborns (37.9 percent) were within the normal limits and four (13.8 infants) had shown an ideal adaption right after birth.
Five minutes after births in the cohort, 8 infants (27.6 percent) were within normal limits and the remaining 21 (72.4 percent) immediately showed an ideal adaption.
In the study group, ten minutes after the severing of the umbilical cord, 4 infants (13.8 percent) were within the normal limits and the remaining 25 (86.2 percent) had shown an ideal adaption.

In the control group, within the first minute, 4 infants (13.7 percent) suffered from severe distress, 5 (17.2 percent) from moderate distress, 13 newborns (44.8 percent) were within the normal limits and 7 (24.1 infants) showed an ideal adaption right after birth.
Five minutes after birth within the control group, one infant (3.4 percent) was still suffering from severe distress, 7 infants (24.1 percent) were within the normal limits and 21 (72.4 percent) already showed an ideal adaption.
In the control group, 10 minutes after the severing of the umbilical cord, 3 infants (10.3 percent) were within the normal limits and the remaining 26 (89.7 percent) showed an ideal adaption.

## 2.3. Conclusion

Summarizing, it can be said, that within the perinatal analysis, the only significant difference ($p = 0.01$) between both groups could be proven within the gestational age. With an average gestational weight in the study group of 1,081 grams, the infants within the control group reached a plus of 19.1 percent with an average weight of 1,288 grams.
Within the single gestational periods, gestational weights of infants in the control group had shown a plus of 4.9 percent in the preterm period and 24.8 percent in the very preterm period, compared to the infants within the study group.

As described in other studies, the process of delayed growth in the context of prematurity could be shown in both groups. As far as the incidence of dystrophy is concerned, at the time of birth 31.6 percent of the children within the study group and 5.3 percent within the control group had been dystrophic; at the time of discharge the percentage of dystrophies increased 69 percent in the study group and 53.8 percent in the control group.

Against all expectations, neither in terms of size, head circumference, adaptation parameters such as acid base state and Apgar scores at time of birth and discharge, nor in relation to cerebral and neurological

abnormalities during hospitalization (58.5 percent in the study group versus 37.9 percent within the control group could a significant difference between the two groups be proven.

| Variable | mean | minimum | maximum | standard deviation | significance (p) | |
|---|---|---|---|---|---|---|
| **Gestational age** (days) | 211 | 173 | 241 | 17,8 | p = 1,0 | study group |
| | 211 | 171 | 252 | 20,99 | | control group |
| **Gestational weight** (grams) | 1081 | 425 | 1495 | 303,4 | p = 0,018 | study group |
| | 1288 | 760 | 2280 | 329,7 | | control group |
| **Gestational seize** (cm) | 38,1 | 29 | 43 | 3,38 | p = 0,07 | study group |
| | 39,9 | 34 | 47 | 3,81 | | control group |
| **Gestational head circumference** (cm) | 26,4 | 20,5 | 30 | 2,54 | p = 0,72 | study group |
| | 27,1 | 21 | 26,4 | 2,48 | | control group |
| **pH value** | 7,27 | 7,12 | 7,47 | 0,062 | p = 1,0 | study group |
| | 7,27 | 7,15 | 7,37 | 0,069 | | control group |
| **Apgar score 1min** | 6,6 | 2 | 9 | 1,82 | p = 0,59 | study group |
| | 6,9 | 1 | 9 | 2,45 | | control group |
| **Apgar score 5min** | 9 | 7 | 10 | 0,94 | p = 0,46 | study group |
| | 8,8 | 5 | 10 | 1,09 | | control group |
| **Apgar score 10 min** | 9,3 | 7 | 8 | 0,8 | p = 1,0 | study group |
| | 9,3 | 10 | 10 | 0,8 | | control group |

Table 10: Statistic analysis of the postnatal period

## 3. Peripartal morbidity

Acquiring all necessary data was possible for 29 infants only, 18 females and 11 males with gestational ages between 24 + 5 and 34 + 3 weeks. The following periods were analysed: the postnatal, hospitalization and discharge, as well as at the age of two years.

To create our control group, these 29 infants were matched to the same number of children with the same gestational terms, except for one late preterm instead of a preterm term infant, due to the fact that no late preterm with neurological long term check ups could be found. The control group included 12 female and 17 male infants with gestational ages between 24 + 3 and 36 + 0 weeks.

During hospitalization at the LKH Graz or the LKH Klagenfurt the following data was collected: the need for intensive care (Intensive care) and cerebral as well as neurological abnormalities (cerebral/neurological abnormalities); as shown in table 11, 12 and 13.

| Term | GA | MOD | GW (g) | Intensive care | Cerebral/Neurological abnormalties |
|---|---|---|---|---|---|
| | | | | | |
| Preterm | 32+2 | S | 1460 | no | Macrocephalus |
| | 33+3 | S | 1300 | no | |
| | | | | | |
| Very Preterm | 29+2 | S | 1060 | no | |
| | 29+4 | S | 824 | yes | |
| | 25+6 | S | 600 | yes | Ventricle asymmetrie (left > right) |
| | 27+1 | S | 820 | yes | PVL I, IVH II, Plexus hemorrhage (both sides) |
| | 28+4 | S | 1130 | no | |
| | 28+4 | S | 760 | yes | |
| | 29+0 | S | 730 | no | PVL I, Microcephalus |
| | 27+2 | S | 930 | yes | |
| | 31+4 | S | 1330 | yes | |
| | | | | | |
| Extremely preterm | 24+5 | S | 425 | yes | |

Table 11: Data of the cohort during hospitalization at the LKH Graz

| Term | GA | MOD | GW (g) | Intensive care | Cerebral/Neurological Abnormalties |
|---|---|---|---|---|---|
| Late preterm | 34+1 | S | 1260 | yes | |
| | 34+3 | S | 1475 | yes | |
| Preterm | 33+0 | S | 1340 | yes | |
| | 33+4 | S | 1450 | yes | |
| | 32+6 | S | 1305 | yes | |
| | 33+1 | S | 1480 | yes | |
| | 32+0 | S | 1360 | yes | |
| Very Preterm | 31+6 | S | 1300 | yes | Ventricle asymmetrie (left > right) |
| | 27+5 | S | 790 | yes | |
| | 27+2 | S | 924 | yes | |
| | 27+3 | S | 760 | yes | Plexus cysts frontal (4 right, 2 left) |
| | 31+4 | V | 1340 | no | |
| | 28+5 | S | 970 | yes | IVHI right with 1 cerebral cyst, Ventricle asymmetrie |
| | 31+3 | S | 1495 | yes | |
| | 30+0 | S | 990 | yes | |
| | 29+0 | S | 870 | yes | |
| | 28+5 | S | 882 | yes | |

Table 12: Data of the cohort during hospitalization at the LKH Klagenfurt

| Term | GA | MOD | GW (g) | Intensive care | Cerebral/Neurological Abnormalties |
|---|---|---|---|---|---|
| Late preterm | 34+6 | V | 2110 | yes | |
| | 36+0 | S | 1410 | no | Alternating, non synchronic spontaneous movements |
| | 35+5 | S | 1250 | yes | |
| Preterm | 32+4 | S | 2280 | yes | IVH I, Hämatocephalus int., PVL I |
| | 32+1 | V | 1740 | no | Hypoxic ischemic encephalopathy II, Ventricle asymmetrie (left > right) |
| | 33+6 | S | 1170 | no | |
| | 26+1 | S | 805 | yes | IVH I |
| | 32+2 | S | 1230 | yes | Ventricle asymmetrie (left > right), |
| | 32+6 | S | 1490 | no | |
| Very Preterm | 31+0 | S | 1420 | no | neurologically conspicious jumpy |
| | 29+2 | S | 1280 | yes | |
| | 28+2 | S | 1070 | yes | Basal ganglia hemorrhage (right) |
| | 31+4 | S | 1410 | yes | |
| | 27+6 | S | 1200 | yes | |
| | 27+3 | V | 1050 | yes | |
| | 31+4 | S | 1080 | no | |
| | 30+0 | S | 1220 | no | |
| | 31+4 | S | 1410 | yes | |
| | 31+6 | S | 1290 | yes | |
| | 26+0 | V | 1000 | no | |
| | 31+4 | S | 1332 | yes | |
| | 29+0 | S | 1440 | yes | Ventricle asymmetrie (left > right), small plexus cyst (right) |
| | 27+1 | V | 990 | yes | IVH I, pseudocystic change (> 20 days) |
| | 27+3 | V | 1080 | yes | Ventricle asymmetrie (right > left), |
| | 28+2 | S | 1110 | yes | PVL III occipital, Ventriculomegaly right |
| | 27+3 | S | 1018 | yes | IVH III, Ventricle wall cyst (left), post hemorrhagic hydrocephalus internus |
| | 28+4 | S | 1350 | yes | |
| | 28+2 | S | 1360 | yes | PVL I > 14 days (fronto-temporal) |
| Extremely preterm | 24+3 | S | 760 | yes | |

Table 13: Data of the control group during hospitalization at the LKH Graz and Klagenfurt

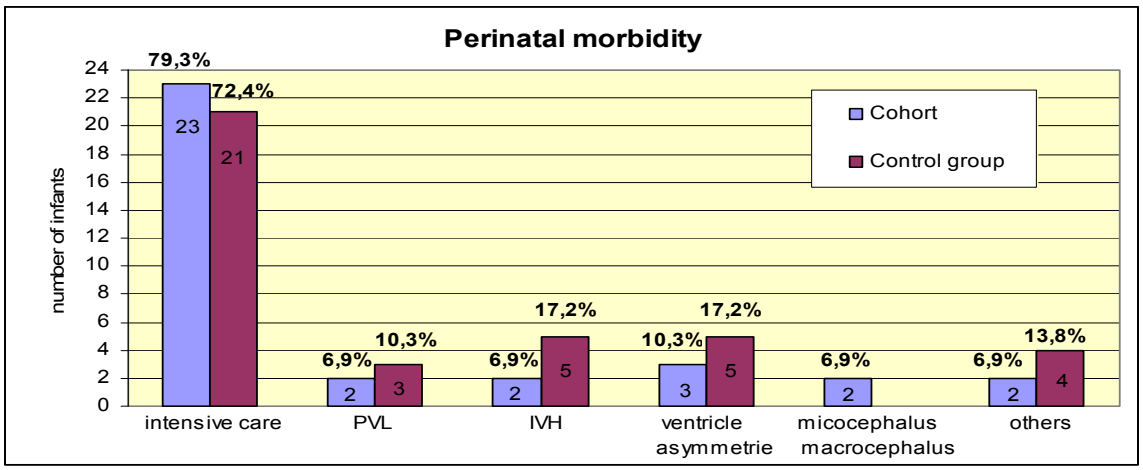


Figure 30: Incidence of: need of intensive care, periventricular leukomalacia (PVL), intraventricular hemorrhage (IVH), ventricle asymmetry, micro- or macrocephalus, and other neurological/cerebral abnormalities in the cohort and control group

Figure 30 shows that the incidence of infants with the need for intensive care was extremely high, with 79.3 percent in the study group and 72.4 percent in the control group; this includes the need for neonatal intensive care only, not prematurity care.

During hospitalization, two infants (6.9 percent) developed a periventricular leukomalacia (PVL) within the study group, in both instances grade I; in the control group, 5 children (10.3 percent), twice with grade I and once with grade III with an additional extensive cystic fronto-parieto-occipital leukomalacia.
Intraventricular hemorrhage (IVH) occurred within the study group in two infants (6.9 percent), once grade I, associated with a single cerebral cyst and the other time grade II with additional plexus hemorrhage on both sides, while in the control group, 5 infants (17.2 percent) developed an intraventricular hemorrhage (IVH), 4 times grade I and once grade III with additional ventricle wall cysts, and as a result, a post hemorrhagic hydrocephalus internus and periventricular echodensities.

Ventricle asymmetries occurred in 10.3 percent of the study group, all three times with the left side greater than the right one, and in 17.2 percent within the control group; 3 times the left ventricle had been larger than the right one, and twice the other way round.

One infant developed a microcephalus, another one a microcephalus, both within the study group, but none within the control group.

