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UNIVERSITY

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Abstract

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The four studies included in this thesis were retrospective cohort studies. Study I used data from the perinatal quality register Perinatal Revision South (PRS) to evaluate the ability of routine ultrasound in GW 32-34 to predict SGA compared to examination on indication. Clinical outcome was analysed in relation to the screening method. Study II investigated the cerebroplacental ratio (CPR) predictive ability for adverse perinatal outcome in GW 32-41, using data from a clinical database with Doppler examinations. Comparisons between the performance of CPR compared to its components, pulsatility index (PI) of middle cerebral artery (MCA) and umbilical artery, were performed. Study III and IV studied neonatal outcome (data from PRS) and school performance (data from the Swedish medical birth register and the school grade register) after late preterm birth. The impact of underlying pregnancy-related conditions on the outcomes was investigated.

Screening for SGA with routine ultrasound and measurement of fetal growth improved detection of SGA at birth compared to ultrasound on indication, but no convincing improvement of clinical outcome was detected. The studied Doppler parameters were found to be of no use in predicting asphyxia/mortality in high-risk pregnancies after 32 GW. CPR had high predictive value for SGA at birth. CPR and MCA PI performed equally in predicting neonatal morbidity. Late preterm infants had increased risk for neonatal mortality and morbidity and special educational needs compared to term infants. The risks decreased for each added GW. A linear association was also found between gestational age at birth (GW34-41) and mean grades or summary scores when graduating compulsory school. The underlying medical conditions accounted for a substantial proportion of the perinatal morbidity and the risk for poorer school performance and special educational needs. Among children born late preterm, those born after preterm prelabor rupture of membranes without any other major pregnancy complication were found to be a group of low risk. However, compared to children born at term they had increased risks for respiratory complications and special educational needs.

Key words: Doppler velocimetry, fetal growth restriction, late preterm, perinatal outcome, preterm, , school performance, ultrasound

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“Rivers know this: there is no hurry, we shall get there some day.”
The House at Pooh Corner, A.A. Milne

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List of original papers

I. “Detection of small for gestational age fetuses in the third trimester – a comparison between routine ultrasound examination and examination on indication”. Anna Bonnevier, Karel Maršál, Karin Källén. Manuscript accepted 2 oct 2021. Acta Obstet Gynecol Scand. doi: 10.1111/aogs.14278.

II. “Cerebroplacental ratio as predictor of adverse perinatal outcome in the third trimester”. Anna Bonnevier, Karel Maršál, Jana Brodszki, Ann Thuring, Karin Källén. Acta Obstet Gynecol Scand. 2020;100:497-503.doi:10.1111/aogs.14031.

III. “Underlying maternal and pregnancy-related conditions account for a substantial proportion of neonatal morbidity in late preterm infants.” Anna Bonnevier, Jana Brodszki, Lars J Björklund, Karin Källén. Acta Paediatrica. 2018; 107:1521-1528.doi: 10.1111/apa.14321.

IV. “School performance and special educational needs among children born late preterm.” Anna Bonnevier, Karin Källén. Manuscript submitted. 2021.

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Abbreviations

AC	abdominal circumference
AGA	appropriate for gestational age
AUC	area under curve
BMI	body mass index
CI	confidence interval
CNS	central nervous system
CPR	cerebroplacental ratio
CS	cesarean section
EFW	estimated fetal weight
FGR	fetal growth restriction
GA	gestational age
GW	gestational week
ICD	International classification of diseases
LGA	large for gestational age
MBR	medical birth register
MCA	middle cerebral artery
OR	odds ratio
PI	pulsatility index
PPROM	preterm prelabor rupture of membranes
PRS	perinatal revision south
ROC	receiver operating characteristic
RR	risk ratio
SGA	small for gestational age
UA	umbilical artery

Summary in Swedish

Populärvetenskaplig sammanfattning

Att födas för tidigt, liksom att födas lätt för tiden, är förknippat med ökad risk för sjuklighet och död i nyföddhetsperioden, men också med sämre långtidsutfall, till exempel kroniska lungproblem och lägre utbildningsnivå jämfört med barn som är födda i fullgången graviditet och som är normalstora för graviditetslängden. Den vanligaste dödsorsaken i världen för barn under 5 år är att dö till följd av komplikationer av för tidig födsel. Mycket forskning har ägnats åt de barn som föds extremt eller mycket för tidigt. De senaste femton åren har dock blicken riktats allt mer mot de barn som föds endast några veckor för tidigt, så kallade lätt underburna (födda i graviditetsvecka 34-36). I detta projekt avsåg vi att undersöka om lätt underburna barn hade ökade risker på kort och lång sikt jämfört med barn födda i fullgången graviditet (dvs graviditetsvecka 37-41). Om vi fann en skillnad ville vi studera hur stor del av riskökningarna, på kort och lång sikt, som kunde hänföras till den kortare graviditetslängden och hur mycket som hängde samman med graviditetskomplikationer eller underliggande sjukdomar hos mamman.

Vi studerade också en undergrupp av barn med ökad risk, nämligen de som föds lätta för tiden. Tillväxthämning, som leder till att fostret inte växer optimalt under graviditeten, är i vår del av världen den vanligaste orsaken till dödföddhet i sen graviditet. Att upptäcka och handlägga dessa graviditeter är en av förlossningsvårdens stora utmaningar. Vi undersökte huruvida screening med tillväxtultraljud de sista månaderna i graviditeten, och vid behov ytterligare ultraljudsundersökning med Doppler av fostrets blodflöde i navelsträng och hjärna, kunde förbättra hälsan vid födseln. Resultaten av ultraljuds- och blodflödesundersökningar leder inte sällan till åtgärder inom förlossningsvården, såsom beslut om igångsättning av förlossning och därmed för tidig födsel orsakad av sjukvården. Potentiellt positiva effekter av dessa åtgärder måste ställas i relation till konsekvenser, både kort- och långsiktiga, av att födas något för tidigt.

I det första delarbetet undersökte vi om screening med rutinultraljud i graviditetsvecka 32–34, med skattning av fostrets vikt, är bättre på att förutsäga om barnet kommer att födas lätt för tiden jämfört med om man endast gör ultraljud då man misstänker att det väntade fostret kan vara tillväxthämmat, det vill säga när det finns en medicinsk indikation. Om vi fann en skillnad i de olika strategiernas träffsäkerhet ville vi studera om detta i sin tur ändrade utfallet för de gravida

kvinnorna och deras nyfödda barn, till exempel om risken för akut kejsarsnitt, att födas mycket liten för tiden eller att ha tecken på syrebrist minskade. Vi jämförde den gravida befolkningen i Lund-Malmöregionen med den gravida befolkningen i Helsingborg-Höganäs-Ängelholm under åren 1995–2009. I Lund-Malmö erbjöds alla gravida en screeningundersökning av fostertillväxt med ultraljud, medan Helsingborg-Höganäs-Ängelholm endast gjorde ultraljud på medicinsk indikation. Vi fann att rutinultraljud med tillväxtmätning var ett bättre sätt att hitta barn som föds små för tiden jämfört med ultraljud på indikation. Däremot fann vi inga betydande skillnader i hur det gick för mödrarna och deras barn vid födseln trots att man identifierade ett större antal med tillväxthämning.

Delstudie två undersökte metoder som används i tillägg till skattning av fostrets vikt med ultraljud för identifiering och övervakning av graviditeter där fostret har ökad risk för tillväxthämning. Detta tillstånd hänger ofta samman med en försämrad funktion av moderkakan (placenta). Här tittade vi på graviditeter med hög risk för tillväxthämning där man mellan graviditetsvecka 32 och 41 gjort blodflödesundersökning med Dopplerultraljud i navelsträngsartären liksom i en artär i fosterhjärnan. Vi undersökte hur väl försämrade värden av dessa undersökningar, liksom en kvot dem emellan (cerebro-placentär kvot), korrelerade till att födas lätt för tiden, att födas med tecken på syrebrist eller att dö i nyföddhetsperioden samt att ha en större sjuklighet under första månaden i livet. Vi fann att ingen av blodflödesundersökningarna med Doppler var bra på att förutsäga risken för död eller syrebrist i dessa graviditetsveckor. Den cerebro-placentära kvoten var bra på att förutsäga att födas lätt för tiden.

I det tredje arbetet studerade vi sjuklighet och död i nyföddhetsperioden bland barn födda i graviditetsvecka 34–36, så kallat lätt underburna, jämfört med fullgångna barn. Vi undersökte hur risken för lungsjukdomar, behov av andningsstöd, inläggning på neonatalavdelning, infektioner och neurologiska sjukdomar påverkades av varje veckas ökning av graviditetslängden. Vi utforskade sedan, inom gruppen av lätt underburna barn, hur orsaken till den för tidiga födseln påverkade risken för sjuklighet. Vi fann att orsaken till den tidiga födseln i stor utsträckning påverkade risken och att de barn som föddes efter en för tidig vattenavgång men utan andra allvarligare graviditetskomplikationer hade lägre risk än övriga. När lågriskgruppen av barn som var födda lätt underburna efter för tidig vattenavgång jämfördes med de som var födda i fullgången tid hade de dock en betydligt ökad risk för andningssjukdomar och behov av andningshjälp.

Det avslutande arbetet undersökte sambandet mellan slutbetyg i grundskolan och graviditetslängd för barn födda i graviditetsvecka 34–41. Vi studerade relationen mellan graviditetslängd och slutbetyg, men också sannolikheten att vara inskriven i grundsärskola eller träningsskola. Vi tittade också på risken att få betyg under medelnivå i de enskilda ämnena svenska, engelska, matematik och idrott, eller att inte få något slutbetyg. Vidare analyserade vi hur underliggande sjuklighet hos mamman, eller graviditetskomplikationer, påverkade slutbetygen och risken att vara

inskriven i grundsärskola inom gruppen av barn födda lätt underburna. Barn födda i graviditetsvecka 34–36 hade ökad risk för att vara inskrivna i särskola och att ha betyg under medel i svenska, matematik, engelska och idrott jämfört med fullgångna barn. Precis som i delarbete tre visade sig riskerna påverkas av underliggande sjuklighet, och barn födda lätt underburna efter för tidig vattenavgång, utan övriga graviditetskomplikationer, var även i denna studie en lågriskgrupp jämfört med övriga barn som var födda något för tidigt. När denna lågriskgrupp av barn födda lätt underburna jämfördes med barn födda i fullgången graviditet hade de dock en ökad risk för att vara inskrivna i särskola. Barn som fötts något för tidigt på grund av att de hade medfödda missbildningar eller att de var små för tiden hade störst risk att vara inskrivna i grundsärskola bland de som var födda lätt underburna.

