Dissertation

Moderate and late preterm infants: a prospective analysis of neonatal morbidities, causes and rates of rehospitalizations within the first year of life, and neurodevelopmental outcome at 12 months

submitted by

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Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organizations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the ***Guidelines of the Medical University of Graz on Good Scientific Practice****.*

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Disclosure

This thesis was written at the doctoral school “Lifestyle-related diseases”.

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Table of content

Abbreviations

Bayley-III	Bayley Scales of Infant Development – Third Edition
Ch	Chaotic (GMs)
CP	Cerebral palsy
CS	Cramped-synchronized (GMs)
cUS	Cranial ultrasound
e.g.	Exempli gratia
FMs	Fidgety movements
GMA	General movement assessment
GMOS	General movement optimality score
GMs	General movements
i.e.	Id est
IQR	Interquartile range
IVH	Intraventricular hemorrhage
LPT	Late preterm
MLPT	Moderate and late preterm
MPT	Moderate preterm
MND	Minor neurological dysfunction
MOS	Motor optimality score
MRI	Magnetic resonance imaging
NEC	Necrotizing enterocolitis
NICU	Neonatal intensive care unit
PPROM	Preterm premature rupture of membranes
RDS	Respiratory distress syndrome
TTN	Transient tachypnea of the newborn
Vs.	Versus

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Abstract

Background and Aim

Moderate and late preterm (MLPT) infants account for nearly 85 % of all preterm infants. It is crucial to identify those MLPT infants who are at risk for an adverse outcome. However, the current knowledge on morbidities and neurodevelopment within the first year is still limited. This thesis therefore aims to investigate neonatal morbidities, General Movements (GMs), rehospitalization rates and neurodevelopment of MLPT infants during the first year.

Methods

This is a longitudinal follow-up study of a group of MLPT infants at a tertiary care hospital. Demographic and clinical characteristics regarding morbidity rates, lengths of stay and rates of as well as reasons for rehospitalization were recorded. GMs were analyzed globally and detailed from one video recording during the neonatal period and a second video recording at 3-4 months post-term age. Videos were rated based on the Prechtl General Movement Assessment and detailed optimality scores (General Movement Optimality Score, GMOS; Motor Optimality Score, MOS) were calculated. Neurodevelopment was assessed at the age of one year with a standardized assessment.

Results

The study population comprised 215 infants (58% males; 60% singletons; 99 moderate preterm (MPT) and 116 late preterm (LPT) infants) with a median gestational age of 34 weeks and birth weight of 2100 grams; 20% of them were small for gestational age. MPT infants more often had a diagnosis of mild respiratory distress syndrome (26% vs. 13%, $p < 0.01$) and feeding problems with longer need for nasogastric tube feeding (median 9.5 vs 4.2 days, $p < 0.01$) and parenteral nutrition (3.5 vs. 2.7 days, $p < 0.01$), and longer duration of stay at either NICU (10.6 vs. 3.7 days; $p < 0.01$) or hospital (13 vs. 11 days; $p < 0.01$). Fifty-two infants (24.3%) were hospitalized at 67 occasions without differences regarding readmission rates and causes between

groups. Median age at readmission was 3 months, median stay 4 days. The most common diagnosis was respiratory illness (43.3%).

The rate of normal GMA within the neonatal period was 45% for MPT and 30 % for LPT infants (37.7% for MLPT infants). 99% had Fidgety Movements (FMs) at 3-4 months post-term age. The GMOS ranged from 12 to 42 (median = 31; IQR 25 - 38.5). The MOS ranged from 12 to 28 (median = 24; IQR 23 - 26) and was reduced in 42% of all infants (e.g., below 25). GMOS and MOS did not differ in MPT and LPT infants. GMs during neonatal period did not correlate with the MOS. The effects of sex, multiple birth, postmenstrual age at assessment, and particular neonatal morbidities or complications varied between gestational age groups. 87.5% of all infants reached normal results at the assessment at the age of one year.

Conclusion

MPT infants had more neonatal morbidities diagnosed, but the same rehospitalization rates than LPT infants. The MLP infants of our study showed a high rate of occurrence of abnormal GMs during neonatal age. All infants except one had FMs. However, in the detailed assessment we found a high number of reduced MOS. None of our children were diagnosed as having severe global developmental delay. However, since 1 in 8 children showed a moderate delay at the corrected age of 1 year, our results suggest that the development of MLPT infants should be monitored after discharge.

Zusammenfassung

Hintergrund und Zielsetzung

Moderate und späte Frühgeborene stellen einen Anteil von fast 85% aller Frühgeburten dar. Es ist wesentlich, diejenigen moderaten und späten Frühgeborenen zu identifizieren, die ein Risiko für ein ungünstiges Outcome haben. Das derzeitige Wissen über Morbiditäten und die neurologische Entwicklung innerhalb des ersten Jahres ist jedoch noch begrenzt. Ziel dieser Arbeit war es daher, neonatale Morbiditäten, General Movements (GMs), Rehospitalisierungsraten und die neurologische Entwicklung von moderaten und späten Frühgeborenen während des ersten Jahres zu untersuchen.

Methoden

Es handelt sich um eine prospektive Follow-up-Studie einer Gruppe von moderaten und späten Frühgeborenen in einem Krankenhaus der Tertiärversorgung. Demographische und klinische Charakteristika hinsichtlich Morbiditätsraten, Verweildauer sowie Raten und Gründe für Rehospitalisationen wurden erfasst. GMs wurden global und detailliert aus einer Videoaufnahme während der Neonatalperiode und einer zweiten Videoaufnahme im Alter von 3 bis 4 Monaten nach der Geburt analysiert. Die Videos wurden anhand des Prechtl General Movement Assessment bewertet und detaillierte Optimalitätsscores (General Movement Optimality Score, GMOS; Motor Optimality Score, MOS) wurden berechnet. Die neurologische Entwicklung wurde im Alter von einem Jahr mit einem standardisierten Assessment beurteilt.

Ergebnisse

Die Studienpopulation umfasste 215 Neugeborene (58% männlich; 60% Einlinge; 99 moderate und 116 späte Frühgeburten) mit einem medianen Gestationsalter von 34 Wochen und einem Geburtsgewicht von 2100 Gramm; 20% von ihnen waren small-for-gestational-age. Moderate Frühgeborene hatten häufiger die Diagnose eines leichten Atemnotsyndroms (26% vs. 13%, $p < 0,01$) und Ernährungsprobleme mit längerem Bedarf an nasogastraler Sondenernährung (median 9,5 vs. 4,2 Tage, $p <$

0,01) und parenterale Ernährung (3,5 vs. 2,7 Tage, p < 0,01) sowie eine längere Aufenthaltsdauer auf der NICU (10,6 vs. 3,7 Tage; p<0,01) oder im Krankenhaus (13 vs. 11 Tage; p < 0,01). Zweiundfünfzig Säuglinge (24,3%) wurden 67-mal hospitalisiert, ohne dass sich die Gruppen hinsichtlich der Wiederaufnahmeraten und -ursachen unterschieden. Das mediane Alter bei der Wiederaufnahme betrug 3 Monate, der mediane Aufenthalt 4 Tage. Die häufigste Diagnose war eine Atemwegserkrankung (43,3%).

Die Rate der normalen GMA innerhalb der Neugeborenenperiode betrug 45% bei moderaten Frühgeborenen - und 30 % bei späten Frühgeborenen (37,7% bei moderaten und späten Frühgeborenen). 99 % hatten Fidgety Movements (FMs) im Alter von 3 bis 4 Monaten nach der Geburt. Die GMOS reichte von 12 bis 42 (Median = 31; IQR 25 - 38,5). Der MOS reichte von 12 bis 28 (Median = 24; IQR 23 - 26) und war bei 42% aller Kinder reduziert (e.g. <25). GMOS und MOS unterschieden sich nicht bei moderaten und späten Frühgeborenen. Die GMs während der Neonatalperiode korrelierten nicht mit dem MOS. Die Auswirkungen des Geschlechts, der Mehrlingsgeburt, des postmenstruellen Alters bei der Beurteilung und bestimmter neonataler Morbiditäten oder Komplikationen variierten zwischen den Gruppen des Gestationsalters. 87,5% aller Kinder erreichten bei der Beurteilung im Alter von einem Jahr normale Ergebnisse.

Schlussfolgerung

Bei moderaten Frühgeborenen wurden mehr neonatale Morbiditäten diagnostiziert, aber die gleichen Rehospitalisierungsraten im ersten Lebensjahr wie bei späten Frühgeborenen. Die moderaten und späten Frühgeborenen unserer Studie zeigten eine hohe Rate von abnormalen GMs während des Neugeborenenalters. Alle Säuglinge außer einem hatten FMs. Bei der detaillierten Untersuchung fanden wir jedoch eine hohe Anzahl von reduzierten MOS. Keines unserer Kinder zeigte eine schwere neurologische Entwicklungsverzögerung. Da allerdings jedes 8. Kind im korrigierten Alter von einem Jahr eine moderate Entwicklungsverzögerung aufwies, legen unsere Ergebnisse nahe, dass die Entwicklung von moderaten und späte Frühgeborenen nach der Entlassung überwacht werden sollte.

Introduction

Preterm birth (< 37 weeks of gestation) is the leading cause of death in children younger than 5 years worldwide and infants born preterm are at an increased risk of a wide spectrum of short- and long-term morbidities (1-3). Preterm birth affects approximately one in 12 (7.7 percent in 2017 (4)) of all births in Austria each year, and even more in the US (9.9 percent in 2016 (5)). It remains the main reason for morbidity during neonatal age and childhood (6), and for neonatal mortality world-wide (7). Rates of neonatal morbidity and mortality, and cognitive, behavior and motor impairments during childhood are particularly high among the very preterm infants, while they decrease with increasing gestational age at birth (8, 9). Thus, the incidence for neurodevelopmental impairment in moderate and late preterm (MLPT) infants (32^{+0}-36^{+6} weeks gestation at birth) is much lower compared to infants born very preterm. However, the group of infants born moderate and late preterm is larger. They represent nearly 85 percent of all preterm infants (4, 10) and may cause considerable liability to the health system during both the neonatal period and childhood (10-12). Recently, increased consideration has been given to better understanding the causes for the high rate of moderate and late preterm birth, as well as the short and long term consequences (13). It is substantial to identify those MLPT infants who are prone to an adverse outcome via clinical indicators, as an early detection of impairment and consequently early-targeted intervention might provide the best possible outcome.

When I started this project, I focused on maternal risk factors and the perinatal and neonatal morbidity of MLPT infants. Apart from collecting their epidemiological data, it was originally planned to assess their neurodevelopment at the corrected age of one year. But, while waiting I felt that a closer follow-up assessment would be beneficial for both the families, and my doctoral thesis. Spittle and colleagues (2008) rated the Prechtl General Movement Assessment (GMA) (14) among the best predictive assessment tools to rate the motor development of preterm infants, and as such, I decided to become trained in its application and to apply the GMA to my study group.

Therefore, my doctoral thesis consists of two parts, part I contains the epidemiological data. And part II which consists of GMA at preterm or term age, at 3 to 4 months and assessment of neurodevelopment at one year.

Moderate and late preterm infants

Definitions

In 1969, preterm birth was defined as, “birth of an infant at less than 37 weeks completed gestation, or 259 days of gestation, counting from the first day of the last menstrual period in women with regular (28-day) menstrual cycles” by the World Health Organization (15). Births after this period were applied to be term and those after 42 completed weeks, post-term (16). The gold standard for precise ascertainment of gestational age is the first trimester ultrasound (17). In the 1970s and 80s the phrase “near term” started to be used in research publications and refers to infants born between 34 and 36^{+6} weeks gestation, and was in relation to experimental animal studies. Such research participants were considered fully mature without any differentiation from full-term infants. Over time, this phrase obtained physiologic association (16). This might have happened due to the standard procedure in obstetrics, which recommended tocolysis and corticosteroids only for women presenting symptoms of preterm labor < 34 weeks of gestation, whereas there are no such interventions in women with the same symptoms > 34 weeks (8). Problematically, the phrase “near term” disguised the physiological and developmental immaturity of these infants. Deficient understanding of the crucial physical and neurocognitive consequences of prematurity could lead to higher numbers of early elective deliveries, less diligent newborn assessment, early discharge, insufficient monitoring, or poor follow-up (18). In 2005 an expert panel succeeded in replacing the phrase with “late preterm” as there is no such thing as a “normal preterm birth”. The new term comprises the risk for higher morbidity and mortality of that group (19) and was able to shift the paradigm, which in turn initiated a huge interest in research (20). In addition, previous research has suggested that even full term infants do not have equal maturity, as infants with 37^{+0}-38^{+6} weeks gestation are at higher risk for neonatal mortality, morbidity and long-term impairment, respectively (16).

Infants born at 32^{+0} to 33^{+6} weeks gestation are defined as “moderate preterm”.

Causes of moderate and late preterm birth

Preterm birth is the outcome of a heterogeneous accumulation of maternal and fetal factors, which are multiple and complex (18). The etiologies of preterm birth seem to be influenced by gestational age, with those of later preterm birth being much more heterogeneous (18, 21). About two thirds of all MLPT births are spontaneous, with causes regularly undetermined. The remaining third of births are due to medical interventions made to assure the well-being of both mother and child. Medical reasons for interventions diversify according to gestational age. This is due to the changing biological processes throughout the pregnancy, which can lead to different kinds of complications at different time points. For instance, several maternal complications such as preeclampsia or diabetes occur more commonly in late pregnancy. There are a lot of challenges in the obstetrical management of women in labor at any preterm gestation. While early delivery leads to higher rates of neonatal mortality and morbidity, expectant management may imply danger for the fetus, as it is in a potentially suboptimal or even adverse uterine environment. The best time to deliver has to be found by weighing these risks against expected benefits (16). Therefore, for clinical decision making, it is of high importance the risks of MLPT birth are fully taken into consideration(18).

Epidemiology of preterm birth

An increasing rate of preterm birth has been reported since 1990, almost completely due to MLPT infants (22). Currently the reasons are not well understood, however several theories have been suggested. The increase of elective inductions and caesarean sections to reduce adverse fetal outcome is one theory. Although more concerns raise by the more invasive medical obstetric management, as the indication for delivery seems to be not always clear and evidence-based (19, 23).

Of particular note, after adopting the phrase “late preterm” instead of “near term” in 2005 (19), guidelines were developed for optimal timing of deliveries in 2011 (23). Further publications were made recommending the prevention of early-term deliveries, which were not medically indicated, before 39 weeks in 2013 (24). Following this, the preterm birth dropped from over 10 percent to 8 percent in the US (25, 26). During the last decade in Austria this trend is also noticeable with rates

of preterm birth between the highest 8.9 percent in 2009, and lowest 7.0 percent in 2020 (27). In the following figure the rates of LPT infants and all other preterm infants are depictured over years (2004 – 2020) in Styria (county of our hospital with approximately 10.000 births per year). In contrast to the increasing preterm birth rates worldwide, the preterm birth rate in Styria remained constant over the last years. However, in general the preterm birth rate is increasing globally (1, 10, 28, 29).

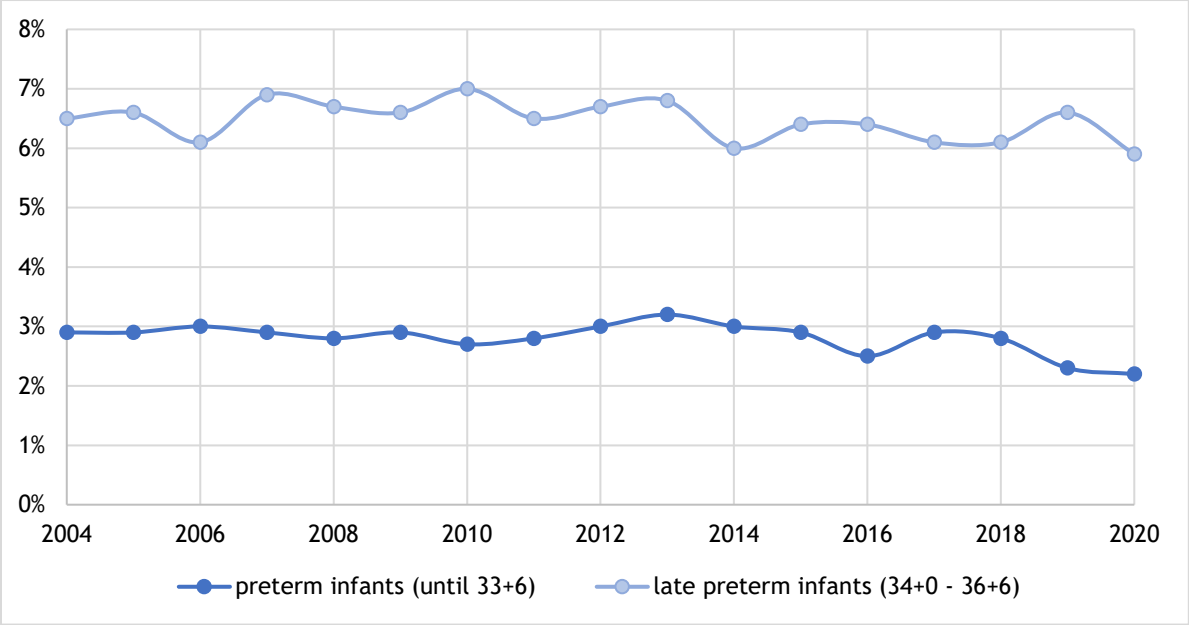

Figure 1: Rates of preterm births in percent in Styria between 2004 and 2020 (30)

Risk factors for moderate and late preterm birth

Multiple gestations

Moderate and late preterm birth occurs more commonly in twins or higher order multiples compared to singletons. Increased use of assisted reproductive technologies due to delayed childbirth is one theory of explanation (31). Assisted reproductive technologies is also associated with higher risk of preterm birth among singletons. However, it is not fully clarified whether this increase is due to assisted reproductive technologies or the underlying causes for infertility (18).

Congenital malformations

There is an association between preterm birth and congenital malformations. In an US-study, congenital malformations were described to be significantly more common in MLPT infants compared to full-term infants (32).

Maternal age

Specific maternal age has been described to be associated with preterm birth. Women of <20 and >35 years are at higher risk for MLPT birth. Diabetes, hypertension, and other diseases, as well as higher multiple birth rates and the use of assisted reproductive technologies may increase the risk for preterm delivery in women beyond 35 years (18, 33). For younger women, biologic immaturity, several lifestyle factors (e.g. smoking), and lower socioeconomic status may be reasons for elevated preterm birth rates (18, 34).

Developmental physiology of moderate and late preterm infants

Maturation is a continuum. As such, maturational milestones are only an invention to facilitate making clinical decisions, if they differ from normal. However, the pace and trajectory of maturation vary between organ systems, as maturation is programmed to ensure an autonomous extra-uterine existence of the organisms at various time points. Currently, the factors that speed up or delay specific fetal organ maturation are not yet known. Certainly, the duration of gestation is only one influencing factor out of numerous, like intrauterine environment, maternal health, diet, nutrition and lifestyle, parity, multiple vs. singleton pregnancy, gender, and medical conditions of the fetus (16, 26). Infants of the same gestational age vary commonly in their degree of maturation. Variation in the degree of maturation among infants of the same gestational ages is very common (20).

Morbidity and mortality rates

Risk of infant morbidity and mortality decreases significantly with increasing gestational age up until term and then increases again post-term (18, 35). MLPT birth

and maternal medical conditions, especially antepartum hemorrhage and hypertensive disorders of the pregnancy are each independent risk factors of newborn morbidity (13, 36). MLPT infants are at lower risk for various medical problems compared to those born prior to 32 weeks gestation. However, their risk for neonatal mortality and morbidity, and for adverse short-term and long-term outcome, respectively, is significantly higher compared to infants born at 39 and 40 weeks gestation (6, 8, 12, 16, 36-55). MLPT infants account for one third of the neonatal intensive care unit admissions in the USA (55). Moderate and late preterm birth increases the risk for rehospitalization after initial hospital discharge, and during infancy due to higher risk for pulmonary illnesses, respectively (37, 42, 56).

Delayed growth of organ systems, neonatal morbidity and neonatal care practices may lead to a consistency of various disorders throughout infancy and adolescence into adulthood (54).

Thermal instability

Maternal thermal homeostasis regulates and controls the fetal thermal homeostasis (57). By effacing its heat through the mother, the fetus' temperature stays about 0.5 - 1.0°C higher than the mother's. Fetal thermoregulation is not working independently but linked to the mother's until birth. Thus, if the mother is hypothermic, the fetus is not capable of generating heat itself or eliminate heat if the mother is hyper thermic. Hypothermia after birth is common, as the "new" environment for the newborn is cold compared to its warm intrauterine environment. In reply, the newborn needs to prevent itself from too much heat loss, increase the generation of heat, and sustain core temperature without consuming too much oxygen (57, 58). Most healthy term infants are able to establish the required physiological responses, while MLPT infants may have difficulty caused by insufficient, immature or non-existent thermoregulatory processes (20, 57-61). Temperature instability is significantly more frequent in LPT infants during the early postnatal period compared to term infants (11, 37, 62).

Respiratory morbidities

MLPT infants are at elevated risk for all forms of pulmonary disorders (38, 39, 41). Between 25 and 36 weeks gestation, a transient 'saccular phase' interrupts the alveolization process. The saccules are compact, thick and primitive. Hence, they are not optimal for gas exchange and vulnerable for barotraumas. From 32 weeks

gestation, the saccules begin to transform into alveoli, which increases dramatically each week and continues through early childhood (63). Developmental immaturity-related respiratory disorders include respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN), pneumonia, pulmonary hypertension in the neonatal period and apnea of prematurity (20). The rates of severe respiratory morbidity requiring assisted ventilation are also higher after moderate and late preterm birth compared to birth after 39 to 41 weeks and seem to decrease with each increasing gestational week until 38 weeks (36, 38, 39, 43, 46, 47). Severe respiratory morbidity in LPT infants is most commonly caused by RDS, with a reported incidence of 5.2 percent compared to 0.4 percent in full term infants (39). Immature antioxidant and surfactant systems as well as delayed intrapulmonary fluid absorption due to developmentally regulated epithelial sodium channel expression may be underlying causes (11, 41, 64). The second most common pulmonary condition in MLPT infants is TTN, as there is a deficiency of instant clearance of the pulmonary fluid from the alveolar airspaces (20). The risk for apnea of prematurity is also higher in MLPT infants compared to term infants, as brainstem regions and control of the breathing apparatus are not completely maturated. This can be compounded by the fact that the chest wall and the upper airways are extremely pliable and inclined to collapse with diaphragm contractions during rapid eye movement sleep (11, 20).

Hypoglycemia

The energy a fetus requires is delivered through the placental transmission of glucose, amino acids, fatty acids, ketone, and glycerol. A fetus' blood glucose concentration remains > 55 mg/dl, although it does not produce glucose endogenously. After birth the placental glucose supply is interrupted and blood glucose concentration falls. Maturation-dependent, the newborn is able to activate glucose from hepatic glycogen, initiates gluconeogenesis and feeds sufficiently (65, 66). MLPT infants are at higher risk for hypoglycemia compared to their full-term counterparts. Reasons for the increased risk include reduced hepatic glycogen stores, immature glucose-regulated insulin response, potentially increased energy demands due to cold stress and hypoxia, inadequate intake due to difficulties in sucking and swallowing, and also caregivers inadvertence of not monitoring them, since many MLPT infants appear like their full-term counterparts (20). The American Academy

of Pediatrics advises the measurement of blood glucose levels prior to each feed in LPT infants during their first 24 hours of life (11, 65).