Furthermore, one newborn in the study group showed six plexus cysts frontal (four on the right side and two on the left). In the control group, four infants had neurological suspicions: one with alternating, non synchronic spontaneous movements, another developed a hypoxic ischemic encephalopathy grade II, one had been neurologically, conspicuously jumpy and the last one developed a single, small plexus cyst on the right side.

## 4. Discharge state

Acquiring all necessary data was possible for 29 infants only, 18 females and 11 males with gestational ages between 24 + 5 and 34 + 3 weeks. The following periods were analysed: the postnatal, hospitalization and discharge, as well as at the age of two years.
To create our control group, these 29 infants had been matched to the same number of children with the same gestational terms, except one late preterm instead of a preterm term infant, due to the fact that no late preterm with neurological long term check ups could be found. The control group included 12 female and 17 male infants with gestational ages between 24 + 3 and 36 + 0 weeks.

The 18 females and 11 males with a gestational age between 24 + 5 and 34 + 3 weeks were analysed at the time of discharge, acquiring the duration of the in-patient stay in days (H (d)), corrected gestational age (cA_d), weight in grams (W_d), length (L_d) and head circumference in centimetres (HC_d), as well as the clinical discharge diagnoses.

| Term | GA | GW < 10p | H (d) | cA_d | W_d | L_d | HC_d | Clinical discharge diagnoses |
|---|---|---|---|---|---|---|---|---|
| Preterm | 32+2 | | 41 | 38+2 | 2040 | 43,0 | 33,5 | |
| | 33+3 | x | 35 | 38+3 | 2210 | 43,0 | 32,5 | status post: small for gestational age |
| Very Preterm | 29+2 | | 53 | 36+5 | 2050 | 42,0 | 32,5 | |
| | 29+4 | x | 65 | 38+5 | 2005 | 45,0 | 32,4 | status post: small for gestational age |
| | 25+6 | | 92 | 39+6 | 2140 | 45,0 | 32,5 | ‚slit ventricle', very immature parenchyma |
| | 27+1 | | 90 | 35+4 | 2212 | 43,0 | 32,6 | status post: plexus hemorrhage |
| | 28+4 | | 46 | 35+0 | 2270 | 45,0 | 32,8 | status post: small for gestational age |
| | 28+4 | x | 71 | 34+2 | 2150 | 44,5 | 32,0 | status post: small for gestational age |
| | 29+0 | x | 87 | 41+4 | 1895 | 42,0 | 31,5 | status post: small for gestational age, PVLI and microcephalus |
| | 27+2 | | 68 | 32+4 | 1830 | - | - | |
| | 31+4 | | 36 | 36+4 | 2060 | - | 30,7 | status post: dystrophy < 3 percentile |
| Extremely preterm | 24+5 | x | 106 | 39+5 | 2095 | 44,0 | 32,6 | |

Table 14: Data of the cohort at time of discharge at the LKH Graz

| Term | GA | GW < 10p | H (d) | cA_d | W_d | L_d | HC_d | Clinical discharge diagnoses |
|---|---|---|---|---|---|---|---|---|
| Late preterm | 34+1 | x | 73 | 40+2 | 2400 | 43,0 | 32,0 | status post: small for gestational age |
| | 34+3 | x | 31 | 39+1 | 1980 | 42,0 | 31,0 | status post: small for gestational age |
| Preterm | 33+0 | x | 44 | 39+2 | 2450 | 47,0 | 32,8 | status post: small for gestational age |
| | 33+4 | x | 34 | 38+2 | 2220 | 45,0 | 32,5 | status post: small for gestational age |
| | 32+6 | x | 42 | 38+4 | 1968 | 45,0 | 31,7 | status post: small for gestational age |
| | 33+1 | x | 31 | 37+4 | 2180 | 46,5 | 31,5 | ventricle asymmetrie (left > right) |
| | 32+0 | x | 44 | 38+2 | 2280 | 48 | 33,3 | |
| Very Preterm | 31+6 | x | 40 | 37+3 | 2130 | 44,0 | 32,2 | ventricle asymmetrie (left > right) |
| | 27+5 | | 91 | 40+5 | 2840 | 47,0 | 35,0 | |
| | 27+2 | | 95 | 36+4 | 3370 | 46,0 | 35,0 | ventricle asymmetrie (left > right), slight periventricular echodensities (occipital) |
| | 27+3 | | 94 | 40+5 | 2410 | 45,5 | 33,0 | status post: small for gestational age, 6 small plexus cysts (frontal) |
| | 31+4 | | 53 | 39+0 | 2155 | 43,0 | 31,0 | |
| | 28+5 | | 74 | 39+0 | 2220 | 47,0 | 33,0 | |
| | 31+3 | | 37 | 38+0 | 2230 | 49,0 | 33,3 | |
| | 30+0 | x | 71 | 40+0 | 2120 | 46,3 | 32,5 | |
| | 29+0 | x | 67 | 39+4 | 2196 | 44,0 | 32 | |
| | 28+5 | | 79 | 38+2 | 2300 | 45,5 | 33 | IVH I (right side) with single cerebral cyst, ventricle asymmetry, fundus demarcation |

Table 15: Data of the cohort at time of discharge at the LKH Klagenfurt

| Term | GA | GA < 10p | H (d) | cA_d | W_d | L_d | HC_d | Clinical discharge diagnoses |
|---|---|---|---|---|---|---|---|---|
| Late preterm | 34+6 | | 36 | 40+0 | 2670 | - | - | |
| | 36+0 | x | 130 | 14+4d (54+4) | 2250 | 46 | 33 | alternating, non synchronic spontaneous movements, status post: small for gestational age and IUGR with dysmorphic face and asymmetry of the face |
| | 35+5 | x | 22 | 38+6 | 1800 | - | - | status post: small for gestational age |
| Preterm | 32+4 | | 29 | 36+5 | 2530 | 49 | 34 | subependymal hemorrhage followed by hematocephalus internus and postischemic lesions (basal ganglia, periventricular infarction (subacute; left side) |
| | 32+1 | | 39 | 37+5 | 2540 | 46 | 31,5 | hypoxic ischemic encephalopathy II, ventricle asymmetry, no IVH |
| | 33+6 | x | 25 | 37+3 | | 40,5 | 30,5 | |
| | 26+1 | x | 93 | 39+3 | 2274 | - | - | subependymal hemorrhage (IVH I), ventricle asymmetry |
| | 32+2 | | 42 | 38+2 | 2000 | - | - | ventricle asymmetry |
| | 32+6 | x | 24 | 36+2 | 1950 | 44 | 31 | physiologically distinct periventricular echodensities |
| Very Preterm | 31+0 | | 31 | 35+3 | 1845 | 43 | 31,3 | Neurologic suspicious jumpy |
| | 29+2 | | 51 | 36+4 | - | 44 | 32 | |
| | 28+2 | | 74 | 38+6 | 2100 | - | - | subependymal hemorrhage grade I (basal ganglia, right side) |
| | 31+4 | | 95 | 44+1 | 2430 | 48 | 32,6 | |
| | 27+6 | | 62 | 36+4 | 2420 | 45 | 32,4 | |
| | 27+3 | | 63 | 36+3 | 2146 | 46 | 32,2 | |
| | 31+4 | x | 74 | 42+1 | 2520 | - | - | |
| | 30+0 | | 46 | 36+4 | 2070 | - | - | |
| | 31+4 | | 61 | 40+2 | 2430 | 48 | 32,6 | |
| | 31+6 | | 68 | 5+5d (45+5) | 2130 | | | |
| | 26+0 | | 68 | 35+5 | 2154 | 45 | 32 | small, periventricular echodensities unknown etiology |
| | 31+4 | | 45 | 38+0 | 2180 | 46 | 31 | |
| | 29+0 | | 35 | 34+0 | 2816 | 47 | 33,2 | ventricle asymmetry (left > right), single small plexus cyst (right) |
| | 27+1 | | 81 | 38+5 | 1080 | - | - | Status post: subependymal hemorrhage grade I |
| | 27+3 | | 30 | 31+5 | 2185 | 45,5 | 31,8 | ventricle asymmetry (right > left) |
| | 28+2 | | 61 | 37+1 | 2885 | 51 | 36,5 | occipital echodensities, PVL III with occipital cysts, ventricle asymmetry (right > left), muscle tone slightly increased |
| | 27+3 | | 88 | 40+1 | 2415 | 48 | 33,5 | both ventricles enlarged, ventricle wall cyst (left), post hemorrhage hydrocephalus internus |
| | 28+4 | | 37 | 33+6 | 2050 | 44 | 30,1 | |
| | 28+2 | | 51 | 35+4 | - | - | - | Echodensities (right, fronto-temporal), no IVH |
| Extremely preterm | 24+3 | | 92 | 37+4 | 2140 | 45 | 31 | |

Table 16: Data of the control group at time of discharge at the LKH Graz and Klagenfurt

## 4.1. Duration of hospitalization and corrected age at discharge

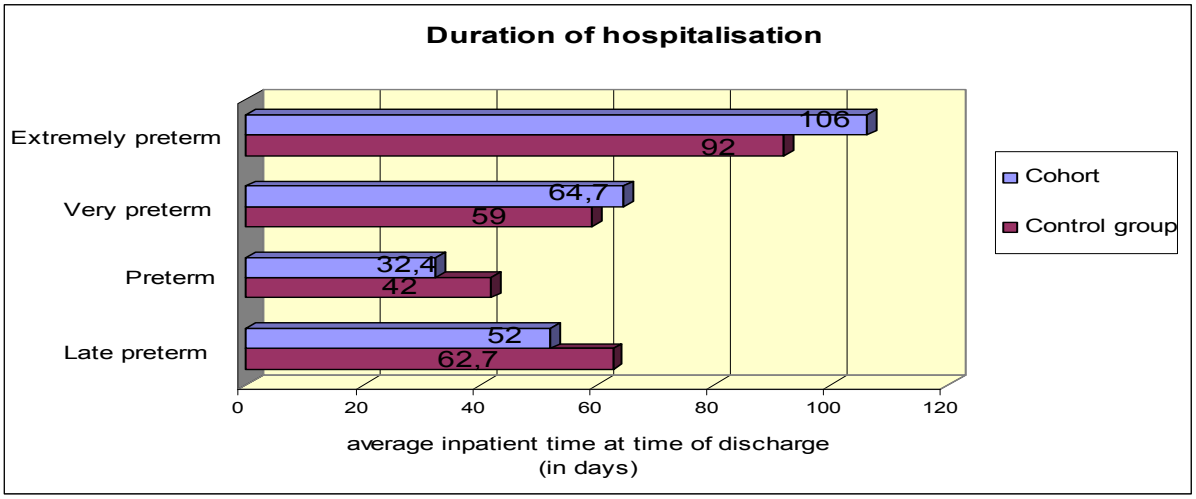


Figure 31: Distribution of weights of the cohort at the LKH Graz and Klagenfurt at time of discharge

Figure 31 indicates the correlation between the average in-patient stay and the gestational periods.
In the study group, the one *extremely preterm* infant had to stay 106 days, in the control group it had been 92 days.

The mean duration of hospitalization of the '*very preterm' period* (between 25 + 1 and 31+ 6 weeks of gestation) was 64.7 days in the study group and 59 in the control group.
Within this gestational period, the longest in-patient stay was 95 days in the study group, as well as in the control group, the shortest duration of hospitalization was 36 days in the study group and 30 in the control group.

The mean duration of hospitalization of the '*preterm' section* (between completed 32 and 33 + 6 weeks of gestation) was 32.4 days in the study group and 42 days in the control group.
Within this gestational period, the longest in-patient stay was 44 days in the control group and 93 in the study group and the earliest discharge had been 31 days in the study group and 24 in the control group.

The mean duration of hospitalization of the '*late preterm' period* (between completed 34 and 37 + 6 weeks of gestation), was 52 days in the study group and 62.7 days in the control group.
Within this gestational period, the longest in-patient stay was 73 days in the study group and 130 days in the control group and the earliest discharge had been 31 days in the study group and 22 days in the control group.