Sammanfattningsvis visade undersökningarna i denna avhandling att tillväxtultraljud under graviditetens sista månader är en bra metod för att hitta foster som inte växer normalt under graviditeten. Vi fann däremot inte att detta påverkade hur det gick för mammorna och barnen vid födseln. Detta kan tala för att de kompletterande metoder eller strategier som används för att veta hur vi bäst ska handlägga en riskgraviditet där vi misstänker tillväxthämning inte är tillräckligt bra. De kompletterande Dopplerundersökningar vi studerade visade sig inte, i vår studie, vara träffsäkra gällande att förutse vilka barn som har en ökad risk för att födas med tecken på syrebrist eller att dö före födseln eller första tiden i livet. Vi fann även att bland de något för tidigt födda barnen så har orsakerna till den för tidiga födseln stor betydelse för hur det går, både som nyfödd men även för skolprestationer på längre sikt. Här visade sig gruppen av barn som föds efter en för tidig vattenavgång men utan andra komplicerande faktorer vara en lågriskgrupp, även om de som nyfödda har ökad risk för andningsproblem. Barn som var födda lätt underburna hade ökad risk att vara inskrivna i grundsärskola. Bland de som var inskrivna i vanlig grundskola var risken att ha något lägre slutbetyg eller betyg under medelnivå i de enskilda ämnena ökad, men dessa skillnader var så små att de rimligtvis inte har någon större praktisk betydelse.

Introduction

Preterm birth and fetal growth restriction (FGR) are both conditions associated with increased risks of perinatal mortality and morbidity, but also with adverse long-time effects on health and cognitive abilities (1-3). Worldwide, 5-18% of all infants are born preterm, the great majority only a few weeks too early, so called late preterm (4, 5). Complications due to preterm birth is the leading cause of death for children under five years of age in the world (6). A considerable proportion of preterm births is further complicated by FGR (7).

Approximately one third of preterm births are iatrogenic, caused by health care providers, and the most common medical indication is FGR, occurring in one third of these cases (7). There is so far no evidence that antenatal detection and induced delivery for late FGR is cost-effective nor that it improves perinatal or long-term outcome (8-12). Thus, clinical management of these pregnancies is a challenge. Elevated risks of adverse perinatal outcome due to FGR, mainly stillbirth, must be weighed against increased risks of iatrogenic preterm delivery (10, 11, 13, 14).

It is also difficult to separate the impact of preterm birth per se and the impact of impaired fetal growth or other pregnancy complications, respectively, on outcome.

This thesis aimed to explore strategies for detection and surveillance of late-onset FGR, after 32 gestational weeks (GW). The project further investigated short- and long-term outcomes after late preterm birth, with special focus on the impact of underlying pregnancy-related conditions.

Fetal growth

Fetal size is dependent on the intrauterine growth velocity as well as the duration of pregnancy. It is determined by several predisposing factors where the placental function plays a central role. Other contributing factors are genetic growth potential, maternal nutrition, infections, environmental factors and fetal structural or chromosomal abnormalities (15). The terminology regarding impaired fetal growth is confusing. Studies refer to small for gestational age (SGA) infants, growth restricted fetuses and infants with low birth weight (<2500 grams).

Placental function

Normal fetal growth requires a well-functioning placenta. Trophoblast invasion and remodelling of the vessel walls of the spiral arteries is crucial for normal placentation. The remodelling of the spiral arteries during the first half of the pregnancy creates a "low-resistance" vascular system with increased uteroplacental perfusion that can meet the needs of the fetus as pregnancy progresses. An impaired artery-remodelling will lead to prevailing high vascular resistance and placental malperfusion associated with pre-eclampsia and FGR (16, 17).

Small for gestational age

Fetuses and newborns are defined as SGA when their size (either estimated by ultrasound or by the actual birth weight) is below a certain threshold for the gestational age (GA) according to a predefined reference curve. There are many definitions of SGA, but the most common in international guidelines is estimated fetal weight (EFW) or abdominal circumference (AC) below the 10^{th} percentile of a predefined reference (18, 19). Other thresholds are weight below the 5^{th} or 3^{rd} percentile. In Sweden the commonly used definition, by both obstetricians and pediatricians, is z-score <-2 (comparable to the 2.3^{rd} percentile) according to the Swedish intrauterine growth curve (20). The etiology of SGA is heterogeneous. Fetuses may be constitutionally small, growth restricted due to structural or chromosomal abnormalities, or suffering from placenta mediated growth restriction. Although there is an association between being born SGA and adverse perinatal outcome, the risks are likely to be most pronounced within the two latter groups.

Fetal growth restriction

FGR is a condition where the fetus does not reach its predefined growth potential. This definition is not very helpful in clinical practice since the clinicians have no information of the hypothetical growth potential. This implicates that not all infants born after pregnancies complicated by FGR will be SGA. A proportion of growth restricted fetuses will be born appropriate for gestational age (AGA), making it even harder to identify them antenatally with available methods (21).

Just as is the case for the term "SGA" there is no consensus on the definition of FGR. The Royal College of Obstetricians and Gynaecologists and American College of Obstetricians and Gynecologists recommend that FGR is defined as an ultrasonographic EFW or AC less than the 10th percentile for GA (18, 19, 22). Another definition was proposed by expert consensus through a Delphi procedure in 2016, differentiating FGR into early- and late-onset FGR with the cut off at 32 GW (23). This latter definition, also proposed by the International Society of Ultrasound in Obstetrics and Gynecology, defines late-onset FGR as EFW or AC

below the 3rd centile in absence of congenital anomalies, or a combination of contributory parameters including the Doppler parameters umbilical artery (UA) pulsatility index (PI) or cerebroplacental ratio (CPR). Then at least two of the following criteria should be present: 1) AC and/or EFW <10th centile. 2) AC and/or EFW crossing centiles >2 quartiles on growth centiles (non-customized). 3) CPR <5th centile or UA PI >95th centile (24).

Early- and late-onset FGR are two conditions with different characteristics. The former is a rare condition, occurring in 0.5-1% of all pregnancies, highly associated with maternal hypertensive disease of pregnancy, typical histopathological findings in the placenta, abnormal umbilical Doppler measures and high perinatal mortality and morbidity risks. Late-onset FGR, is much more common, occurring in 5-10% of all pregnancies, more difficult to detect and differentiate from physiologically small fetuses. Abnormal umbilical Doppler findings are rare, the association with preeclampsia is weak and the perinatal mortality and morbidity risks are elevated although lower than in early-onset FGR (12, 23-25).

Pregnancies complicated by FGR are considered high risk compared to pregnancies with normally grown fetuses. FGR is estimated to be present in 30 % of preventable stillbirths (26, 27). Infants born growth restricted are at increased risk of perinatal morbidity, but also morbidity during childhood and as adults (28-32). They may have adverse neurodevelopment and poorer academic achievements (33-35).

Fetal circulation and hemodynamic changes in FGR

The fetus receives nutrients and oxygenated blood from the placenta by the umbilical vein. The blood passes the ductus venosus, one of the three fetal shunts that closes after birth, through the inferior vena cava to the right atrium of the heart. Most of the oxygenated blood then passes the second shunt, foramen ovale, into the left atrium, then into the left ventricle to the aorta and further to the brain and the systemic circulation. Deoxygenated blood from the fetus is transported through the right atrium and ventricle, to the pulmonary trunk and through the third fetal shunt, ductus arteriosus, and the descending aorta through the two umbilical arteries back to the placenta.

A growth restricted fetus suffers from low nutrient supply and hypoxia (36). As the condition aggravates the fetus will respond to its intrauterine environment with a series of physiological changes. These adaptations will increase the chance of fetal survival. Unfortunately, they may have negative long-term effects leading to chronic diseases and adverse neurocognitive development (31, 32, 37).

The response to hypoxia will be a prioritization of blood supply to the brain, adrenal glands and heart at the expense of reduced blood supply to kidneys, skeletal muscles and gastrointestinal organs (37, 38). Some of the adaptive changes have immediate effects that can be observed antenatally and used in surveillance of the pregnancies

with suspected FGR. The increased blood supply to the brain is enabled by intracerebral vasodilatation and can be detected by Doppler ultrasound examination of the middle cerebral artery (MCA) as changed blood velocity waveform, the so called “brain sparing effect”. The diastolic velocity will increase and consequently the PI will decrease (39).

Another hemodynamic adaptation is the increase in the blood flow from the umbilical vein via ductus venosus, foramen ovale to the left atrium and left ventricle. This will increase the cardiac output. When the situation deteriorates changes in the ductus venosus waveform can be detected with Doppler ultrasound and be used in decision making for timing of delivery (40, 41).

Screening for SGA

Strategies to estimate intrauterine fetal size and growth vary. Serial measurements of symphysis-fundus height are routine in many countries despite the unsatisfactory detection rate (42, 43).

Another strategy is to screen for SGA fetuses by estimating fetal weight or fetal AC as a part of a third trimester routine ultrasound examination, but no randomized trials have shown that routine ultrasound improves perinatal outcome compared to other strategies (8). Several guidelines recommend selective ultrasonography when risk factors for giving birth to an SGA-infant are present, e.g., former pregnancy complicated by FGR, essential hypertension or clinical suspicion of FGR (18, 19).

There are several studies on screening for growth restriction in the first or second trimester with a combination of uterine artery Doppler velocimetry, biochemical analyses, and maternal characteristics. This early screening has not yet proved to be an effective tool in detecting late-onset FGR (12, 44, 45). Individualized growth assessment to differentiate fetal growth into a certain number of growth patterns, hereby distinguish infants with elevated risks, is another strategy proposed (46, 47).

Doppler ultrasound

The Doppler effect was described in 1842 by Christian Doppler. In the late 1970s Doppler ultrasound examinations were introduced in obstetrics and are nowadays routine in surveillance of high-risk pregnancies (48, 49). The standard method used to describe the blood flow velocity waveform in fetal and umbilical vessels is PI (50).

PI is defined as: $PI = \frac{v_{max} - v_{min}}{v_{mean}}$

V_{max} is the peak systolic velocity, v_{min} the minimum diastolic velocity and v_{mean} is the mean velocity over the heart cycle.

Umbilical artery Doppler

Two umbilical arteries transport deoxygenated blood from the fetus to the placenta. In the normal fetoplacental circulation the resistance will decrease with increasing GA implying that the UA PI must be evaluated according to reference values taking GA in account (51).

When the resistance in the utero-placental vascular system remains high despite increasing GA, as in the case of abnormal placentation and placenta insufficiency, it will result in a higher than normal UA PI, reflecting a higher velocity of the blood flow in systole and a lower in diastole. With increasing resistance, end-diastolic blood flow becomes absent or even reversed, so called ARED flow, leading to a substantial decline in placental function.

The use of UA Doppler in surveillance of pregnancies with suspected FGR decreases risks of adverse perinatal outcome (52). However, in late-onset FGR the occurrence of abnormal UA PI is rare and search for other methods for monitoring these pregnancies is proceeding.