Hepatic immaturity and jaundice

LPT infants are most frequently re-admitted to the hospital after discharge due to jaundice developing after their initial hospital stay. Increased bilirubin production and reduced metabolism and elimination lead to hyperbilirubinemia, which is facilitated by the immature liver in MLPT infants (64). Feeding difficulties, also a known problem in MLPT infants, may be additional reasons raising the risk of hyperbilirubinemia in this population, as they cause a deferral in the resolution of the enterohepatic re-circulation of bilirubin, which results again in increasing the hepatic bilirubin load (20). Rates of hyperbilirubinemia were reported to decrease from 76 percent for infants born at 30 weeks to 48 percent at 34 weeks gestational age (51).

Gastrointestinal immaturity and feeding difficulties

Oral-motor function is already present in utero, as the fetus swallows amniotic fluid. However, more complex functioning of the central nervous system of the newborn is required to accomplish the coordination of sucking, swallowing, and breathing (67). Particularly, the establishment of successful breastfeeding is difficult in this population (68, 69). Feeding difficulties are common in MLPT infants, as swallowing mechanisms, peristalsis and sphincter control mechanisms are immature (64). Preterm infants in general have elevated rates of gastro-esophageal reflux, which leads to further reduced food intake and problems in gaining weight and may result in dehydration and hypernatremia throughout the first weeks of life (20). Feeding problems in preterm infants may not only be caused by immaturity, but also from neurologic dysfunction due to injury of the central nervous system (67). Furthermore, several procedures that involve breathing and swallowing mechanisms, such as tube feeding, any form of respiratory support, and suctioning, might interrupt feeding development in preterm infants (70).

There has been reported increased risk of necrotizing enterocolitis (NEC) with decreasing gestational age from 36 to 34 weeks (43). However, NEC occurs rarely in MLPT infants with reported rates ranging from 0.3 to 0.7 percent (47, 51).

Immunological maturation

Studies have suggested a significantly higher risk of culture-proven infections in MLPT infants compared to full-term infants (6, 43, 51, 62). Newborns are not able to generate an adequate T-cell response, as they have no contact with antigens during their intrauterine life (20). However, T-cell responses of full-term and preterm infants are similar, although the absolute counts of naïve helper T-lymphocytes were reported to increase with gestational age (71). A healthy fetus obtains its predominant circulating immunoglobulins via the placenta. After birth, colostrum and human milk are the main sources of immunological protective agents (72). Yet, MLPT infants may not receive adequate amounts of human milk due to difficulty in establishing successful breastfeeding, which increases their risk for infection, sepsis and NEC (20). Other reasons for the receptivity of MLPT infants for infection may be associated with invasive procedures and maternal chorioamnionitis (11).

Intraventricular hemorrhage and periventricular leukomalacia

In many NICUs, cranial ultrasound is not a standardized performed screening for MLPT infants. Rates of ultrasound imaging vary from 38 to 60 percent (73). Thus, an evaluation of the incidence of intraventricular hemorrhage (IVH) is hampered in this population. Nonetheless, higher rates for any IVH and especially severe (> grade 2) IVH in MPT compared to term infants have been demonstrated (43, 47, 48, 51, 74). Intrauterine growth retardation seems to be an important predisposing factor for IVH in the LPT infant (75). The MLPT infant' s brain is still vulnerable to periventricular leukomalacia (PVL), as the maturation of the cerebral white matter is incomplete (76). The identification of cystic PVL rates is again complicated by the inconsistent use of cranial ultrasound. Studies have reported rates from 1.4 to 1.5 percent in infants born 30 to 33 weeks gestational age (74, 77). Data showed that a quarter of all preterm infants with cystic PVL has been diagnosed in infants of 33 to 35 weeks of gestation (78).

Mortality

The absolute incidence of neonatal mortality in infants born MLPT is low, but the incidence is significantly higher compared to full-term infants (43, 44, 79). Infant mortality rates further decrease until 39 to 41 weeks gestational age, as described by epidemiologic studies. The rate of infant mortality is 8 times higher in infants

born at 32 to 33 weeks and 3 times higher in infants born between 34 to 36 weeks gestation (18). These infants are also at higher risk of death within their first year of life compared to full-term infants (43). Reported rates for neonatal death among MLPT infants are 16.2 and 7.1 per 1000 live births, respectively, compared to 2.1 per 1000 live births in infants born at 39 to 41 weeks gestational age (11, 18).

Long-term outcomes of moderate and late preterm infants

Hospital readmissions

MLPT infants were reported to have significantly higher readmission rates than their full-term counterparts (37, 56, 80-82). However, the literature is limited regarding outcomes of MLPT infants after discharge from the hospital and mainly focuses on LPT infants, since MPT infants are frequently grouped with less mature infants (82). Escobar studied all readmissions within the first two weeks after discharge from the NICU and reported significantly higher rehospitalization rates for MLPT infants compared to term infants. In this study MLPT infants comprised 9 percent of NICU discharges, but 19 percent of NICU rehospitalizations (80). It has also been suggested, that it might be risky to discharge LPT infants early after birth (< 48 hours), as they need hospital readmission 1.5 times more often and have a higher risk of neonatal morbidity compared to term infants (56). The most prevalent causes for early readmissions included hyperbilirubinemia (56, 80), feeding difficulties (80), infection (56), respiratory morbidity, specifically respiratory syncytial viral infections (83, 84), and dehydration (46).

Hospitalization after the neonatal period has been less well studied (85). Still, MLPT infants require more frequent hospital admissions within the first year of life than full-term infants. Health care related costs were demonstrated to be higher for LPT infants due to hospital admissions (83). Only recently, it has been reported that 20.9 percent of MLPT infants were admitted to the hospital during the first year after birth due to respiratory infection compared to 6.9 percent of full-term infants (86). Beside respiratory disorders, gastrointestinal problems including infection and gastro-esophageal reflux were reported to be common reasons for hospitalization

within the first year of life (83, 85). Small-for-gestational age was outlined as an independent risk factor for higher readmissions rates (87). The odds of requiring a rehospitalization between nine months and five years of age were also reported to be higher in infants born MLPT than in those born at term (88).

Neurodevelopmental, neurobehavioral and cognitive outcomes

MLPT infants are not routinely followed in neurodevelopmental centers due to the large number of infants and their comparatively little pathology. However, over the past years, there has been rising perception that MLPT infants are at significantly higher risk for developmental impairment throughout childhood (11, 54). Prematurity seems to disturb microstructural and neural connectivity processes, which could result in atypical differentiation of neuronal pathways (89). After 32 weeks of gestation structural changes occur particularly in the limbic system and the cerebellum. Thus, later problems controlling complex motor or mental tasks may be explained by the missing 4 to 8 weeks of intrauterine brain growth and development due to premature birth (53, 90-92). Accordingly, there is a lack of reports dealing with the neurological outcome of MLPT infants during early infancy, especially during the first year of life (93-95).

It is not yet clear whether there is a correlation between MLPT birth and worse cognitive functioning or whether there are other mechanisms that account for the impaired cognitive outcome in addition to prematurity (96). A recent large cohort study demonstrated via magnetic resonance imaging (MRI) that MLPT birth has an effect on brain size and maturation at term-equivalent age compared with full-term infants (97). MLPT infants have smaller brains, less developed myelination of the posterior limb of the internal capsule, more immature gyral folding and larger extracerebral spaces. Thus, the curve of intrauterine brain growth during the last months prior to birth seems to be disturbed by MLPT birth. These findings could be helpful to clarify the foundation of long-term neurodevelopment impairment of MLPT infants, as studies in very preterm infants (<32 weeks gestation) have indicated that brain metric measurements correlate with cognitive and motor development (97, 98). An association between larger volumes of total brain tissue, white matter, and cerebellum with better cognitive, language, and motor scores at 2 years corrected age in MLPT infants has been demonstrated (99).

The following summarizes some of the findings of international studies of MLPT infants regarding neurodevelopmental impairment based in age at assessment and other possible contributing factors.

Outcome up to the age of 2 years

With the Hammersmith Neonatal Neurological Examination (HNNE) scales, which are a simple and structured method for neurological assessment of infants after the neonatal period between 2 and 24 months of age (98, 103, 104), MLPT infants showed both less trunk and flexor tone, and worse head control and quality of movement at newborn age and at term-equivalent age. The results demonstrated generally a wider range of findings in MLPT infants compared to their full-term counterparts (100-102). On the NICU Network Neurobehavioral Scale (NNNS), MLPT infants had poorer arousals, regulation, and quality of movement, more lethargy, and non-optimal reflexes. Stress and hypotonic muscular tone occurred more often. (93, 102, 103). Spittle et al. showed an association between neurobehavior of MLPT at term-equivalent age. This was assessed with HNNE scales and NNNS as well as the cognitive development assessed with the Bayley-III at 2 years. Infants with suboptimal HNNE scores were at three times higher risk for having cognitive delay. Suboptimal excitability and regulation scale scores in the NNNS were also associated with minimum three times higher odds of cognitive delay. In addition, increased odds of language and motor delays were associated with suboptimal lethargy scores in the NNNS (93, 102). Only recently, a study group applied the Hammersmith Infant Neurological Examination (HINE) scales taken at the corrected age of 6 and 12 months to a group of LPT infants admitted to the NICU (105). Additionally, the global score increased between 6 and 12 months in this study population. 74.6 percent of the infants showed suboptimal scores. It is worth noting though, the neurological scores altered gradually from 6 to 12 months corrected age as the infants showed an increase in global and optimal scores which indicates a successive change towards normality at 12 months corrected age. The study group assumed that there is a correlation between HINE suboptimal scores and suboptimal long-term neurodevelopmental outcomes (104).

Johnson et al. showed that MLPT infants are at twice the risk of neurodevelopmental impairment compared with term infants at 2 years of age for most impairment in the cognitive domain. Male sex, socioeconomic disadvantage,

and preeclampsia are independent predictors of low cognitive scores after MLPT birth (52). Cheong et al. confirmed the developmental neurological deficits at the age 2 years, which were most evident in the area of language. In addition, MLPT infants were reported to have worse overall social-emotional competence, with odds of 3.9 compared to term infants (105).

Outcome at preschool-age and school-age

Kerstjens et al. examined the outcome of MPT infants at preschool age and showed twice the prevalence of developmental delay for MPT infants compared with full-term infants. MPT infants experienced problems with fine motor skills, communication, and personal and social skills more frequently than full-term infants (106).

Regarding long-term cognitive outcomes, cognitive and emotional regulation difficulties were found to affect the functioning of MLPT infants. Compared with term infants, they exhibited school problems, slightly lower IQ, and attention and behavior problems (107-112). Odd et al. found an increased risk for special education needs but did not find evidence of lower IQ in MLPT infants (108).

Influence of neonatal morbidity and socioecomic factors on outcome

It is not clear if neonatal morbidities contribute to neurodevelopmental sequelae, but there is evidence that they do. An association between complicated LPT birth with poorer cognitive performance has been demonstrated (113). Only recently, neonatal respiratory morbidity after LPT birth has been described to be related with higher risk of deficits in the communication domain in the Ages & Stages Questionnaires at the age of 4 years (114). Additionally to the communication deficit, an association with gross motor delay in the Ages & Stages Questionnaires was also demonstrated at the age of 12 months in a Canadian population of LPT infants (115).

By contrast, Kerstjens at al. do not approve the understanding that neonatal morbidities have a considerable impact on developmental outcome (116). They found only hypoglycemia to be related to a higher risk of parent-reported developmental delay at the age of 4 years in a group of MPT infants. Differences in socioeconomic status may be an explanation for the association of moderate prematurity with developmental delay. This is because low socioeconomic status could additionally increase the consequences of MPT birth on development (53, 117, 118). Potijk et al. reported low socioeconomic status to be a significant risk factor for delay in overall

development and for delay in domains fine motor, communication, personal-social and problem-solving skills. They also found that socioeconomic status and gestational age had multiplicative effects which could lead to developmental delays. However, socioeconomic status neither weakened nor strengthened the correlation between MPT birth and developmental delay, which supports the hypothesis that gestational age is directly related to developmental delay (53).

Normal developmental results

There are some studies that did not report any impairment and differences in the development of MLPT infants compared to their full-term counterparts (119-122). Romeo et al. reported a significant difference in the HINE at 3, 6, 9, and 12 months corrected age for global scores and tone and at 3 months for the subsections “cranial nerve” and “posture” for MLPT infants compared to term infants. However, MLPT infants showed the same results as full-term infants in the neurological assessment at 2 years. (119). The same study group assessed the mental developmental index (MDI) of the Bayley Scales of Infant Development second edition in a group of MLPT infants (33 to 36 weeks of gestation) and term infants at 12 and 18 months (103). The results at the corrected age showed no differences between groups. Only when comparing the preterm infants’ results of the uncorrected age with term infants were the scores significantly lower at both 12 and 18 months (120). In the study by Hughes et al., there were no differences in the neurodevelopmental and physical outcomes at one year age between LPT and term infants (122). The results of a study by Gurka et al. suggest that LPT infants born otherwise healthy have no real disadvantage for cognition, achievement, socioemotional, or behavioral development from ages 4 to 15 years compared with their full-term counterparts. However, these results may probably be generalized only to a healthy group of LPT infants with families of higher socioeconomic status similar to Gurka’s study population (121).

Basic concepts of developmental neurology

Well into the middle of the 20th century, classical neurophysiology focused predominantly on the study of sensory input and reflexive motor output. To facilitate this research, de-cerebrated animals were used for experiments to avoid any interference from spontaneous activity from the nervous system. However, from a contemporary view it is logical, that reflexes cannot fully reflect brain function and dysfunction , as the nervous system is the most complex and complicated organ of any organism (123). These approaches represented one way of systematically understanding the brain. Advances in techniques and approaches allowed these paradigms to shift. Beginning in the 1940s, the new interest of neurophysiology was the observation of the un-stimulated infant. In human infants there is no phase of either uncoordinated or amorphic movements (124, 125). From 8 to 9 weeks postmenstrual age, movement patterns, which are endogenously generated by the unstimulated nervous system, can be observed. This repertoire of movement patterns continue toward birth unchanged for the first two to three months of life (126). Hence, spontaneous movements are an important indicator of brain dysfunction at very early age (127, 128). The concept of ontogenic adaptation was a significant new paradigm for the functional development of the human nervous system. (129). It confirmed that the functional repertoire of the developing neural structure must conform to the demands of the organism and its environment. When it comes to non-vital functions the human neonate is little adjusted to the environment after birth. The infants' movements in the first two months after birth are very similar to its fetal behavior. Three months after birth an important transformation in many functions of the nervous system is initiated to achieve a better behavioral adaptation to the demands of extra-uterine life (130, 131). Any neurological examination must be suitable for each developmental stage of the human nervous system with its stage-dependent differences in structure and functional repertoire. As there are age-specific signs and symptoms there need to be age-specific diagnostic procedures. In the late 1950s and the early 1960s, Prechtl tried to evolve an early assessment of brain function, which takes account of the age

specificity and the ontogenetic adaptation. During the following years, he concentrated on the spontaneous motor patterns seen in the newborn. By comparing them between low and high-risk preterm infants he soon realized that it was not the quantitative differences but rather the qualitative differences in movements are that really count when it comes to assessing neurological function. This marked the beginning of a completely new approach: The qualitative assessment of spontaneous motor activity (123).

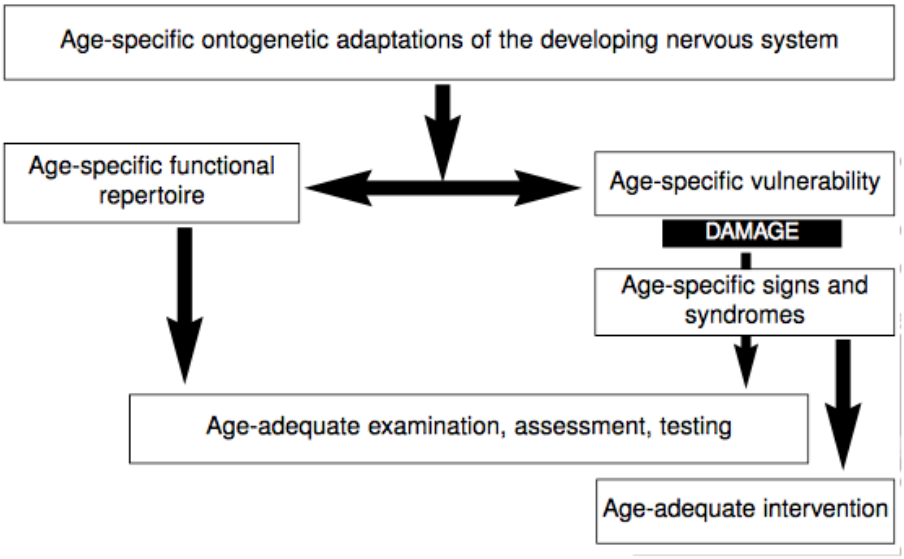

Figure 2: Basic concept of ontogenetic adaptation and its consequences.

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Spontaneous motility in fetuses, pre-term and term infants

Central pattern generator

The existence of endogenously generated activity is evidenced by modern neurobiology. Although it is not yet fully resolved how spontaneous movements are generated, central pattern generators (CPGs) seem to play an important role. CPGs are networks of neurons, which are most likely found in the brainstem and the spinal cord. They generate specific rhythmic movements without being provoked by specific sensory input (132). Well-known examples of CPGs are the central

mechanisms for breathing, sucking, and chewing, and for locomotion such as swimming, crawling and walking (123). Supraspinal projections immediately as the sensory feedback activate, inhibit and modulate the CPG activity which leads to variability in the motor output (123, 133). Less variable (i.e. abnormal) movements can be explained by reduced modulation of the CPGs.

Prenatal and postnatal development of spontaneous movements

The breakthrough for fetal movement studies was achieved after the introduction of the advanced ultrasound equipment in the 1980s. Prechtl and co-workers observed fetuses in frequent intervals from 7 to 8 weeks postmenstrual age to monitor the fetal motor repertoire (124, 134-137). The first fetal movements could be observed at this early age (sideward bending of the head). Yet, at 9 to 10 weeks postmenstrual age complex and generalized movements occur (124, 134). The first isolated movements of the limbs can be monitored at 10 to 11 weeks and appear simultaneously in arms and legs It also became apparent that fetal movements are not amorphic and random, but specific, distinct and differentiated. Some patterns of the fetal movement repertoire like stretches and yawns, which occur as early as 10 weeks, remain unchanged for the whole life. For a brief outline of the fetal motor repertoire see Table 1.

In general, there is a continuance of the prenatal motor repertoire during the first 2 months after birth (126, 131, 138). However, some endogenously generated motor patterns come under sensory control. For example, prenatally, sucking movements always lead to drinking amniotic fluid. Postnatally, sucking movements need to be provoked by the feeding situation. There are also new patterns in the motor repertoire after birth, as reflexes for protection of the airway as well as the communication signal of crying. In preterm infants this continuance lasts until the same postmenstrual age as in full-term infants; thus, the time of birth seems to be irrelevant. The corrected age for preterm age is the relevant factor when observing movement patterns in infants. After 3 months, a significant transformation of motor and sensory patterns emerge, which is important for the infant to meet the requirements of the life after birth (130).

Table 1: Fetal motor repertoire between 10 and 20 weeks of gestation

10 weeks	12 weeks	14 weeks	20 weeks
Startle	Startle	Startle	Startle
GMs	GMs	GMs	GMs
Isolated arm ms	Isolated arm ms	Isolated arm ms	Isolated arm ms
Isolated leg ms	Isolated leg ms	Isolated leg ms	Isolated leg ms
Hiccup	Hiccup	Hiccup	Hiccup
	Breathing ms	Breathing ms	Breathing ms
	Hand-face contact	Hand-face contact	Hand-face contact
	Head rotation	Head rotation	Head rotation
	Head anteflexion	Head anteflexion	Head anteflexion
	Stretch	Stretch	Stretch
	Yawn	Yawn	Yawn
		Sucking and swallowing	Sucking and swallowing
			Eye ms

Age is given in postmenstrual weeks; GMs = General movements, ms = movements.

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General Movements

As mentioned above, general movements are part of the endogenously generated early spontaneous motor repertoire of infants. The integrity of the young nervous system can be most effectively evaluated by the GMs (127). They are frequently occurring, long-lasting and complex spontaneous movement patterns and therefore suitable for observation. Assessment is based on visual Gestalt perception of normal and abnormal GMs in preterm infants and infants from term up to the age of 5 months post term (139). When applying the visual Gestalt perception to the assessment of GMs, in the first instance a differentiation between normal GMs and abnormal GMs needs to be carried out. GMs are regarded to be normal if the sequence, amplitude,

speed, and intensity are variable. Abnormal GMs are distinguished by the absence of variability, particularly in the movement sequence (140, 141).

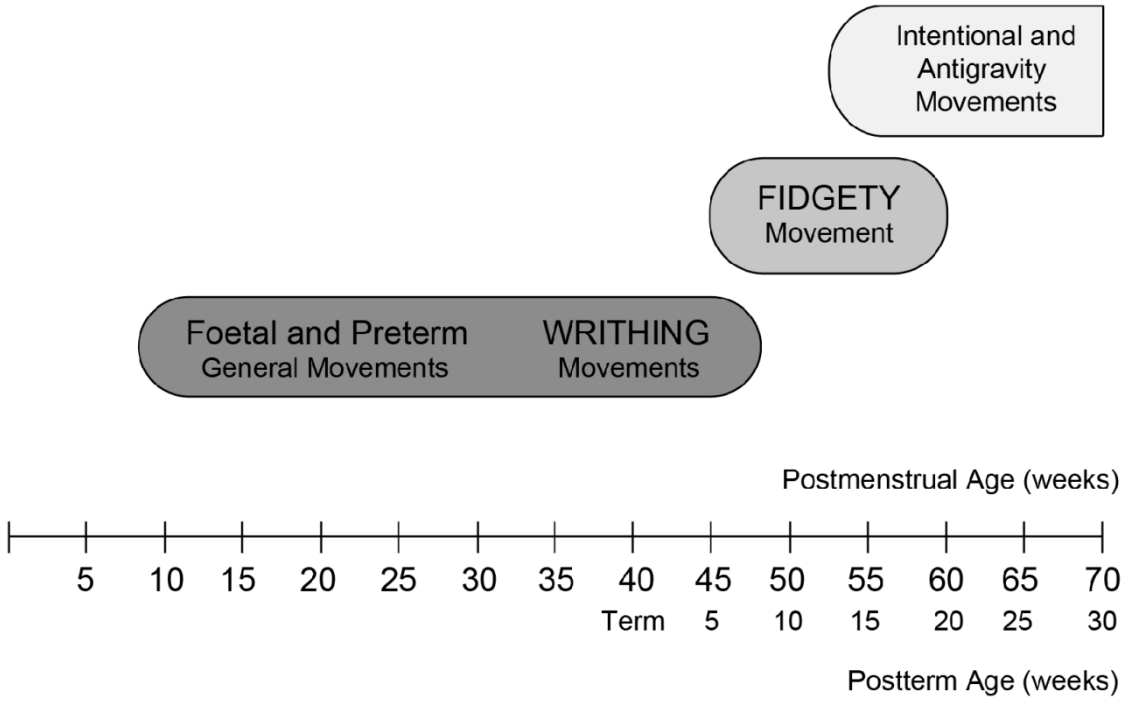

Figure 3: Developmental course of GMs.

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GMs during the neonatal period

GMs before term are called preterm GMs, while at term age until about 6 to 9 weeks post term age, they are called writhing movements (142). Minor differences exist, but GMs look similar from early prenatal life until two to three months postmenstrual age (123).