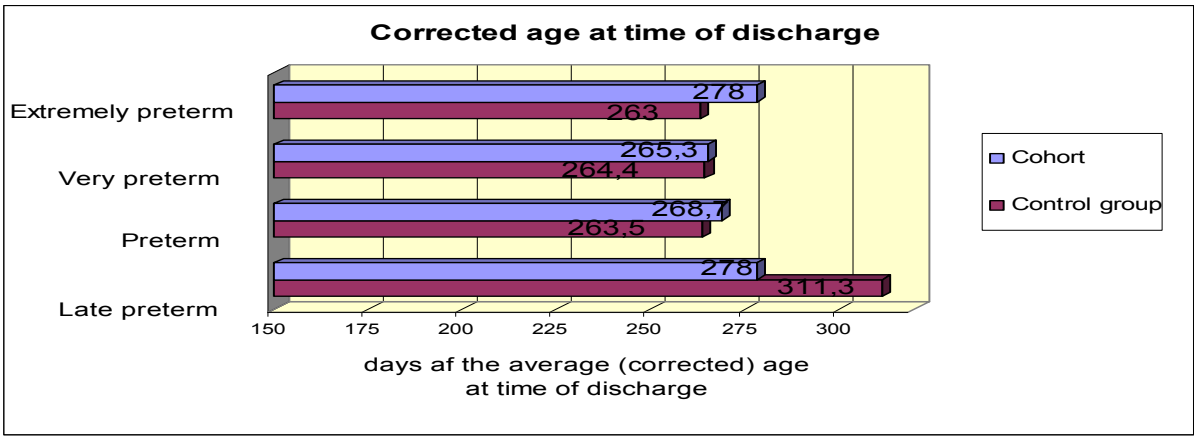


Figure 32: Distribution of weights of the cohort, depending on gestational periods, at the LKH Graz and Klagenfurt at time of discharge

Although the duration of hospitalization had shown large differences, depending on the gestational periods, the corrected ages at discharge were very close.

In the study group, the one *extremely preterm* infant in the cohort had been in the hospital until a corrected age of 278 days (corrected 39 + 5 gestational weeks) the one from the control group had been 263 days (corrected 37+4 gestational weeks) at the time of discharge.

At the time of discharge, the mean corrected gestational age in the '*very preterm' period* (between 25 + 1 and 31+ 6weeks of gestation) had been 265 gestational days (corrected 37 + 6 gestation weeks) in the study group and 264 gestational days (corrected 37 + 5 gestational weeks) in the control group.
Within this gestational period, the oldest child had been 291 gestational days (corrected 41+4 gestational weeks) in the study group and 320 days (corrected 45+5 weeks of gestation) in the control group at the time of discharge. At this time, the youngest infant had been 228 gestational days (corrected 32+4 gestational weeks) in the study group and 222 gestational days (corrected 31+5 gestational weeks) in the control group.

At the time of discharge, the mean corrected gestational age of the '*preterm' section* (between completed 32 and 33 + 6 weeks of gestation) had been 269 gestational days in the study group and 263.5 gestational days in the control group.
The youngest infants leaving the hospital had been 263 gestational days (corrected 37+4 weeks of gestation) in the study group and 254 gestational days (corrected 36+2weeks) in the control group, while the oldest had been 274 gestational days (corrected 39+2 weeks) in the study group and 276 gestational days (corrected 39+3 weeks of gestation) in the control group.

At the time of discharge, the mean corrected gestational age *late preterm' period* (between completed 34 and 37 + 6 weeks of gestation), had been 278 gestational days in the study group and 311 gestational days in the control group.

The youngest infants leaving the hospital has been 274 gestational days (corrected 39 + 1 weeks of gestation) in the study group and 272 gestational days (corrected gestational age of 41+4 weeks) in the control group, while the oldest had been 282 gestational days (corrected 40 + 2 weeks) in the study group and 320 days (corrected gestational age of 45+5 weeks) in the control group already.

## 4.2. Distribution of weight, size and head circumference at time of discharge

### 4.2.1. Weight at discharge

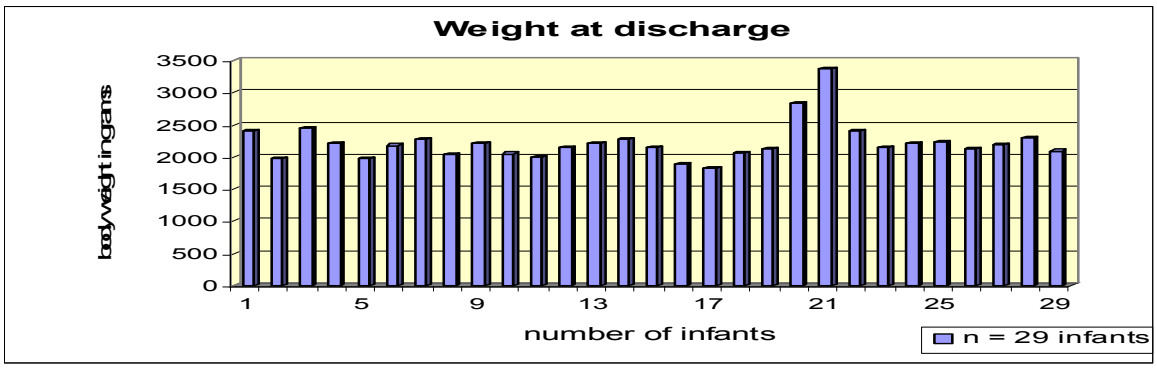


Figure 33: Distribution of weights of the cohort at the LKH Graz and Klagenfurt at time of discharge

The mean discharge weight of all 29 infants within the study group had been 2,221 grams. The weights of 20 infants (69 percent) had been below this average, while the remaining 9 children (31 percent) had been more than 2,221 grams at time of discharge.

At discharge, the heaviest infant reached a weight of 3,370 grams at a corrected gestational age of 36 + 3 weeks, the lightest infant with a corrected age of 27 + 2 weeks of gestation, weighed 1,830 grams.

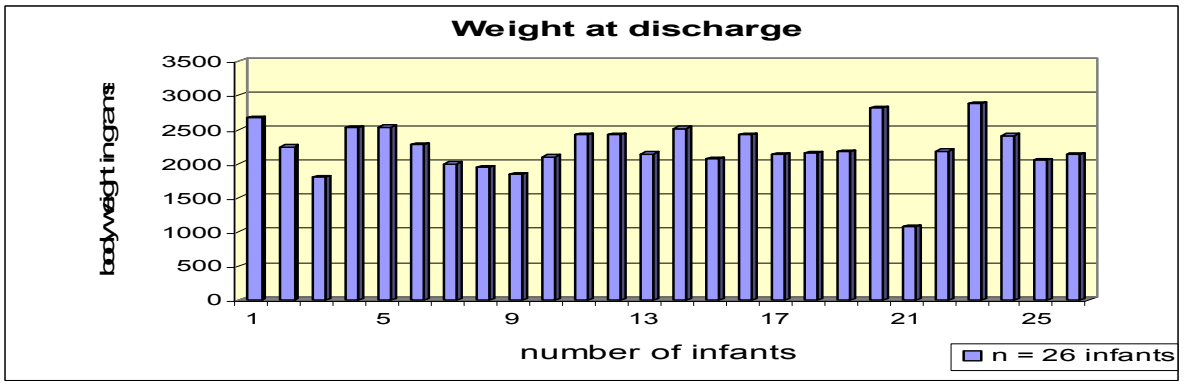


Figure 34: Distribution of weights of the control group at time of discharge

In the control group, the mean discharge weight of 26 infants had been 2,231 grams. The discharge weights of 14 infants (53.8 percent) had been below this average, while the remaining 46.2 percent (12 children) had been above 2,231 grams.

The heaviest infant reached a weight of 2,885 grams at a corrected gestational age of 37+1 weeks, the lightest infant weighted 1,080 grams at a corrected gestational age of 38 + 5 weeks.

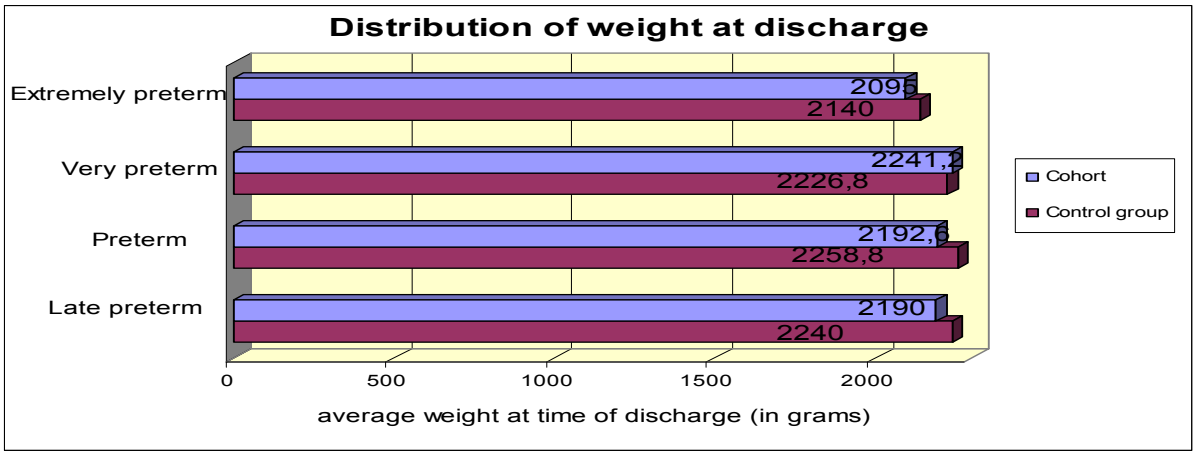


Figure 35: Comparison of the cohorts' and control groups' weights at discharge

The mean discharge weight of the '*late preterm' period* (between completed 34 and 37 + 6 weeks of gestation) had been 2,190 grams in the study group and 2,240 grams in the control group.
Within this gestational period, the heaviest infant has reached a weight of 2,400grams in the study group and 2,670 grams in the control group, and the lightest infant had been 1,980 grams in the study group and 1,800 grams in the control group at the time of discharge.

The mean discharge weight of the '*preterm' section* (between completed 32 and 33 + 6 weeks of gestation) had been 2,192 grams in the study group and 2,259 grams in the control group.
Within this gestational period, the heaviest infant had reached a weight of 2,450 grams in the study group and 2,540 grams in the control group, and the lightest infant had been 1,968 grams in the study group and 1950 grams in the control group, at the time of discharge.

The mean discharge weight of the '*very preterm' section* (between 25 + 1 and 31+ 6 weeks of gestation) had been 2,241 grams in the study group and 2,227 grams in the control group.
Within this gestational period, the heaviest infant had reached a weight of 3,370 grams in the study group, at a corrected age of 36+4 weeks of gestation and 2,885 grams in the control group, with 37+1 weeks of corrected gestational age. The lightest infant had been 1,830 grams at an age of 32 + 4 weeks of corrected gestational age in the study group, and 1,080 grams with a discharge age of 38+5 weeks, of corrected gestational age in the control group, at the time of discharge.

Under completed 25 weeks of gestation, in the '*extremely preterm' group*, the mean and only discharge weight had been 2,095 grams in the study group, but 2,140 gram in the control group.

### 4.2.2. Seize at discharge

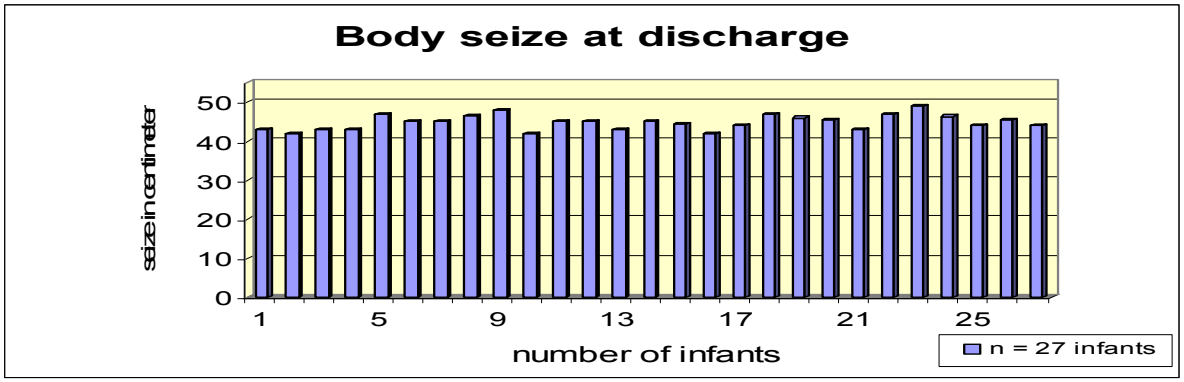


Figure 36: Distribution of body lengths within the control group at time of discharge

In the study group, the body length of 27 infants, born at the LHK Graz or Klagenfurt had been analysed at the time of discharge and the average had been 44.2 centimetres. 12 infants (44.4 percent) had been smaller and 15 infants (55.5 percent) larger than 44.2 centimetres.