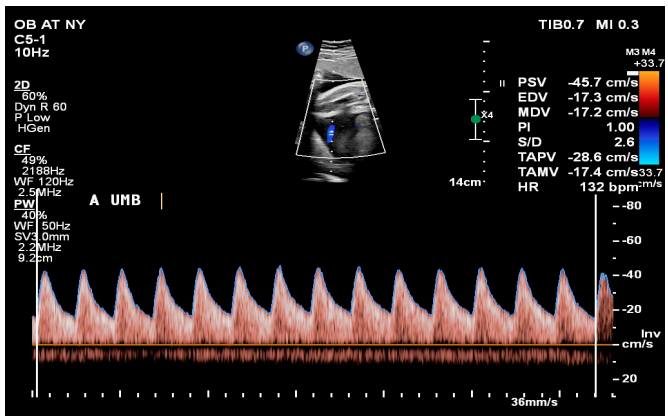

Figure 1. Doppler recording of blood flow velocity from the umbilical artery in gestational week 36. Normal blood flow velocity waveform with positive diastolic velocity and normal pulsatility index.

Middle cerebral artery Doppler

In a situation of fetal blood flow redistribution, as in the case of hypoxia, the intracerebral vessels dilate and blood flow to the brain increases, the “brain sparing effect”. This can be assessed by Doppler examination as higher blood flow velocities in diastole, resulting in a lower MCA PI (39).

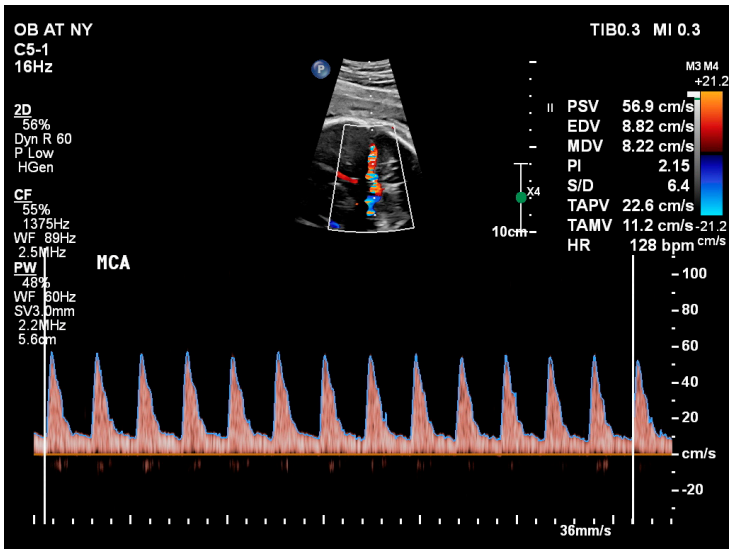

Figure 2. Doppler recording of blood flow velocity from the middle cerebral artery in gestational week 36. Normal pulsatility index.

Cerebroplacental ratio

CPR is defined as MCA PI divided with UA PI and is thought to reflect both the fetal hemodynamic redistribution and the increase in placental resistance (53, 54). Fetuses with an abnormal MCA and/or UA PI will consequently have an abnormal CPR, but MCA and UA PI in the lower and upper range of the reference curve, respectively, will also result in an abnormal CPR. It is rare that UA PI is abnormal in late-onset FGR due to the large compensatory capacity of the placenta (55). Since more subtle changes in the UA PI in combination with signs of brain sparing generate an abnormal CPR it has been suggested to be a better predictor for adverse perinatal outcome in late FGR compared to its components alone. The first studies of CPR appeared in the early 1990s (54). Since then, many studies have been published and the results are inconsistent (56-58). It has been suggested that the reversed ratio, so called umbilical-cerebral ratio (defined as UA PI divided with MCA PI) is to prefer (59). The great heterogeneity of reported CPR cut-off values, and the risk of publication bias have been pointed out by several meta-analysis (60-62). There is an ongoing debate on the usefulness of this Doppler parameter.

Fetal biometry

By two-dimensional ultrasound, EFW can be assessed by different formulas estimating fetal growth of the head, body (abdomen) and femur. Internationally the formula of Hadlock is often used (63), incorporating measures of biparietal diameter, abdominal circumference, and femur length. In study one and two of this

thesis the EFW was calculated according to the formula of Persson and Weldner (64), which includes fetal biparietal diameter, measured from the outer edge of the proximal parietal bone to the inner edge of the distal parietal bone (65), femur length (66), and mean abdominal diameter (67). The obtained EFW was then compared to the Swedish ultrasound based intrauterine growth curve according to Maršál et al (20).

Short-term consequences of late FGR

FGR increases the risk of stillbirth and neonatal morbidity compared to fetuses with normal growth (3, 14). The risks for neonatal morbidity are elevated at all gestational ages (68), and the infants with the most severe growth restriction are at highest risk (69). The risk for stillbirth is highest among undiagnosed fetuses (14). Studies reveal that growth restricted infants more often suffer from hypoglycemia, hyperbilirubinemia, hypothermia, respiratory distress syndrome, intraventricular hemorrhage, necrotizing enterocolitis, and morbidity related to hypoxic events compared to non growth-restricted infants (1, 3, 68).

Long-term consequences of late FGR

There is evidence that impaired fetal growth has influence on the cardiovascular system and increases the risks for cardiovascular disease and type 2 diabetes later in life (28-32, 37). Just like in the case of neonatal morbidity this association depends on low birth weight in relation to GA, and can be found across the whole range of birth weights, i.e., it is not only an effect of preterm birth. Deficient nutrient and oxygen supply will generate several changes in the fetus; the hemodynamic changes have been described earlier, but metabolic and structural changes with persistent effects may also occur. The fetus will slow down cell division resulting in a reduced number of cells in certain organs, e.g., in pancreatic tissue, with permanent changes in the body (31, 32).

The association between growth restriction and poorer neurocognitive outcome is also well established (33-35). Several studies have reported poorer neurocognitive tests during childhood and poorer academic performance in adulthood. The cause of this association is not completely clarified but both metabolic and morphologic changes seem to be of importance. Despite this association it is not yet established that antenatally detected growth restricted fetuses have better outcome than those born undetected (10, 70).

Gestational age and preterm birth

Preterm birth is defined as birth before 37 completed GW with the sub-categories of infants born extremely (<28 GW), very (GW 28-31), moderately (GW 32-34) and late (GW 34-36) preterm. The incidence of preterm birth ranges from 5% to 18% in the world and the rates increase (4, 5). In Sweden the incidence of preterm birth in 2019 was 5.8%. The incidence has been stable during the last decade and is rather declining than increasing (71).

Normal duration of gestation is 37^{+0} to 41^{+6} $GWs^{+days.}$ Lately, this arbitrary definition of GA into preterm, term and post term with non-physiological cut-offs has been questioned in favour of an approach to look on GA as a continuum (72). Numerous reports, both on neonatal morbidity risks and risk of adverse neurodevelopmental outcome, show a linear association between risks and GA, persisting into term without thresholds.

Table 1. Gestational age classification

Classification		Gestational weeks+days	Infants born in Sweden 2019* n (%)
Preterm	Extremely preterm	<28+0	1076 (0.9)
	Very preterm	<32+0	
	Moderate	32+0-33+6	5468 (4.7)
	Late preterm	34+0-36+6	
Term	Early term	37+0-38+6	103 337(88.4)
	Full term	39+0-40+6	
	Late term	41+0-41+6	
Post term	Post term	≥42+0	6932 (6.0)

***Live born and stillborn infants registered in the Swedish Medical Birth Register (71)**

There are different causes of preterm birth. Approximately two-thirds of preterm births in the world are spontaneous, occurring after preterm labor or preterm prelabor rupture of membranes (PPROM) (73, 74). It is estimated that one third of preterm births are iatrogenic, caused by induction of labor or prelabor cesarean delivery for a variety of fetal and/or maternal indications, such as FGR, preeclampsia and maternal diabetes (73). Preterm birth is a leading cause of neonatal mortality and morbidity, but also an important risk factor for morbidity later in life and for learning difficulties. The risks for adverse outcomes decrease with each GW along the full spectrum of GA, from extreme prematurity till full term pregnancy (75, 76). It is therefore an important goal to reduce preterm births, both spontaneous and iatrogenic. The impact of extremely and very preterm birth on neonatal morbidity and cognitive ability is extensively studied in several cohorts, e.g., the

extremely preterm infants in Sweden study (EXPRESS) (77, 78). During the last 15 years there has been a growing interest in late preterm births, accounting for three quarters of all preterm deliveries.

Late preterm births

In 2005 there was a consensus decision to change the nomenclature of infants born in 34^{+0} – 36^{+6} $GW^{+\ days}$ from "near term" to "late preterm" in an attempt trying to change the attitude among obstetricians and neonatologists (79). That was an answer to a steadily increasing number of late preterm births in the world, and a growing awareness of the challenges these infants face (80-82). The last six weeks of gestation represent a critical period for fetal maturation and growth. Since then, more studies have confirmed higher risks for neonatal morbidity and mortality, childhood asthma, cerebral palsy, neuropsychiatric diagnoses, neurodevelopmental disabilities, and underperformance in school among children born late preterm compared to children born at term (2, 83-86). The incidence of late preterm birth varies in the world. In Sweden the incidence is comparatively low. In 2019 moderate and late preterm infants accounted for 4.7% of all live-births which implies that consequences of late preterm birth will affect a substantial number of individuals causing great suffering for families and considerable costs for the society (71, 87). Nevertheless, it is important to remember that most infants born late preterm will have an uncomplicated outcome.

Neonatal mortality and morbidity after late preterm birth

Late preterm infants have increased risks for neonatal mortality and morbidity compared to infants born at term, and the risks decrease with each GW increment (88, 89). Infants born late preterm are more likely to die within their first year of life (89-92). A French study detected an almost doubled risk, while an American study showed a three-fold higher mortality rate among infants born late preterm compared to infants born at term (91, 92). The typical neonatal morbidities associated with preterm birth such as intraventricular hemorrhage, retinopathy of prematurity, bronchopulmonary dysplasia, periventricular leukomalacia and necrotizing enterocolitis are rare among late preterm infants. However, they have elevated risks for other adverse neonatal outcomes compared to term infants. They suffer from respiratory problems, hypoglycemia, hyperbilirubinemia, apnea, temperature instability, feeding difficulties and re-hospitalization to a higher extent then term infants (80, 85, 89, 93).

Respiratory complications are the most common morbidity among infants born late preterm, including respiratory distress syndrome, transient tachypnea of the newborn, pneumonia, and persistent pulmonary hypertension (94, 95). The risk for

respiratory complications decreases with increasing GA among infants born late preterm or early term and seems to be associated to the prematurity per se (86, 93). A systematic review including 22 studies (29 375 675 late preterm infants) reported on increased risks for respiratory complications among infants born late preterm, and the risk for respiratory complications approximately halved for each GW within the late preterm period (86). This is in concordance with the third study in this thesis. The same association was found in a French study, where a halving of the respiratory complication risk was seen until full term gestation (93).