Global scoring

Usually, the GMs of a preterm or term infant involve the whole body in a variable sequence of arm, leg, neck and trunk movements and have a gradual beginning and end. They appear and cease gradually, varying in intensity, speed, and range of motion. Rotations and frequent slight variations of the direction of movement make

them look complex but elegant (123, 143). GMs are present in all infants, irrespective of their medical history (144), but they differ in their quality, as they lose their complex and variable character when becoming abnormal (123, 140, 143). GMs cannot be assessed if the infant is agitated (fussy or crying) or hypokinetic (123).

Abnormal GMs are classified into (1) “poor repertoire GMs”, whereby the sequence of movement components is repetitive and monotonous; the amplitude, speed, and intensity lack the normal variability; (2) “cramped-synchronized GMs”, which appear rigid as they lack the usual smoothness and fluent character; the limb and trunk muscles contract almost simultaneously and relax almost simultaneously; characterized by a stop-start quality with minimal or absent rotations; and (3) “chaotic GMs”, which appear jerky and abrupt due to their large amplitude and high speed; they also lack the usual smoothness and fluent character (123).

Detailed scoring

Apart from this global GM categorization, looking at different aspects and components of GMs can be meaningful, particularly if they are abnormal. Thus, a semi-quantification of the quality of GMs can be achieved (145). Associations between small changes in the quality of the GMs and other clinical factors can be documented by means of a detailed semi-quantitative approach (139) which might be helpful to distinguish preterm infants with low and high risk for brain-damage or adverse neurological outcome. Furthermore, it provides an opportunity for the short-term prospects of improvements versus deterioration within an specific GMs trajectory, respectively (145) In addition, therapeutic interventions can be evaluated by means of detailed scoring (145, 146).

In 1990, Ferrari et al. initiated a detailed assessment of GMs at preterm and term age (144). Subsequently, an association between a reduced motor optimality score (MOS) and more severe motor impairments a few years later was determined (147). Hitzert et al. (2012) reported an association between dexamethasone therapy in preterm infants at risk for bronchopulmonary dysplasia and higher general movement optimality scores (GMOS) (146). The detailed approach was also used to examine a relation between placental pathologies and the quality of movements, which could not be demonstrated (148). Another study reported on an association between intra-uterine exposure to selective serotonin reuptake inhibitors and the

infant's lower GMOS (149). Using a slightly different detailed scoring procedure, a differentiation between infants whose poor repertoire GMs will have normalized and those whose poor repertoire GMs will have deteriorated was not possible (150).

In 2015, several hundred video recordings of GMs were reassessed in a multi-center study to compare global with detailed GMA. For this purpose, the score sheet for detailed GMA was newly designed in order to score neck and trunk, upper and lower extremities separately (145). The detailed score sheet is described within the method section.

Movements and postures of infants aged 3 to 5 months

At 6 to 9 weeks post term age, GMs with a writhing character progressively disappear while GMs with a fidgety character, the so-called fidgety movements (FMs), appear (142). The chance of identifying infants at risk for developing CP is considerably improved by assessing the GMs at the age of 3 to 5 months. (139). There is no neurodevelopmental impairment to be expected if such FMs are present and normal, even if a brain ultrasound shows distinctive features. By contrast, there is a high risk for the occurrence of impaired neurological outcome in infants without FMs, even if their ultrasound is without pathological findings (141). Yuge et al. (2011) reported that the absence of FMs and a cramped-synchronized movement character were the most protruding features to forego CP. The same study group found normal FMs along with smooth and variable motor performance only in infants with an unimpaired neurological development. Normal FMs seem to indicate an optimal brain development (139).

Global scoring

Normal FMs

FMs are small in amplitude, moderate speed and variable acceleration of neck, trunk and limbs in all directions (123). At times, they are already seen at 6 weeks post term but usually appear around 9 weeks and then remain until 15 to 20 weeks (123). Yet they can be observed up to the end of the first half-year of life when deliberate and antigravity movements are foregrounded (140, 142). FMs appear despite the position of the infants but can be best observed if the infant is in a supine or in a

semi-upright position in a relaxing chair. They are only present if the child is awak. If the child cries, sleeps, is fussy or tired, FMs are not detectable. Hence, the child needs to be in the right state to be observed (123, 141).

The temporal organization of FMs can be defined as follows: (151)

- Continual FMs: Continual FMs are frequent, though intermittent with short (1-2s) pauses. They involve the whole body, particularly the neck, shoulders, wrists, hips, and ankles. Depending on the actual body position, especially the position of the head, FMs may occur asymmetrically. When infants focus on the environment, their FMs are mainly shown in the hips and ankles (152, 153).
- Intermittent FMs: Intermittent FMs occur in all body parts, though with longer pauses (up to 10 seconds). FMs seem to be only present during half of the observation time (152, 153).
- Sporadic FMs: Isolated fidgety bursts of 1 second to 3 seconds are intermittent with long pauses of up to 1 minute. Sporadic FMs are age-adequate between 6 and 8 weeks post term age and during the 5th month when FMs fade out (152, 153) (154).

Prechtl (1986) tried to ascertain the potential biological function of the transient movement pattern of FMs and accredited them to the postnatal adjustment of the proprioceptive system (123, 155). Accurate control of the co-occurring visual hand regard, of intentional reaching, visually controlled manipulation of objects and fine motor skills can only be reached via ideal re-calibration of the sensory domain. There is evidence that children who show less distinct or even abnormal FMs evolve impairment in their fine motor activity (156, 157). However, a recent study suspects FMs to exert influence on the mother-infant-interaction because well-pronounced FMs may trigger a more affectionate handling (158).

Abnormal FMs

- Abnormal FMs: Abnormal FMs look like normal FMs, however with a greater amplitude, speed, and jerkiness (123, 140, 141). Abnormal FMs are not often observed; they appear more often in infants born preterm who show

uncoordinated sucking (67). They are mainly seen in infants with hypotonia (123), for example children with Down syndrome or intra-uterinely exposed to maternal opiate abuse and/or HIV (159). However, the predictive value of abnormal FMs is not yet clear (160), as infants with abnormal FMs may develop normally (94, 140, 157, 161), but could also develop CP (140, 153), coordination difficulties and/or fine manipulative disabilities, respectively (94, 156, 157). Recent studies additionally indicate an association between abnormal FMs and later diagnosed autism spectrum disorder (159, 162-164).

- Absent FMs: If FMs cannot be observed in infants from 9 to 20 weeks post term age, this abnormality is called *absent FMs*. Absent FMs are highly predictive of later neurological deficits (141), particularly of CP (123, 140, 143, 165-167). Specific motor patterns, postures or movement character may give evidence for determination of the eventual type of CP and the anatomical location. Infants with an increased risk of non-spastic CP showed circular arm movements (168). Asymmetries of distal segmental movements, which were reduced or absent on the contralateral side of the lesion, provide an indication for later unilateral CP (169-171). A cramped-synchronized movement character was reported to always result in CP, whereas absent FMs did not: 13% of the cohort with no FMs did not have later neurodevelopmental impairment (139). A cramped-synchronized movement character combined with repetitive opening and closing of the mouth, repetitive kicking, and abnormal finger postures characterized children who would later show poor self-mobility (172, 173).
- Sporadic FMs: FMs are limited to a few body parts and never last longer than 3 s (median: 1s). There is no evidence that intermittent isolated fidgety bursts from 9 to 16 weeks post term age indicate milder neurodevelopmental impairment. There seem to be no difference in the functional mobility and activity limitation of 3-5-year old children with CP after demonstrating sporadic or absent FMs (153).

Detailed scoring

Besides the FMs there are also other movements and postural patterns at the age of 3 to 5 months (Table 2). The prediction of the GMA can be increased by analyzing

qualitative and quantitative aspects of the motor patterns (139). The detailed analysis focuses also on the assessment of the concurrent motor and postural patterns and the overall quality of the movement character. The motor optimality score (MOS) with a maximum value of 28 indicates the best performance; the minimum value of the MOS is 5.

Table 2: Movement patterns, which may occur together with FMs

Movement pattern	**Definition**	**Period of occurrence**
Wiggling-oscillating arm movements	Irregular, oscillatory, waving like movements; most noticeable in partially or fully extended arms, where they have a frequency of 2 to 3 Hz; small amplitude and moderate speed; should be clearly distinguished from tremendous movements, which are less smooth in appearance and have more regular rhythm	6 to 14 weeks post-term
Saccadic arm movements	Jerky, zigzag movements, which continually vary in direction; most noticeable in partially or fully extended arms; moderate to large amplitude and moderate speed	6 to 15 weeks post-term age
Swiping movements	Movements with a sudden but fluid onset and smooth offset with a ballistic-like appearance; can go in downward or upward direction; most noticeable in extended arms, but also in partially or fully extended legs; large amplitude and high speed	6 to 20 weeks post-term age
Mutual manipulation of fingers	Both hands are brought together in the midline and the fingers of both hands repetitively touch, stroke or grasp each other	From 12 weeks post term age onward
Manipulation (fiddling) of clothing	The fingers of one or both hands repetitively touch, stroke or grasp some object or the clothing	From 12 weeks post term age onward

Reaching and touching	One or both arms extend to some object in the immediate environment. The fingers contact the surface of the object	From 12 weeks post term age onward
Legs lift	Both legs lift vertically upward; partial or full extension at the knees; hips are slightly tilted upward; one or both hands touching or grasping the knees; sometimes with anteflexion of the hand	From 15 weeks post term age onward
Trunk rotation	As a result of the soles of the feet pushing down on the lying surface, one side of the hips is lifted and rotated	From 12 weeks post term age onward
Axial rolling	The whole body is turned from supine to prone lying in a movement started by the head. Sometimes the infant returns to prone lying	From 18 weeks post term age onward

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Prediction of outcome

Cerebral palsy

CP is a general term for a lifelong motor impairment due to a non-progressive cerebral lesion acquired early in life. It is the most common motor disorder among children, affecting about 2 of 1000 live births (174). The injuries to the developing brain, which lead to neurological disorder of movement and posture, can have their origin in the pregnancy or early childhood (175). However, their full etiological causal pathways are not completely clear. It is important to discriminate early whether there is a mild or nonspecific motor delay, developmental coordination disorder, a genetic syndrome, a metabolic and progressive condition, or CP with its various types present. Still, CP is diagnosed with an average age of 19 months (61).

Early recognition of infants who are at risk for brain dysfunction and therefore require intervention and treatment is important, as early management of CP can lead to improved functional outcomes (176, 177). Therapeutic interventions could then be applied even prior to the development of pathological features. In addition,

providing a realistic prognosis regarding their infant's development is important for the parents. The GMA is able to meet the described demands (178).

The predictive validity

Since the 1990s Prechtl's GMA has been known as a method which allows substantive predictions about neurological outcome, mainly CP, even prior to the first signs of spasticity, as the sensitivity of GMA is extremely high (140). Reviews reported sensitivity values over 90 percent (165, 178-180). Recently, a review by Kwong et al. (2018) confirmed the predictive validity of FMs. However, they confirmed a low specificity of the writhing movements, indicating a high presence of false positive results (180). This finding was already described by Prechtl et al. (1997) (140) and shows the importance of trajectories of GMs, as abnormal writhing movements may normalize until the fidgety age. Even the distribution (179) and severity of CP may be predicted by means of GMA and the detailed scoring, respectively (172, 173). However, specificity is lower (46 to 65 percent) during preterm and writhing movements as abnormal GMs, mainly with poor repertoire, are observed frequently, which partially have the potential to normalize over time (178). This means that specificity increased with increasing age with specificity values between 82 and 100 percent during the fidgety age, when normal FMs predict a normal neurological outcome (123).

GMs and neurological examinations, brain ultrasound and MRI

Neurological examination has never been completely replaced by neuroimaging techniques. This is because the results provided by neurological examination of newborns provide crucial information about which types of imaging or other examinations are needed, as well as to give prognosis and monitor the development of an impairment (181). Cioni at al. (1997) (184) compared GMA with the traditional neurological assessment by Dubowitz in term infants and found quite a high overall agreement (81.5 percent) between the two techniques. However, the sensitivity and specificity at almost all ages with respect to outcome at 2 years was slightly higher in the GMA than in the neurological examination. Sensitivity was additionally higher than specificity for both techniques (181). GMA also has benefit over the Motor

Assessment of Infancy, reported in a review by Bosanquet et al. (2013) (179). The predictive precision was significantly better in the GMA (sensitivity 87-100 percent vs. 74 percent; specificity 82-100 percent vs. 63 percent). Neurological examination seems to be less valuable at preterm age for the later outcome, as it determines signs that may be temporary (e.g., jitteriness and dystonia), which are not good predictors for CP. Furthermore, neurological examination does not appear to be reliably reproducible and lacks satisfactory inter-user reliability.

Magnetic resonance imaging has a precise prediction of CP at term age (sensitivity 86-100 percent; specificity 87-97 percent). Evidence also suggests that MRI may predict the severity of CP. So far, there is no evidence for the use of MRI prior to term (179).

Cranial ultrasound is also an important tool to predict CP, as it is commonly used in the neonatal intensive care setting due to its readily availability and good toleration by the infants. The predictive values are much lower than the GMA (sensitivity 66-79 percent, specificity 92 percent) (179, 182).

GMA is one of the most cost-effective and sensitive tools available for early prediction of CP. However, it is important to use the combination of clinical assessment methods and frequent follow-up for a clinical diagnosis (179). Skiöld and co-workers (2013) reported a sensitivity and specificity of 100 percent, when combining GMA and MRI findings (183).

GMs and minor neurological dysfunction

Aside from the prediction of severe motor dysfunction, GMA can also be used to predict minor neurological dysfunction (MND), albeit with a lower predictive power (123). MND implies the occurrence of neurological symptoms such as dysfunctional posture and muscle tone, fine manipulative disability and dis-coordination without any evident neurological pathology (184). Its prevalence accounts for 7 to 20 percent of healthy term born children (185). The more severe form, complex MND, has been associated with learning disabilities, behavioral and motor problems (184, 186). Abnormal FMs signify a high risk for developing MND. Bruggink et al. (2008) reported that 64 percent of all infants of their study had abnormal FMs had MNDs at school age (7-11 years). Additionally, qualitative aspects of the early motor repertoire may be predictive since the study by Bruggink showed a risk of 30 percent for MND after

having a monotonous motor repertoire at fidgety age. By contrast, the risk for developing MND is low (5 percent), if the concomitant motor repertoire is smooth and variable (187). It has also been reported that quantitative aspects of the motor repertoire at 11 to 16 weeks post term age can be coherent to the neurological outcome at 7 to 11 years of age. However, of all movement patterns, only the asymmetrical tonic neck posture was predictive independently to neurological outcome, but only in combination with normal FMs. In infants with normal FMs and an abnormal concurrent motor repertoire, the presence of the asymmetrical tonic neck increased the risk for MND to 75 percent, whereas the absence of an asymmetrical tonic neck decreased the risk to 15 percent (188). Normally, the obligatory asymmetrical tonic neck posture is only present until 3 months post term age (189). Thus, the presence of the asymmetrical tonic neck after 3 months of age may be a sign of affected maturation of the nervous system or of neurological damage (188). The occurrence of MND is known to be age-specific: The rate at toddler age is low. Subsequently, the frequency of MND increases with a peak on the verge of the onset of puberty. Supposedly, the age-dependent increase is linked up with gaining complexity of brain function during childhood. The incidence decreases again with the onset of puberty (185). Hence, it can be anticipated, that the data collected at the preschool and school age could not be expanded to puberty (157). Einspieler et al. (2007) (157) could not show a relationship between abnormal FMs and complex MND in 13 to 15 years old children. Their results affirmed the low predictive value of abnormal FMs, as previously mentioned (123, 141, 178). However, abnormal FMs seem to be associated with fine manipulative disabilities at puberty (157).

GMs, cognitive dysfunction and language development

Aside from neurodevelopmental impairment, deficits in cognitive skills are often described challenges after preterm birth with an occurrence rate between 25 and 50 percent (52, 190, 191). Early identification of children with estimated problems in cognitive skills is difficult, as there is no distinct association between neuro-imaging scans and cognitive functions. Additionally, while movement quality is strongly associated with damage of the central nervous system, behavior and intelligence are strongly related to environmental factors such as the quality of home environment,

and the parents' sympathy and view of social support (192, 193). However, there is evidence that early motor status may also reflect the integrity of brain areas involved in emotional and cognitive control (194), which has been recently confirmed in several studies (193, 195). Abnormal GMs, which last up to the post term age of 8 weeks, give strong evidence for lower intelligence quotients at school age compared to children with an early normalization of the GMs (195-197).

So far, a direct relation between FMs and cognition has not been described. Several qualitative and quantitative aspects of the concurrent motor repertoire, including postural patterns and the overall movement character, have been shown to be predictive of later intelligence (193, 198, 199). Poor movement quality might not result directly in cognitive impairment, but an abnormal motor repertoire in the first weeks after birth might mirror global brain functioning. Thus, pre-/perinatal brain injuries, which lead to global brain impairment, might appear in abnormal motor repertoire and be an early clinical sign of later motor and cognitive dysfunction (198). Prenatal and neonatal factors might also influence the quality of movements and the later cognitive outcome, respectively. Infants with monotonous, jerky and/or stiff movements were more often small-for-gestational-age singletons than infants with a smooth and fluent movements character. Fetal growth restriction, including the brain, may lead to impaired cognitive functioning at school age (199). Spontaneous movements may therefore have prognostic value not only for motor development, but also for cognitive outcome (193). White matter injury correlates with the quality if GMs and might result into affected cortical development (200). Preterm infants have higher risk for reduced cortical volumes at school-age which are associated with impaired intelligence (201).

Only recently, a correlation between GMA and language development has been reported. Several aspects of the early motor repertoire at 3 to 5 months of healthy term infants are associated with both expressive and receptive language skills at 4 years and 10 years. The strongest predictor of language performance seems to be qualitative characteristics of movement character (202).

GMs prior to term and individual developmental trajectories

As described by de Vries and Bos in 2011, GMs assessed early (preterm) may give a prediction of the neurodevelopmental outcome at 2 years of age (203). However,

there is restricted comprehension concerning the neurodevelopment prior to term. The identification of neurodevelopmental impairment prior to term during the NICU stay could help to identify children with the necessity of developmental surveillance and early intervention, respectively. Serial GMs assessments give a more distinct impression of the infant's development than assessing an infant only once (141). Perinatal factors, infant behavioral states and clinical interventions may change the quality of GMs temporarily. Assessing the GMs of an infant's several time helps to accomplish higher informative value and to recognize clinical factors that influence the early neurodevelopment. An individual developmental trajectory can indicate the consistency or inconsistency of abnormal results (143). By grouping infants' similar trajectories, the specific prediction of the individual outcome can be improved. For example, a normalization of the GMs over serial assessments showed an association with higher birth weight, lower gestational age, and lower Neurobiological Risk Score (204-206). Previous studies have described high rates of poor repertoire GMs prior to term, which tend to normalize with increasing postmenstrual age (205, 206). These high rates of abnormal GMs seem to be explained by the infant's immaturity (207), instability and the influence of acute perinatal factors (205) rather than by adverse central nervous system development. Poor repertoire GMs prior to term are also hypothesized to mirror early brain function, such as transient ultrasound abnormalities (144), and transitory changes to the neural subsystems confirming the central pattern generators of GMs (181) (206). Olsen et al. reported the normalization of GMs in infants older than 29 weeks PMA, prior to that age they could not find normal GMs in their cohort (206).

GMs in moderate and late preterm infants

MLPT infants represent more than 80 percent of all preterm infants in the US (31), and in Austria (4). In the US, the incidence has increased over the last two decades whereas the number of younger preterm infants remained constant (5). It consistently is the case that especially LPT, but also MPT infants, are treated like full-term infants. However, their risk of both short term and long-term adverse outcome is increased (11, 45, 49, 53, 208). On this account, there is a great interest to detect early signs of developmental disorders in MLPT infants. There has been a lot of research about the quality of GMs in preterm infants <32 weeks gestation and

in term infants with hypoxic ischemic encephalopathy. However, little is known about the GMs in MLPT infants and their prognostic value. To our knowledge, there is one study that is specifically dedicated to the GMA of LPT infants. Brogna et al. (2013) included nearly 600 LPT infants and performed 3 assessments: cranial ultrasounds at one week post-natal age and term-equivalent age; GM video-recordings at 1 and 3 months post-term age and neurological and developmental scale assessment at 24 months post-term age (94). The GMA showed good sensitivity and specificity in predicting CP in LPT infants at the age of 3 months. However, sensitivity and specificity were lower during the writhing period as indicated in other studies (123, 140) due to numerous false positive results. The study also showed a high frequency of poor repertoire GMs followed by normal GMs during the fidgety age with a further normal outcome, which explains the lower specificity. In Brogna's study GMs correlated better with the neurological outcome compared to cranial ultrasound. Data confirmed that constantly abnormal GMs have very good predictive power for CP. Also, constantly normal GMs seem to lead to normal outcomes (95 percent). However, the cohort of this study reported a much higher rate of CP (4 percent) compared to other study populations with a CP prevalence of less than 1 percent (35, 49). A study by Spittle et al. (2016) reported 25 percent and 32 percent of normal GMs for MPT and LPT infants, respectively, compared with a rate of 9 percent normal GMs in full-term infants. For MPT infants they found a decreasing odds ratio for abnormal GMA with increasing gestational age at birth and a decreasing odds ratio for abnormal GMA with increasing postmenstrual age at assessment (102). The results of Brogna's and Spittle's studies underline the importance of the last weeks of fetal development for the cerebral maturation, as in this period thalamo-cortical and cortico-cortical fibers develop forming synapses with subplate neurons (94, 102).

Inter-observer agreement

It is important that the inter-observer agreement is sufficiently high, as the qualitative GMA is based on pattern recognition. An agreement between 89 and 93 percent has been reported. Cohen's kappa is used to assess inter-rater agreement when observing qualitative variables. Kappa is considered to be an improvement over using percentage agreement to evaluate this type of reliability (123). The GMA has

been reported to achieve kappa values as high as 0.88; values higher than 0.75 can be rated excellent agreement. Valentin et al. demonstrated the effectiveness of training of Prechtl's method in GMA. After evaluating 700 scoring sheets they reported an accurate differentiation between normal and abnormal GMs in 92 percent and 83 percent correct assessments after a 4-to 5-day training course, respectively.

Previous studies reported a high inter-observer reliability for the assessment of FMs (Cohen's Kappa= 0.75-0.91); a moderate to very high agreement for the assessment of the age adequacy of the motor repertoire (0.51-0.89); similar values were accomplished in the assessment of the quality of other movement patterns (0.51-0.91); the lowest agreement was reported for the assessment of posture (0.39-0.56); moderate to very high inter-observer reliability was found for the assessment of the overall quality of the motor repertoire (0.54-0.91). Inter-observer reliability in the assessment of the motor optimality score was very high with intra-class correlation coefficients ranging between 0.80 and 0.94 (139, 187, 188, 209, 210).

Assessment and recording technique

GMA could be performed by directly observing the movements by watching the infant. However, standardized recording and assessment procedure has been developed in order to achieve best reliability and to have the possibility to document for the future (123). The video camera should be placed high above the infant, which should not distract the infant with e.g., blinking light during recording. Generally, any interference with the child should be avoided (parents, examiner, equipment, surroundings). The infant should lie in a supine position in the incubator, bed or on a changing mat on the floor. The infant's face must be visible for the observer to distinguish between rigid face movements and crying, as the later assessment is done without sound. The infant should be dressed lightly and comfortably; the arms and legs should be bare. The room temperature should therefore also be convenient for the infant's clothing, as the behavioral state is affected, if the child is too hot or cold. Appropriate behavioral states for recording are active sleep (state 2) and active wakefulness (state 4) (211). The recording must be interrupted during episodes of fussing and crying, during drowsiness and episodes of hiccupping. The infant should also not suck on a dummy, as it results in the sucking posture (flexed arms, fisting,

and extended legs). The duration of the recording depends on the infant's age. For a reliable assessment about three GMs are required. From the writhing period onwards, five to ten minutes of ideal recording is usually enough. It is not recommendable to record an infant during the first three days of life due to string fluctuation of physiological variables and instability of the behavioral states during these early days (123).