At discharge the largest infant in the study group had reached a size of 49 centimetres at a corrected gestational age of 38+0 weeks, the smallest only a size of 42 centimetres at a corrected age of 41 + 4 weeks of gestation.

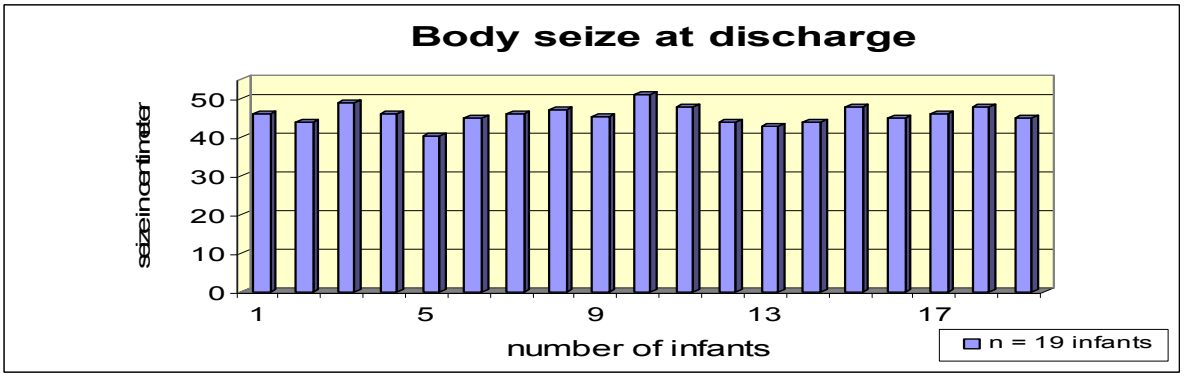


Figure 37: Distribution of body lengths within the control group at time of discharge

The average size in the control group with a total of 19 infants had been very close to the mean of the study group; 45.5 centimetres. Eight infants, 42.1 percent, had been below this average and 11 children (57.9 percent) had been larger at the end of hospitalization.

The maximum length had been a body height of 51 centimetres at a corrected gestational age of 37+1 weeks, the smallest infant with an age of 37 + 3 weeks of gestation had been 40.5 centimetres long.

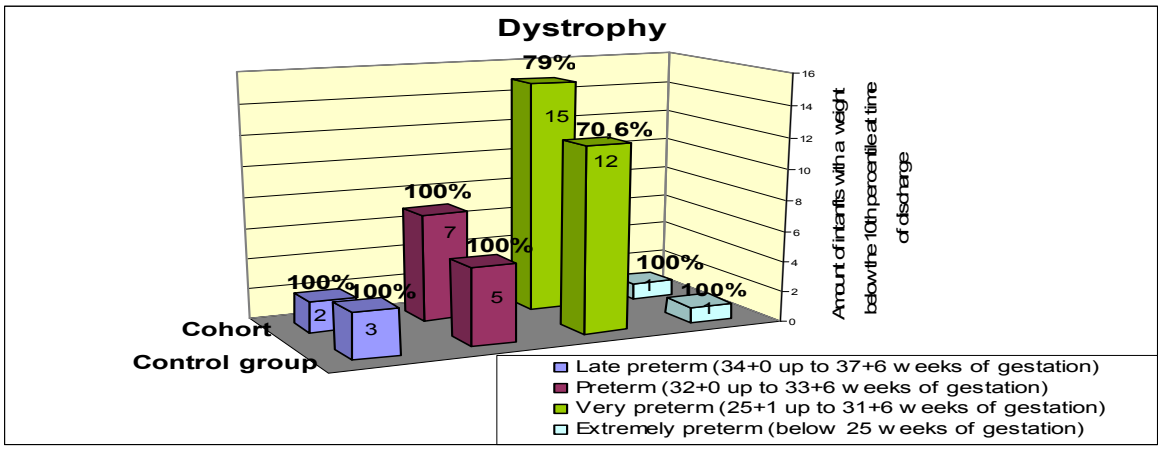


Figure 38: Incidence of growth retardation in severe maternal preeclampsia, at time of discharge

At the time of discharge, in the late preterm, the preterm, as well as in the extremely preterm period, the percentage of dystrophic children was 100%, both in the study group and in the control group.

In the very preterm period, between a corrected age of 25 +1 and 31 + 6 weeks of gestation, the number of growth retarded infants was 79 percent within the study group (15 out of 19 children) and 70.6 percent in the control group (12 out of 17).

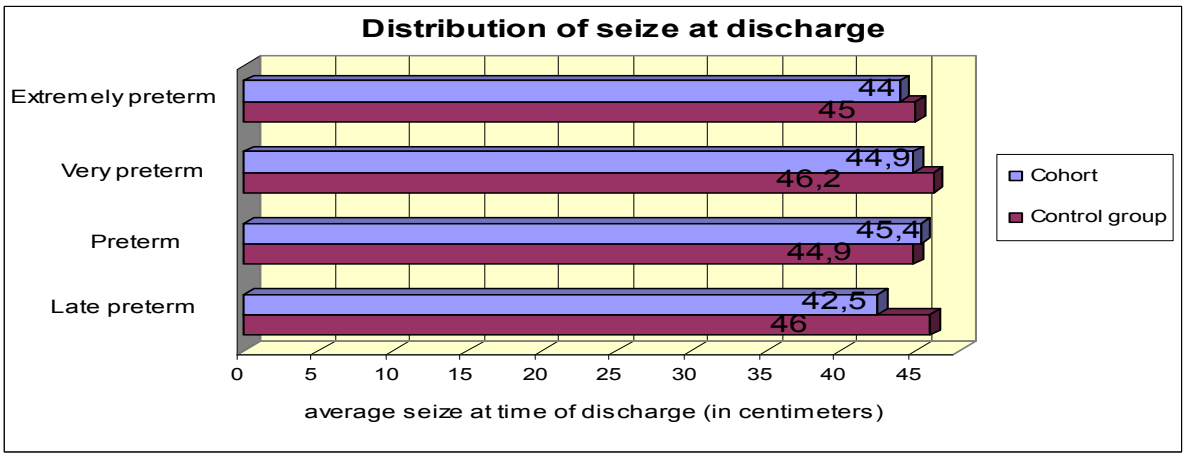


Figure 39: Comparison of average seizes of the cohort and control group at time of discharge

The mean discharge size of infants in the '*late preterm' period* (between completed 34 and 37 + 6 weeks of gestation) was 42.5 centimetres; the largest infant was 43 centimetres, the smallest 42 centimetres within the study group. The control group consisted of one child only, with a discharge size of 46 centimetres.

In the '*preterm' section* (between completed 32 and 33 + 6 weeks of gestation) the average length at discharge had been very similar in both groups, 45.4 centimetres in the study group and 44.9 in the control group. In the study group, the largest infant had reached a size of 48 centimetres and in the control group, 49 centimetres, while the smallest infant was 43 centimetres in the study group and 40.5 centimetres in the control group, at the end of hospitalization.

In the '*very preterm' section* (between 25 + 1 and 31+ 6 weeks of gestation) the average sizes at discharge were 44.9 centimetres in the study group and 46.2 centimetres in the control group. The largest infant in the study group within this gestational period had reached a length of 49 centimetres and in the control group 51 centimetres. The smallest child in the study group measured 42 centimetres and in the control group only 40.5 centimetres, at the time of discharge.

Under the completed 25 weeks of gestation, in the '*extremely preterm' group*, the study group as well as the control group included one child each, with a body length of 44 and 45 centimetres.

### 4.2.3. Head circumference at time of discharge

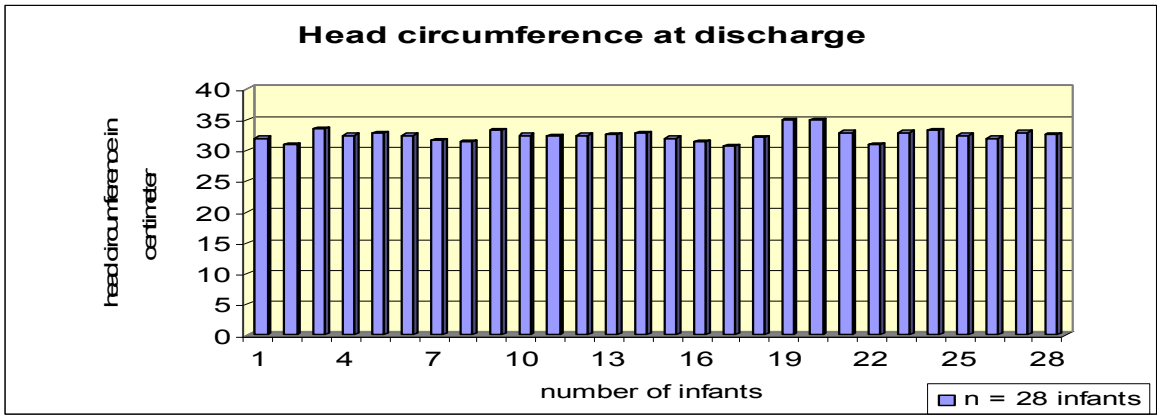


Figure 40: Distribution of gestational head circumference of the cohort at the LKH Graz and Klagenfurt at time of discharge

In the study group, the average head circumference of 28 infants at the time of discharge had been 32.3 centimetres. Eight infants (28.6 percent) were below and the remaining 20 children (71.4 percent) were above this mean head circumference at the end of hospitalization.

The largest circumference in the study group was 35 centimetres at the time of discharge; the smallest was 30.7 centimetres.

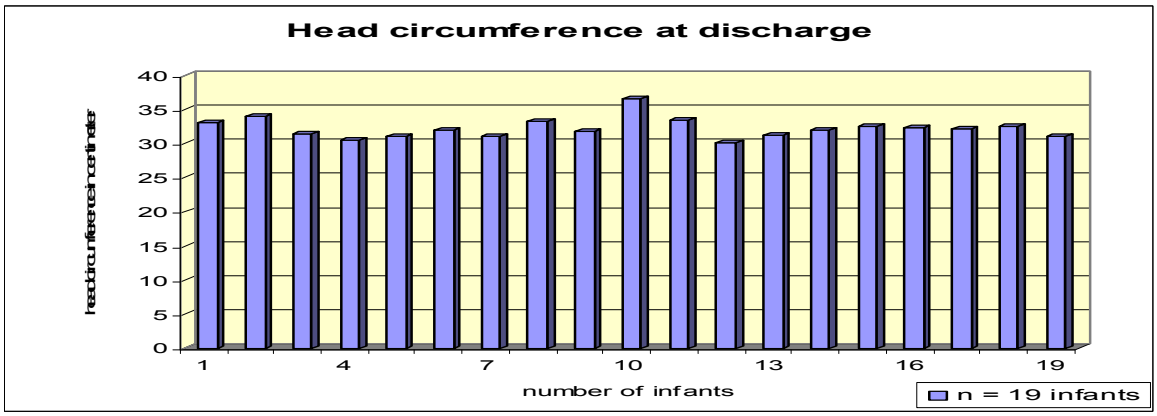


Figure 41: Distribution of gestational head circumference of the control group at the LKH Graz and Klagenfurt at time of discharge

In the control group, the average head circumference of 19 children at the time of discharge was close to the study group, 32.1 centimetres. Eight infants (42.1 percent) were below and 11 above this mean gestational head circumference at the end of hospitalization.

The largest circumference in the control group was 36.5 centimetres; the smallest was only 30.1 centimetres.