The third trimester of pregnancy represents an important period in the development of the lungs, and their growth during the last months of pregnancy are impressive. At 34 GW the lungs have reached less than 50% of their final volume and important stages in the development of the lung take place in the transition from the so-called saccular phase (from GW 24 until term) to the alveolar phase (from GW 36 until 2-3 years of age). The formation of primitive alveoli begins at the end of the saccular phase and surfactant production starts. In case of late preterm birth, these important processes are interrupted, and the infant is born with a more or less structurally immature lung and at best a marginally sufficient surfactant pool. This makes it more difficult for the infant, who has relatively weak respiratory muscles and a compliant chest wall, to establish and retain lung gas volume, in turn a prerequisite for opening of the pulmonary circulation and achieving a normal oxygen saturation of the blood. Also, incompletely developed epithelial sodium channels leads to re-entry of liquid into the airspaces and a delayed liquid clearance from the lung. The clinical picture may have features of both respiratory distress syndrome (surfactant deficiency), transient tachypnea of the newborn ("wet lung"), and sometimes persistent pulmonary hypertension. There is also evidence that long-term lung function may be compromised, especially if the clinical course is complicated by respiratory tract infection (94-99).

Neurodevelopmental outcomes after late preterm birth

Children born late preterm are at higher risk for neurodevelopmental problems, special educational needs and poor academic performance compared to children born at term (76, 100-103). Two Swedish studies by Lindström et al. found increased risks for neuropsychiatric diagnoses and mental illness among children and adults born late preterm compared to those born at term (104, 105). This is in concordance with a recently published large Danish national cohort study (106). However, there are also studies indicating that late preterm infants have no disadvantage in long-term cognition and behavioural development (107-109). The reported risk estimates differ considerably between studies and that could, to a certain extent, depend on the variety of reported outcome measures and different ages at follow-up (103). The origin of long-term neurodevelopmental problems is

probably multifaceted: First, the prematurity itself, since the last six weeks of pregnancy are a critical period for brain growth and maturation. At 34 GW the brain has reached 65% of its weight at term, the cortical volume will increase with 50% during the late preterm and term period and crucial cerebellar development will happen (110, 111). Second, neonatal morbidity related to late preterm birth, e.g., hypoglycemia, hyperbilirubinemia and hypoxia might have negative effects on the vulnerable preterm brain. Finally, the underlying cause of the preterm delivery, e.g., FGR, infection, and congenital malformations may have adverse effects on fetal brain development (83, 110).

Aims

The aims of the thesis were to investigate short- and long-term outcomes after late preterm birth and to study a sub-group of pregnancies contributing to a large number of iatrogenic late preterm births, those complicated by suspected late-onset fetal growth restriction.

Specific aims:

I. The primary aim was to evaluate SGA detection rates obtained with routine ultrasound examination of fetal weight in GW 32-34 compared to the rate achieved with a risk-based method, using ultrasound examination on indication. The secondary aim was to investigate the clinical outcome in relation to the screening method, with a special focus on the sub cohort of infants born SGA.

II. To investigate the ability of cerebroplacental ratio (CPR) to predict adverse perinatal outcome in GW 32-41. Another aim was to evaluate if CPR had a better predictive value than its components: middle cerebral artery pulsatility index and umbilical artery pulsatility index.

III. To study the risk for neonatal morbidity after late preterm birth compared to birth at term and the impact of maternal and pregnancy-related conditions and gestational age itself on the risk estimates.

IV. To investigate the association between school performance at the age of 16 years or not being enrolled in compulsory school and gestational age among infants born in GW 34 to 41, with special focus on late preterm birth and the impact of underlying pregnancy-related conditions.

Material and Method

Epidemiological methods

In Sweden every resident who is registered in the Swedish Population Register receives a unique personal identification number. The Swedish authorities administer several national registers of the entire population including information on migration, birth and death, education, health care, employment and income. The personal identification number makes linkage between different registers at an individual level possible. The registers are an important source for epidemiological studies. The four national registers used in this study as data sources are presented briefly later.

There are several ways to design a study and analyse effects of exposure or treatment on an outcome. In epidemiology, studies can be classified as interventional/experimental or observational. Intervention studies interfere with participants e.g., giving them different treatments and then analyses the outcome. A common experimental study design is the randomized controlled study. Observational studies are divided into cross-sectional or longitudinal and the study design can be cohort- or case-control. Depending on how data is obtained they are prospective or retrospective (112).

In this thesis all four studies are observational, retrospective cohort studies.

However, even though the studies are retrospective the analysed exposure data was collected prospectively and not biased by the pregnancy outcome. For example, data on maternal smoking, weight and height in the current registers are gathered at the woman´s first visit to the antenatal clinic. This is more reliable than if these data should be collected after the woman gave birth when the pregnancy outcome might bias the information.

Data sources

The Swedish Medical birth register

The Swedish Medical Birth Register (MBR), kept by the Swedish National Board of Health and Welfare, was established in 1973 and contains prospectively collected data on approximately 96-99% of all births in Sweden since then (113, 114). It is mandatory for every health care provider to report certain predetermined information from the prenatal, delivery and neonatal care. All pregnant women in Sweden are offered free antenatal care. At the first antenatal visit, information regarding the women's weight and height, smoking habits, chronic diseases, and use of medical drugs are gathered and reported to the MBR. Information on maternal smoking and body mass index (BMI) is available in MBR from 1983.

Diagnoses from the obstetrical and neonatal care are recorded using International Classification of Diseases (ICD) version 8 (1973-1986), version 9 (1987-1997), and version 10 (1997 and onwards), with the exception of the region of Skåne who changed from ICD-version 9 to 10 in 1998. For a number of conditions check boxes are used.

The Swedish School grade register

The School Grade Register, kept by Statistics Sweden, started 1988 and contains data on all school grades for each child leaving the Swedish compulsory school, usually at the age of 16 years. Municipal, and since 1993 also private schools, are obliged to register the grades yearly. Children fulfilling criteria for intellectual disability do not enter the Swedish compulsory school. They are educated in special schools and are not reported to the School Grade Register. Sweden has changed the grade system twice since the school grade register was founded, 1998 and 2015.

Swedish Educational Register and the Total Population Register

The Swedish Educational Register and the Total Population Register are both kept by Statistics Sweden. The educational register contains data on the highest final educational level for all Swedish citizens since 1985. The Total Population Register started in 1968 and includes information on date of death, immigration and emigration. The calculated coverage of the register is high, 100% of all deaths and 91-95 % of migration are estimated to be reported (115).

Perinatal Revision South

The quality register Perinatal Revision South (PRS), founded in 1994, contains data from all obstetric and neonatal units, including antenatal maternal care in the Southern Healthcare Region of Sweden (116). Medical conditions and diagnoses were reported through check boxes and by ICD-codes. Information about tocolytic and steroid use is available in the register from 2005.

Clinical database of Doppler examinations

All obstetric Doppler examinations performed at the Laboratory for Obstetric Doppler Velocimetry at Lund University Hospital since 1995, and at the University Hospital of Malmö since 1990 are registered in a clinical database.

Hierarchical system

In study three and four, we aimed to evaluate the impact of underlying fetal and maternal medical conditions and pregnancy complications on neonatal morbidity risk and risk of special educational needs and overall school performance among infants born late preterm. A hierarchical classification system was developed and the hierarchies were arranged by severity and probability as a cause of preterm birth. In many pregnancies more than one of the considered complications are present, but by making the classification hierarchical one has to decide which one is the most probable cause of the preterm birth. Analyses were made within the cohort of late preterm births, allowing us to evaluate conditions, e.g., PPROM, only present in preterm births. Another advantage with this analysis is that it takes in account the fact that we believe that each condition present in premature birth is likely to be more severe than the corresponding condition at term birth.

The system allows each infant to appear in one group only. The group of infants born with congenital malformations were put first to exclude the possibility of anomalies at birth being a source of bias for the results of the other classification-groups. The second group were pregnancies complicated by antepartum hemorrhage, since we assume that in case of e.g., placental abruption this will be the immediate cause of a preterm birth even though other conditions could be present, such as hypertensive disease. The rationale for putting pregestational diabetes as group three was that this group is comparatively small and even though it is most likely that pregestational diabetes itself will not be the main cause of a preterm birth the condition will even in presence of hypertensive disease or PPROM have a major impact on the neonatal morbidity. Therefore, we did not want interference from infants to diabetic mothers among the subsequent hierarchical groups. Hypertensive disease of pregnancy was chosen as group four followed by

infants born SGA (and none of the previous conditions present such as pregestational diabetes or preeclampsia). Group number six were pregnancies complicated by PPROM. The seventh group, used as a reference group among infants born late preterm, was called “none of the complications listed”. An AGA infant, born after preterm labor following an uncomplicated pregnancy, would belong to this group.

For information regarding the ICD-diagnoses considered, see table 2.

Table 2. ICD-diagnoses considered in the hierarchical classification system.

Hierarchical group	Explanation	ICD-8	ICD-9	ICD10
1. Congenital malformations	Congenital malformations except congenital deformities of hip, undescended testicles, patent ductus arteriosus, single umbilical artery and accessory auricle	740-759 except:74709,75210, 7556, 74510	740-759 except: 7470, 7525, 7475, 7543, 7441	Q00-Q99 except Q65, Q53, Q250, Q270, Q170
2. Antepartum hemorrhage	Placental abruption, placenta praevia with bleeding,	65177	641	044-045
3.Pregestational diabetes	Diabetes type 1 and type 2 diagnosed before pregnancy	76110	6480	O240-0241
4. Hypertensive disease of pregnancy	Essential and gestational hypertension, preeclampsia, eclampsia	637	642	O10, O139,O14
5. SGA,	Birth weight <-2SD			
6. PPROM	Amniotic fluid leakage before onset of contractions	63495	6581-6582	O42
7. None of the complications listed	None of the diagnoses listed present and birth weight ≥-2 SD			

PPROM, preterm prelabor rupture of membranes; SD, standard deviation;SGA, small for gestational age.

Statistical analyses

Diagnostic tests

Diagnostic tests are used to estimate the ability of an examination e.g., an ultrasound parameter or a biochemical analysis to identify a disease/condition. The statistical concepts sensitivity and specificity are often used to describe the reliability of a test. **Sensitivity** is the probability that an individual having the disease will have a positive test (true positive), while **specificity** is the probability that a healthy individual will have a negative test (true negative). The definition referring to the cross-table, table 3, will be: sensitivity =a / (a+b) and specificity = d / (c+d)

Another way to express this is to use the positive and negative predictive value of a test. **The positive predictive value** (PPV) being the probability of an individual with positive test to have the disease and the **negative predictive value** (NPV) the probability of an individual with a negative test to be healthy. Referring to table 3, PPV=a / (a+c) and NPV= d / (b+d).