Aims

The primary aim of the project was the investigation of morbidities and neurodevelopment of MLPT infants during the first year of life.

We divided our study into two parts:

1. Epidemiological part

The aims of the epidemiological part of the study were:

1.1. To document the epidemiological data of MLPT infants born at the Department of Obstetrics and Gynecology of the Medical University of Graz, Austria, between April 1, 2013, and March 31, 2014.
1.2. To evaluate maternal and perinatal risk factors of moderate and late preterm infants who were admitted to the Division of Neonatology at the Department of Pediatrics and Adolescent Medicine, Medical University of Graz, Graz, Austria.
1.3. To evaluate neonatal morbidity and lengths of stay of MLPT infants and compare data between the two age groups.
1.4. To evaluate rehospitalization rates and reasons for rehospitalization within the first year of MLPT infants and compare again these data between the two age groups.

2. Neurodevelopmental part

The aims and null hypotheses of the neurodevelopmental part of the study were:

2.1. To provide a perinatal optimality score for the description of prenatal, perinatal, and neonatal conditions of MLPT infants for neurodevelopmental assessments.
2.2. To describe GM patterns (based on global and detailed analyses) in MLPT infants and to compare these data between the two age groups.
2.3. To analyze the association between GMs at preterm and term age and GMs at the age of 3-5 months (based on global and detailed analyses).
Null hypothesis 2.3 The results of the GMA applied during preterm and term

age are not associated to the results of the GMA at 3-5 months.

2.4. To analyze to what extent the perinatal optimality score and selected clinical characteristics (with a special focus on (a) the neonatal presentation at birth and (b) placental pathologies) are related to GMs (global and detailed analyses) in MLPT infants.

Null hypothesis 2.4 The perinatal optimality score and selected clinical characteristics are not related to GMs in MLPT infants.

2.5. To describe the neurological development at the corrected age of 12 months in MLPT infants and to compare it between the two age groups.

Null hypothesis 2.5 There is no difference in the neurological development at the corrected age of 12 months in MLPT infants between the two age groups.

2.6. To investigate the association between selected clinical characteristics and the neurological development at the corrected age of 12 months in MLPT infants.

Null hypothesis 2.6 Neurological development at the corrected age of 12 months in MLPT infants is not associated with selected clinical characteristics.

2.7. To analyze to what extent the GMs (global and detailed analyses) are related to the neurological development at the corrected age of 12 months in MLPT infants.

Null hypothesis 2.7 The GMs are not related to the neurological development at the corrected age of 12 months in MLPT infants

Methods

Parts of this section were similarly published in an article by Scheuchenegger et al. (212).

Participants

This exploratory study was conducted between April 2013 and March 2014. The study included infants with a gestational age between 32^{+0} and 36^{+6} weeks, who were born at the Department of Obstetrics and Gynecology of the Medical University of Graz, Graz, Austria. Participants originated from the postnatal wards and the neonatal unit of the Department of Pediatrics' Division of Neonatology, which provided tertiary neonatal care. We excluded infants with congenital abnormalities or known genetic syndromes.

The study protocol, participant information sheet, and consent form were approved by The Ethical Review Board of the Medical University of Graz (EK 25-082 ex 12/13 extended until November 2015). The parents of all participants gave written informed consent.

Gestational age was assessed on the basis of the mother's last menstrual period, as confirmed or modified by routine early antenatal ultrasound examination if necessary. In Austria, pregnancy care is free of charge, and practically all pregnant women follow a standardized antenatal care program beginning early in the pregnancy. Routine performance of cranial ultrasound after the first week of life did not show IVH and PVL in any of the infants enrolled.

Procedure of the epidemiologic part

Maternal and perinatal data

Maternal data were collected by reviewing medical records at the time of recruitment regarding maternal age, history of previous pregnancies, as well as problems of the current pregnancy including hypertensive diseases of pregnancy

(chronic arterial hypertension, pregnancy-induced hypertension, pre-eclampsia, eclampsia and HELLP-syndrome), diabetes (gestational and pre-existing diabetes mellitus), chorioamnionitis (infection of suspected infection of the amniotic cavity as determined by clinical criteria by the attending physician), placental abruption, placenta previa, preterm and premature rupture of membranes (PPROM), oligo-and anhydramnion, corticosteroids for induction of lung maturation (induced in mothers with imminent preterm birth after 23 completed through 34 completed weeks gestation), and presence of intrauterine growth restriction (IUGR).

Pertinent perinatal information included the cause for premature birth, mode of delivery, infant's presentation at birth (i.e., cephalic presentation; breech presentation), gender, birth weight and information concerning the children's adaptation phase (Apgar scores, umbilical artery pH, respiration, need for mechanical ventilation), umbilical cord, placenta, amniotic liquor and its potential pathologies, if a report was available (see below).

Placental lesions

After moderate preterm birth all placentas were routinely examined by a perinatal pathologist pursuant to the Amsterdam international consensus criteria for placental diagnosis (213). The pathologist did not know the clinical outcome of the infant. We included all the placental lesions that were found in the placentas of our study group. The lesions were: placental pathology consistent with malformation of the maternal vascular bed, delayed villous maturation, umbilical cord anomalies, fetal vascular mal-perfusion and ascending intrauterine infection of the placenta. Table 3 presents definitions and scoring criteria.

Table 3: Diagnostic terminology and definition of the placental lesions.

Diagnostic terminology	Definition and scoring criteria
Malformation of the maternal vascular bed (MVM)	Uteroplacental malperfusion, hypertensive disorders and preeclampsia, small for gestational age placenta and abnormal placental location, infarcts, infarction hematoma, retroplacental hemorrhage (placental abruption), distal villous

	hypoplasia, decidual artheriopathy, intervillous thrombus, accelerated villous maturation, increased perivillous fibrin. (214-218)
Delayed Villous Maturation	Insufficient or abnormal branching of villous tree, mesenchymal dysplasia, chorangiomatosis, chorangiosis, distal villous immaturity, and maturation disorders due to fetal (viral) infection. (219, 220)
Umbilical cord anomalies	Abnormal insertion, obstruction or disruption of the umbilical blood flow, abnormal amount of Wharton jelly, marginal/velamentous insertion, true knots, hyper/hypo-coiling, thin cord. (221, 222)
Fetal vascular malperfusion	Placental parenchymatous changes due to hypoxic fetal conditions: fetal vascular thrombosis, intimal edema of chorionic plate vessels and stem villi vessels, stem vessel obliteration, hemorrhagic endovasculitis, avascular villi, chronic villitis, intramural fibrin disposition. (223, 224)
Infection	Ascending infection and vertical in utero transmission of maternal infection across placenta, infection of membranes, umbilical cord and chorionic plate, fetal villitis. (225)

Neonatal data

Neonatal details and adverse events were determined until discharge by the hospital. These included hyperbilirubinemia, respiratory morbidity (transient tachypnoea of the newborn, respiratory distress syndrome, necessity for mechanical ventilation), nervous system disorders (IVH, PVL; detected via cranial ultrasound), metabolic disorders (hypoglycemia, hyperglycemia), infection (neonatal infection, sepsis, pneumonia) and feeding problems.

Definitions of neonatal morbidities

Hyperbilirubinemia was defined as need for phototherapy based on laboratory measurement of serum bilirubin concentration. Age-specific Total Serum Bilirubin - thresholds for phototherapy were used (infants born between 32+6 and 34+6 weeks: 8 mg/dl in the first 24 hours, 10 mg/dl between 24 and 72 hours, 12 md/dl after 72 hours; infants born between 35+0 and 36+6 weeks: 10 mg/dl in the first 24 hours, 14 mg/dl between 24 and 72 hours, 16 md/dl after 72 hours) Respiratory distress syndrome (RDS) was diagnosed in infants with respiratory distress (necessity for oxygen supplementation by reason of tachypnoea (respiratory rate > 60 breaths/min), retractions, grunting, nasal flaring, and/or cyanosis) including chest X-Ray. The four gradations of RDS are shown in table 4.

The diagnose TTN was made in infants with clinical signs, such as the incidence of tachypnoea appearing in the first 24 hours after birth and radiographic results of perihilar streaking, fissure edema, and congestion (75). Hypoglycemia was defined as blood glucose level <35 mg/dl within the first 24 hours after birth and < 45 mg/dl afterwards. Sepsis was defined as blood culture and/or clinical and laboratory (C-reactive protein >8 mg/L) positive bacterial infection. Clinical signs of sepsis were defined as the presence of 3 or more of the following: apnea/tachypnoea, nasal flaring, retractions, cyanosis, respiratory distress, bradycardia (<100/min)/ tachycardia (>180/min), hypotonia, seizures; poor skin color, capillary refilling time > 3 s; irritability/lethargy (50). Feeding problems were defined as ineffective sucking, feeding intolerance, and/or need for parenteral nutrition >7 days.

Table 4: RDS grades in X-Ray (226)

Grade 1	Fine granularity, some air bronchograms
Grade 2	More apparent, distinct, coarse granularity to the lung fields, more extensive bronchograms
Grade 3	Increasing opacity, decreasing air bronchograms and granularity, visible heart borders
Grade 4	Diffuse bilateral opacification, lack of apparent heart boarders, loss of air bronchograms

Readmissions to the hospital within the first year

Throughout the first year of life data regarding readmission to the hospital was documented. These included the number of rehospitalization, infant's age at the rehospitalization, diagnoses for readmission, and results of any performed microbiologic test during the hospital stay. The causes of rehospitalization were classified according to *International Classification of Disease* codes and divided into respiratory causes (upper and lower respiratory tract disorders, including pharyngitis, laryngitis, bronchiolitis, lower respiratory tract infections, and wheezing), surgery, digestive diseases (feeding difficulties, vomiting, gastroenteritis, and cow milk allergy), infections (viral and bacterial infections, urinary tract infection), and other causes.

In Austria, parental healthcare insurance covers children's health care costs and includes outpatient care and hospitalization. Insurance companies cover remaining health costs fully.

Procedure of the neurodevelopmental part

The inclusion criterion for this part of the study was participation in at least one of the assessments described below. Again, the study protocol, participant information sheet, and consent form were approved by The Ethical Review Board of the Medical University of Graz (EK 25-082 ex 12/13 extended until November 2015). The parents of all participants gave written informed consent. Clinical data of the participants were documented as described in the first part of the study, as all participants of the second part are also included in the first part of the study. The protocol consisted of the following assessments: (a) video recording and global and detailed assessment of GMs during the neonatal period; (b) video-recording and global and detailed assessment of GMs at 3-4 months post-term age; and (c) developmental assessment at 12 months post-term age.

Perinatal optimality score

To combine all clinical data each participant was given a neonatal optimality score with a maximum value of 42 points based on Prechtl's optimality concept (227). An infant received one point whether the respective criterion of optimality was met

(indicated in brackets, as shown below). The higher the score the better the maternal, perinatal, and neonatal events were.

The score consisted of the following 38 aspects:

1. Maternal age (22-31 years)
2. prior pregnancies: interruption (no); abortion (no); intrauterine death (no)
3. single pregnancy (yes)
4. diabetes of the mother (no)
5. operation during pregnancy (no)
6. severe disease or infection (no)
7. alcohol and drug abuse (no)
8. blood pressure (<135/85; >105/70)
9. first pregnancy (no)
10. proteinuria (no)
11. early contractions (no)
12. spontaneous onset of labor (yes)
13. delivered at term (yes)
14. gestational age (37^{+1} to 42^{+0} weeks)
15. premature rupture of membranes (no)
16. caesarean section (no)
17. instrumental delivery (no)
18. amniotic fluid (clear)
19. breech presentation (no)
20. time of placental separation (<30min)
21. placental weight (10^{th} to 90^{th} percentile)
22. umbilical cord anomalies (no)
23. sex (female)
24. birth weight (10^{th} to 90^{th} percentile)
25. Apgar 1 (8-10)
26. Apgar 5 (9-10)
27. breathing in the first two minutes (40-50 breaths per minute)
28. heart rate in the first two minutes (100-160 beats per minute)
29. indication for resuscitation (no)
30. body temperature after birth (>36°C)
31. traumatic fractures after birth (no)

32. necessity of mechanical ventilation or prolonged apneas (no)
33. neonatal seizures (no)
34. parenteral nutrition (no)
35. necessity for phototherapy (no)
36. coordinated sucking during nursing and bottle feeding (yes)
37. NICU stay (no)
38. severe disease or infection (no)

Recording and evaluation of GMs during the neonatal period

Spontaneous movements were observed using the standard procedure of the Prechtl method for the GMA (123). The used recording technique is described above (page 46). Each infant was videoed once for 3 to 10 minutes between the 4th day of life and the day of discharge from the hospital to record at least three GMs. The infants were partially clothed, lying supine, not using a pacifier and during periods of active wakefulness or during active sleep. The videos were edited according to the GMA standards, so that only the GMs that are relevant for the analysis remain (178). Crying episodes were excluded from further assessment. GM sequences were analyzed by two trained GM scorers certified for the basic and advanced levels of GMA training. The description of normal and abnormal GMs is described above.

Apart from a global GM categorization (normal/abnormal GMs), we performed a detailed scoring that focused separately on neck and trunk, upper and lower extremities (amplitude, speed, spatial range, proximal and distal rotations, onset and offset, tremulous and cramped components of the upper and lower extremities). The first part of the detailed scoring referred to the global categories as mentioned above (i.e., normal, poor repertoire, cramped-synchronized, chaotic). 'Hypokinetic' indicated that GMs could not be observed during the whole recording (123). The movement sequence was related to the global movement category: 'variable' for normal GMs; 'monotonous and/or broken' for poor repertoire GMs; 'synchronized' for cramped-synchronized GMs; and 'disorganized' for chaotic GMs. The detailed scoring concentrates separately on neck and trunk, upper and lower extremities. For each item a description of optimal performance was given and scored with 2 points (e.g., tremulous movements are absent). Less optimal performance was scored with 1 point (e.g., tremulous movements were unilaterally present). Non-optimal

performance was scored with 0 points (e.g., tremulous movements were bilaterally present). The involvement of the neck was only scored with 2 points (involved in the sequence) or 1 point (hardly/not involved in the sequence). Also, the amplitude and the speed of upper and lower limb movements were scored with 2 points (variable) or 1 point (predominantly small/large/mainly one range; predominantly slow/fast/mainly one speed), as there is no absence of amplitude or speed in children who show GMs. Adding the scores of each item within a category gives the General Movement Optimality Score (GMOS) *(provided in Appendix 1)* with a maximum value of 42, declaring optimal GM performance. The minimum score (worst performance) is 5 (145). A GMOS between 38 and 42 was considered optimal; and a GMOS below 38 was considered reduced.

Recording and evaluation of movements and postures at the age of 3 to 4 months

A second videotape recording was made between 11- and 19-weeks post term. The video was either recorded during an appointment at our clinic or by the parents at home following detailed instructions concerning age, behavioral stage, posture and length of the video. Recordings were made during active wakefulness according to the Prechtl GMA standards (123, 178). Periods of fussing, crying, hiccupping, and using a pacifier were excluded. The duration of the video recordings was between 5 and 10 minutes. Global and detailed assessments were again performed. The global analysis refers to the assessment of normal, abnormal, or absent FMs. FMs (normal, abnormal, absent) are described above. The detailed analysis focused also on the assessment of the concurrent motor and postural patterns and the overall quality of the movement character. The motor optimality score (MOS) (provided in Appendix 2) with a maximum value of 28 indicates the best performance; the worst possible performance is scored with 5 (123, 139). A MOS between 25 and 28 was considered optimal; and a MOS below 25 was considered reduced.

The score sheet comprised five sub-categories:

1. FMs were classified as normal (12 points); abnormal (i.e., excessive amplitude, speed, and jerkiness; 4 points); or absent (1 point)
2. An age-adequate motor repertoire scored 4 points (e.g., wiggling-oscillating arm movements, kicking, swipes, hand-to-hand contact, fiddling with the

clothes, reaching out and touching, leg lifting with or without hand-knee contact, trunk rotation, axial rolling, hand regard, and visual exploration). From the post term age of 10 weeks an infant's repertoire should consist of at least 4 normal motor patterns. Midline movements are not obligatory at this age. From the post term age of 12 weeks midline movements in the form of foot-foot contact should be present additional to at least 3 normal motor patterns. From the post term age of 14 weeks midline movements should be present in the form of foot-foot and hand-hand contact additional to at least 2 normal motor patterns. From the post term age of 16 weeks midline movements should be present in the form of foot-foot, hand-hand additional to legs lift and at least 1 other normal motor pattern (228). A reduced repertoire scored 2 points. If less than four (or three, if the infant was younger than 12 weeks post term age) patterns were observed, the motor repertoire was scored as absent (1 point).

3. The quality of movement patterns (other than FMs): each of above-mentioned patterns can have normal or abnormal appearance. Abnormal patterns further include circular arm movements (168) and asymmetrical segmental movements (169, 170). Predominantly normal movement patterns scored 4 points; an even number of normal and abnormal movement patterns scored 2 points; predominantly abnormal patterns scored 1 point.
4. Posture scored 4 points if normal patterns (of the head, trunk, limbs, and fingers) predominated. Normal postural patterns included head held in the midline and varied finger patterns (fingers move independently of each other). Abnormal postural extended arms and /or legs on surface and invariant finger patterns (fingers curled inwards to form a fist or extended and spread) (193). Equal as with the quality of movement patterns (see above), an even number of normal and abnormal postural patterns scored 2; 1 point was given if abnormal patterns predominated.
5. The overall quality of the motor repertoire was regarded normal if all movements were smooth, variable in sequence, and fluent (4 points); jerkiness, stiffness and reduced complexity were rated as abnormal (2 points); a cramped-synchronized movement character (rigid movements; limb and trunk muscles contracting almost simultaneously and relaxing almost simultaneously (229)) scored 1 point.

Assessment of trajectories

If both video recordings of infants were available, we also assessed the trajectories of their GMs by looking at the percentage that was reached of the maximal GMOS and MOS. We divided those infants into 3 groups: (1) improvement from GMOS to MOS of more than 2 percent; (2) deterioration from GMOS to MOS of more than 2 percent; and (3) no change (the infant reached an equal percentage +/- 2 percent of the maximum MOS and GMOS).

Outcome assessment at 12 months of age

At one year of age – as corrected for preterm birth – the developmental functioning was assessed using the German translation of the Bayley Scales for Infant and Toddler Development - Third Edition (Bayley-III) with regard to the manual guidelines (230). The Bayley-III is commonly used in research and clinical settings, and is age standardized. The assessment was originally created by psychologist Nancy Bayley, first published in 1969 and revised in 1993, and is used to assess the development of infants and toddlers between 1 and 42 months of age. It comprises a series of developmental play tasks using engaging toys and activities. Its primary purposes are to identify children with developmental delay and to provide information for intervention planning (231). The German version's normative information is based on a national standardization sample (n = 1009) representative of the German population for infants 2 through 42 months of age. There are Dutch infants included in the standardization sample between 16 days and 2 months old due to difficulties recruiting enough German infants. The Bayley-III German version has been reported to have good test reliability (r = 0.77 - 0.89) (232).

We used the German translation of the most recent edition, the Bayley-III, which has three main subtests: The Cognitive Scale, which comprises items such as ringing a bell, pushing a car, picking up blocks, finding hidden objects, removing a lid, for example, monitors sensorimotor development, exploration and manipulation, object relatedness, concept formation, memory, and other aspects of cognitive processing. The Language Scale (including the Receptive and Expressive communication subtests) assesses preverbal behavior, receptive vocabulary development, such as being able to identify objects and pictures, preverbal

communication, such as babbling, gesturing, joint referencing, and turn taking, expressive vocabulary development, such as naming objects, pictures, and attributes. The Motor Scale (including the Fine and Gross Motor subtest), which comprises items as grasping toys or food pellets in different ways (e.g., whole hand, thumb-fingertip grasp), turning pages of a book, stacking blocks, crawling, raising, and walking, for example, monitors the increasing posture and movement control, and the fine motor skills associated with prehension, perceptual-motor integration, motor planning, and motor speed. In total, the Bayley-III consist of 326 items (91 in the cognitive, 97 in the language, and 138 in the motor subtest). Each scale has fixed item order, as they are ordered with increasing difficulty; however, the order of the subtests can be altered (230, 233). For children up to 13 months, administration time for the entire assessment is about 50 minutes (233). The items should easily arouse the children's interest. The clinical examiner observes the child's apparent behavioral reactions and should be able to estimate the developmental level of the child. Raw scores of successfully completed items are converted to scale scores and to composite scores. These scores are used to assert the child's performance compared with norms taken from usually developing children of their age calculated in months (233, 234). In every subtest, new tasks are presented to the child until 5 in a row cannot be solved. The most optimal test environment was provided, and the assessment took only place when the infant was alert and cooperative. Aside from the child and the assessor, a caregiver was present during the assessment.

Developmental delay was classified "at risk" if a Bayley-III score was below 85 on any of the language, cognitive, or motor scales and as a "delayed" if a Bayley-III score was below 70 on any of the subscales. The mean score of the German Bayley-III population for all indices was 100 with a standard deviation of 15 (232).

Statistical analysis

Descriptive statistics (median, interquartile-range) were used to document subject characteristics. The Shapiro Wilk test was used to check normality. To evaluate associations between nominal data, Fisher's exact test and the Pearsons's Chi-square test were used. Non-parametric tests were applied because the data were not normally distributed. The Mann-Whitney-U test and the Kruskal-Wallis test were applied to put the medians of the non-normally distributed continuous data (e.g.,

gestational age, birth weight, optimality scores) in relation to nominal data (e.g., moderate/late preterm, singleton/multiple birth, small for gestational age). Spearman's rank order correlations (ρ) were applied to analyze the association between ordinal variables with a monotonic relationship between the two. Data analyses was conducted using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA); *p*-values below 0.05 were considered significant.

Results

Parts of this section were similarly published in an article by Scheuchenegger et al. (212).

Of the 3194 live births at the Department of Obstetrics and Gynecology of the Medical University of Graz, Austria, during the study period (April 1, 2013 – March 31, 2014), 480 infants (15 percent) were born preterm, 2712 infants (84.9 percent) were born full term, and 2 infants (0.1 percent) were born post term. 99 and 273 births occurred at 32 to 33 and 34 to 36 completed week's gestation (11.6 percent), respectively. Of those 372 MLPT infants, 225 infants (60.5 percent) were admitted to the Department of Neonatology at the Children's Hospital in Graz. From these 225 records, we excluded ten: 1 infant died after birth before discharge, 1 infant was transferred to another hospital during its' NICU stay and 8 infants were diagnosed with chromosomal aberrations.

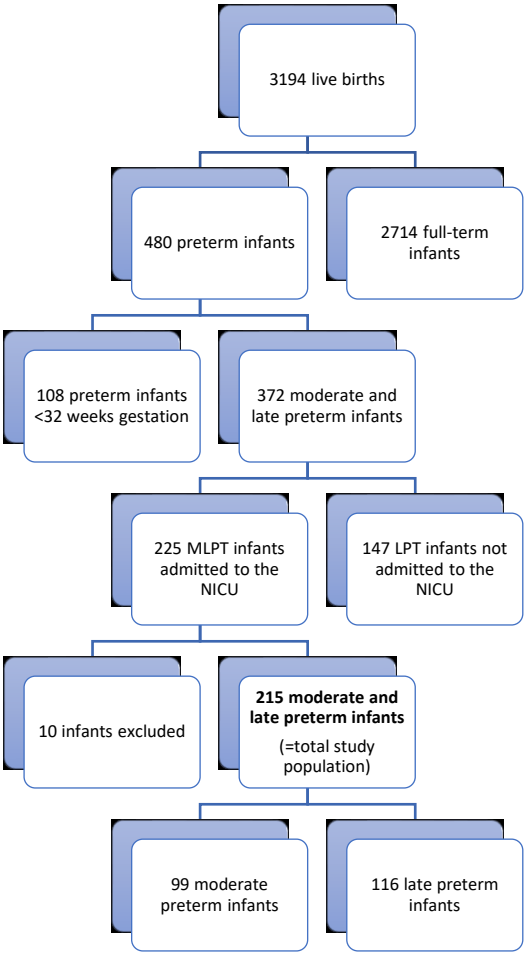

Figure 4: Flow diagram of the epidemiological study population.