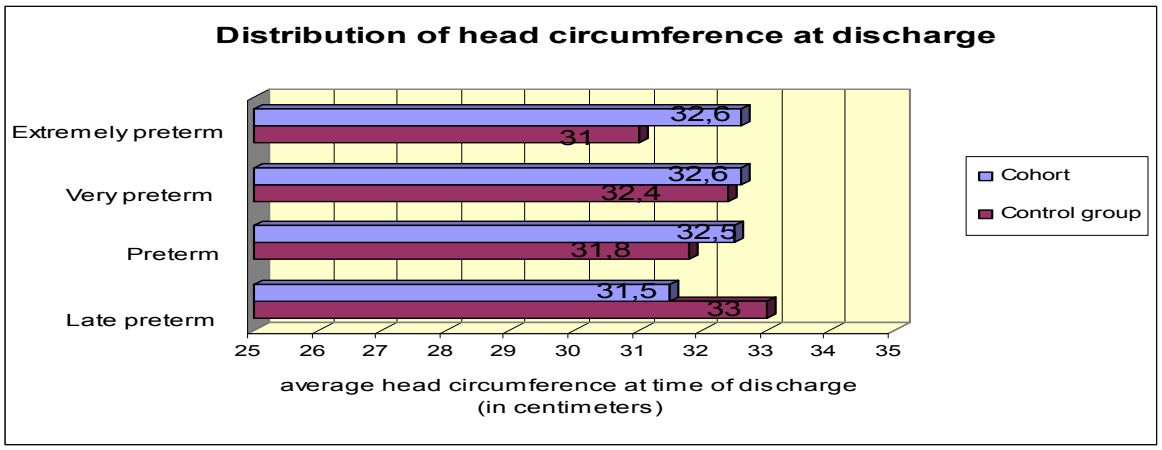


Figure 42: Comparison of average head circumferences of the cohort and control group at time of discharge

In the *'late preterm' period* the mean discharge head circumference of two infants in the study group was 31.5 centimetres, the larger one with 32, the smaller with 31 centimetres at the time of discharge. The control group included only one child with a head circumference of 33 centimetres at the time of discharge.

In the '*preterm' section* (between completed 32 and 33 + 6 weeks of gestation) the average head circumference of 7 children was 32.5 centimetres in the study group and 31.8 centimetres (four infants) in the control group.

Within this time period, the largest infant's head in the study group had reached a circumference of 33.5 centimetres and 34 centimetres in the control group. The smallest head circumference in the study group was 31.5 centimetres and in the control group only 30.5 centimetres.

In the *'very preterm' section* the average head circumference at the time of discharge was 32.6 centimetres in the study group and 32.4 centimetres in the control group.

The largest child's head circumference reached 35 centimetres in the study group and 36.5 centimetres in the control group. The smallest head circumference in the study group was 30.7 centimetres; in the control group 30 centimetres at the time of discharge.

Under the completed 25 weeks of gestation, in the '*extremely preterm' group*, consisted of only one infant each, with a head circumference of 32.6 centimetres in the study group and 31 centimetres in the control group at the time of discharge.

## 4.3. Conclusion

The high rate of Caesarean sections (96.6 and 82.8 percent), as well as the need of intensive care in both groups, (79.3 and 72.4 percent) can be explained by the ante partum management of preeclamptic women and the iatrogenic prematurity of the foetus/newborn.

No significant difference between both groups, but a clear distribution of length of hospital stay depending on gestational period was found. Infants, born extremely preterm had to stay longest, followed by children, born very preterm and late preterm. The shortest in-patient stay had been within the preterm period, with an average of 32.4 days in the study group and 42 day in the control group.

The mean corrected age at discharge was 38 + 4 weeks of gestation, the same in both the study group and the control group, without correlation to gestational periods of the infants.

| Variable | mean | minimum | maximum | standard deviation | significance (p) | |
|---|---|---|---|---|---|---|
| **corrected age (days)** | 267 | 34+2 | 41+4 | 14,1 | p = 0,7 | study group |
| | 269 | 33+6 | 54+4 | 20,9 | | control group |
| **Weight (grams)** | 2224 | 1830 | 3370 | 265,6 | p = 0,8 | study group |
| | 2233 | 1080 | 2885 | 12,38 | | control group |
| **Seize (cm)** | 44,6 | 42 | 49 | 1,78 | p = 0,07 | study group |
| | 45,8 | 40,5 | 51 | 2,37 | | control group |
| **Head circumference (cm)** | 32,5 | 30,7 | 35 | 1 | p = 0,4 | study group |
| | 32,2 | 30,5 | 36,5 | 1,46 | | control group |
| **Hospitalization (days)** | 267 | 31 | 106 | 14,2 | p = 0,7 | study group |
| | 269 | 22 | 130 | 29,77 | | control group |

Table 17: Statistic analysis at time of discharge

# 5. Neurodevelopmental outcome at the age of two years

The study group (18 females and 11 males with gestational ages between 24 + 5 and 34 + 3 weeks, born after severe maternal preeclampsia) as well as the control group (including 12 female and 17 male infants with gestational ages between 24 + 3 and 36 + 0 weeks, without any form of maternal hypertension of pregnancy) have regularly visited the LKH Graz or Klagenfurt for their neuropediatric follow ups. At a corrected age of 24 month, a final examination with all children, except one, had been performed; the Bayley infant neurodevelopmental screening test (Bayley test).

The neurological analysis included the overall results of the Bayley test, with the following possible results: no developmental delay (0), mild developmental delay (1), moderate developmental delay (2), or severe developmental delay (3), as well as the individual results of the subcategories, from which the Bayley test is composed.

These are: Remit of task management (B_T), language skills (B_L), motor skills (B_M) divided into fine motor (F) and gross motor skills (G) and accessibility of the child (B_A). Every category had been evaluated with numbers from 0 (no developmental delay in this subcategory) to 3 (severe developmental delay), as in

the overall in the Bayley test. For assessment of the accessibility of the child, terms such as friendly, shy, extremely shy (extr. shy), difficult, hesitant, strong headed and others have been used to describe this subcategory. Additional notes or explanations in the final medical report have been collected and listed in the table as well (N_notes).

| Term | GA | GW | IC | Clinical discharge diagnose | Bayley | B_T | B_L | B_M | B_A | N_notes |
|---|---|---|---|---|---|---|---|---|---|---|
| Preterm | 32+2 | 1460 | no | | 1 | n.k. | 1 | 0 | difficult | extremely deffensive, impression of mild developmental delay |
| | 33+3 | 1300 | no | status post: small for gestational age | 0 | 0 | 0 | 0 | shy | |
| Very Preterm | 29+2 | 1060 | no | | 0 | 0 | 0 | 0 | extr. shy | |
| | 29+4 | 824 | yes | status post: small for gestational age | 1 | 1 | 1 | 0 | shy | needs loads of motivation and help, mild developmental delay |
| | 25+6 | 600 | yes | ‚slit ventricle', immature parenchyma | 0 | 0 | 0 | 0 | friendly | |
| | 27+1 | 820 | yes | status post: plexus hemorrhage | 3 | 3 | 3 | F2 G2 | friendly | |
| | 28+4 | 1130 | no | status post: small for gestational age | 0 | 0 | 1 | 0 | 0 | only mild speech delay |
| | 28+4 | 760 | yes | status post: small for gestational age | 0 | 0 | 1 | 0 | 0 | dyslalia, child slightly dystrophic |
| | 29+0 | 730 | no | status post: small for gestational age, PVLI and microcephalus | 1 | 1 | 1 | 0 | hesitant | very hesitant, tasks take a long time, mild developmental delay |
| | 27+2 | 930 | yes | | 0 | 0 | 0 | 0 | extr. shy | |
| | 31+4 | 1330 | yes | status post: dystrophy < 3 percentile | 0 | 0 | 0 | 0 | friendly | dyslalia |
| Extremely preterm | 24+5 | 425 | yes | | 3 | 3 | 1 | 3 | tantrum, hyperactive | severe developmental delay, dystrophy, hyperactive, suspected sensory disorder |

Table 18: Neurological outcome at the age of two years of the cohort at the LKH Graz

| Term | GA | GW | IC | Clinical discharge diagnose | Bayley | B_T | B_L | B_M | B_A | N_Anmerk |
|---|---|---|---|---|---|---|---|---|---|---|
| Late preterm | 34+1 | 1260 | yes | status post: small for gestational age | 1 | 0 | 0 | F1 G1 | friendly | mild developmental delay (correspond to 22 month), dystrophy |
| | 34+3 | 1475 | yes | status post: small for gestational age | 0 | 0 | 0 | 0 | lively | |
| Preterm | 33+0 | 1340 | yes | status post: small for gestational age | 0 | 0 | 0 | 0 | friendly | |
| | 33+4 | 1450 | yes | status post: small for gestational age | 0 | 0 | 0 | 0 | friendly | |
| | 32+6 | 1305 | yes | status post: small for gestational age | 0 | 0 | 0 | 0 | curious | |
| | 33+1 | 1480 | yes | ventricle asymmetrie (left > right) | 0 | 0 | 0 | 0 | friendly | |
| | 32+0 | 1360 | yes | | 1 | 1 | 1 | 0 | friendly | |
| Very Preterm | 31+6 | 1300 | yes | ventricle asymmetrie (left > right) | 0 | 0 | 0 | 0 | friendly | |
| | 27+5 | 790 | yes | | 0 | 0 | 0 | 0 | friendly | |
| | 27+2 | 924 | yes | ventricle asymmetrie (left > right), slight periventricular echodensities (occipital) | 0 | 0 | 0 | 0 | friendly | |
| | 27+3 | 760 | yes | status post: small for gestational age, 6 small plexus cysts (frontal) | 0-1 | 0 | 0 | 0 | stranger anxiety | incipient stuttering (increasing), strong stranger anxiety, progress in motoric with physiotherapy (start with 7 months) |
| | 31+4 | 1340 | no | | 0 | 0 | 0 | 0 | friendly | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| 28+5 | 970 | yes | | 0 | 0 | 0 | 0 | stronghead | |
| 31+3 | 1495 | yes | | 0 | 0 | 0 | 0 | friendly | |
| 30+0 | 990 | yes | | 0 | 0 | 0 | 0 | friendly | |
| 29+0 | 870 | yes | | 0 | 0 | 0 | 0 | friendly | |
| 28+5 | 882 | yes | IVH I (right), single cerebral cyst, ventricle asymmetry | 1 | 1 | 0 | F1 G1 | shy | mild developmental delay, need of early intervention |