Screening is an examination with purpose to identify individuals with disease or high-risk of disease among a mostly healthy population in order to offer early intervention to prevent disease or treatment for better long-term prognosis. The optimal screening test should have a high sensitivity i.e., should not miss individuals with disease. The initial test is then often followed by other examinations to confirm disease. A high specificity is important in order to keep down the proportion of false positive results since this will cause both anxiety for the patients and suffering and costs from further examinations.

ROC-curves

Receiver operating characteristic (ROC) curve is a diagram showing the interplay between sensitivity and specificity of a test (figure 3). It could be used on quantitative tests to illustrate how different cut-offs values affect the sensitivity and specificity. Sensitivity (true positive rate) is plotted against 1-specificity (false positive rate). Area under the ROC-curve (AUC) is often used as a measure to express the overall ability of the test to classify individuals as having disease or being healthy, the outcome is binary. In a perfect test AUC is 1.0 with 100 % sensitivity and 0% false positive test results. The line of identity (y=x line), AUC 0,5, represents the chance performance. If a test has AUC<0.5 then chance is better than the test in predicting disease.

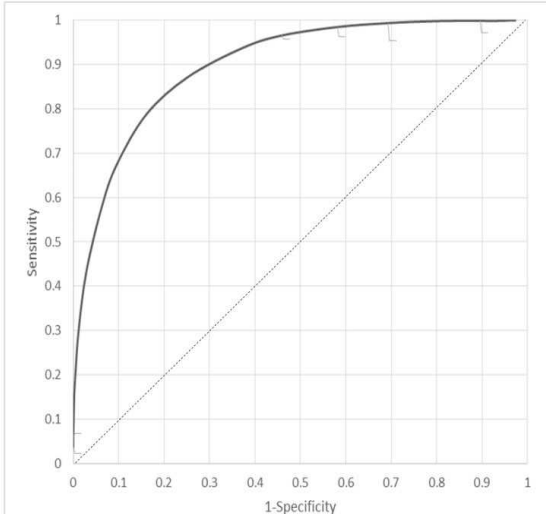

Figure3. ROC curve

Type of outcome variable

The outcome data can be divided into different types: numerical (quantitative), categorical (qualitative) and rates. The type of outcome determines the way data are best displayed and analysed.

A **numerical** variable is either continuous or discrete. A continuous variable might take any value on a continuous scale, e.g., birth weight or height and a discrete variable can have a limited number of values, often whole numbers, e.g., parity. The distribution of a continuous outcome variable can be presented by the measurements mean or median (as the average) and range or standard deviation (as measure of the spread of values).

A **categorical** variable on the other hand is non-numerical and comprises a number of classes, e.g., country of birth. A binary (dichotomous) categorical outcome variable has two possible values, this is a common outcome variable, for example being enrolled in compulsory school (yes/no) or sex (male/female). It is common that categorical outcome variables are transformed to binary variables.

Association between exposure and outcome

When we aim to compare an outcome measure in different exposure-groups such as "respiratory problems" among infants born preterm compared to infants born at term, there are different measures. We can compare absolute differences, for example risk differences, or often used relative differences, by counting the odds or

risk ratios. The odds being the quota between event and no event (a/c). The risk defined as the number of events of the total number, a/ (a+c).

Odds ratio and Risk ratio

Odds ratio (OR) and risk ratio (RR), also named relative risk, are two different measures used to compare odds or risks between exposure groups. If an outcome is rare the odds and the risk ratios will be practically equal since the total number of events (a+c and b+d, respectively) will be almost the same as the number of no events (c and d, respectively). In case-control studies ORs are the method of choice. The RR and OR are calculated as follows, see table 3.

RR= a/(a+c)/b/(b+d)

OR=(a/c)/(b/d)

Table 3. Four field contingency table.

	Event/Disease	No event/Healthy	Total
Exposed/Positive test	a	c	a+c
Unexposed/Negative test	b	d	b+d
Total	a+b	c+d	

Regression analyses

Regression analysis are statistical methods used to investigate how exposure (independent) variables can explain or predict an outcome (dependent variable). Depending on the number of explanatory variables the model will be univariable or multivariable. The nature of the outcome variable will determine which type of regression model should be used. Logistic regression is used for binary outcomes and linear regression for continuous outcomes when the time for follow-up is constant.

Linear regression

This model is used to describe the relationship between an exposure and a continuous outcome, e.g., in study four, how each GW (exposure, x) is associated with the outcome “mean grade percentile” (outcome, y). The analyses will generate a slope coefficient, a higher slope coefficient indicate a stronger association. The linear regression model can estimate the outcome variable from a change in the exposure variable.

Logistic regression

A logistic regression model is chosen when the outcome variable is binary. It is often used to examine the association between a binary outcome and various exposures, and to control for confounding in the analysis. A logistic regression model can predict the probability of an outcome (with two possible results).

Poisson regression model

This regression model can be used to compare rates in different exposure groups, two or more, and to control for confounding. Rates are defined as number of events per unit time. The Poisson distribution describes the number of events during a period given that the events occur randomly and independently of one another. However, if the time unit is a constant (=1) the rate will be equated to the risk and the model can be used to analyse RRs.

Hypothesis testing

To examine if a detected difference between groups depends on a true difference or if it is just explained by chance, several statistical tests can be conducted. The tests yield a p-value. The p-value is the probability of getting the observed outcome if the null hypothesis is true. The noll hypothesis defined as no association between exposure and outcome. In other words, the probability is 5 % that we reject the null hypothesis (meaning that the exposure/treatment have no effect) even though it is true.

It is important to remember that differences found between groups can be statistically significant albeit of low clinical importance, as might be the case in large study populations.

Chi-squared test

This method could be used for hypothesis testing when we aim to estimate the differences between expected and observed frequencies. The test assumes a total number of observations of equal or more than 40 and there must be at least five expected observations in every cell in the contingency table. If the hypothesis is true then the frequencies should be similar and the squared difference between expected and observed frequencies will be close to zero. The Chi-squared test will yield a value, given the number of degrees of freedom, (the number of groups -1) x (the number of outcomes-1), that yields a p-value. If any cell in the cross-table have less than five observations then Fisher´s exact test can be used instead.

Mann Whitney U-test

This could be used to estimate whether a continuous outcome variable differs between two groups. The data does not have to be normal-distributed and it is a so called non-parametric test. The test compares the difference between the mean rank, i.e., the actual measures are ranked, which means that the test is less sensitive to extreme values/outliers. The analysis result in a p-value.

T-test

This method compares the means of two groups and can be used if the mean gives a correct description of the center of the values and both groups have a normal distribution or if the both groups are large and. It is the parametric counterpart to Mann-Whitney U-test.

In the describing of statistical methods “Essential medical statistics” by BR Kirkwood was used (117).

Paper-specific methods

I

Data was retrieved from the quality register PRS. We utilized the fact that different perinatal centres in the Skåne region had different antenatal programs for the pregnant women in the use of third trimester routine ultrasound screening during the years 1995-2009. Pregnant women in the catchment area of Malmö-Lund were offered a third trimester routine ultrasound with estimation of fetal weight in GW 32-34 (population A). Pregnant women living in the catchment area of Helsingborg, Höganäs, and Ängelholm were not offered routine ultrasound in the third trimester with assessment of EFW. Instead, they were referred to an ultrasound examination in case of suspicion of FGR, based on a deviating symphysis-fundus curve or presence of maternal risk factors (population B). In population A, 99 265 pregnancies were identified, the corresponding number in population B was 24 868 pregnancies.

The definition of SGA was birth weight z-score <-2 according to the Swedish intrauterine growth curve (20). Fetuses with EFW z-score <-1 at the ultrasound examination were followed up according to local clinical guidelines. The surveillance protocols at the different perinatal centres could have minor differences but were based on the same principles (118). The screening examination was performed between 32^{+0} and 34^{+6} GW^{+days}. We decided to include ultrasound examinations on medical indication in population B between 32^{+0} and 36^{+6} GW^{+days} since the risk-based detection method is not restricted to a limited time span in the same way as the screening examination.

The ability of routine ultrasound to predict SGA at birth was estimated by a ROC curve.

Differences in maternal characteristics between the two populations were compared using Chi-squared-test. Descriptive comparisons between populations regarding continuous outcome measures were performed using Mann-Whitney U test.

To evaluate the clinical outcome in relation to the SGA screening method univariable and multivariable Poisson regression analyses were conducted. Crude and adjusted RRs, with 95% confidence interval (CI), for selected outcome variables were computed comparing the two populations. Analyses were also performed comparing the subcohort of pregnant women participating in the screening with the population with ultrasound on indication.

The outcome measures considered were duration of gestation (preterm or post-term compared to term), start of delivery (cesarean section (CS) before contractions or induction compared to spontaneous), mode of delivery (emergency CS or instrumental vaginal compared to spontaneous vaginal), birth weight z-score (<-3 -

≥-4 or <-4 compared to ≥ -3), Apgar score <7 at 5 minutes (compared to Apgar score≥ 7 at 5 min), UA pH <7.05 (compared to UA pH ≥7.05), early neonatal death (compared to alive at one week).

In the multivariable analysis adjustments were made for maternal age (continuous variable), parity (parity 0 and parity 2+, compared to parity 1), smoking (ordinal, semi-continuous variable: 1=no, 2=1-9 cigarettes per day, 3=more than 10 cigarettes per day) and BMI (continuous variable).

We evaluated the outcome measures in the cohort of infants born SGA and among infants born AGA or large for gestational age (LGA).

Statistical analyses were performed using IBM SPSS Statistics version 26.0. (Armonk, NY: IBM Corp, USA) and Gauss (Aptech Systems Inc., Arizona, USA).

II

Data on Doppler measurements was retrieved from the clinical database of Doppler examinations at the Laboratory for Obstetric Doppler Velocimetry at Skåne University Hospital in Lund and Malmö. Records of 6049 examinations with data on UA PI and MCA PI in 32^{+0}-40^{+6} GW^{+days} between December 1994 and December 2017 were identified. Exclusions were made for multiple pregnancies, major fetal malformations, chromosomal abnormalities, fetal arrhythmias and isoimmunization since the conditions might influence the fetal hemodynamic situation themselves. Records were linked to the quality register PRS to obtain data on perinatal outcome. We further excluded pregnancies with ≥14 days between examination and delivery, post-term delivery and absent or reversed end-diastolic flow at Doppler examination. The latter because that is an established indication for delivery after 32 GW. The study population finally included 1573 pregnancies. Two subgroup analyses were computed, the first subgroup included 1241 pregnancies with trial of labor (prelabor CS was excluded) and the second was a subgroup of 814 pregnancies with spontaneous onset of labor (inductions and prelabor CS excluded).

The Doppler measures are GA specific. Before conducting analyses, the actual values were transformed to GA specific z-scores according to published reference values of Ebbing et al (119). SGA was defined as birth weight z-score <-2 according to the Swedish intrauterine growth curve (20).