Epidemiological part

The study population of the epidemiological part was therefore comprised of 215 MLPT infants (58 percent males; 60 percent singletons): 99 moderate (53 percent males, 55 percent singletons) and 116 late preterm infants (62 percent males, 66 percent singletons). The median birth weight was 2100 grams (1840 - 2423 grams), 20 percent of the infants were small for gestational age (birth weight <10th percentile). The birth weight of singletons (median = 2185 grams) was higher compared to multiples (median = 1940 grams) (Mann-Whitney-U test; p<0.01). There was no gestational age difference (moderate/late preterm) between singletons and multiples (Pearson's Chi-square test; p = 0.16). Perinatal characteristics are presented in tables 5 and 6.

Table 5: Distribution of the gestational age and perinatal data of 215 study infants.

Number of participants	**215**
Gestational age in weeks	
32 $^{0/7}$-32$^{6/7}$	36 (17)
33 $^{0/7}$-33$^{6/7}$	63 (29)
34 $^{0/7}$-34$^{6/7}$	55 (26)
35 $^{0/7}$-35$^{6/7}$	34 (16)
36 $^{0/7}$-36$^{6/7}$	27 (12)
Birth weight in grams	2100 (1840-2423)
Male	124 (57%)
Apgar score 1 min	9 (8-9)
Apgar score 5 min	9 (9-10)
Singletons	130 (60)
Multiples	85 (40)

Data are given as medians (interquartile ranges) or numbers (%)

Table 6: Perinatal data of 99 moderate and 116 late preterm infants.

	Moderate preterm infants n=99	Late preterm infants n=116	*p* value
Male	52 (53%)	72 (62%)	n.s.
Birth weight in grams	1918 (1745-2190)	2290 (1995-2635)	<0.05*
Small for gestational age	11 (11)	33 (28)	<0.05*
Apgar score 1 min	8 (8-9)	9 (8-9)	n.s.
Apgar score 5 min	9(9-10)	10 (9-10)	n.s.
Singletons	54 (65)	76 (64)	n.s.
Twins	34 (34)	42 (36)	n.s.
Triplets	11(11)	0	<0.05*

Data are given as medians (interquartile ranges) or numbers (%). *Pearson's Chi-square test. n.s., not significant.

Maternal and perinatal data

The median maternal age was 31 years (IQR 28.1 - 34); 113 (65 percent) of the 174 women were nulliparous. Antenatal steroids (i.e., Bethametason) were given to 93 (53 percent) women (61 singleton and 32 multiple pregnancies) to induce lung maturation. With increasing gestational age, the frequency of administered antenatal steroids decreased, with the exception of 33 gestational weeks. In 86 percent of pregnancies with preterm birth after 32, 88 percent after 33, 51 percent after 34, 21 percent after 35, and 19 percent after 36 completed weeks antenatal steroids were given. Reasons for preterm birth included:

- preterm premature rupture of membranes (36 percent)
- early contractions (20 percent)
- intrauterine growth retardation (15.6 percent)
- preeclampsia, HELLP syndrome, or pregnancy induced hypertension (9.8 percent)
- vaginal bleeding, placenta previa, or placental abruption (5.6 percent)
- pathological Doppler ultrasonography (1.7 percent)
- other fetal reasons (3.5 percent; i.e., an/oligohydramnion, diabetic fetopathy, tachycardia)

- other maternal reasons (5.8 percent; i.e., intrahepatic cholestasis of pregnancy, multiple pregnancy, dyspnea, status post multiple caesarean sections, severe back pain, and Parvovirus infection).

Preterm premature rupture of membranes and early contractions were the most prevalent reasons for preterm birth at any gestational age. 118 women were delivered by caesarian section (68 percent of all deliveries), resulting in 125 MLPT infants (72 percent of all infants). 49 percent were elective caesarean sections. Caesarean deliveries before the onset of labor were peaking at 82 percent at 36 weeks gestation and were least frequent at 36 percent for 32- and 34-weeks gestation. In singleton pregnancies the caesarean delivery rate was 62 percent; in multiple pregnancies 88 percent. Other maternal factors, pregnancy complications, and delivery characteristics are given in table 7 and 8.

Table 7: Incidence of maternal complications during pregnancy and delivery characteristics.

PPROM	69 (39.7)	
Hypertensive diseases of pregnancy	31 (17.8)	
Diabetes	15 (8.6)	
Oligo-/anhydramnion	15 (8.6)	
Chorioamnionitis	10 (5.7)	
Placenta praevia	7 (4)	
Placental abruption	6 (3.4)	
Delivery characteristics		
	Spontaneous preterm birth	56 (32)
	Caesarean section	118 (68)
	Breech presentation	42 (19.5) *

Data are given as numbers (%). PPROM, preterm premature rupture of membranes. *Number in relation to number of the total study population (n=215); other numbers in table in relation to number of pregnancies (n=174).

Table 8: Incidence of maternal complications during pregnancy and delivery characteristics according to gestational age.

	$32^{0/7}$-$32^{6/7}$ (n=28)*	$33^{0/7}$-$33^{6/7}$ (n=48)*	$34^{0/7}$-$34^{6/7}$ (n=45)*	$35^{0/7}$-$35^{6/7}$ (n=31)*	$36^{0/7}$-$36^{6/7}$ (n=22)*
PPROM	15 (53.6)	25 (52.1)	16 (35.6)	7 (22.6)	6 (27.3)
Hypertensive diseases of pregnancy	5 (17.9)	11 (22.9)	6 (13.3)	9 (29)	0
Diabetes	1 (3.6)	5 (10.4)	5 (11.1)	2 (6.5)	2 (9.1)
Oligo-/anhydramnion	2 (7.1)	2 (4.2)	5 (11.1)	2 (6.5)	4 (18.2)
Chorioamnionitis	1 (3.6)	2 (4.2)	4 (8.9)	2 (6.5)	1 (4.5)
Placental abruption	1 (3.6)	0	2 (4.4)	1 (3.2)	2 (9.1)
Placenta previa	1 (3.6)	3 (6.3)	0	1 (3.2)	2 (9.1)
Delivery characteristics					
Spontaneous preterm birth	9 (32.1)	18 (37.5)	12 (26.7)	9 (29)	8 (36.4)
Caesarean section	19 (67.9)	30 (62.5)	33 (73.3)	22 (71)	14 (63.6)
*Breech presentation***	4 (11.1)	14 (22.2)	12 (21.8)	7 (20.6)	5 (18.5)

Data are given as numbers (%). PPROM, preterm premature rupture of membranes. *Numbers in relation to the number of pregnancies (n=174); ** Numbers in relation to number of the total study population (n=215).

Respiratory support immediately after birth was provided to 104 infants (48.4 percent) of the total study population. The number of infants requiring respiratory support during resuscitation phase declined with increasing gestational age (67 percent at 32, 52 percent at 33, 49 percent at 34, 38 percent at 35, and 26 percent at 36 weeks gestation). In 13 infants (6 percent) heart rate was below 100 beats per minute in the first minute after birth; however, no infant required chest compressions. Median umbilical cord pH was 7.31 (IQR 7.28-7.34).

There were two infants with an umbilical cord pH below 7.0 after placental abruption. The male infant with an umbilical cord pH of 6.74 was born after 34 completed weeks. Apgar scores after 1 and 5 minutes were 1 and 6, respectively. The male infant with an umbilical pH of 6.82 was born after 36 completed weeks. Apgar scores after 1 and 5 minutes were 4 and 8, respectively. Both infants required

respiratory support during the resuscitation phase but no chest compressions were required. Both infants needed respiratory support for 6 days after birth. Both were diagnosed with mild hypoxic-ischemic brain injury due to asphyxia. The umbilical cord pH of another 2 male infants, who were born after 33- and 34-weeks gestation, respectively, was below 7.1 (7.08 and 7.09). Their Apgar after 1 minute was 4 and 8, respectively, and their Apgar after 5 minutes was 9 and 10, respectively. One of those infants needed respiratory support immediately after birth, but not during the further NICU stay. Cranial ultrasounds of all 4 described infants were normal.

Aside from the need for respiratory support and/or monitoring, it is hospital policy that all infants born less than 34 weeks gestation or with a birth weight less than 2000 grams shall be admitted to the neonatal unit.

Placental lesions

A perinatal pathologist examined all placentas after preterm birth until 33 completed weeks gestation (n = 99) as it was hospital policy during our study period. The median weight was 400 grams (IQR 353.8 - 427.5), which is approximately the 25th percentile (235). 86 placentas (86.9 percent) were diagnosed with one or more pathologies, which is 86 percent and 87 percent of the placentas at a gestational age of 32 and 33 completed weeks, respectively (Pearson's chi-square test; p=0.71). The incidence of placental pathologies is presented in table 9. Placentas of girls were more likely to be diagnosed with any pathology compared to placentas of boys (Fisher's exact test; p=0.02). We also found an association between placental lesion and lower birth weight (Mann-Whitney-U test; p=0.01). Placentas of infants with a birth weight < 10th percentile had no increased rates of pathologies (Fisher's exact test; p = 0.35). We did not find any associations between pathologic placental features and neonatal outcome (i.e., hyperbilirubinemia*, hypoglycemia*, early-onset-sepsis*, respiratory morbidity*, Apgar scores**, feeding problems**, length of NICU stay**; *Fisher's exact test/Pearson's Chi-square test, p = 0.13-0.34; ** Mann-Whitney-U test, p = 0.12-0.71).

Table 9: Presence of placental pathology.

Placental pathology	
Malformation of the maternal vascular bed	68
Delayed villous maturation	28
Umbilical cord anomalies	13
Fetal vascular malperfusion	15
Infection	19

Data are given as numbers.

Neonatal data

Of all MLPT infants born within our study period, 225 (61.1 percent) were admitted to the NICU. The admission rate increased with decreasing gestational age, with 100 percent after 32 and 33 completed weeks gestation (see hospital policy described above), 82.1 percent after 34 weeks, 43.6 percent after 35 weeks, and 22.3 percent after 36 weeks gestation, respectively, compared to 3.7 percent of their full-term counterparts. The median length of stay (LOS) was 18 days (IQR 10 - 24) in the total population of 215 infants and was decreasing with increasing gestational age. This was the same as the LOS at the NICU, which was also decreasing with increasing gestational age at birth.

Neonatal morbidity was not coercively decreasing with increasing gestational age. Hyperbilirubinemia was peaking at more than 30 percent at 33 completed weeks gestation. Hyperglycemia occurred most frequently in infants of 36 weeks gestation. The frequency of early-onset sepsis increased with increasing gestational age between 34 and 36 weeks, peaking at 40.7 percent at 36 weeks. Minor respiratory problems (i.e., TTN and wet lung) were most frequently diagnosed in infants of 34 weeks gestation. Major respiratory problems (i.e., IRDS) requiring surfactant treatment and respiratory support occurred more frequently at lower gestational age and its incidence decreased with each advancing week of gestation. This was with the exception of infants of 34 weeks gestation, who required respiratory support more frequently than infants of 33 weeks. Also, feeding problems (i.e., delayed enteral nutrition, need for nasogastric feeding tube and/or parenteral nutrition) were decreasing with increasing gestational age. NEC and IVH did not occur in any of

our included infants. PVL I° was diagnosed in one male infant, who was born with a gestational age of 33 completed weeks due to PPROM. However, the infant was not diagnosed with sepsis and did not require antibiotic therapy. He required respiratory support for 4 days after IRDS III and surfactant treatment after birth. He was also diagnosed with hyperbilirubinemia requiring phototherapy. His LOS at the NICU was 6 days. Unfortunately, he was lost for follow-up for our assessments. However, we have the report of his follow-up check at 4 years of age at our outpatient department. He was diagnosed with a mild form of spastic tetraplegia.

Median postmenstrual age upon discharge from the neonatal care unit was 36.7 weeks. MPT infants were significantly younger at the time of discharge compared to LPT infants (median postmenstrual age: 36.4 vs. 37.0 weeks) (Mann-Whitney-U test; $p<0.01$).

Nine LPT infants were not admitted to the NICU immediately after birth, but between the second and fifth day after birth due to feeding problems (n = 3), sepsis (n = 2), hyperbilirubinemia (n = 2), hypoglycemia (n = 2), and apnea (n = 1). None of those infants was discharged home, but they stayed with their mothers at the obstetric ward of the clinic after birth prior to the admission to the neonatal care unit.

Table 10: Neonatal characteristics of the study population according to moderate and late preterm birth.

	Moderate preterm infants (n=99)	**Late preterm infants** (n=116)	*p*-value
Hyperbilirubinemia	30 (30.3)	31 (26.7)	n.s.
Hypoglycemia	1 (1)	14 (12.1)	<0.01***
Early-onset sepsis	19 (19.2)	25 (21.6)	n.s.
Late-onset sepsis	0	1 (8.6)	n.s.
TTN/wet lung	25 (25.3)	34 (29.3)	n.s.
IRDS Grades 1 and 2	26 (26.3)	15 (13)	0.01***
IRDS Grades 3 and 4	11 (11.1)	8 (6.9)	n.s.
Surfactant treatment	12 (12.1)	9 (7.8)	n.s.
Infants requiring respiratory support*	42 (42.4)	38 (32.8)	n.s.

Duration of respiratory support (in days)	0 (0-1.5)	0 (0-0.5)	n.s.
Duration of antibiotics (in days)	2 (0.5-3.5)	0 (0-1.5)	n.s.
Duration of nasogastric tube (in days)	10 (5.5-14.5)	5 (0-10)	<0.01*** *
Duration of parenteral nutrition (in days)	4 (2-6)	3 (0.5-5.5)	0.01****
Delayed enteral nutrition**	47 (47.5)	12 (10.3)	<0.01***
LOS (in days)	22 (17-27)	12.5 (6.5-18.5)	<0.01*** *
LOS in NICU (in days)	9 (5-13)	3 (1-5)	<0.01*** *
PMA at discharge in weeks	36.4 (35.7-37.1)	37.0 (36.1-37.4)	<0.01*** *

Data are given as medians (interquartile ranges) or numbers (%). TTN, transitory tachypnoea of the newborn; IRDS, infant respiratory distress syndrome; LOS, length of stay; NICU, neonatal intensive care unit; PMA, postmenstrual age; n.s., not significant. * non-invasive and/or invasive respiratory support for at least 1 day; **parenteral nutrition for >7days. ***Pearson's Chi-square test; ****Mann-Whitney-U-test.

Table 11: Neonatal characteristics of the study population according to age group

	$32^{0/7}$-$32^{6/7}$ (n=36)	**$33^{0/7}$-$33^{6/7}$** (n=63)	**$34^{0/7}$-$34^{6/7}$** (n=55)	**$35^{0/7}$-$35^{6/7}$** (n=34)	**$36^{0/7}$-$36^{6/7}$** (n=27)	**Total** (n=215)
Hyperbilirubinemia	10 (27.8)	20 (31.7)	15 (27.3)	9 (26.5)	7 (25.9)	61 (28.4)
Hypoglycemia	0	1 (1.6)	7 (12.7)	3 (8.8)	4 (14.8.)	15 (7)
Early-onset sepsis	8 (22.2)	11 (17.4)	5 (9.1)	9 (26.5)	11 (40.7)	44 (20.5)
Late-onset sepsis	0	0	1 (1.8)	0	0	1 (0.5)
TTN/wet lung	9 (25)	16 (25.4)	20 (36.4)	8 (23.5)	6 (22.2)	59 (27.4)
IRDS Grades 1 and 2	13 (36.1)	13 (20.6)	7 (12.7)	6 (17.6)	2 (7.4)	41 (19.1)
IRDS Grades 3 and 4	4 (11.1)	7 (11.1)	6 (10.9)	1 (2.9)	1 (3.7)	19 (8.8)
Surfactant treatment	5 (13.9)	7 (11.1)	6 (10.9)	1 (2.9)	2 (7.4)	21 (9.8)

Infants requiring respiratory support*	19 (52.8)	23 (36.5)	21 (38.2)	9 (26.5)	8 (29.6)	80 (37.2)
Duration of respiratory support (in days)	1 (0-4)	0 (0-1)	0 (0-1.5)	0 (0-0.75)	0 (0-1)	0 (0-2)
Duration of antibiotics (in days)	3 (0-4)	0 (0-3)	0 (0-3)	3 (0-4.75)	3 (0-6)	2 (0-3)
Duration of nasogastric tube (in days)	12 (8-20)	7 (2-13)	8 (2.5-12.5)	2.5 (0-5)	2 (0-5)	6 (2-12)
Duration of parenteral nutrition (in days)	4 (2.75-6.25)	3 (2-5)	3 (2-5)	3 (0-4)	2 (0-4)	3 (2-5)
Delayed enteral nutrition**	23 (63.9)	24 (30.1)	8 (14.5)	2 (5.9)	2 (7.4)	59 (27.4)
LOS (in days)	26 (22-34)	20 (16-24.5)	17 (11-23)	9 (6-13.75)	7 (5.5-12)	18 (10-24)
LOS in NICU (in days)	12.5 (6.75-15)	8 (4-11)	4 (3-7.5)	4 (2-5)	3 (2-5)	5 (3-9.5)
PMA at discharge in weeks	36.0 (35-37)	36.4 (35.9-37)	36.7 (36-37.59	36.9 (36.3-37.5)	37.4 (36.9-37.9)	36.7 (36-37.2)

Data are given as medians (interquartile ranges) or numbers (%). TTN, transitory tachypnoea of the newborn; IRDS, infant respiratory distress syndrome; LOS, length of stay; NICU, neonatal intensive care unit; PMA, postmenstrual age. * non-invasive and/or invasive respiratory support for at least 1 day; **parenteral nutrition for >7days.

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Readmissions to the hospital within the first year

214 infants of the total study population (n=215) were followed up for rehospitalization throughout the first year of life. One male infant (36 weeks gestational age) was lost to follow-up due to change of residence to another country. No infant died within the first year of life.

52 infants (24.3 percent) were hospitalized at 67 occasions during their first year of life, 10 of 36 infants of 32 weeks gestation (27.8 percent), 14 of 63 infants of 33 weeks gestation (22.2 percent), 14 of 55 infants of 34 weeks gestation (25.

percent), 10 of 34 infants of 35 weeks gestation (29.4 percent), and 4 of 26 infants of 36 weeks gestation (15.4 percent). We found no significant difference in the readmission rate between MPT and LPT infants (Pearson's Chi-square test; p = 0.74). Furthermore, we did not find any association between readmission within the first year and gender, single/multiple birth, small for gestational age, respiratory morbidity, early-onset sepsis (Pearson's Chi-square test; p = 0.41-0.96), postmenstrual age at discharge after birth hospitalization, and birth weight (Mann-Whitney-U test; p = 0.33 - 0.48). Infants with longer stays at the NICU after birth were at higher risk for readmission within their first year (Mann-Whitney-U test; p = 0.03). Reasons for readmission are presented in table 11. Median length of stay was 4 days (IQR 3 - 5 days); and median age at readmission was 3 months (IQR 2 - 9 months).

Respiratory illness

26 infants (12.1 percent) were admitted to the hospital at 29 occasions due to respiratory illness within the first year of life: 7 infants born at 32 weeks gestation (19.4 percent), 5 infants born at 33 weeks gestation (7.9 percent), 9 infants born at 34 weeks gestation (16.4 percent), and 5 infants born at 35 weeks gestation (14.7 percent). In general, infants with respiratory symptoms are tested for RSV and influenza at our clinic. Depending on the physician on duty, other respiratory viruses or pathogens are screened for. One infant was tested RSV positive (35 weeks gestational age), one infant was tested Metapneumovirus positive, and one infant was tested Rhinovirus positive (both 32 weeks gestational age). RSV infection immune prophylaxis (palivicumab) is covered by medical health insurance and is given at the start of the epidemic period, pursuant to national guidelines. Forty-six infants (21.5 percent) received palivicumab. We did not find any differences between infants who did receive palivicumab and those who did not receive RSV infection immune prophylaxis regarding rehospitalization rates. We found no significant difference in the readmission rate due to respiratory illness between MPT and LPT infants (Pearson's Chi-square test; p = 0.55). Additionally, we could not find any association between readmission due to respiratory illness within the first year and gender, single/multiple birth, small for gestational age, respiratory morbidity, early-onset sepsis (Pearson's Chi-square test; p = 0.56-0.92), postmenstrual age at

discharge after birth hospitalization, and birth weight (Mann-Whitney-U test; p = 0.44-0.92). There was a trend for infants with longer stays at the NICU after birth to be at risk for readmission due to respiratory morbidity within their first year (Mann-Whitney-U test; p = 0.09). Median length of stay of infants with respiratory illness was 5 days (IQR 3 - 5 days); and median age at readmission was 6 months (IQR 3 - 10 months).

Table 12: Reasons for rehospitalizations within the first year of life.

Number of rehospitalizations	**67**
Respiratory illness	29 (43.3)
Upper respiratory tract infection	16 (23.9)
Acute bronchitis	10 (14.9)
Bronchiolitis	2 (3)
Pneumonia (bacterial)	1 (1.5)
Feeding problems*	13 (19.4)
Hyperbilirubinemia	1 (1.5)
Viral infection	8 (11.9)
Surgery **	6 (9)
Urinary tract infection	2 (3)
Other diagnoses***	9 (13.4)

Data are given as numbers (%). *i.e., gastroesophageal reflux, poor weight gain, meteorism (one of the infants with feeding problems required phototherapy); **due to inguinal hernia or testicular hydrocele; ***i.e., concussion, epilepsy, burn, aspiration, apnea after vaccination, latent heart failure due to VSD/ASD.

Neurodevelopmental part

Characteristics of the study population of the neurodevelopmental part

The sample that participated in this part comprised of 162 participants, 90 (56 percent) were male and 72 (44 percent) were female. The MPT group comprised of 81 infants (42 male), the LPT group comprised of 81 infants (48 male). Gender distribution was equal between MLPT infants (Pearson's Chi-square test; p = 0.35). Perinatal characteristics of the infants are presented in table 13 and 14.

Table 13: Perinatal data of the 162 infants participating in the neurodevelopmental part of the study

Number of participants	**162**
Gestational age in weeks	33,9 (33,1-35,4)
32 $^{0/7}$-32$^{6/7}$	30 (19%)
33 $^{0/7}$-33$^{6/7}$	51 (31%)
34 $^{0/7}$-34$^{6/7}$	29(18%)
35 $^{0/7}$-35$^{6/7}$	24(15%)
36 $^{0/7}$-36$^{6/7}$	28(17%)
Birth weight in grams	2130 (1840-2435)
Male	90 (55%)
Apgar score 1 min	8 (8-9)
Apgar score 5 min	9 (9-10)
Small for gestational age	31 (19%)
Singletons	89 (55%)
Twins	62 (38%)
Triplets	11(7%)

Data are given as medians (interquartile ranges) or numbers (%).

Table 14: Perinatal data of the infants participating in the neurodevelopmental part of the study according to age group.