Table 19: Neurological outcome at the age of two years of the cohort at the LKH Klagenfurt

| Term | GA | GW | IC | Clinical discharge diagnose | Bayley | N_T | N_L | N_M | N_A | N_note |
|---|---|---|---|---|---|---|---|---|---|---|
| Late preterm | 34+6 | 2110 | yes | | 0 | 0 | 0 | 0 | blusters | |
| | 36+0 | 1410 | no | alternating, non synchronic spontaneous movements, status post: small for gestational age and IUGR with dysmorphic face and asymmetry of the face | 2 | 2 | 2 | 2 | restless | moderate developmental delay (corresponds to an age of 16 month), alternating, non synchronic spontaneous movements |
| | 35+5 | 1250 | yes | status post: small for gestational age | 0 | 0 | 0 | 0 | friendly | |
| Preterm | 32+4 | 2280 | yes | IVH I followed by hematocephalus internus and postischemic lesions | 0 | 0 | 0 | 0 | friendly, active | |
| | 32+1 | 1740 | no | hypoxic ischemic encephalopathy II, ventricle asymmetry, no IVH | 0 | 0 | 0 | 0 | extr. shy | |
| | 33+6 | 1170 | no | | 0 | 0 | 0 | 0 | attentive | slightly dystrophic |
| | 26+1 | 805 | yes | IVH I, ventricle asymmetry | 0 | 0 | 1 | 0 | shy | clear speech delay (bilingual), denied some tasks |
| | 32+2 | 1230 | yes | ventricle asymmetry | 0 | 1 | 0 | 0 | friendly, active | short attention, clear deficit in naming pictures, vocabulary consists of 10 words, yet age-appropriate development |
| | 32+6 | 1490 | no | physiologically distinct periventricular echodensities | 2 | 2 | 2 | 0 | friendly | headstrong, moderate developmental delay, needs early intervention |
| Very Preterm | 31+0 | 1420 | no | neurologic suspicious jumpy | 0 | 0 | 0 | 0 | friendly | vague language, short attention, suspicious jumpy |
| | 29+2 | 1280 | yes | | 0 | 0 | 0 | 0 | extrem. shy | language skills difficult to perform because of shyness |
| | 28+2 | 1070 | yes | IVH I (basal ganglia, right side) | 0 | 0 | 0 | 0 | selfconfident | no developmental delay with physiotherapy |
| | 31+4 | 1410 | yes | | 0 | 0 | 0 | 0 | shy | development corresponds to an age of 22 month |
| | 27+6 | 1200 | yes | | 3 | 3 | 2 | 0 | defendent | severe developmental delay (corresponds to an age of 16 month), behavioural problems since parents divorce |
| | 27+3 | 1050 | yes | | 0 | 0 | 0 | 0 | friendly, gut | |
| | 31+4 | 1080 | no | | 1 | 1 | 1 | 1 | friendly, gut | mild developmental delay (corresponds to an age of 22 month), learns from siblings – no intervention |
| | 30+0 | 1220 | no | | 0 | 0 | 0 | 0 | friendly | |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | 31+4 | 1410 | yes | | 0 | 0 | 0 | 0 | shy | development corresponds to an age of 23 month |
| | 31+6 | 1290 | yes | | 0 | 0 | 0 | 0 | friendly | |
| | 26+0 | 1000 | no | small, periventricular echodensities unknown etiology | 0 | 0 | 0 | F0 G0 | disobedient | |
| | 31+4 | 1332 | yes | | 0 | 0 | 0 | F0 G0 | shy | |
| | 29+0 | 1440 | yes | ventricle asymmetry (left > right), single small plexus cyst (right) | 1 | 0 | 0 | F0 G1 | friendly | G1: asymmetry to the left side, motoric intervention started |
| | 27+1 | 990 | yes | status post: IVH I | 0 | 0 | 1 | F0 G0 | friendly | mild speech delay |
| | 27+3 | 1080 | yes | ventricle asymmetry (right > left) | 1 | 1 | 1 | F1 G1 | defensive | mild developmental delay , speech delay, test difficult to perform, no need of early intervention |
| | 28+2 | 1110 | yes | occipital echodensities, PVL III with occipital cysts, ventricle asymmetry (right > left), muscle tone slightly increased | 3 | 1 | 1 | F3 G3 | friendly | spastic tetraparesis (right > left), severe developmental delay, slightly improvement because of early interventions, and physiotherapy |
| | 27+3 | 1018 | yes | both ventricles enlarged, ventricle wall cyst (left), post hemorrhage hydrocephalus internus | 2 | 1 | 2 | F2 G2 | friendly | moderate developmental delay, dystrophy, slightly improvement because of early interventions, and physiotherapy |
| | 28+4 | 1350 | yes | | 0 | 0 | 1 | F0 G0 | shy | psychomental and speech delay , speech therapy started |
| | 28+2 | 1360 | yes | echodensities (right, fronto-temporal), no IVH | 1 | 0 | 0 | F2 | friendly | mild developmental delay (corresponds to an age of 18 – 20 month), hemiparesis (left side), increased muscle tone, increased self-reflexes |
| Extremely preterm | 24+3 | 760 | yes | | 1 | 1 | 0 | 0 | friendly | mild statomotoric delay with sensory disorder (corresponds to an age of 20 month) |

Table 20: Neurological outcome at the age of two years of the control group at the LKH Graz and Klagenfurt

## 5.1. Survey of long-term neurological outcomes using the Bayley test

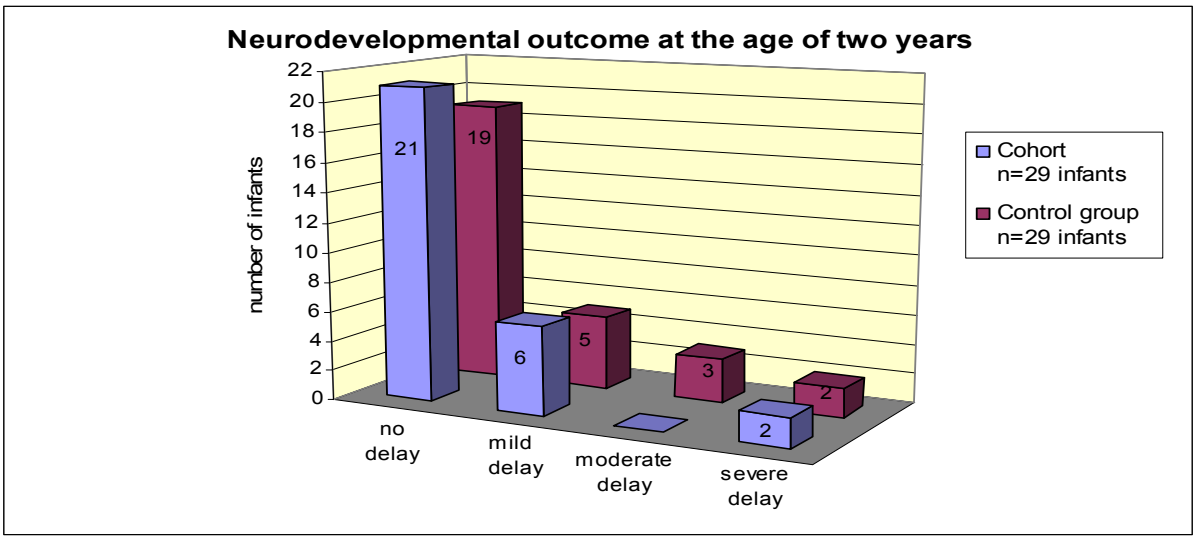


Figure 43: Neurodevelopmental outcome at the corrected age of 24 month

Within the study group 72.4 percent (21 infants) had shown an inconspicuous development without any neurodevelopmental delays at a corrected age of 24 months, in the control group it had been 65.5 percent (19 children). Within the study group, 20.7 percent of a total of 21 children had been diagnosed with 'mild neurodevelopmental delay', which has been observed less frequently in the control group with only 17.2 percent. Moderate developmental delay occurred only within the control group, with a percentage of 10.3. The number of children suffering from severe delay in neurological development at an age of 24 months has been equal in both groups with two infants (6.9 percent).

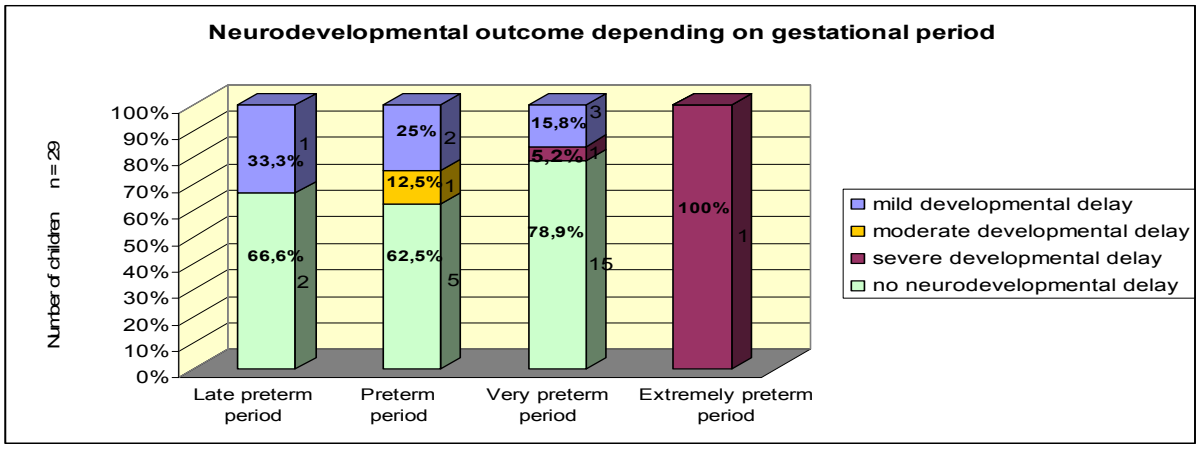


Figure 44: Neurodevelopmental outcome of the cohort depending on gestational periods at the corrected age of 24 month

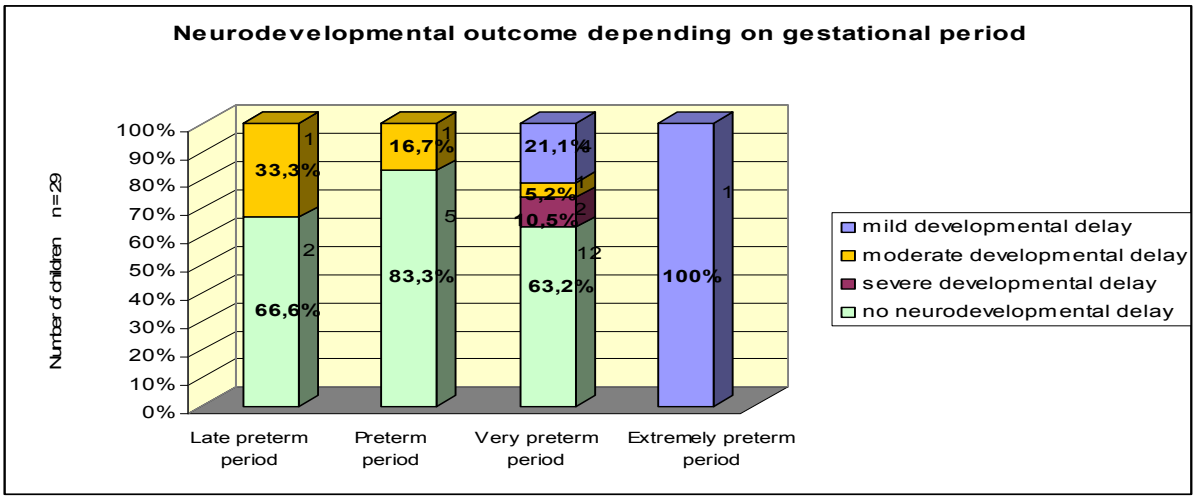


Figure 45: Neurodevelopmental outcome at the corrected age of 24 month of the control group depending on gestational periods

Figures 44 and 45 compare the distribution of neurological outcomes in the study group with the control group, based on gestational periods.

In the *late preterm* period (between completed 34 and 37+6 weeks of gestational age) within the study group, one child (33.3 percent) had shown a mild delay while the remaining two toddlers (66.6 percent) had not shown any neurodevelopmental delays at all. In the control group one child (33.3 percent) had been suffering from moderate developmental delay and as in the study group, the remaining two children (66.6 percent), had been without any neurological abnormalities.

In the *preterm period* (between completed 32 and 33+6 weeks of gestational age) the distribution had been the following: 62.5 percent of the toddlers had been healthy within the study group and 83.3 percent in the control group. Among the 37.5 percent of children with neurological delays in the study group, 12.5 percent (one child) had shown a moderate and 25 percent (2 children) a mild neurodevelopmental delay. In the control group, only one child (16.7 percent) had suffered from moderate delay.

In the *very preterm period* (between 25+1 and 31+6 weeks of gestational age) 78.9 percent of the toddlers in the study group had been healthy, and 62.3 percent in the control group. Within this gestational period, 16.8 percent (3 toddlers) had shown mild and 5.2 percent (1 child) severe delay in the study group. In the control group, 21.1 percent (4 children) with mild, 5.2 percent (1 toddler) with moderate and 10.5 percent (2 children) with severe neurodevelopmental delay in the control group.

*Below the completed 25 weeks* of gestation every group includes only one child, with a severe delay in the study group and a mild delay in the control group.

## 5.2. Selective analysis of segment of the Bayley Test

At a corrected age of 24 months, all toddlers who received neurological long term check ups either at the LKH Graz or LKH Klagenfurt, had been subjected to a final neurological examination; the Bayley Test, which is composed of the following individual tests:

- Task performance evaluates the child's ability to solve simple tasks and follow instructions without foreign help
- Language skills by which the development of vocabulary and pronunciation is assessed
- Motor skills, divided into gross and fine motor skills
- Accessibility and social behaviour evaluates if the toddler is friendly, alert and curious or very shy, defensive, and non-compliant.