We aimed to investigate the predictive ability of CPR on four perinatal outcomes and investigate whether CPR had better predictive value than its components, MCA PI and UA PI.

The primary outcome was a composite outcome for perinatal asphyxia/mortality, defined as at least one of: stillbirths, Apgar score<7 at 5 min, neonatal death during hospitalization, seizures and hypoxic ischemic encephalopathy grades II or III. The secondary outcomes were birthweight SGA (yes/no) among infants with no

asphyxia/mortality, and two composite outcomes of neonatal morbidity among live-born infants born AGA/LGA or SGA, respectively. In the latter two composite outcomes neonatal morbidity was defined as at least one of: admission to neonatal care unit, mild respiratory disturbance, respiratory distress syndrome, meconium aspiration syndrome, bronchopulmonary dysplasia, persistent pulmonary hypertension of the newborn, supplementary oxygen at discharge, intraventricular hemorrhage grades 3 and 4, periventricular leukomalacia or seizures.

We used ROC curves to examine the predictive ability of the Doppler measures of the four outcomes. Further analysis was made to examine the variance of each ROC AUC as well as the difference between two dependent ROC AUCs by a method suggested by De Long (120).

Statistical analyses were performed using SPSS Statistics 24 (SPSS Inc., Chicago, IL, USA) Gauss (Aptech Systems Inc., Arizona, USA).

III

Data was retrieved from the quality register PRS. The late preterm study group included 14 030 and the term control group consisted of 294 814 singletons born alive. GA was assessed on ultrasound estimates in the second trimester. Medical conditions and diagnosis were reported to the register using ICD-codes (ninth and tenth revision) and checkboxes.

Differences in baseline maternal and infant characteristics between the study groups were tested using Chi squared-test and Mann-Whitney U-test for binary and continuous outcome measures, respectively.

The outcomes considered were: 1) Neonatal mortality (early and late neonatal death). 2) Central nervous system (CNS) complications (intraventricular hemorrhage grades 3-4, other intracranial nontraumatic hemorrhage of fetus and newborn, hypoxic ischemic encephalopathy grades 1-3, seizures). 3) Respiratory disease (respiratory distress syndrome, transient tachypnea of the newborn, other respiratory distress/mild respiratory disturbancy, mechonium aspiration syndrome, bronchopulmonary dysplasia, persistent hypertension of the newborn, pneumothorax, apnea, unspecified respiratory condition of newborn). 4) Respiratory support (mechanical ventilation, continuous positive airway pressure). 5) Infections: (septicemia, pneumonia). 6) Admission to neonatal unit.

Neonatal outcome was analysed in relation to GA, both within the group of infants born late preterm and between infants born late preterm and term, using simple and multiple logistic regression analyses. In the analysis adjustments were made for year of birth (continuous variable), maternal age (continuous variable), parity (parity 0 and parity 4+, compared to parity 2-3), smoking (ordinal, semi-continuous variable:

1=no, 2=1-9 cigarettes per day, 3=more than 10 cigarettes per day), BMI (continuous variable) and infant gender (male/female).

To explore the impact of underlying maternal and pregnancy-related conditions on neonatal outcome within late preterm births a hierarchical system was developed. The classification system is explained earlier in the method-chapter. We used multiple logistic regression analyses to compute ORs for the neonatal outcomes (except mortality due to small numbers) for different classification groups in the hierarchical system compared to the seventh group in the hierarchy for which none of the reported complications were reported. We computed three analyses, crude OR, adjusted OR and finally, a restricted model where we included factors with p-value <0.2. Adjustments were made for the same variables as listed above with addition of GA (continuous variable). In the outcomes related to respiratory disease and infection adjustments were also made for CS. In the restricted model adjustments were made as follows: CNS complications: year of birth; Respiratory disease: year of birth, maternal age, primipara, smoking, gender, GA, elective and emergency CS; Respiratory support: primipara, smoking, gender, GA, elective and emergency CS; Infection: year of birth, BMI, GA, emergency CS; Neonatal admission: year of birth, maternal age, primipara, gender, GA, elective and emergency CS.

Statistical analyses were carried out using Gauss software (Aptech Systems Inc, Chandler, AZ, USA).

IV

In the fourth study we aimed to investigate the association between GA at birth and school performance or need for education in special schools for children with intellectual disabilities, with special focus on late preterm birth and impact of underlying obstetric conditions. We intended to measure the mean grades or summary scores as well as four subject-specific school grades (mathematics, English, Swedish, and physical education).

We used data from several national registers, described earlier in the methods chapter. A cohort of singletons (with information on their mother´s personal identification number), born alive in GW 34-41 from 1973 to 2002, was established from the MBR (information on maternal background, pregnancy, delivery, and neonatal period) by the Swedish National Board of Health and Welfare. A linkage was then performed by Statistics Sweden with the school grade register (information on the compulsory school leaving certificate) the total population register (information on date of death or/and emigration) and the educational register (information on maternal highest level on education). The cohort consisted of 2 640 416 children.

Exclusions were made for children who died or emigrated before graduating school.

Sweden changed the grade system twice during the study period. The children completing school between 1988 and 1997 (born between 1973 and 1981) received numerical grades, ranging from 1-5. Their final summary grade was the average across completed subjects. The numerical grades were comparative, meaning that, for each subject, they were expected to have a normal distribution, with three as the mean. The second grade system between 1998 to 2014 (born between 1982 and 1998) had four levels: not passed (0 points) passed (10 points), passed with distinction (15 points) and passed with excellence (20 points) and the final grade a summary score with maximum 320 points. The third system refers to grades from 2015 and onwards (children born in 1999 and onwards). This grade system has six levels: A (20 points), B (17,5 points), C (15 points), D (12,5 points), E (10 points), F (0 points) and the final grade, just like the second grade system, a summary score of maximum 320 points. The grades in system two and three are criterion-referenced. Those grades are not expected to have a normal distribution.

The children completing school 1988-1997 chose between a common or an advanced course in the subjects English and mathematics. In the second and present grade system all children completed the same course in these subjects. Therefore, the results presented for English and mathematics represents system two and three. For the first school grade system RR for choosing common course in these subjects are presented instead.

To evaluate the overall school performance over the three grade systems measured as the mean grades (first grade system) and summary scores (grade system two and three), the original measures were converted into percentile rank units. First, the grade percentiles for each grade system period were determined, and then each child's original grades were converted into unit of percentiles.

Outcome measures: 1) Risk for not being enrolled in compulsory school (proxy for need for education in special school) or leaving school without any grades. 2) Overall school performance measured as mean grades (system 1) or summary score (system two and three), converted into percentiles. 3) Risk of having scores $\leq 25^{th}$ summary score percentile for the corresponding grade system period. 4) Risk of having scores under the median for the corresponding grade system period in the subjects Swedish, mathematics, English, and physical education. 5) Risk of choosing common course, versus advanced course, in English or mathematics (first grade system).

Differences in maternal and infant characteristics between the populations of infants born late preterm and at term were compared using Chi-squared-test, and 95% CI for proportions were obtained using normal approximation.

Crude and adjusted RR for special educational needs, not receiving any grades, or having grades below or above the median in the four selected subjects were calculated, comparing children born late preterm with those born at term. For period one, crude and adjusted RR for choosing common course in mathematics or English were computed comparing children born late preterm to children born at term.

Linear regression analysis was conducted to evaluate the overall effect of GA (GW 34 to 41) on school performance by comparing percentiles of mean grades or summary scores (see above) for each GW.

RRs for binary outcomes were obtained using univariable and multivariable modified Poisson regression analyses. Three analyses were computed: crude RR, adjusted RR with adjustments for maternal age (continuous), year of birth (continuous), infant gender (male/female), parity (nullipara, parous), school-grade system (class variables 1,2,3), the mother´s highest educational level (ordinal, 5 classes), and the mother´s country of birth (Nordic/non-Nordic). Finally, analyses with adjustments for the variables mentioned above were conducted with addition of BMI (continuous) and smoking (yes/no), restricted to births from 1983 and onwards (fully adjusted RRs) since these data are available in MBR from 1983 and onwards. For analyses within the late preterm group, adjustments for GW were also made in all three analyses. Missing values for maternal BMI and smoking were replaced with the overall means.

Within the group of children born late preterm analysis of the effects of underlying obstetric conditions on school performance were evaluated by comparing the risks for not attending compulsory school, or for mean grades/summary scores ≤25th percentile, respectively, between the groups in the hierarchical system of obstetric complications described above in the method-chapter and methods of study III.

Tests of homogeneity of aRRs over k strata were performed where the aRRs were weighted by precision (1/Standard Error of aRRk), and compared to the Chi2(k-1) distribution. Possible linear trends of k independent aRRs were investigated using linear regression, weighted by precision as previously described.

Statistical analyses were performed using Statistical analyses were performed using IBM SPSS Statistics version 27.0. (Armonk, NY: IBM Corp, USA).

Ethical considerations

Data in the studies were deidentified before analyses were performed. The cohorts were also very large, particularly in study I, III and IV, making the ethical consideration regarding personal integrity less of a problem.

Study I was approved by The Swedish Ethical Review Agency on December 9, 2020 (reference no. 2020-06088). Study II and III were approved by the Research Ethics Committee of Lund University, Sweden, 26th February 2015 (reference number 2015/82). Study IV was approved by the Research Ethics Committee of Lund University, Sweden, 26th February 2015 (reference number 2015/82) and the Swedish Ethical Review Agency on July 2, 2020 (Reference number 2020-02983).

Results and Comments

Paper I

Results

In population A (women offered routine ultrasound examination), 99 265 records were identified from the PRS register. Of these, 59 452 (59.9%) pregnancies had undergone a screening ultrasound with measurement of EFW at 32^{+0} - 34^{+6} GW (population A1). Another 3408 women in population A had an ultrasound examination on other indication during 32^{+0}-34^{+6} GW, hence they did not participate in the routine ultrasound screening. In population B (ultrasound examination on indication), 24 868 singleton pregnancies were identified, among them 5792 (23.3%) had an indicated ultrasound for measurement of EFW at 32^{+0} - 36^{+6} GW. Overall, the population demographics of populations A and B were similar. There was no difference in maternal age or body mass index distributions between the populations, but there were more nulliparous women, and less smokers in population A than in population B.

The median GA at ultrasound examination was 32^{+5} GW in population A and 34^{+2} in population B ($p<0.001$). The median GA at delivery did not differ between population A and B (39^{+6}) nor between the subcohorts of infants born SGA (39^{+3} GW). The median birthweight in population A was 3550 g (range: 610-6360 g) and 3.0% of the infants were born SGA compared to population B where the median birth weight was 3530 g (range 995-6110 g) and 3.5% of the infants were born SGA ($p<0.001$).