	Moderate preterm infants n=81	Late preterm infants n=81	*p*-value
Male	42 (52%)	48 (59%)	n.s.
Birth weight in grams	1900 (1740-2190)	2370 (2047-2633)	*<0.01**
Small for gestational age	10 (12%)	21 (26%)	*<0.01**
Apgar score 1 min	8 (8-9)	8 (8-9)	n.s.
Apgar score 5 min	9 (9-10)	10 (9-10)	n.s.
Singletons	40 (49%)	49 (60%)	n.s.
Twins	30 (37%)	32 (40%)	n.s.
Triplets	11(14%)	0	*<0.01**

Data are given as medians (interquartile ranges) or numbers (%). *Pearson's chi-square test. n.s., not significant.

Median birth weight was 2137 grams (1840 - 2490). The lowest birth weight was 1218 grams at 32 weeks of gestational age, which is below the 3rd percentile. The highest birth weight was 3380 grams at a gestational age of 36 weeks, which is the 90th percentile. 20 percent were small-for-gestational-age with a birth weight below the 10th percentile. LPT infants were more often small-for-gestational-age (Pearson's Chi square test; p = 0.009) compared to MPT infants. 55 percent of the infants were singletons, 45 percent were multiples (38 percent twins and 7 percent triplets). The birth weight of singletons (median = 2190 grams, IQR 1887-2493) was higher compared to multiples (median = 1960 grams, IQR 1679-2241) (Mann-Whitney-U test; p < 0.01). There was no significant difference in the gestational age at birth (MPT/LPT) between singletons and multiples (Pearson's Chi-square test; p = 0.13). Maternal data are presented in table 15. Neonatal outcome is presented in table 16.

Table 15: Maternal data of the infants participating in the neurodevelopmental part of the study according to age group.

	Moderate preterm births n=60	Late preterm births n=65	Total births n=125*
Maternal age	30 (27.3-33.1)	31.3 (29.3-34)	30.6 (28.2-33.9)
Antenatal steroids	56 (93)	19 (29)	75 (60)
PPROM	30 (50)	20 (30.8)	50 (40)
Hypertensive diseases of pregnancy	14 (23.3)	12 (18.5)	26 (20.8)
Diabetes	6 (10)	5 (7.7)	11 (8.8)
Oligo-/anhydramnion	3 (5)	6 (9.2)	9 (7.2)
Chorioamnionitis	1 (1.7)	2 (3.1)	3 (2.4)
Placental abruption	1 (1.7)	2 (3.1)	3 (2.4)
Placenta previa	3 (5)	1 (1.5)	4 (3.2)
Delivery characteristics			
Spontaneous preterm birth	19 (31.7)	21 (32.3)	40 (32)
Caesarean section	41 (68.3)	44 (67.7)	85 (68)
Breech presentation**	13 (16)	20 (27)	33 (20.4)

Data are given as medians (interquartile ranges) or numbers (%). PPROM, preterm premature rupture of membranes. *90 singleton pregnancies, 35 multiple pregnancies. ** Numbers in relation to number of the study population with follow-up data (n=162).

Table 16: Neonatal characteristics of the infants participating in the neurodevelopmental part of the study according to age group.

	Moderate preterm infants n=81	Late preterm infants n=81	MLPT infants n=162	*p* - values
Hyperbilirubinemia	24 (29.6)	24 (29.6)	48 (29.6)	n.s.
Hypoglycemia	1 (1.2)	9 (11.1)	10 (6.2)	*<0.05**
Early-onset sepsis	14 (17.3)	12 (14.6)	26 (16)	n.s.
Late-onset sepsis	0	1 (1.2)	1 (0.6)	n.s.
TTN/wet lung	20 (24.7)	22 (27.3)	42 (26)	n.s.
IRDS Grades 1 and 2	24 (29.6)	9 (11.1)	33 (20.4)	*<0.05**
IRDS Grades 3 and 4	5 (6.2)	3 (3.7)	8 (4.9)	n.s.
Surfactant treatment	9 (11.1)	6 (7.4)	15 (9.3)	n.s.

Duration of respiratory support (in days)	0 (0-2)	0 (0-2)	0 (0-2)	n.s.
Infants requiring respiratory support***	34 (42)	28 (34.6)	62 (38.3)	n.s.
Duration of antibiotics (in days)	0 (0-3)	1 (0-3)	0 (0-3)	n.s.
Duration of nasogastric tube (in days)	10 (3-13)	5 (1-9.5)	7 (2-13)	*<0.05***
Duration of parenteral nutrition (in days)	4 (2-6)	3 (1.5-5.5)	3 (2-5)	n.s.
Delayed enteral nutrition****	44 (54.3)	7 (8.6)	51 (31.5)	*<0.01**
LOS (in days)	23 (19-28)	13 (6-18.5)	18.5 (11-25)	*<0.01***
LOS in NICU (in days)	10 (6-14.25)	4 (2-5.25)	6 (3.5-11)	*<0.01***

Data are given as medians (interquartile ranges) or numbers (%). *Pearson's chi-square test. ** Mann-Whitney-U test. n.s., not significant. *** non-invasive and/or invasive respiratory support for at least 1 day; ****parenteral nutrition for >7days.

Perinatal optimality score

The perinatal optimality scores ranged from 25 to 39 (median = 32; IQR 30-34) in the total sample. We found a significant association between lower gestational age and a lower perinatal optimality score, with median perinatal optimality scores of 30 (IQR 29-32) and 34 (IQR 31.5-35) in the moderate and late preterm birth group, respectively (Mann-Whitney-U test; $p < 0.01$). The minimal scores of 26 and 25, respectively, were similar in the moderate and late preterm group, while the maximal score was 34 in the moderate preterm and 39 in the late preterm group. There was also an association between lower birth weight and lower perinatal optimality score (Spearman Rho's correlation coefficient $r = 0.45$; $p < 0.01$).

General movement patterns in moderate and late preterm infants

Each infant was videoed for about 10 minutes (range 3 to 15 minutes) between the 4th and the 27th day after birth (median = 7, IQR 5 - 11.25), so that at least 3 GMs were recorded. We tried to record all GMs at the same age but, eventually, the recording age differed for logistic and patient-related reasons (e.g., wrong

behavioral state, feeding schedule, early discharge from the hospital). The infants were during periods of active wakefulness (93 recordings; 60 percent) or during active sleep (62 recordings; 40 percent). Due to inappropriate behavioral state video recordings of seven infants had to be excluded from the analysis. Therefore, a total of 154 video sequences containing a minimum of three GM sequences were analyzed by two GM scorers certified for the basic and advanced levels of GMA training. None of the infants was given steroids, sedatives, or narcotic analgesics during the period of GMA video recording in order not to influence the quality of GMs.

Global assessment

Writhing age

In total, 154 video clips were available that met the criteria for assessment. The median postmenstrual age at the recording was 34.4 (IQR 34 - 35 weeks) and 36.3 weeks (IQR 35.5 - 36.9 weeks) in MPT infants and LPT infants, respectively. Table 17 provides the distribution different GM qualities in MLPT infants. The GMs of two of the earlier described infants with an umbilical pH below 7.1 were assessed and scored PR.

Table 17: Distribution of normal and abnormal general movement patterns according to the different age groups.

	Normal GM	PR GM	CS GM	Chaotic GM	Total
Moderate preterm infants	36	40	2	2	80
Late preterm infants	22	50	1	1	74
Total	58 (38)	90 (58)	3 (2)	3 (2)	154

Data are given in numbers (%). GM, general movements; PR, poor repertoire; CS, cramped-synchronized.

Video recordings were made during the 4th and the 27th postnatal day (median=7; IQR 5 - 11.25). MPT infants were older, when they were recorded (median = 10 postnatal days; IQR 6.25 - 15.75) compared to late preterm infants (median = 5 postnatal days; 4-8) (Mann-Whitney-U test; $p < 0.01$). Infants with abnormal GMs were recorded earlier after birth (median = 6 postnatal days, IQR 5 - 9.75) than infants with normal GMs (median = 9 postnatal days, IQR 6.75 - 15.25) (Mann-Whitney-U test; $p < 0.01$).

Fidgety age

One hundred and twenty infants were videoed at the corrected age of 3 to 5 months. All except one had normal FMs; one infant had abnormal FMs. 42 children were lost for follow-up. It was not possible to video these infants during the predetermined age period due to organizational challenges. The average length of the video recordings that were provided for analysis was 7 minutes.

Detailed Scoring

General Movement Optimality Score (GMOS)

In the total sample of 154 videos, the GMOS ranged from 12 to 42 (median = 31; IQR 25 - 38.5). Table 18 provides the GMOS for each global GM category. The postnatal age of the video recording correlated with the GMOS. Infants with a higher postnatal age achieved higher GMOS in the total sample of our study population (Spearman-Rho's correlation coefficient r = 0.29, p < 0.01) as well as in LPT (Spearman-Rho's correlation coefficient r = 0.28, p < 0.01) and MPT (Spearman-Rho's correlation coefficient r = 0.3, p = 0.013) infants.

Table 18: General Movement optimality scores according to the different categories of GMs.

GMOS	**Normal GM** n=58	**PR GM** n=90	**CS GM** n=3	**Chaotic GM** n=3
Maximum	42	35	14	25
P75	38	30	13	21.5
Median	40	27	12	18
P25	41	24	12	16
Minimum	35	19	12	14
p-values	*<0.01**	*<0.01**		
			*0.03**	

P, centile rank; GM, general movements; PR, poor repertoire; CS, cramped-synchronized. *Mann-Whitney-U test.

The Motor Optimality Score (MOS)

The MOS ranged from 12 to 28 (median = 24; IQR 23 - 26). In 42 percent of all infants the MOS was reduced (< 25). The number of normal movement patterns (e.g., hand-to-hand contact, kicking, leg lifting, hand regard) varied between 0 and 11 (median = 4; IQR 3 - 6). The movement repertoire was evaluated as age-adequate in 42 infants

(35%), as reduced in 52 infants (43 percent), and as absent in 26 infants (22 percent). Posture was scored as predominantly normal in 83 infants (69 percent) and predominantly abnormal in 13 infants (11 percent). 24 infants (20 percent) exhibited an even number of normal and abnormal postures. The overall movement character was assessed normal in 49 infants (41 percent) and abnormal but not cramped-synchronized in the remaining 71 infants (59 percent).

Comparison of GMs of moderate and late preterm infants

LPT infants more often had abnormal GMs compared to MPT infants (Pearson's Chi-square test; p = 0.05) at preterm or term age. There was no significant difference between the GMOS of MPT infants and LPT infants (Mann-Whitney-U test; p=0.23). In addition, no significant difference could be found between the MOS of MLPT infants (Mann-Whitney-U test; p=0.29). Data are provided in table 19 and 20.

Table 19: Age-specific general movement optimality scores.

	Moderate preterm infants n=80	**Late preterm infants** n=74	*p*-value
Maximum	42	42	
P75	40	38	
Median	32	30	*0.23**
P25	25	25	
Minimum	12	14	

P, centile rank. *Mann-Whitney-U test.

Table 20: Age-specific motor optimality scores.

	Moderate preterm infants n=45	**Late preterm infants** n=75	*p*-value
Maximum	28	28	
P75	27	26	
Median	24	24	*0.29**
P25	23.5	23	
Minimum	20	12	

P, centile rank. *Mann-Whitney-U test.

There was no significant difference in the movement repertoire between MPT and LPT infants (Pearson's Chi-square test, p = 0.23). However, LPT infants more often had predominantly abnormal movement patterns (other than FMs) or a balanced number of normal and abnormal movement patterns (Pearson's Chi-square test; p = 0.03). In the LPT group, significantly less infants (11 percent of the LPT infants) showed hand-to-hand contact during the video recording compared to the MPT group (33 percent of the MPT infants) (Pearson's Chi-square test, p < 0.01). Furthermore, LPT infants showed less normal movement patterns (median = 4; IQR 3 - 5) compared to their MPT counterparts (median = 5; IQR 3.5 - 7) (Mann-Whitney-U test, p < 0.01). No difference was found between the two age groups in other characteristics of movement patterns or posture (foot-to-foot contact, hand-to-mouth contact, head in midline, body symmetry, extended arms) (Pearson's Chi-square, p values from 0.14 to 0.6). No significant difference in the overall movement character between MPT and LPT infants (Pearson's Chi-square test, p = 0.16) was found.

Infants with CS and Ch GMs and their developmental trajectory

Characteristics of the six infants with CS and Ch global score are given in table 20. We did not assess trajectories of those six infants with CS and Ch movements within the writhing period. We therefore do not know whether and at what time their writhing movements improved. Four infants came for FM assessment, and all had normal FMs; however, their MOS was reduced. The remaining two infants did not come for FM assessment.

Table 21: Characteristics of the infants with cramped-synchronized and chaotic GMs.

GMA	CS	CS	CS	Ch	Ch	Ch
Age at recording (postnatal days)	12	6	12	20	6	4
GMOS	12	12	14	18	14	25
MOS	n.a	22	19	n.a.	21	21
GA	32	33	34	32	33	35
Gender	Male	Male	Female	Male	Male	Male
Birth weight in grams	2226	2230	2630	1700	2200	2770

Reason for preterm birth	Early contractions	Maternal cholestasis	Early contractions	Placenta previa	Maternal cholestasis	Early contractions
Delivery mode	Spontaneous birth	Caesarean section	Caesarean section	Caesarean section	Caesarean section	Caesarean section
Breech presentation	No	Yes	Yes	Yes	Yes	No
Apgar 1	1	8	9	8	8	9
Apgar 5	5	8	9	9	10	9
Umbilical pH	7.21	7.29	7.41	7.21	7.29	7.33
*Cranial ultrasound**	Normal	Normal	Normal	Normal	Normal	Normal
LOS (in days)	35	15	14	25	15	3

GMA, general movement assessment; CS, cramped-synchronized; Ch, chaotic; GMOS, general movement optimality score; MOS, motor optimality score; n.a., not available; GA, gestational age in completed weeks; LOS, length of stay. *Performed on the 8th postnatal day.

Infant with abnormal FMs and his developmental trajectory

The infant with abnormal FMs was male with a gestational age of 36^{+4} weeks. Preterm birth was indicated (caesarean section in breech position) due to intrauterine growth restriction. His birth weight was 1750 grams (< 3rd percentile). During his neonatal phase he was diagnosed with hypoglycemia and was treated with antibiotics for 7 days due to infection. He did not need any respiratory support. He spent the first 3 days after birth at the NICU and was discharged at 12 days after birth. At term age, his GMs were assessed as PR with a GMOS of 29/42 (37^{+4} weeks postmenstrual age). The MOS, which was assessed at 13 weeks corrected age, was 12/28 (no midline movements, asymmetric body posture, absent movement repertoire). Unfortunately, he was lost for follow-up after the second video recording. We only know that throughout his first year he was not readmitted to the hospital.

Association between GMs at preterm and term age and GMs aged 3 to 5 months

There was no significant association found between the (normal or abnormal) GMs during the neonatal period and the MOS (Mann-Whitney-U test; p = 0.94; table 22). Neither was there a significant correlation between the GMOS and the MOS (Spearman-Rho's correlation coefficient r = 0.49; p = 0.62). In addition, we did not

find a significant association between infants with optimal/reduced GMOS and infants with optimal/reduced MOS (Pearson's Chi-square test; p = 0.89).

Table 22: Motor optimality scores according to normal or abnormal GMs at preterm and term age.

MOS	Normal GM	Abnormal GM (PR, CS, Ch)
	n=43	n=69
Maximum	28	28
P75	26	26
Median	24	24
P25	23	23
Minimum	18	12
p-value	*p=0.94**	

P, centile rank; GM, general movements, PR, poor repertoire, CS, cramped-synchronized, Ch, chaotic. *Mann-Whitney-U test.

From GMOS to MOS: improvement or deterioration?

One-hundred and twelve trajectories allowed longitudinal assessment: 74/112 infants (66.1 percent) showed an improvement; 8/112 infants (7 percent) did not change; and 30/112 infants (27 percent) had diminished in their motor performance from their preterm or term period until they reached 3 to 5 months of age. Infants, with cramped components in their lower extremities during the first video recording, more often showed improvement in the second video recording; the result did not turn out to be significant, (Pearson's Chi-square test; p = 0.08). Infants, who had foot-to-foot and hand-to-hand contact and did not have extended arms by the age of 3 to 5 months, presented more often improvement between the two video recordings (Pearsons's Chi-square test; p-values from 0.052 to 0.06). Infants who had their head in midline during their second video recording showed improvement more often from the first to the second recording (Pearsons's Chi-square test; p < 0.01). No significant effect was found of gestational age at birth on the trajectory (Pearsons's Chi-square test; p = 0.66).

Association between the perinatal optimality score, clinical characteristics and GMs

There were no associations between the perinatal optimality score and the GMs at preterm and term age (Mann-Whitney-U test; p = 0.24 in the total sample; p = 0.79

in MPT infants; and p = 0.91 in LPT infants) or the GMOS (Spearman-Rho's correlation coefficient r = -0.039, p = 0.63). Additionally, the perinatal optimality score did not correlate with the MOS (Spearman-Rho's correlation coefficient r = 0.08; p = 0.39).

No significant association was found between sex or small-for-gestational-age and the global score of GMs at preterm or term age (Pearson's Chi-square test; p-values from 0.15 to 0.76) or the GMOS (Mann-Whitney-U test; p-values from 0.15 to 0.88), either in the total sample or in the MLPT group. Male infants had a significantly lower MOS (median = 24; IQR 22 - 26) compared to female infants (median=25; IQR 24-28) (Mann-Whitney-U test, p = 0.018). We found the same result in the LPT group (Mann-Whitney-U test, p = 0.02), with a median MOS of 24 (IQR 22 - 26) in males and a median MOS of 26 (IQR 23.25 - 28) in females. However, this sex difference was not found in the MPT group.

LPT males had reduced MOS (MOS < 25) more often than LPT females (Pearson's Chi-square test, p = 0.03). MPT born males showed significantly less likely foot-to-foot contact compared to MPT females (Pearson's Chi-square test, p = 0.01).

The item small-for-gestational-age had no significant effect on the MOS (Mann-Whitney-U test; p = 0.73). Sex did not significantly affect trajectories (Pearsons's Chi-square test; p = 0.17).

There was no significant association between birth weight and GMs at preterm or term age (Mann-Whitney-U test; p = 0.96). In addition, we also found no such correlation between birth weight and the GMOS (Spearman-Rho's correlation coefficient r = 0.01, p = 0.91).

Multiples had abnormal GMs more often than singletons; however, only after moderately preterm birth, but this result did not reach significance (Pearson's Chi-square test; p = 0.07). No significant difference was detected between the GMOS or the MOS of singletons and multiples (Mann-Whitney-U test; p-values from 0.75 to 0.8). Single/multiple birth did not significantly affect trajectories (Pearsons's Chi-square test; p = 0.95).

Delayed enteral nutrition and longer need for nasogastric feeding tube were significantly associated with abnormal GMs in MPT infants at preterm or term age (Pearson's Chi-square test, p = 0.03; Mann-Whitney-U test, p = 0.02). MPT infants with abnormal GMs at writhing age were fed through nasogastric tube for 10 days (median; IQR 5 - 15), compared to a median duration of 4.5 days (IQR 0 - 10) in infants with normal GMs. MPT infants who needed to be fed through nasogastric tube

also had abnormal GMs more often compared to MPT infants who did not need any feeding support via nasogastric tube (Pearson's Chi-square test; $p < 0.01$). MPT infants with nasogastric feeding tube had significantly lower GMOS compared to MPT infants without nasogastric feeding tube (Mann-Whitney-U test; $p = 0.02$). The median GMOS of MPT infants with need for nasogastric feeding tube was 31 (IQR 24.75 - 39) compared to a median GMOS of 40 (IQR 38 - 40.25) in infants without nasogastric feeding tube. The need for a nasogastric feeding tube or delayed enteral nutrition was not significantly associated with the MOS (Mann-Whitney-U test; p= 0.22 - 0.83). No significant associations were detected between feeding problems and GMs in the total sample or in LPT infants.

We could not find any significant associations between hypoglycemia, hyperbilirubinemia, or early-onset sepsis and GMs at preterm and term age (Pearson's Chi square test, p-values from 0.14 to 0.82 in the total sample; p-values from 0.12 to 0.95 in MPT infants; p-values from 0.28 to 0.76 in LPT infants) or the GMOS (Mann-Whitney-u test, p-values from 0.13 - 0.37 in the total sample; p-values from 0.1 to 0.7 in MPT infants; p-values from 0.53 to 0.69 in LPT infants). Six infants were still under antibiotic treatment due to sepsis during the time of video recording but this did not affect their GMs (Fisher's exact test; $p = 0.56$).

In the total sample, a trend was detected for infants who required respiratory support in the first minute after birth during resuscitation phase to have lower GMOS (Mann-Whitney-U test; p=0.06). Median GMOS of infants with respiratory support was 29.5 (IQR 24-38) compared to a median GMOS of 32 (IQR 26-39) in infants without respiratory support during resuscitation phase. The global score at preterm or term age was not related to the need for respiratory support immediately after birth, though (Pearson's Chi-square test; p=0.68).

Breech presentation

Thirty-three infants (20 percent) were in breech presentation; 13 infants in breech presentation were born moderately preterm; 20 were born late preterm. They were all delivered via caesarean section. The type of breech was not documented by the obstetricians (i.e. frank breech, complete breech, incomplete breech (236)). We did not detect any significant association between the incidence of breech presentation and gender or gestational age at birth (grouped in moderate and late preterm birth) (Pearson's Chi-square test; p-values from 0.17 to 0.26). Infants in breech

presentation had abnormal GMs more frequently at preterm or term age (Fisher's exact test; p=0.05). As described in the method section, two items of the GMOS refer to cramped components in the upper and lower extremities. Cramped components in the lower extremities were observed in 32 infants (21 percent) of the total sample and in 13 infants who were in breech presentation (40 percent of all breech infants). Hence, a significant association between cramped components in the lower extremities and breech presentation (Pearson's Chi-square test; $p < 0.01$, table 23) was found. There was no correlation between breech presentation and cramped components in the upper extremities (Fisher's exact test; $p = 0.3$).

Table 23: Comparison between cramped components and fetal presentation at birth.

	Cephalic presentation	Breech presentation	Total	*p*-values
Cramped components lower extremities				
Present	19	13	32	*0.003**
Absent	102	20	122	
Cramped components upper extremities				
Present	3	2	5	*0.288***
Absent	118	31	149	

*Pearson's Chi-square test; **Fisher's exact test.

Infants born breech had a significantly lower MOS (Mann-Whitney-U test; $p < 0.01$) with a median 22.5 (IQR 21 - 26) compared to the median MOS of 24 (23.75 - 26) in infants with cephalic presentation at birth. Infants with breech presentation showed significantly less normal patterns co-occurring with FMs (Mann-Whitney-U test; $p < 0.01$). The above-described male infant with abnormal FMs, who was in breech presentation, did not show any normal movement pattern. We found a significant association between fetal presentation and motor repertoire. Infants in breech presentation at birth were more likely to have reduced or absent motor repertoire between the ages of 3 to 4 months (Pearson's Chi-square test; $p < 0.01$). We additionally found a trend towards abnormal posture in breech infants compared to infants in cephalic presentation (Pearson's Chi-square test; $p = 0.059$). There was no significant association between fetal presentation at birth and overall movement quality (Pearson's Chi-square test; $p = 0.15$), with 72 percent of infants in breech

presentation and 56 percent of infants with cephalic presentation, respectively, showing abnormal movement character. There was also no significant association between fetal presentation and foot-to-foot contact during the fidgety video recording (Pearson's Chi-square test; p = 0.16), 7 percent of infants in breech presentation and 61 percent of infants in cephalic presentation, respectively, showed no foot-to-foot contact during the recording. However, we did find an association between fetal presentation and head in midline during the fidgety video recording and this was just below the threshold to be significant. Infants in breech presentation were more often unable to put their head in midline (18 percent of infants in breech presentation) compared to infants in cephalic presentation at birth (6 percent) (Pearson's Chi-square test; p = 0.07). There was no significant effect of fetal presentation on the trajectory (Pearsons's Chi-square test; p = 0.87).