### 5.2.1. Task performance

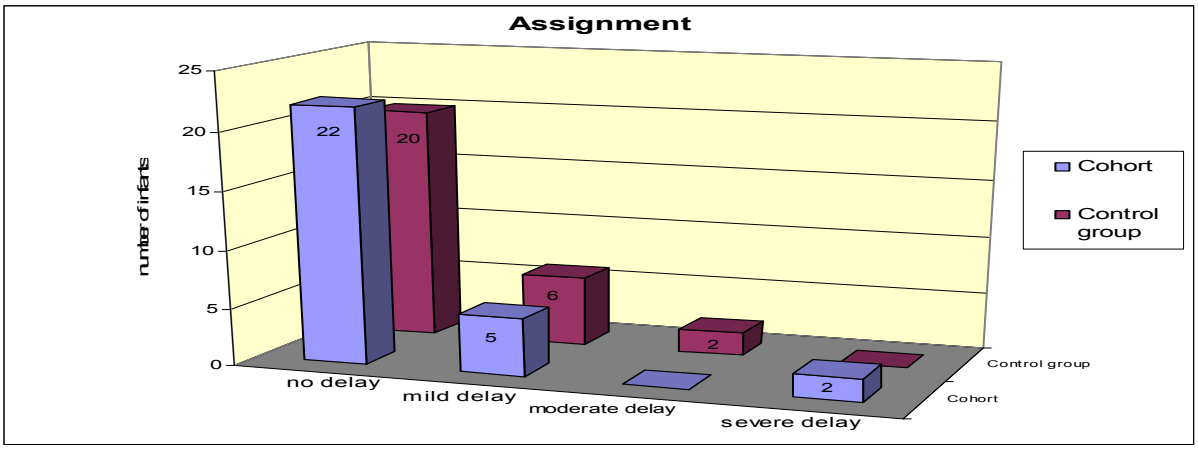


Figure 46: Neurological outcome referring to task performance

The ability to follow easy instructions and solve simple tasks without the parents' help have been evaluated from 29 children in each group. In the study group, 75.9 percent of the toddlers performed this test without any problems, 17.2 percent (5 children) had shown mild delays, such as the need for strong motivation, help and extra explanations and with the need of early intervention in 6.9 percent (2 children), which had suffered from severe delays, such as hyperactivity or sensory delays. In the control group 69 percent of the children (20 children) had been tested without any delays, 20.7 percent (6 children) had shown mild delays, and remaining 6.9 percent (2 toddlers) showed moderate delays in this category.

### 5.2.1. Language skills

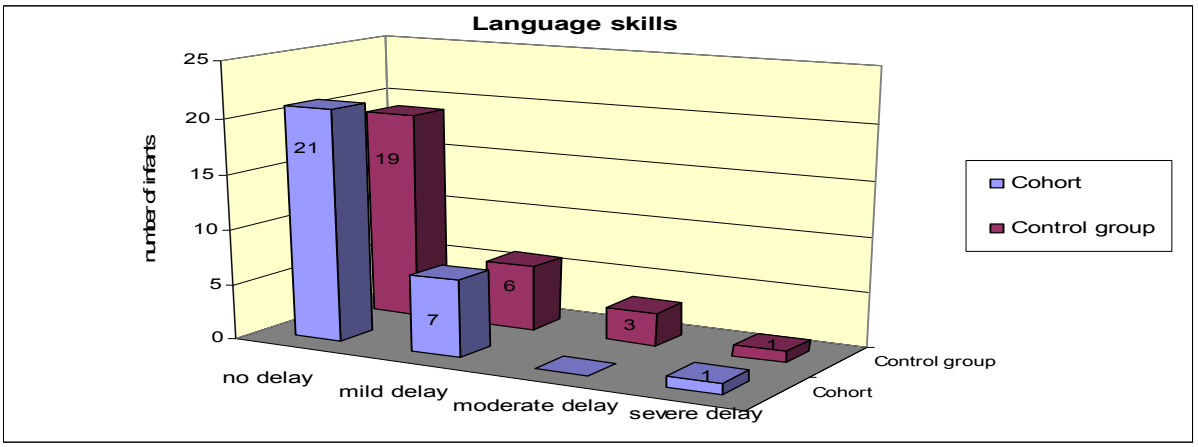


Figure 47: Neurological outcome referring to language skills

In this subtest, the development of vocabulary, word comprehension, pronunciation, picture naming, combination of two words, and carrying out instructions had been assessed from 29 toddlers in both groups. In the study group, 72.4 percent of the toddlers performed this test without any problems, 24.1 percent (7 children) had shown mild delays, such as dyslalia, the need for strong motivation or stuttering, and only 3.4 percent (1 child) suffered from severe delays, such as limited vocabulary or hardly speaking at all, by using only 2 to 3 words at a corrected age of 24 months.

In the control group, 65.5 percent of the toddlers had been tested without any delays, 20.7 percent (6 children) showed mild delays in language skills, 10.3 percent (3 toddlers) moderate delays such as difficulties in naming pictures or body parts and no meaningful 2-word-combinations with the need of early intervention and or logo therapy and 3.4 percent (1 toddler) with severe developmental language delays.

### 5.2.2. Motor skills

Motor skills are divided into 2 subcategories: fine motor skills and gross motor skills.

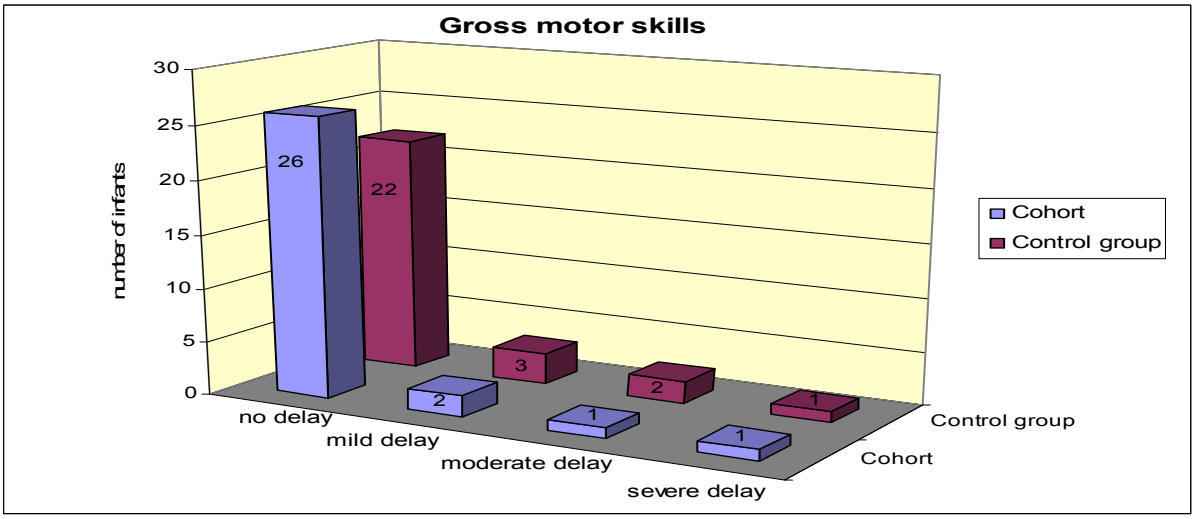


Figure 48: Neurological outcome referring to gross motor skills

In the subcategory of gross motor skills, the following abilities were evaluated from 29 toddlers from each group, the study group as well as the control group: running backwards, throwing a ball over the head, hopping on the spot, playing soccer, going up a staircase, standing on one leg, e.g.

Within the study group, 89.7 percent of the children passed the test without any difficulties, 6.9 percent (2 toddlers) had shown mild delays, such as slight lateral asymmetry, and only one child each (3.4 percent) had shown moderate and severe delays, with the need for early intervention and physiotherapy.

In the control group, 75.9 percent (22 toddlers) showed no delays in gross motor, but 10.3 percent (3 children) with mild delays, 6.8 percent (2 toddlers) with moderate delays such as no free stair climbing, increased/decreased muscle tone and 3.4 percent (one child) with severe delays such as no ability to sit up or to turn from stomach to back without help, and no standing alone.

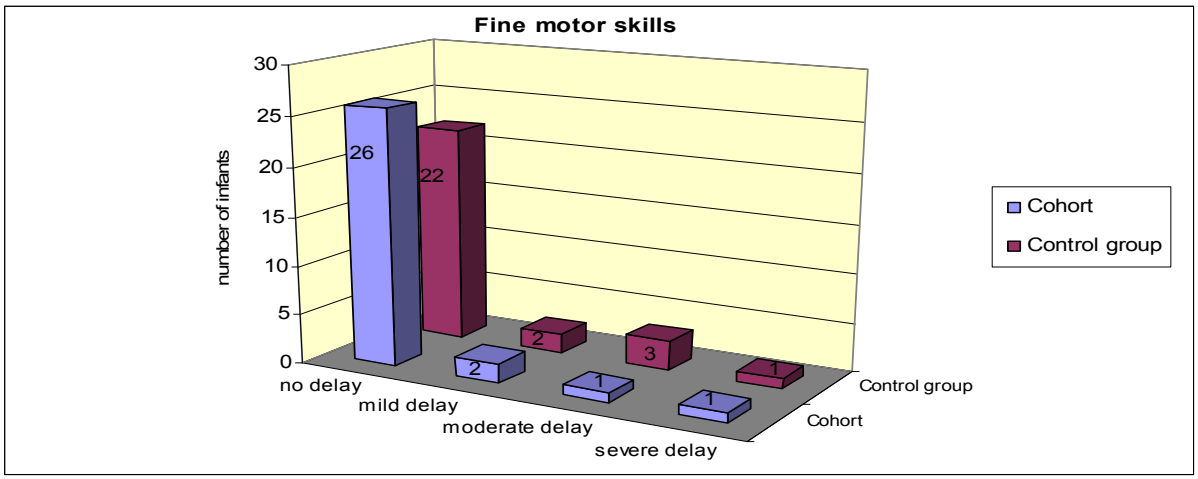


Figure 49: Neurological outcome referring to fine motor skills

The subcategory of fine motor skills evaluated abilities such as spontaneous scribbling, building a tower with 4-8 blocks, tracing a cross, a circle, a vertical line, the ability to tilt raisins out of a bottle, etc.

Out of the 29 toddlers from the study group, 89.7 percent showed no delays at all, 6.9 percent (2 toddlers) showed mild delays and 3.4 percent each had moderate and severe delays in fine motor skills.

In the control group, 75.9 percent (22 children) passed the test without any problems, 6.9 percent (2 toddlers) showed mild delays, 10.3 percent (3 toddlers) were diagnosed with moderate delays, and one toddler (3.4 percent) with severe delays in fine motor skills.

### 5.2.3. Accessibility

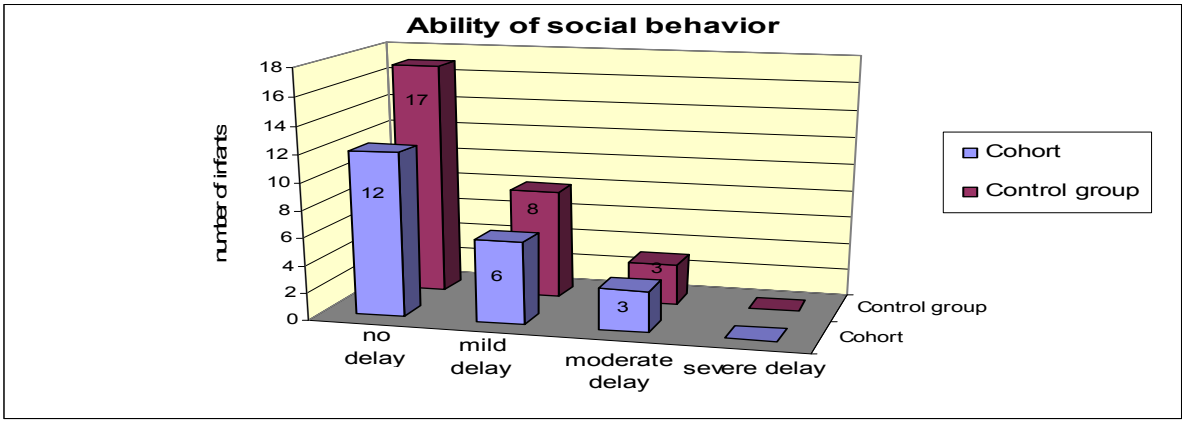


Figure 50: Neurological outcome referring to the social behaviours

In the subcategory of accessibility, the social contact and behaviour of the children had been evaluated, such as accessibility itself, behaviour towards the parents and playmates, ability to play tag, behaviour when separated from the mother, hand washing ability, undressing and subsequent dressing, etc.