The ability of routine ultrasound in GW 32-34 to predict SGA was assessed by ROC curve, see figure 4. The overall SGA prediction ability was high, with area under the ROC-curve 0.90 (95% CI 0.89-0.91). The highest ‘height over identity line’ was obtained for the EFW z-score -0.75 (sensitivity 79%, specificity 84% false positive rate 16%). In order to reduce the false-positive rate, the EFW z-score -1.0 was arbitrarily chosen as the optimum cut-off level. At the EFW z-score -1.0, the sensitivity for SGA was 67.3% (95% CI 65.0-69.5%), specificity 90.5% (95 %CI 90.2-90.7%), and false positive rate 9.5% (95 %CI 9.3-9.8%).

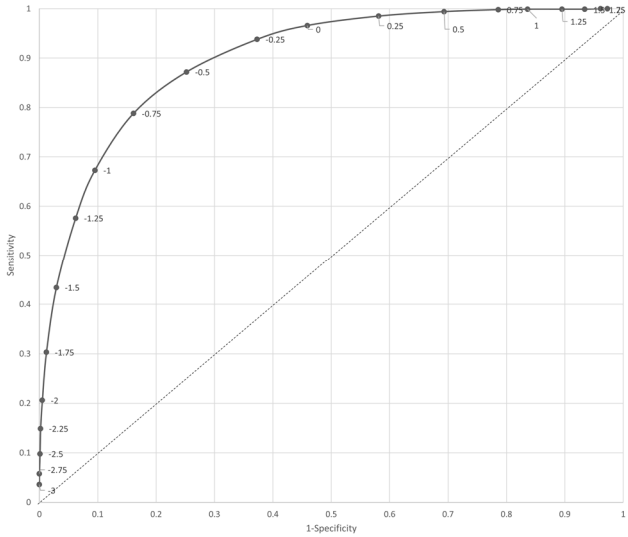

Figure 4. ROC curve for the detection of SGA by EFW z-score cut-off at routine ultrasound examination performed at 32-34 gestational weeks.

Abbreviations: EFW, estimated fetal weight; ROC, receiver operating characteristic; SGA, small for gestational age

Analysis based on the whole population A, irrespective of whether a routine ultrasound scan was performed, revealed that 46.5% (95% CI 44.7-48.3) of all SGA infants were detected antenatally using the cut-off EFW z-score of -1.0, with false positive rate 6.3% (95% CI 6.1-6.4). The corresponding SGA detection rate in population B was 34.3% (95% CI 31.1-37.5) with the false positive rate 3.4% (95% CI 3.2-3.6). Adjusted RR was 1.35 (95% CI 1.22-1.50) for intrauterine detection of SGA in population A compared to population B. For details on detection rates, including those for the subgroup of women participating in screening, see table 4.

Table 4. Detection of SGA infants

	SGA infants								
	Total	Detected antenatally		Non-detected antenatally					
	N	n	%	n	%	RR	95%CI	aRR	95%CI
Routine ultrasound population (A)	2951	1371	46.5	1580	53.5	1.35	1.22-1.50	1.35	1.22-1.49
Scanned population (A1)	1678	1129	67.3	549	32.7	1.96	1.78-2.16	1.96	1.78-2.17
Ultrasound on indication population (B)	860	295	34.3	565	65.7	1.00	Reference	1.00	reference

aRR, adjusted risk ratio; CI, confidence interval; RR, risk ratio; SGA, small-for-gestational age (infant with birth weight z-score <-2.0).

Table 5 and 6 shows comparisons of perinatal outcome between routine ultrasound and ultrasound on indication for all infants (table 5) and infants born SGA (table 6). The risk of being born preterm was lower, and the risk of being born post-term was higher in the population offered screening (A) than in population B (ultrasound on indication). Induction of labor was less likely in population A. The risk for birthweight z-score <-3.0, low Apgar score, and low umbilical artery pH, respectively, was significantly lower in population A compared to population B. There was no difference in perinatal death between group A and B.

Among infants born SGA, no significant difference in the gestational duration was detected between populations A and B. Spontaneous start of delivery was more common and induction of labor was less frequent in population A than in population B. The birthweight distribution and risk of perinatal death among children born SGA did not differ between populations.

Comparisons between the population who participated in the screening program (A1) and population B showed similar results to those for populations A and B.

Table 5. Comparison between routine ultrasound and ultrasound on indication; all infants.

		Routine ultrasound (A) (n=99 265)		Ultrasound on indication (B) (n=24 868)					
		n	%	n	%	RR	95%CI	aRR	95%CI
Gestational duration (weeks)	Preterm delivery (<37)	4588	4.6	1315	5.3	0.88	0.83-0.93	0.87	0.82-0.92
	Term delivery (37-42)	89 124	89.8	22 329	89.8	reference		reference	
	Post term delivery (≥42)	5553	5.6	1224	4.9	1.13	1.06-1.20	1.12	1.06-1.19
Start of delivery	CS before contractions	5169	5.2	1159	4.7	1.08	1.01-1.15	1.08	1.01-1.14
	Induction	6280	6.4	2419	9.7	0.65	0.63-0.68	0.66	0.63-0.69
	Spontaneous start	87 816	88.5	21 290	85.6	reference		reference	
Mode of delivery[a]	Emergency CS	7444	7.9	1690	7.1	1.11	1.05-1.16	1.09	1.04-1.15
	Instrumental vaginal	3742	4.0	1016	4.3	0.94	0.88-1.00	0.92	0.86-0.98
	Spontaneous vaginal	81 112	86.2	21 003	88.6	reference		reference	
	Missing information	1798		0					
Birth weight z-score	<-3 – ≥-4	315	0.32	102	0.41	0.76	0.62-0.94	0.75	0.61-0.93
	<-4	32	0.03	12	0.05	0.67	0.34-1.30	0.64	0.33-1.25
	≥-3	98 918	99.6	24 754	99.5	reference		reference	
Neonatal outcome	5-min Apgar score <7	1101	1.1	353	1.4	0.78	0.69-0.88	0.77	0.68-0.87
	5-min Apgar score ≥7	98 164	98.9	24 515	98.6	reference		reference	
	UA pH <7.05 [b]	1390	1.9	569	2.8	0.69	0.63-0.76	0.68	0.62-0.75
	UA pH ≥7.05 [b]	71 314	98.1	19 925	97.2	reference		reference	
	Perinatal death	326	0.3	84	0.34	0.97	0.76-1.24	0.97	0.76-1.24
	Alive at one week	98 939	99.7	24 784	99.7	reference		reference	

[a] CS before contractions excluded; [b] Percentages and risk estimates based on known values only (population A: n=72 204; missing n=26 561; population B: n=20 494, missing 4374). aRR, adjusted risk ratio; CI, confidence interval; CS, cesarean section; RR, risk ratio; UA, umbilical artery.

Table 6. Comparison between routine ultrasound and ultrasound on indication; infants born SGA.

		Routine ultrasound (A) n=2951		Ultrasound on indication (B) n=860					
		n	%	n	%	RR	95%CI	aRR	95%CI
Gestational duration (weeks)	Preterm delivery (<37)	460	15.6	149	17.3	0.92	0.78-1.08	0.90	0.76-1.06
	Term delivery (37-42)	2309	78.2	674	78.4	reference		reference	
	Post term delivery (≥42)	182	6.2	37	4.3	1.40	1.00-1.98	1.40	0.99-1.96
Start of delivery	CS before contractions	167	5.7	32	3.7	1.41	0.97-2.04	0.75	0.65-0.88
	Induction	475	16.1	188	21.9	075	0.65-0.87	0.75	0.65-0.88
	Soontaneous start	2309	78.2	640					
Mode of delivery[a]	Emergency CS	710	25.5	195	23.6	1.06	0.93-1.21	1.04	0.91-1.19
	Instrumental vaginal	114	4.1	33	4.0	1.28	0.85-1.92	1.20	0.80-1.80
	Spontaneous vaginal	1898	68.2	600	72.5	reference		reference	
	Missing information	62		0					
Birth weight z-score	<-3 – ≥-4	315	11.8	102	13.3	0.89	0.73-1.08	0.88	0.72-1.07
	<-4	32	1.1	12	1.4	0.77	0.40-1.48	0.72	0.37-1.39
	≥-3	2604	88.2	746	86.7	reference		reference	
Neonatal outcome	5-min Apgar score <7	124	4.2	39	4.5	0.93	0.65-1.32	0.86	0.60-1.23
	5-min Apgar score ≥7	2827	95.8	821	95.5	reference		reference	
	UA pH <7.05 [b]	48	2.4	26	4.0	0.60	0.38-0.96	0.58	0.36-0.95
	UA pH ≥7.05 [b]	1956	97.6	625	96.0	reference		reference	
	Perinatal death	73	2.5	15	1.7	1.42	0.82-2.46	1.39	0.80-2.40
	Alive at one week	2878	97.5	845	99.2	reference		reference	

[a] CS before contractions excluded; [b] Percentages and risk estimates based on known values only (population A: n=2004; missing n=947; population B: n=651, missing 209). aRR, adjusted risk ratio; CI, confidence interval; CS, cesarean section; UA, umbilical artery, RR, risk ratio; SGA, small for gestational age.

Comments

FGR is a major risk factor for adverse perinatal outcome and most growth-restricted fetuses are born SGA. Thus, an efficient antenatal screening for SGA fetuses in the third trimester could have a major impact on perinatal health.

The current study showed that third trimester routine ultrasound in GW 32-34 improved the detection of SGA antenatally compared to selective ultrasound, but no convincing improvement in perinatal outcome was identified neither in the total populations nor in the populations of infants born SGA. The results are consistent with other studies. A Norwegian randomized controlled study found that routine ultrasound screening in GW 33 improved detection of SGA from 46% to 80%, compared to ultrasound on indication, but no difference in perinatal outcome was detected (9). Despite reports of high detection rates the 13 trials reviewed in the Cochrane Library in 2015 could not show that routine ultrasound screening for SGA in the third trimester would reduce perinatal mortality or adverse perinatal outcomes in general (8).

One limitation in our study was the lack of detailed information on the clinical protocols for surveillance of suspected growth restricted fetuses used at the different perinatal centres during the study period. A strength of the study was the large size of a non-selected population and that we evaluated the total populations, not only the pregnant women that took part in the screening, since the coverage is a matter of concern for all screening programs. Only 60% of the pregnant women who were offered routine ultrasound in GW32-34 participated in the screening. The screening coverage varied between 57-67% with no time trend, during the study period. Within population A, we compared the characteristics of pregnant women who attended the offered ultrasound screening (population A1) and those who did not. The absolute differences were small although statistically significant due to large numbers. Thus, we have no explanation for the low participation rate in the screening population A.

In this study we evaluated the SGA prediction rates achieved with routine ultrasound in GW 32-34 compared with the corresponding rate using a method with selective ultrasonography when medically indicated. It has been proposed that ultrasound examination in late pregnancy could have positive effects besides measuring the fetal weight e.g., improved detection of structural fetal anomalies or malpresentation. However, the Cochrane review from 2015 found no evidence for this suggestion (8). In the present study we had no possibility to evaluate this topic.