Placental pathologies

The pathologist described one or more pathologies in 70 (86 percent) of all examined placentas; 90 percent of the placentas at a gestational age of 32 and 84 percent at 33 completed weeks were diagnosed with one or more pathologies (Pearson's Chi-square test; p = 0.47). Malformation of the maternal vascular bed occurred in 47 placentas; delayed villous maturation occurred in 15 placentas; umbilical cord anomalies occurred in 9 placentas; fetal vascular malperfusion occurred in 14 placentas; and ascending intrauterine infection of the placenta occurred in 12 placentas. 25 placentas showed more than one category of placental histopathology. Median placental weight was 420 grams (IQR 356 - 480 grams), which is approximately the 25th percentile at a gestational age of 32 - 33 weeks (235). Birth weight of infants with any placental lesion was significantly lower compared to infants without placental lesion (median = 1848 grams (IQR 1818 - 1078) vs. 2190 grams (IQR 1919 - 2461); Mann-Whitney-U; p < 0.01). Placental pathology had no relation with small-for-gestational-age (Pearson's Chi-square test; p = 0.21). Placentas of multiples were more often diagnosed with any pathology compared to placentas of singletons (Fisher's exact test; p = 0.03). However, due to sample size, we did not distinguish between monochorionic and dichorionic multiples. We could not detect any association between placental lesions and neonatal morbidity (i.e., hyperbilirubinemia, need for respiratory support, IRDS, hypoglycemia, sepsis,

feeding problems) (Pearson's Chi-square test; p- values from 0.13 to 0.35). Placenta pathology was not related to the perinatal optimality score (Mann-Whitney-U test; p=0.134). No associations were found between placental pathology and (normal and abnormal) GMs at preterm or term age (Pearson's Chi-square test; p = 0.49; table 24). There was also no significant association between placental pathology and the GMOS (Mann-Whitney-U test; p = 0.9) or the MOS (Mann-Whitney-U test; p = 0.67). Infants with placentas with more than one lesion did not have abnormal GMs more often at preterm or term age (Pearson's Chi-square test; p = 0.94). The number of placental lesions did not influence the GMOS (Mann-Whitney-U test; p = 0.92) or MOS (Mann-Whitney-U test; p = 0.23). However, lower placental weight was associated with abnormal GMs during the preterm or term age (Mann-Whitney-U test; p = 0.03). Median placental weight of infants who showed normal GMs was 465 grams (IQR 380 - 515) compared to 392 grams (IQR 355 - 462) of infants with abnormal GMs. No significant association was found between infants with or without placental pathology and the GM trajectory (Pearsons's Chi-Square test, p = 0.94).

Table 24: Association between infants with and without any placenta lesion and normal and abnormal GMs during the neonatal period.

	Normal GMs n=36	**Abnormal GMs** n=44	*p*-value*
no placenta lesion	6	5	
			0.49
one or more placenta lesions	30	39	

GMs, general movements; *Pearson's Chi-square test.

No statistically significant association was found between the global score of the writhing movements (distributed as normal vs. abnormal) and any of the five observed placental lesions (Pearson's Chi-square test for malformation of the maternal vascular bed and delayed villous maturation, fetal vascular malperfusion, and infection, p-values from 0.15 to 0.71; Fisher's exact test for umbilical cord anomalies, p = 0.73).

We could not find a significant association between the observed placenta lesions and a GMOS < 38 or a MOS < 25 (table 25).

Table 25: Association between placental lesion and GMOS and MOS.

	Reduced GMOS (GMOS<38)	**Reduced MOS** (MOS<25)
Malformation of the maternal vascular bed	*p*=0.38*	*p* =0.21*
Delayed villous maturation	*p*=0.63*	*p*=0.4**
Umbilical cord anomalies	*p*=0.9**	*p*=0.1**
Fetal vascular malperfusion	*p*=0.79*	*p*=0.28**
Infection	*p*=0.22*	*p*=0.71**

GMOS, general movement optimality score; MOS, motor optimality score. *Pearson's Chi-square test, ** Fisher's exact test.

Neurological development at the corrected age of 12 months

Sixty-four children volunteered to participate at the outcome assessments. The other participants were lost to follow-up due to impossibility to test these infants because of organizational challenges (no suitable appointment date could be found within the planned period). We assessed the participating children at a median corrected age of 12.1 months (IQR 11.8 - 12.6). In our study, administration time varied between 45 and 60 minutes, dependent on the individual development of the child. The data were not normally distributed. Our sample did not differ from the normative sample of the German version in respect to language and motor development but scored 10 points lower in the cognitive scale (table 26). 87.5 percent of all infants reached normal results in all subscales of the Bayley-III. The results of the language and motor scales match the normative data, while the results of the cognitive scale are 10 points below the normative data of the German version of Bayley-III, as the normative data is 100 in all scales (232). No child reached a composite score below 70 for any of the subscales tested. However, eight children (12.5 percent) scored below 85 in one or more subscales (i.e., moderately delayed): four children in both the cognitive as well as the language scales, one child only in the cognitive scale and another three children only in the language scale. All children scored at least 85 in

the motor scale. Neurological examination did not reveal any child with cerebral palsy.

No significant difference could be found between the Bayley-III results of any subscale of children who were born at moderate or late preterm age (Mann-Whitney-U test; p-values from 0.18 to 0.96, table 27). We could also not detect a difference between the two age groups regarding infants, who reached scores above 85 or below 85 in one or two of the three Bayley-III subscales (Pearson's Chi-square test; p = 0.56),

Table 26: Bayley-III scores

Number of participants	**64**	
	Median	IQR
Bayley-III Cognitive scale	90	85-95
Bayley-III Language scale	100	94-105.25
Bayley-III Motor scale	100	92-103

IQR, interquartile range.

Table 27: Bayley-III scores in moderate and late preterm infants.

Number of participants	**Moderate preterm infants** 25		**Late preterm infants** 39		
	Median	IQR	Median	IQR	*p*-value
Bayley-III Cognitive scale	90	85-92.5	90	85-95	0.67*
Bayley-III Language scale	100	97-106	97	94-103	0.18*
Bayley-III Motor scale	100	94-104.5	100	92-103	0.96*

IQR, interquartile range. *Mann-Whitney-U test.

Association between clinical characteristics and the neurodevelopment at 1 year

We found a trend towards lower scores in the language scale in children, who were small for gestational age at birth (Mann-Whitney-U test; p = 0.07). However, the median score of 94 (IQR 84 - 98.5) (compared to 100 (IQR 84 - 106) in infants with age-adequate birth weight) was within the normal range in those children. Multiples had lower Bayley-III scores in the cognitive scale than singletons (Mann-Whitney-U test; p = 0.04). Both groups reached the same first quartiles of 85 and median scores of 90; however, the third quartile was 90 in multiples compared to 101.25 in singletons, which conducted the significant difference. We also found a trend in twins and triplets to score lower in the cognitive scale compared to singletons. Triplets had lower scores in the motor scale with a median of 85 (IQR 85 - 85), compared to twins (median = 100; IQR 96 - 103) and singletons (median = 101.5; IQR 92 - 106). Since we tested only one set of triplets, we could not perform any statistical calculations.

Sex, fetal presentation, respiratory morbidity, and placental lesion did not influence any of the Bayley-III subscales (Mann-Whitney-U test; p-values from 0.29 to 0.94).

Association between GMs and the neurodevelopment at 1 year

We did not find a correlation between the global GMA, the GMOS or MOS and any Bayley subscale, as represented in tables 28 and 29. Children who did not show variable finger postures at 3 to 5 months of age had significant lower scores in the cognitive scales (median = 90, IQR 85 - 93.75) compared to children, who had variable finger postures during infancy (median = 90, IQR 90 - 101.25) (Mann-Whitney-U test; p=0.05). There was also a trend in children, who did not show variable finger postures during infancy to score below 85 in one or more subscales, compared to their counterparts with variable finger postures (Pearson's Chi-square test; p = 0.09). No association between infants with or without reduced GMOS (GMOS < 38) (Pearson's Chi-square test; p = 0.21) and with or without reduced MOS (MOS < 25) (Pearson's Chi-square test; p = 0.33), and infants, who scored below 85 in one or two subscales.

Table 28: Comparison between the groups with different GMs with Bayley-III scales.

GMs	Infants (n)	Median	IQR	*p*-value*
		Bayley-III Cognitive scale		
normal	24	90	85-105	
				0.4
abnormal	35	87.5	85-91.25	
		Bayley-III Language scale		
normal	24	100	96.25-103.75	
				0.38
abnormal	35	97	94-103.75	
		Bayley-III Motor scale		
normal	24	100	92-111	
				0.8
abnormal	35	97	92-103	

GMs, general movements; IQR, interquartile range; *p*, probability. *Mann-Whitney-U test.

Table 29: Correlation between GMOS and MOS and Bayley-III scores.

	GMOS	MOS
Bayley-III Cognitive scale		
Correlation coefficient	-0.037	0.117
*p**	0.78	0.39
Bayley-III Language scale		
Correlation coefficient	0.064	0.074
*p**	0.63	0.59
Bayley-III Motor scale		
Correlation coefficient	0.067	0.14
*p**	0.61	0.30

GMOS, general movement optimality score; MOS, motor optimality score. *Spearman-rho.

Discussion Part I

Parts of this section were similarly published in an article by Scheuchenegger et al. (212)

Neonatal morbidity

We found that MLPT infants had a median 68 percent rate of cesarean section, a 60 percent admission rate to the NICU, a median length of stay of 18 days ranging from 29 to 7 days and a median stay at the NICU ranging from 12.5 to 3 days with increasing gestational age, respectively. Nearly half of the infants needed respiratory support after birth and 10 percent received surfactant replacement therapy (without differences between MPT and LPT infants). Frequencies of respiratory morbidities were wet lung in 25 vs. 29 percent, mild RDS in 26 vs. 13 percent and severe RDS in 11 vs. 7 percent regarding moderate vs. late preterm infants, respectively. MPT infants had higher rates of mild RDS, longer time of tube feeding and parenteral nutrition, but less rates of hypoglycemia. Rates of hospitalization throughout the first year of life were respiratory illness in 43 percent, feeding problems in 20 percent, other viral infections in 12 percent and surgery in 9 percent. Less than a third developed hyperbilirubinemia that had to be treated with phototherapy without differences according to gestational age.

In general, our short-term results concur with previous studies that reported higher rates of morbidity immediately after birth relative to infants born at term (8, 122, 237). Having knowledge of week-specific risks for neonatal complications might be useful for parental counselling regarding expected outcomes.

An interesting finding was the relatively high rate of breech presentation at birth when compared to other studies; it remained high even with increasing gestational age which contrasts with published data (238, 239). The high rate of breech presentation contributed to the high rate of delivery by cesarean section. The latter might be also due to the relatively high occurrence of PPROM, which was the most common reason for preterm birth in our cohort. Cesarean section is indicated in many cases after PPROM, e.g., due to signs of infection (240, 241).

We observed that 44 percent of all late preterm infants were admitted to the NICU after birth, which is a higher rate than reported by Mally et al. (242), and documents high neonatal morbidity for this age group.

Generally, parents are informed that they can expect their preterm infants to be discharged around the due date (8). The infants of our study were generally discharged 3-4 weeks prior to the due date, corresponding to findings of Manuck et al. (8). The median postmenstrual age at discharge was 36^{+5} weeks in our total sample and, unexpectedly, increased for each increasing week the infant was born being significantly lower in MPT infants, although their median length of stay was nearly twice as long as in LPT infants. The age at discharge in our study was similar with the age at discharge of infants delivered from 28 to 31 weeks of gestation in the study by Manuck et al (8). It could be that the age of discharge of our infants was affected by our inclusion criterion. Only LPT infants who had to be admitted to the NICU due to their medical condition were included, while all MPT infants were included due to our hospital policy. The earlier age of discharge in our study indicates that perinatal problems and neonatal morbidity of MLPT infants were most likely of moderate extent. It seems that MLPT infants can be cared for at home without constant health profession-based support even prior to the due date. Our results may help when counselling parents, as they can plan for their infant being at home soon after birth. This crucial discharge date could be estimated and discussed with the parents soon after their infant had been admitted to the neonatal care unit (243). However, since safe discharge is the primary concern of neonatal care, an individualized approach needs to be found for every MLPT infant (243).

While most of the full-term infants need no assistance in transitioning from the intrauterine to the extra uterine environment, this transition is more difficult for preterm infants. According to the literature, only 5 percent of infants born at term require positive pressure ventilation (244). In our sample, respiratory support during the adaptation phase was required in 50 percent of the infants. The risk of receiving resuscitation decreased with each increasing gestational week the infant was born; though, still 26 percent of the infants at 36 weeks gestation received oxygen or continuous positive airway pressure. These results are in agreement with previous studies that evidenced increased intensity of delivery room interventions in MLPT infants (245, 246). Since we only included infants with admission to the neonatal care unit, it is not unexpected that the rate of delivery room resuscitation

in LPT infants was higher in our study (40 percent) compared to the findings by Boyle et al. (246). These authors reported only 15 percent of the infants having required delivery room resuscitation with a NICU admission rate of 35 percent. We also found higher rates of delivery room resuscitation in MPT infants (58 percent vs. 37 percent in Boyle's study), although MPT infants were generally admitted to the neonatal care unit in both studies. These findings may reflect a different approach to delivery room resuscitation.

Literature suggests a distinction between moderate and late preterm infants as several studies have reported substantially different outcomes (247). For example, Bastek et al. found a 23 percent decrease in adverse outcomes with each week of advancing gestational age between 32 and 39 completed weeks (248). Although, we found decreasing rates in several morbidities with increasing gestational age, some morbidity rates were even higher at higher gestational age. The overall rate of hypoglycemia was 7 percent confirming other reports (50, 116, 237). While only one MPT infant with 33 weeks of gestational age was diagnosed with hypoglycemia, low blood glucose levels occurred most frequently at 35 weeks of gestational age. This finding may correlate to the fact that more MPT infants primarily received intravenous glucose infusions or parenteral nutrition and therefore experienced less hypoglycemia compared to LPT infants. Furthermore, early-onset sepsis was diagnosed most frequently in LPT infants, peaking in infants at 36 weeks gestation (40 percent), which is distinctly higher than in other studies (237). Maternal chorioamnionitis as an etiology of preterm labor might be an explanation, since PPROM occurred frequently in our cohort. Yet again it should be noted that our LPT group is less comparable to other studies because we only included infants with the need of admission to the neonatal care unit. However, the overall rate of early-onset sepsis is in line with other studies (122, 237).

MPT birth has been suggested as an independent risk factor for neonatal morbidity when compared with LPT infants, since the relationship between gestational age and morbidities characterizes continuity (237). Although one would expect that infants born moderately preterm would have higher rates of neonatal morbidities, need for respiratory support, and antibiotic treatment, the two age groups were widely comparable with few differences. Both age groups had similar rates of sepsis, hyperbilirubinemia, need for respiratory support and length of antibiotic treatment. Only mild IRDS was diagnosed more frequently in infants born

moderately preterm. Even the incidence of surfactant treatment was similar between MPT and LPT infants. Overall, respiratory morbidity of MPT infants compared well with previous studies, while respiratory morbidities were more prevalent in the LPT group compared to others (47, 50, 122), most probably due to our inclusion criterion. We found feeding difficulties more often in MPT infants. It can be assumed that in our study, longer length of stay at the NICU and longer length of stay in general in MPT infants was due to the longer need for parenteral nutrition, feeding via nasogastric tube, and problems concerning enteral nutrition. Wang et al. (62) stated feeding problems as the main reason for a delay of discharge. Length of stay of MPT infants was comparable with the results of Manuck et al. (8).

In conclusion, and in contrast to the literature, the majority of morbidities did not differ between MPT and LPT infants. Feeding difficulties and more days on parenteral nutrition as well as on respiratory support in MPT infants might have contributed to a longer neonatal stay.

Rehospitalization during the first year of life

Rehospitalization occurred in 25 percent of the MLPT infants, indicating a generally high rate compared to previous studies with rates between approximately 8 and 16 percent (46, 82, 83, 249). The higher readmission rate might be explained by the study period of one year, while other studies focused on shorter periods after birth. Furthermore, other health units might have other post discharge home visiting programs. To the best of our knowledge, only Olaberrieta et al. (86) reported similar readmission rates (33 percent in MPT infants and 17.6 percent in LPT infants); they also focused on the first year of life. Only focusing on the first three months after birth, the rate of rehospitalization was still higher in our cohort (15 percent) than reported by Escobar et al. (47), although they included only preterm infants born from 33 to 34 weeks gestation (11.3 percent). Hyperbilirubinemia was reported as the main reason for re-admission of MLPT infants soon after discharge (42, 56, 81), which was not the case in our study. Again, this might be explained by our inclusion criterion. Since all included infants were admitted to the NICU after birth, decreasing bilirubin levels were aimed for before discharge, and complications associated to jaundice like feeding difficulties were most likely already resolved during hospitalization after birth. Additionally, outpatient lactation and feeding support

might have been adequately followed by the families of our study. In this aspect, our results correspond to findings of Oddie et al. (250) who also reported a low rehospitalization rate due to jaundice. The main reason for rehospitalization (12 percent) in our study was respiratory morbidity which confirms previous findings (83, 251, 252). Interestingly, although a majority of the infants of our study did not meet the criteria for receiving respiratory syncytial virus (RSV) prophylaxis, only one infant was diagnosed with RSV infection. Others reported distinctly higher rates (83, 84, 86, 252). It is possible that annual variations in RSV rates (26) explain the low incidence in our cohort. Furthermore, not all our cases were tested for RSV, which could have led to underestimation of the RSV rate and is a well-known phenomenon (253). Some studies reported that male sex (46, 251) and growth restriction (81) may be risk factors for higher rates of rehospitalization in preterm infants, which we could not confirm. The only factor associated with re-hospitalization in our cohort was a longer NICU stay, which might have been related to feeding difficulties.

Discussion Part II

GMs in moderate and late preterm infants

In our cohort of MLPT infants, PR represented the most common GM pattern (58.5 percent) during the neonatal period followed by normal GMs (37.7 percent). CS and Ch GMs were equally rare. These results differ from Brogna et al. (2013) (94), who found that 82 percent of 574 infants had normal GMs; only 13 percent of their infants had PR GMs. However, it needs to be mentioned that Brogna et al. assessed only LPT infants at 1 month corrected age. We, however, assessed the first GMs at a median age of 7 postnatal days, which was still before term equivalent age. A high rate of occurrence of PR GMs during the first 10 days of life of preterm infants was also reported by de Vries et al. (2010) (205) Thereafter, the frequency of abnormal GMs decreased with increasing postnatal age. High rates of PR GMs prior to and at term were also reported by other authors (102, 206, 207, 254, 255). By contrast, Mehler et al. (2014) (256) reported 97 percent normal GMs between 2 and 10 days of life in a population of MLPT infants. The high rate of normal GMs was not further explained by the authors (256).

A distinct relation between gestational age and GMs was also reported by Spittle et al. (2016) (102): MPT infants had a decreasing odds ratio for abnormal GMs with increasing gestational age at birth and increasing postmenstrual age at assessment. The relationship between GMs and postnatal age (between 2 days and 2 weeks) was not assessed by Spittle et al. Unexpectedly, our results concerning the effect of gestational age on GMs were contrary to Spittle's results. We found abnormal GMs more often in LPT infants, although a lower gestational age is an often-described risk factor for adverse neonatal outcome (36, 50, 247, 248). We might be able to explain our findings by considering the study of de Vries et al., who frequently described abnormal GMs in the first 2 weeks after birth (205). All infants of our sample were at least 4 days old when videoed, although the precise day of video recording was not pre-determined. Hence, MPT infants (median length of stay = 23 days) were significantly older when videoed as their length of stay was longer than their late preterm peers (median length of stay = 13 days). As we found more abnormal GMs at a younger postnatal age, independent of the week an infant was

born, we need to be cautious when drawing conclusions from GMA too shortly after birth. Even a group of low-risk infants born at term were observed with abnormal GMs during the first days of life, which normalized within a week (254). Physiological instability and other factors that influence brain function during this time might cause early abnormal GMs without any clinical significance (123, 204).

The rates of CS and Ch GMs in our study were comparable to the results of Brogna's study (94). Two of the three infants who were scored as Ch had their assessment during the first week of life. De Vries and Bos (205) (2010) reported a correlation between early chaotic features and reduced serum calcium, which is commonly found early in life in extremely preterm infants (257). Thus, neuronal hyperexcitability might be an explanation for the chaotic movements of our infants. Additionally, hyperbilirubinemia was associated with Ch GMs (38) but none of the three infants of our study who had Ch GMs required phototherapy due to hyperbilirubinemia. We must mention two moderate preterm twins that were scored as having CS and Ch, respectively. Their mother had cholestasis, which was the indication for their preterm delivery. Maternal cholestasis might have induced an intermediate phase of encephalopathy in these twins. Intrahepatic cholestasis of pregnancy is a known as a risk factor for impaired neonatal outcome, although the underlying mechanisms of these perinatal and neonatal complications are not entirely clear (258). Sepulveda et al. (259) suggested a vasoconstrictive effect of bile acids on placental circulation which might cause an impairment of the fetal perfusion and oxygenation. However, we must be cautious about such a conclusion, as we do not have any information about the bile acid level of these infants.

In our sample, all infants except one had FMs. However, when we conducted a detailed assessment, we found several distinctive features in posture and movement character and a high number of infants with reduced MOS. We even found deterioration from GMs at neonatal age through to GMs at 3 to 4 months in nearly one third of our study population. Our data therefore goes in the same direction as Romeo et al. (2016) (260) who described alterations in tone and posture and lower global scores at the neurological examination in LPT infants during the first year of life compared to their term born peers. Contrary to Romeo et al., who reported no differences between very preterm and LPT infants, we found several differences between MPT and LPT infants. To our surprise, LPT infants were more likely to show non-optimal performance in some features of the detailed scoring at 3 to 4 months.

Their movement repertoire was less adequate for the age, usually expressed by a lack of antigravity movements towards the midline. Additionally, they had a higher occurrence of less optimal and even abnormal movement patterns compared to LPT infants. One can speculate that deviances in (motor) development are not that easily recognized in LPT infants relative to MPT infants. Infants at lower gestational ages more often meet criteria for outpatient care due to their lower birth weight and/or other perinatal and neonatal risk factors. Hence, their development is more frequently professionally assessed and developmental impairment might be detected more easily. As a limitation of our study, we do not know whether our infants received early childhood intervention, or had ambulatory physiotherapy. Thus, our explanation is only conjectural and needs further clarification.

Another interesting finding was that we did not find a relationship between GMs assessed during the neonatal period and at 3 to 4 months. On the other hand, there are several studies showing that infants with PR GMs during neonatal age have a high potential to normalize at the age of 3 to 4 months (94, 140, 261, 262). Additionally in the study by Brogna et al. (2013) (94), 78 percent of the LPT infants with PR GMs showed normal FMs. Neurobehavioral and neurological presentation have been stated to change within the first few weeks of life, including alternation and mostly improvement in quality of movements, self-regulation, and tone and reflexes/reaction (102, 206, 263).