Within the study group, only 41.4 percent (12 toddlers) had been friendly, agile and curious, and were able to fulfil the tasks listed above. 20.7 percent (6 children) had shown a mild delay, such as extreme shyness, anxiety, fixation on the mother or the need for extra motivation to cooperate and 10.3 percent (3 children) had been moderately delayed by using defensive behaviour, being hardly compliant, non obedient, raging or showing minimal social behaviour.

In the control group, 58.6 percent (17 toddlers) had been healthy, 27.6 (8 children) had been diagnosed with a mild, and 10.3 percent (3 children) with a moderate delay. No toddler had been diagnosed with a severe delay in the area of social behaviour.

# IV Discussion

## 1. Incidence of preeclampsia and clinical manifestation in prematurity and dystrophy

Between 1999 and 2005, 28,264 women gave birth at the LKH Graz or Klagenfurt, which correlates to an average of 4,037 infants per year. In our retrospective study, the actual number of women affected with mild or severe preeclampsia, numbered 572 out of 28,264 women who delivered at the LKH Graz or Klagenfurt. This retrospective result correlates to a total of 2.02 percent and therefore falls within the lower limit of incidence of preeclampsia in the general population

In relation to the incidence of prematurity, 82.6 percent of the newborns were between the completed 24 to 38 weeks of gestational age. Only 17.4 percent (out of 161 births) were mature infants older than the completed 38 weeks of gestation. In the general population as in our study group of 161 women, the incidence of premature birth was almost 6 times lower, with 14.2 percent suffering from severe preeclampsia. Therefore it can be assumed that preterm birth is a significant impact on this type of maternal disease.

Furthermore, we have been able to show a significant increase of dystrophy in infants with severe maternal preeclampsia, compared to the general population. Within a number of 161 children, 49 percent of the newborns fulfilled the criteria of 'small for gestational age' and only 51 percent of the newborns were either appropriate or even large for gestational age.

## 2. Outcomes from birth until discharge

In relation to the subsequent chapters of perinatal, postnatal, discharge periods and neurological outcome at the corrected age of 2 years, it must be said, that due to the small sample size, it was not possible to identify significant differences of the comparative two groups in many cases. The detection of weaker group differences was not given at all because of the lack of the necessary statistical data.

Only in relation to the birth weights, was it possible to prove a significant difference ($p = 0.01$). With an average gestational weight of 1,081 grams of in the study group, the control group reached a plus of 19.1 percent with an average of 1,288 grams.

Within the study group, 58.6 percent of the newborns were below this average of 1,081 grams, whereas within the control group, only 20.7 percent had been below the mean of 1,288 grams.

The single gestational periods confirmed that infants within the control group had shown a plus of 4.9 percent in the preterm and 24.8 percent in the very preterm period compared to the gestational weight of the study group. The sample sizes of infant born late preterm and extremely preterm had been too small and therefore not significant.

In the very preterm period, the incidence of dystrophy in infants with severe maternal preeclampsia had been six times higher at 31.6 percent compared to the control group with 5.3 percent of dystrophic infants.

Within the preterm period it was 71.4 percent in the study group compared to 50 percent in the control group.

Against all expectations, in terms of gestational size, a significant level of only 90 percent ($p = 0.066$) could be achieved between infants with severe preeclampsia and the control group and was, as the head circumference, adaptation parameters such as acid base state and Apgar score, not significant enough to confirm a difference between these two groups.

As expected, the rate of Caesarean sections were extremely high with 96.6 percent within the study group and 82.8 percent in the control group, as well as the need for intensive care, with 79.3 percent in the study group and 72.4 percent within the control group.

Due to the small sample size, no meaningful explanations could be made in relation to cerebral and neurological abnormalities during hospitalization, neither in relation to gestational age, gender nor gestational weight. Within the control group 58.5 percent of the infants developed cerebral or neurological disabilities, in comparison to only 37.9 percent in the study group.

As described earlier, in other studies a decrease in percentiles of body length, body weight and head circumference was revealed regarding premature infants during hospitalization. At the time of birth, 31.6 percent of the children within the study group and 5.3 percent within the control group had been dystrophic, whereas at the time of discharge, the percentage of dystrophies increased to 69 percent in the study group and 53.8 percent in the control group.
In this study, no data had been collected between discharge and final neurological examinations at a corrected age of 24 months, hence, no statements could be made regarding the catch-up rate of children in correlation to their body weight, size or head circumference.

Concerning the length of hospitalization, although there is no significant difference between the infants with severe maternal preeclampsia and the study group, a clear distribution of length of hospital stay depending on gestational period has been shown in both groups. Infants, born extremely preterm stayed the longest, followed by children born very preterm and late preterm. The shortest in-patient stay had been within the preterm period, with an average of 32.4 days in the study group and 42 days in the control group.
The mean corrected age at discharge was 38 + 4 weeks of gestation, the same in both the study group and control group, without correlation to the gestational periods of the infants.

## 3. Neurological outcome at the age of 2 years

Due to the small sample size, it was not possible to identify significant differences between the study group and the control group nor could the results be transferred to the general population.

Significant however, is that 72.4 percent within the cohort and 65.5 percent of the control group passed the Bayley's Test without any disabilities at all.
Most abnormalities could be seen in 'social skills', with 58.6 percent within the study group and 41.4 percent within the control group, followed by disabilities in 'language skills' with 27.6 percent in the study group and 34.5 in the control group. In the study group, 24.1 percent had shown deficits in 'task performance', compared to 31 percent in the control group. The smallest number of disabilities occurred within the ‚gross and fine motor skills' with a percentage of 10.3 in the study group and 24.1 percent in the control group.

No correlation could be revealed between gestational age, discharge diagnosis or gestational weight and the delays in the neurological outcome at the age of two years. Therefore, no statement can be made, regarding the impact of the peripartal period to the neurological long-term outcome of the children with/without severe preeclampsia.

## 4. Summary

Neonatal care has changed over the passage of time, resulting in improved survival rates, which eventually results in delays of neurodevelopmental long-term effects in cases of children after severe maternal preeclampsia; as we assumed.
In this study, neurodevelopmental outcome did not differ between the study group, including children with severe maternal preeclampsia only, and the control group, with infants, of the same gestational age but without any form of hypertensive disorders of pregnancy. Hence, a significant correlation between severe maternal preeclampsia and a neurological developmental delay could not be revealed.
Therefore, future studies with correspondingly larger sample sizes are necessary to confirm the influence of preeclampsia on the infants' neurodevelopmental long-term outcome, to improve quality of perinatal care, for early detection of disabilities and initiation of early intervention, which would lead to a better quality of life for the child as well as for the mother/parents.

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# VI Appendix

## 1. List of figures

## 2. List of tables



## 3. Curriculum vitae

See below

# CURRICULUM VITAE

## *Persönliche Daten*

| | |
|---|---|
| Name: | Dobretsberger Anna |
| Geburtsdatum: | 23.03.1984 |
| Hauptwohnsitz: | Leechgasse 86, 8010 Graz, Österreich |
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| Religion: | römisch katholisch |
| Familienstand: | ledig |

| | |
|---|---|
| Vater: | Dr. Franz Dobretsberger:<br>selbständig, Bestattung Dobretsberger |
| Mutter: | Madelaine Dobretsberger:<br>kaufmännische Angestellte, Lebens- und Sozialberaterin |

## Ausbildung

Hochschulausbildung

| | |
|---|---|
| Mai 2010 | Sponsion an der Medizinischen Universität Graz |
| 10/2002 – 05/2010 | Studium an der Medizinischen Universität Graz (Humanmedizin) |

Schulische Ausbildung

| | |
|---|---|
| 2002 | Schulabschluss mit Matura |
| 1994 - 2002 | WRG, Körnerstraße 9, 4020 Linz |
| 1990-1994 | VS IV Mozartschule, Volksfeststraße 7 - 11 |

## Famulaturen/Praktika

| | |
|---|---|
| 03/2010 – 04/2010 | 5 wöchiges Praktikum in der Lehrpraxis (Allgemeinmedizin) |
| 12/2009 – 01/2010 | 5 wöchiges Praktikum im LKH Graz (allgemeine Pädiatrie) |
| 09/2009 – 12/2009 | 11 wöchiges Nef - Praktikum am LKH Graz (Akut- und Notfallmedizin) |
| 04/2009 – 06/2009 | 4 monatiges Internship of internal medicine im University hospital of Pennsylvania, Philadelphia |
| 09/2008 | 2 wöchige Famulatur in der Landes und Frauenklinik Linz (allgemeine Pädiatrie) |
| 08/2008 | 4 wöchige Auslandsfamulatur im Kasr Alainy University Hospital in Kairo (Gynäkologie und Geburtshilfe) |
| 02/2008 | 2 wöchige Famulatur im LKH Graz (Kinderchirurgie) |
| 07/2007 | 4 wöchige Famulatur im AKH Linz (Onkologie) |
| 09/2006 | 2 wöchige Famulatur im LKH Graz (Kinderradiologie sowie Sonographie) |
| 09/2003 | 3 wöchige Famulatur im AKH Linz (Pulmologie) |

## Auslandserfahrung

| | |
|---|---|
| 04/2009 – 07/2009 | 4 monatiges Internship in internal medicine im University hospital in Pennsylvania, Philadelphia |
| 08/2008 | 4 wöchige Auslandsfamulatur im Kasr Alainy University Hospital, Kairo (Geburtshilfe) |

## Wissenschaftliche Mitarbeit

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|---|---|
| 11/2007 bis 04/2010 | Mitglied der Studiengruppe für Präeklampsie am LKH Graz und LKH Klagenfurt unter der Leitung von Univ. Prof. Dr. Schlemmbach und O.A. Dr. Mörtl |

## Vertiefte Ausbildungen

Akut - und Notfallmedizin

| | |
|---|---|
| Seit 01/2010 | ITLS (International Trauma Life Support) Provider |
| Seit 10/2009 | PEPP (Pediatrics education for prehospital professionals) Provider |

Innere Medizin

| | |
|---|---|
| 06/2008 – 12/2008 | (Sonographie in der inneren Medizin, erweiterter EKG Kurs) |

Gynäkologie und Geburtshilfe

| | |
|---|---|
| 04/2008 | (Sonographie, CTG, Mutter-Kind-Pass Untersuchungen) |

Medical English

| | |
|---|---|
| 12/2007 – 02/2009 | (Medical English I und II, English in clinical practice I und II) |

Neurologie

| | |
|---|---|
| 10/2007 – 02/2009 | (Ausgewählte Schmerzsyndrome, Neuromuskuläre Erkrankungen, Elekrophysiologische Diagnostik, Neurochirurgie) |

Pädiatrie

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|---|---|
| 04/2007 – 03/2008 | (Pädiatrische Infektiologie, Kinderchirurgie) |

Radiologie

| | |
|---|---|
| 1/2006 – 12/2006 | (konventionelle Röntgendiagnostik, Strahlenschäden am Menschen) |

Pathologie

| | |
|---|---|
| 12/2005 – 1/2006 | (Gerichtsmedizin, Verkehrsmedizin, Pathologie) |

## Ehrenamtliche Tätigkeiten

| | |
|---|---|
| Seit 8/2008 | Rettungssanitäter beim Österreichischen Roten Kreuz |
| 2002 - 2004 | Mitarbeit bei Planung und Durchführung von Jungscharlagern der Diözese Linz |
| 1992 - 2002 | Mitglied der katholische Jungschar der Diözese Linz |
| 1992 - 1999 | Ministrant der Diözese Linz |