In the present study, two of the three infants with CS GMs who were video recorded at 3 to 4 months had normal FMs. This is in contrast to a number of previous findings that CS GMs are highly predictive for an adverse outcome, especially spastic CP, (140, 229) and in LPT infants (94). However, the high predictive value of CS GMs is only given if CS occurs several weeks after a brain lesion and remains for several weeks. Our single video recording, soon after birth, cannot reveal whether the CS pattern was only transient or present for several weeks (264). Olsen et al. (2015) (206), described fluctuations in the quality of GMs during preterm age tending to normalize over time. They also observed transient CS GMs in a group of preterm infants <30 weeks gestation. We therefore assume that the CS GMs only occurred transiently in the three infants described above.

Association between the perinatal optimality score, clinical characteristics and GMs

In contrast to Yuge et al. (51), who described a correlation between the perinatal optimality score and the MOS in a high-risk group, we did not find an association between the perinatal optimality score and the GMs of MLPT infants. However, we found single factors to be related with a less optimal motor repertoire at 3 to 5 months. Male infants more often had a motor repertoire not appropriate for their age than female infants. Foot-to-foot contact in supine position is typically the first movement to the midline to occur and should be present from 12 weeks after term (equivalent) age onwards (123). Sixty-six percent of our infants did not have foot-to-foot contact, which we consider a surprisingly high rate of occurrence with an overrepresentation of male infants (75 percent). Gender-dependent differences both in normal development, but also in the pathophysiology of diseases have been reported in several previous studies (260, 265, 266). One of the explanations might be the greater biological vulnerability of male preterm infants, which leads to a higher risk for an adverse neurodevelopmental outcome (267, 268).

Another single factor which was associated with abnormal GMs of MPT infants at their neonatal age was feeding difficulties. Oral feeding in MPT infants has been described as being difficult and sometimes less efficient compared to full-term infants (62, 269). As abnormal GMs reflect neurological dysfunctions, feeding difficulties in MPT infants are most probably related to discrete dysfunctions as previously stated (67, 270). Additionally Zahed-Cheikh et al. (2011) (207) found a correlation between the duration of parenteral nutrition and GMs at neonatal age in preterm infants born < 28 weeks gestation. Interestingly, in our cohort such an association was no longer found at the age of FMs. Nieuwenhuis et al. (2012), in contrast, described that infants with uncoordinated sucking patterns tend to more often have abnormal FMs (67). Their cohort was, however, distinctly younger with a median gestational age at birth of 29 weeks. Feeding difficulties of our cohort were also not related to neurodevelopment assessed at the age of 1 year. As mentioned already, the association between feeding difficulties and less optimal to abnormal neonatal GMs was only found in MPT infants. In this respect, it is surprising, as writhing GMs were more often associated with the chronological age at the video recording than with the gestational age at birth.

By extension, multiple preterm birth was related to abnormal writhing GMs in MPT infants. These results confirm previous studies that found a higher risk for impaired outcome in twins (271-273). Dostanic et al. (2018) (274) discussed that the prevalence of adverse outcome in twins might primarily be due to the higher risk of preterm birth in multiple pregnancies. This corresponds to our findings since multiple birth was only associated with GMs in MPT infants. In addition, the multiples of our cohort were younger at birth than the singletons.

In contrast to other studies (204, 206, 207), we could not find an association between hyperbilirubinemia, hypoglycemia, sepsis, or respiratory morbidity and the quality of GMs. This might be also related to the partially low rate of occurrence of these complications (e.g., hypoglycemia). No infant required respiratory support at the age of GM assessment. Five of 26 infants (19 percent) who had sepsis were receiving antibiotic treatment when their GMs were recorded. They did not differ from the other infants concerning rate of abnormal GMs.

Breech presentation

With 20.4 percent our study recorded a relatively high rate of breech presentation compared to rates between 6 and 14 percent in the same age group that have been reported by others (238, 275, 276). Our results were in contrast to others (238, 275, 276) as we could not find a relation between gestational age and breech presentation. Notably, we also found that infants born in breech presentation had a higher rate of abnormal writhing movements, especially cramped components in the lower extremities. The effect of breech presentation on the development of motor function has been already reported by Prechtl et al. (277), (278). They described higher extensor-activity in the legs of infants born breech, even when not moving (67). Also, our infants born in breech position appeared to have stiff legs that were mostly extended. This could be most probably due intra-uterine movement restriction. In turn, this might alter the development of motor functions (277). Our study even documented an effect of breech presentation on FMs; also, their MOS was significantly lower than in infants not born in breech. Infants born in breech presentation had also frequently abnormal postures, such as the inability to maintain the head centered while in supine. They more often had a reduced or absent motor repertoire and showed less normal patterns. The only infant with abnormal FMs in

our study population was born in breech presentation. Sival et al. (278) also reported an effect exceeding the neonatal age: leg reflexes were altered until the age of 26 weeks and the posture of the hips was altered until the age of 12 to 18 months. The authors explained these findings by the existence of a limited extension of the hip joint during the first 3 months after birth in breech position, and consequently alterations in the proprioceptive feedback mechanisms (278). The infants of our study with cramped components in the lower extremities showed some improvement from the GMOS to the MOS. This might indicate that the impact of breech position on motor function gets less severe over time. In any case, our children born in breech were not different at the 1-year examination than those not born in breech. Similarly, Sival and et al. did not report any differences at ages at which developmental milestones (i.e. rolling from supine to prone and reverse, sitting, standing, and walking) were reached (278).

Placental pathologies

We demonstrated a high rate of placental pathologies in our group of MLP infants. This corresponds with previous findings that placental pathology frequently accompanies preterm birth (279, 280). Frequencies of placental lesions are typically diverse according to the gestational age at birth (281, 282). The most common lesion in our study was maternal vascular malperfusion, which concurs with Nijman et al. (2016) (281); here it was found that maternal vascular malperfusion is the most common placental lesion in MLPT birth. There is evidence that placental vascular lesions of maternal malperfusion cause a high percentage of spontaneous preterm births (280, 283). We were surprised that in our study, placental pathology was related to female gender. It might very well be that male and female fetuses have different approaches to cope with adverse maternal environment; males have a higher risk of intrauterine growth restriction, preterm delivery, and intrauterine death (284). Only recently, male infants have been also reported to be at high risk for placental lesions (285). On the other hand, similar to our results, Leon-Garcia et al. (2016) (286) also described higher rates of certain lesions in placentas of female fetuses and attributed this to maternal obesity. Additionally, we also found multiples to be at risk for placental pathologies. Taking into account the higher risk for perinatal morbidity and adverse outcome of twins (273), a higher risk for placental

lesions might contribute to neonatal and developmental complications. On the other hand, the rate of occurrence of placental pathology in twins is still inconclusive as both lower and higher rates have been reported (287, 288). What seems to be consistent is that placental lesions differ between twins and singletons (289). Placental lesions obviously also contribute to fetal mortality (290). Although less clear-cut, several studies indicate that placental lesions are also associated with neonatal morbidity, at least among very preterm infants (291-294). This corresponds to our finding that placental lesions were related to lower birth weight. This might explain the higher rates in multiples as they have a lower birth weight than singletons. Contrary to Roescher et al. (2011) (279), we could not find an association between placental pathology and gestational age at birth. However, as examinations of placentas were only conducted after moderate but not after preterm birth, there was not much of a gestational age difference in the examined placentas. Roescher et al. (279) also described an association between placental lesions and more severe illness during the neonatal phase which we could not confirm.

Like Roescher et al. (69), we found no association between placental pathologies and GMs, although their cohort was born < 32 weeks gestation (148). By contrast to Redline et al. (2015) (295) we did not find any difference in the outcome whether there was one or even more placental lesions diagnosed. However, this result was not unexpected, since the co-occurrence of lesions seem to be associated with earlier preterm birth accompanied by severe neonatal morbidity (280). In our study, lower placental weight correlated with abnormal GMs indicating that low placental weight in MLPT infants corresponded with early brain dysfunction. In this aspect we agree with Roescher et al. (148) who also evidenced placental weight being related to the GMs of preterm infants < 32 weeks gestation. In our cohort, placental lesions were not associated with GMs at 3 to 4 months. Redline et al. (2000) (296) reported that maternal vascular underperfusion was not associated with neurological impairment in term infants. One can assume that placental lesions seem to have crucial impact on the outcome of pregnancies up to 32 weeks gestation and on the neonatal outcome of very preterm infants (< 32 weeks), respectively (290). The impact of placental pathologies on the infants' outcome might be modest after moderate and late preterm birth, as long the infant was delivered before any deterioration of lesions or occurrence of new lesions experiencing acute in utero hypoxia, which is more common in full-term placentas (282) and might have led to

fetal death. Placental examination only retrospectively elucidates pathomechanisms of perinatal morbidity and therefore is difficult to integrate in the decision making of potential induced preterm delivery. Our results indicate that after MPT birth other conditions than placental lesions could have impact on GMs. Despite several studies (291, 296, 297), which report the effect of placental lesions on the neurological outcome, one might not disregard that adverse clinical outcome cannot be simply explained by placental lesions (298). Stanek et al. (2013) (282) reported clinical differences among different gestational ages occur more frequently than placental differences. They concluded that pathomechanisms of the third-trimester pregnancy cannot be decisively explained by the placental pathologic condition.

Neurodevelopment at 1 year

We did not split the 1 - year Bayley-III results into two groups as by that time the effect of moderate vs. late preterm birth is not anymore evident.

MLPT infants performed average or slightly above average in motor and language domains but as a group below average in the cognitive domain (median score = 90) in comparison to test norms, using the mean scaled score of 100 (232). Ramdin et al. (2018) (299) found similar Bayley-III results at 16 months in a cohort of LPT infants. Coletti et al. (2015) (300) reported slightly higher cognitive scores (mean = 102.7) and lower motor scores (mean = 91.11) in a group of LPT infants. Our findings are consistent with those of others reporting normal neurodevelopmental and physical outcomes of LPT infants at the age of 9 months or 1 year, respectively (120, 122, 301). In a recent study by Cheong et al. (2017) (105), MLPT infants exhibited developmental delay at 2 years corrected age relative to full term infants. Yet mean scores in all Bayley-III scales were comparable to our results with mean cognitive scores being even slightly lower in our cohort. Contrary to other studies with similar study populations (94, 299), none of our children showed severe neurodevelopmental delay. This result was not unexpected, since we did not find any high grade perinatal hemorrhage or periventricular leukomalacia, which are the most common causes for adverse motor and/or cognitive outcomes (302). However, 12.5 percent of our children were diagnosed as being moderately delayed at 1 year (Bayley-III scores between 70 and 85 in at least one domain) indicating the need for a longer monitoring

of MLPT infants. Coletti et al. (300) reported an even higher rate of 30 percent with moderate delay at 1 year of age in a group of children born late preterm.

In our cohort, the majority of children with moderate developmental delay demonstrated cognitive delay, while most of the children with developmental delay in Coletti's study demonstrated motor delay. Since impaired long-term outcome after moderate and preterm birth has been has been described (12, 35, 53, 112), we assume that some developmental delay in our cohort might not be apparent until a later age (96, 303, 304). Furthermore, several developmental assessments including the Bayley-III have been discussed to underestimate rates of developmental impairment especially when applied to early (304-306). Severe neurodevelopmental sequelae are unlikely in our study population, as none of our study cases had a lack of FMs during the 3-to 4-month GMA. However, Hodel et al. (2017) (301) found subtle alterations in the cognitive skills assumed to be dependent on prefrontal cortex in MLPT infants at 9 months of age under the circumstances of low medical and environmental risk and normal Bayley-III results. The authors suggested that those alterations might be accountable for long-term variations in the development of the executive function (301). Contrary to the literature (12, 35, 307), we could not detect a relation between gestational age at birth and neurodevelopment at the corrected age of 1 year. An explanation might be the homogeneity of our cohort since we only included MLPT infants with need for admission to the neonatal care unit. This is consistent with the results of others (115, 308-310), suggesting that NICU admission is a more affecting factor associated with neurodevelopment compared to gestational age. The same reason might apply for the lack of any relation between perinatal and neonatal morbidity and Bayley-III results in our study. This is consistent with Ramdin's (299) results who did not detect any link between neonatal or obstetric factors and Bayley-III scores at 16 months in LPT infants. We found a trend for an association between a birth weight < 10^{th} percentile with lower Bayley-III language scores. Small for gestational age is a known risk factor for developmental impairment among preterm and full-term infants (311-313). Recently, small for gestational age has been reported to influence neuromotor outcome at 12 months in LPT infants adversely (104). Kerstjens et al. (2011) (12) found an association between small for gestational age status and developmental delay up to 4 years in MPT infants. We found multiples to have worse results in the cognitive Bayley-III scale results and triplets to have worse results in the motor scale. This corresponds to findings of

previous studies, which stated higher risk for long-term developmental problems after multiple birth (272, 273, 314, 315). Lower birth weight compared to singletons and a higher risk for preterm birth are common explanations for impaired outcome in multiples (274). Since multiples in our study population were not significantly younger at birth compared to singletons, lower gestational age does not explain the adverse neurodevelopmental outcome compared to singletons, although birth weight was significantly lower in our multiples. It is still inconclusive whether being a multiple in and of leads to an increased risk for impaired outcome (274, 316).

Association between GMs and neurodevelopment at 1 year

Neither global nor detailed assessment of GMs at neonatal age was related to Bayley-III results. Manacero et al. (2011) (264) reported an only fair to moderate association between GMs assessed at 36 weeks and motor outcome at 14 months. Contrary to our results, previous studies (197, 255, 261, 317) found significant correlations between writhing GMs and the motor performance at 1 year. However, in the present study, all MLPT infants with normal writhing GMs already normalized before the age of FMs and demonstrated normal motor scores at 12 months. This is comparable to others (255, 261) who reported high specificity but low sensitivity of writhing GMs predicting the 12-month motor outcome. In the present study, abnormal writhing GMs were mostly PR. Thus, our results are consistent with Song et al. (2018) (255) suggesting that infants with PR GMs can be expected to have normal motor development at 1 year. The prediction of neurological development is based on developmental trajectories of GMs (123). We assume that all infants with PR GMs had normalized throughout the writhing period as all of them showed normal FMs. Additionally, PR GMs early in life have been stated as not necessarily leading to impaired neurological outcome, as PR GMs have a wide spectrum and a low predictive value, especially if they occur before term-equivalent age (150). However, the outcome at 1 year may be preliminary and impaired neurodevelopment might occur later in childhood.

The detailed assessment of GMs at 3 to 4 months was not related to Bayley-III results, either. Our data are again contrary to others (197, 255, 318, 319) that reported a correlation between GMs at 3 to 4 months and motor performance at 12 months. One reason could be that the infants studied by others were younger (mean gestational age from 29 to 31 weeks) compared to our cohort. In addition, others

reported abnormal or absent FMs in 23 percent to 54 percent of their study population (197, 255, 318) while all our infants had normal FMs. Crowle et al. (2018) (320) also reported a high specificity of GMA at 3 to 4 months regarding the 1-year outcome in a neonatal surgical population. Variable finger movements is one of the postural patterns which normally appear between 11 and 16 weeks post term age (123). Interestingly, we found that our MLPT infants who had a lack of variable finger postures also had lower cognitive Bayley-III scores; even more, their cognitive development at 1 year was more often moderately delayed compared to infants with variable finger postures at 3 to 4 months. With this finding we support Butcher et al. (2009) (193) who found variable finger postures at the period of FM associated with better cognitive outcome at 7 to 11 years old. In contrast to Adde et al. (2016) (319), who reported worse fine motor development at 1 year of age in infants with few finger postures, we did not reveal such an association.

Even though, in the present study, global and detailed scores of GMA were not significantly associated with neurodevelopment at 1 year. We therefore assume that brain dysfunction was mostly of transient nature. We hypothesize that transient abnormalities might have been present not detectable by cranial ultrasound of our infants within the first week. As a limitation of our study we acknowledge that a 1-year outcome assessment is not able to predict motor or cognitive developmental delays or deficits as precise as for the motoric system the 2-years outcome corrected for prematurity does (96). The risk of developmental delay in MLPT infants has not been resolved (35). Altered or damaged brain growth are common complications in very preterm infants, but are supposedly uncommon in late preterm infants (321). It has been suggested that the brain of MLPT infants might be more resilient to damage caused by certain neonatal morbidities or treatment procedures than the brain of more immature infants (116).

Limitations

This research, however, is subject to some limitations. Firstly, not all assessments were performed in all infants included in our study. This was especially true in the last assessment at the corrected age of one year where considerably fewer children participated. It is possible that some of the defaulters had worse Bayley-III scales or

even CP. However, it can be assumed that the pediatricians in private practice would have referred the children to our clinic if developmental problems had occurred.

Another limitation is that we cannot provide proper long-term follow-up. The short follow-up period made it difficult to determine the presence of a developmental delay. The clinical picture of CP at one year of age is not always distinct, and some disorders may not be diagnosed until later in childhood (322). Furthermore, we do not know whether our infants received outpatient physiotherapy or vaccinations according to the vaccination schedule as this information is only available to the pediatricians in private practice.

The current study only included LPT infants who had been admitted to the NICU. The neurological development of apparently healthy LPT infants discharged to their mothers after birth are not known because they were not followed up.

Conclusion

In conclusion, we have shown contemporary neonatal outcome data across the spectrum of moderate and late preterm gestational ages. Our study provides detailed gestational age specific data on neonatal outcomes that could assist neonatologists in individualized risk assessment. At the corrected age of one year, 12.5 percent, or one in eight children, showed moderately delayed development. Based on our findings, we believe that closer observation and follow-up assessments after discharge should not be restricted to the more immature group of preterm infants but should also be considered for MLPT infants.

The knowledge of week-specific risks for neonatal morbidity and the neurological development of MLPT infants can be useful for parental counseling regarding expected outcomes.

Appendix

Appendix 1

Detailed Assessment of General Movements (GMs) During Preterm and Term Age

The GM Trust

Name		**Date of Birth**	
Recording Date		**Postmenstrual Age**	weeks
Behavioural State (Coincidence)	☐ State 2 (Active Sleep)	☐ State 4 (Active Wakefulness)	

Global Assessment	☐ Normal	**Sequence**	☐ 2 variable
	☐ Poor Repertoire		☐ 1 monotonous and/or broken
	☐ Cramped-Synchronised		☐ 0 synchronised
☐ Hypokinetic	☐ Chaotic		☐ 0 disorganised

Detailed Scoring

	Neck	Trunk
	☐ **2 involved in the sequence**	☐ **2 fluent and elegant rotations**
	☐ **1** hardly or not involved	☐ **1** just a few rotations
		☐ **0** almost no rotations
	Upper Extremities	**Lower Extremities**
Amplitude	☐ **2 variable, full range**	☐ **2 variable, full range**
	☐ **1** predominantly small range	☐ **1** predominantly small range
	☐ **1** predominantly large range	☐ **1** predominantly large range
	☐ **1** neither small nor large but monotonous	☐ **1** neither small nor large but monotonous
Speed	☐ **2 variable**	☐ **2 variable**
	☐ **1** monotonously slow	☐ **1** monotonously slow
	☐ **1** monotonously fast	☐ **1** monotonously fast
	☐ **1** neither small nor fast but monotonous	☐ **1** neither small nor fast but monotonous
Spatial range	☐ **2 full space variably used**	☐ **2 full space variably used**
	☐ **1** limited space	☐ **1** limited space
	☐ **0** in one plane only	☐ **0** lifted-released
Proximal rotatory components	☐ **2 present, fluent and elegant**	☐ **2 present, fluent and elegant**
	☐ **1** just a few rotations	☐ **1** just a few rotations
	☐ **0** almost no rotations	☐ **0** almost no rotations
Distal rotatory components	☐ **2 present, fluent and elegant**	☐ **2 present, fluent and elegant**
	☐ **1** just a few rotations	☐ **1** just a few rotations
	☐ **0** almost no rotations	☐ **0** almost no rotations
Onset	☐ **2 smooth and fluctuating**	☐ **2 smooth and fluctuating**
	☐ **1** minimal fluctuations	☐ **1** minimal fluctuations
	☐ **0** predominantly abrupt	☐ **0** predominantly abrupt
Offset	☐ **2 smooth and fluctuating**	☐ **2 smooth and fluctuating**
	☐ **1** minimal fluctuations	☐ **1** minimal fluctuations
	☐ **0** predominantly sudden release	☐ **0** predominantly sudden release
Tremulous movements	☐ **2 absent**	☐ **2 absent**
	☐ **1** unilaterally present	☐ **1** unilaterally present
	☐ **0** bilaterally present	☐ **0** bilaterally present
Cramped components	☐ **2 absent**	☐ **2 absent**
	☐ **1** occasionally present	☐ **1** occasionally present
	☐ **0** predominantly present	☐ **0** predominantly present

Optimality subscores	**Upper extremities (max 18)**		**Lower extremities (max 18)**	
	Neck and Trunk (max 4)		**Sequence (max 2)**	

GM Optimality Score (max. 42) ☐☐☐

Appendix 2

Preterm and Term General Movements

Christa Einspieler, Peter B Marschik and Yayohi Nakajima 2004/2008

Name: _____ State / Coincidence _____

Postmenstrual Age: _____ weeks Recording date: _____

Global judgement

- ☐ Normal
- ☐ Normal, non-optimal
- ☐ PR
- ☐ CS
- ☐ Ch
- ☐ Hypokinetic

Sequence:

- ☐ 2 variable, complex
- ☐ 1 broken (some parts are not involved)
- ☐ 1 monotonous, repetitive
- ☐ 0 synchronised
- ☐ 0 dysorganised

Detailed scoring of Neck and Trunk

	Neck		Trunk	
Rotatory components	involved in the sequence	☐ 2	present, fluent and elegant	☐ 2
	hardly / not involved	☐ 1	just a few rotations	☐ 1
			almost no rotations	☐ 0

Detailed scoring of Limbs

	Upper Limbs		Lower Limbs	
Amplitude	variable, full range	☐ 2	variable, full range	☐ 2
	predominantly small range	☐ 1	predominantly small range	☐ 1
	predominantly large range	☐ 1	predominantly large range	☐ 1
	mainly one range	☐ 1	mainly one range	☐ 1
Speed	variable	☐ 2	variable	☐ 2
	predominantly slow	☐ 1	predominantly slow	☐ 1
	predominantly fast	☐ 1	predominantly fast	☐ 1
	mainly one speed	☐ 1	mainly one speed	☐ 1
Space	variable	☐ 2	variable	☐ 2
	limited	☐ 1	limited	☐ 1
	in one plane only	☐ 0	lifted-released	☐ 0
Proximal rotatory components	present, fluent and elegant	☐ 2	present, fluent and elegant	☐ 2
	just a few rotations	☐ 1	just a few rotations	☐ 1
	almost no rotations	☐ 0	almost no rotations	☐ 0
Distal rotatory components	present, fluent and elegant	☐ 2	present, fluent and elegant	☐ 2
	just a few rotations	☐ 1	just a few rotations	☐ 1
	almost no rotations	☐ 0	almost no rotations	☐ 0
Onset	smooth	☐ 2	smooth	☐ 2
	minimal fluctuations	☐ 1	minimal fluctuations	☐ 1
	abrupt	☐ 0	abrupt	☐ 0
Offset	smooth	☐ 2	smooth	☐ 2
	minimal fluctuations	☐ 1	minimal fluctuations	☐ 1
	sudden release	☐ 0	sudden release	☐ 0
Tremolous movements	absent	☐ 2	absent	☐ 2
	unilaterally present	☐ 1	unilaterally present	☐ 1
	bilaterally present	☐ 0	bilaterally present	☐ 0
Cramped components	absent	☐ 2	absent	☐ 2
	from time to time present	☐ 1	from time to time present	☐ 1
	predominantly present	☐ 0	predominantly present	☐ 0

Optimality score	Upper limbs (max 18)		Lower limbs (max 18)	
	Neck and Trunk (max 4)		Sequence (max 2)	

Optimality Score for General Movements (max. 42) ☐☐

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