Paper II

Results

After exclusions, 1573 high-risk singleton pregnancies were included, of which 734 (46.7%) were born SGA and 52 (3.3%) died in utero or during neonatal hospitalization, or had postnatal signs of asphyxia. Of the live-born AGA or LGA infants 250 (16.0%) suffered from at least one neonatal morbidity. The corresponding number for SGA live-born infants was 431 (27.6%). For information on characteristics of the study population and perinatal outcome see table 7.

Figure 5 shows the ROC curves for the z-scores of the three Doppler variables as predictors of the four outcome measures. The performance in predicting perinatal asphyxia/mortality was poor for all three variables, and did not significantly differ. The ROC AUC for CPR z-scores to predict SGA was 0.73, which was significantly higher than that for both UA PI and MCA PI. The ability of CPR and the MCA PI z-scores to predict AGA/LGA infant morbidity was similar and significantly better than that of UA PI. The predictive capacity of CPR for SGA neonatal morbidity was similar to that for MCA PI. Both were significantly better than UA PI ROC AUC.

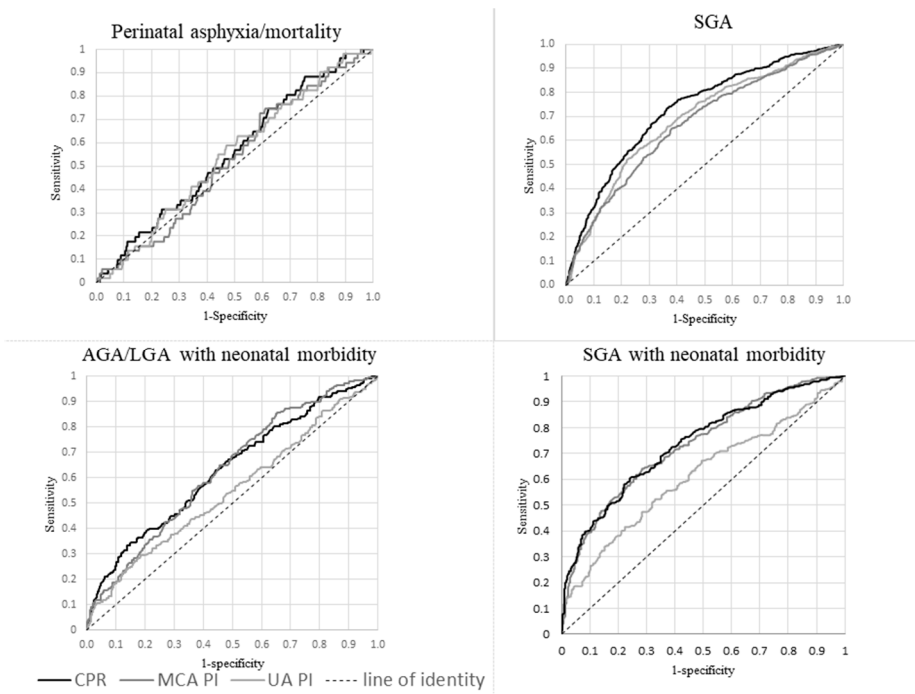

Figure 5. ROC curves of gestational age specific z-scores for CPR, UA PI and MCA PI, respectively, for the four outcomes. Abbreviations: AGA, appropriate for gestational age; CPR, cerebroplacental ratio; LGA, large for gestational age; MCA, middle cerebral artery; PI, Pulsatility index; SGA, small for gestational age; UA, umbilical artery

Table 7. Characteristics of the study population and information on perinatal outcome.Data presented as n (%) or median [range]

		n	%
Maternal characteristics	Maternal age, years	30.0	[14-46]
	<20	43	(2.7)
	≥35	322	(20.5)
	Maternal BMI, kg/m	23.2	[15.4-50.0]
	<18.5	56/1342	(4.2)
	≥30.0	166/1342	(12.4)
	Maternal smoking	222/1431	(15.5)
	Nullipara	944	(60.0)
Interval Doppler examintion to delivery, days		3	[0-13]
Delivery start	Spontaneous	814	(51.8)
	Induction	427	(27.2)
	CS before contractions	332	(21.1)
Delivery mode	Spontaneous	755	(48.6)
	Operative vaginal	49	(3.2)
	Emergency CS	572	(36.8)
	Elective CS	177	(11.4)
	Missing	20	
Gestational age at delivery		37+6	[32^{+0}-41^{+6}]
	GW 32-33	140	(8.9)
	GW34-36	385	(24.5)
	GW 37-39	851	(54.1)
	GW 40-41	197	(12.5)
Infant characteristics	Birth weight,g	2495	[1025-5242]
Infant gender	male	785	(49.9)
Perinatal outcome	Apgar score<7 at 5 min	44	(2.8)
	Stillbirth	9	(0.6)
	SGA	734	(46.7)
	Admission to neonatal unit	681	(43.3)
	BPD	26	(1.7)
	RDS	26	(1.7)
	TTN/mild respiratory disturbancy	34	(2.2)
	Meconium aspiration syndrome	0	0
	IVH grade 3-4, PVL	2	(0.13)
	Seizures	7	(0.4)
	HIE grade 2-3	1	(0.06)
	Death during neonatal hospitalization	6	(0.4)
Composite adverse outcome	Perinatal asphyxia/mortality[a]	52	(3.3)
	AGA/LGA live-born with neonatal morbidity[b]	250/1564	(16.0)
	SGA live-born with neonatal morbidity[b]	431/1564	(27.6)

AGA, birth weight appropriate for gestational age; BPD, bronchopulmnonary dysplasia; CS, cesarean section; GW, gestational week; HIE, hypoxic ischemic encephalopathy; LGA, birth weight large for gestational age; RDS, respiratory distress syndrome; SGA, small for gestational age (infant with birth weight z-score <-2.0); PPHN, persistent pulmonary hypertension of newborn; IVH, intraventricular hemorrhage; PVL, periventricular leukomalacia. [a]Perinatal asphyxia/mortality: Stillbirth, death during neonatal hospitalization , Apgar score <7 at 5 min, seizures, HIE II-III; [b]Neonatal morbidity; At least one of following: Admission to neonatal care unit, BPD, meconium aspiration syndrome, RDS, mild respiratory disturbance/transient tachypnea of newborn, PPHN, IVH grade 3-4, PVL, seizures.

The subgroup analyses showed some differences in the performance of predicting perinatal asphyxia/mortality compared to the analysis of the whole study group. In the subgroup with trial of labor, the ROC AUC was 0.57, 0.60, 0.51 for CPR, UA PI and MCA PI z-scores, respectively. Among pregnancies with spontaneous onset of labor UA PI performed significantly better than CPR and MCA PI. The corresponding ROC AUC was 0.54, 0.60 and 0.46 for CPR, UA PI and MCA PI, respectively. For the other outcomes the results from the subgroup analyses were similar to those from the whole study population. For detailed information on ROC AUC and CI for the whole study population and the two subgroup analyses see table 8.

Table 8. Area under the curve (AUC) for receiver operating characteristics (ROC) curves according to perinatal outcome and Doppler measures for the total study population and two sybgroup analyses.

		UA PI z-score		MCA PI z-score		CPR z-score		Significance of difference, p-value	
		ROC AUC	95% CI	ROC AUC	95% CI	ROC AUC	95% CI	CPR-UA PI	CPR-MCA PI
The whole study population N=1573	Perinatal asphyxia/mortality[a]	0.55	0.48-0.63	0.53	0.45-0.60	0.56	0.48-0.64	0.38	0.082
	SGA (no asphyxia/mortality)	0.69	0.66-0.72	0.67	0.64-0.70	0.73	0.70-0.76	<0.001	<0.001
	AGA/LGA liveborn with neonatal morbidity[b]	0.55	050-0.59	0.63	0.59-0.67	0.63	0.59-0.67	<0.001	0.44
	SGA liveborn with neonatal morbidity[b]	0.62	0.58-0.66	0.73	0.70-0.77	0.74	0.70-0.78	<0.001	0.48
Subgroup: Trial of labor N=1241	Perinatal asphyxia/mortality[a]	0.60	0.51-0.68	0.51	0.43-0.59	0.57	0.49-0.66	0.22	0.012
	SGA (no asphyxia/mortality)	0.69	0.65-0.72	0.66	0.62-0.69	0.72	0.69-0.75	0.002	<0.001
	AGA/LGA liveborn with neonatal morbidity[b]	0.54	0.48-0.59	0.65	0.60-0.69	0.63	0.58-0.68	<0.001	0.23
	SGA liveborn with neonatal morbidity[b]	0.61	0.56-0.66	0.74	0.70-0.78	0.74	0.70-0.78	<0.001	0.50
Subgroup: sponataneous start N=814	Perinatal asphyxia/mortality[a]	0.50	0.50-0.71	0.46	0.34-0.57	0.54	0.42-0.66	0.04	0.008
	SGA (no asphyxia/mortality)	0.69	0.65-0.72	0.67	0.63-0.71	0.73	0.69-0.76	0.001	<0.001
	AGA/LGA liveborn with neonatal morbidity[b]	0.54	0.47-0.60	0.64	0.58-0.70	0.63	0.58-0.69	<0.001	0.40
	SGA liveborn with neonatal morbidity[b]	0.65	0.60-0.71	0.75	0.70-0.80	0.76	0.72-0.82	<0.001	0.26

AGA, appropriate for gestational age; CI, confidence interval; CPR, cerebroplacental ratio; LGA, large for gestational age; MCA, middle cerebral artery; PI, pulsatility index; SGA, small for gestational age; UA, umbilical artery. [a]Perinatal asphyxia/mortality - At least one of following: Stillbirth, neonatal death, Apgar score <7 at 5 min, seizures, HIE II-III; [b]Neonatal morbidity - No perinatal asphyxia/mortality and at least one of following: Admission to neonatal care unit, BPD, meconium aspiration syndrome, RDS, mild respiratory disturbance/transient tachypnea of newborn, PPHN, IVH grade 3-4, PVL, seizures.

Comments

In the second study the aim was to investigate the ability of CPR to predict adverse perinatal outcome in moderate, late preterm, and term high-risk pregnancies and to investigate if the CPR had better predictive value than its components, MCA PI and UA PI. CPR emerged as a suitable predictor of fetal hypoxia in the early 1990s because it was the Doppler parameter that was found to be the best one in following immediate pO_2changes in sheep fetuses (53, 54). Since then, a large number of studies have been published on the performance of CPR regarding adverse pregnancy outcome. The results are contradictory (57, 58, 121, 122).

In our study on a high-risk population of singleton fetuses with positive end-diastolic velocity in the UA born in GW 32-41 CPR showed a relatively high predictive capacity for SGA birthweight. CPR was a better predictor for SGA than its components UA PI and MCA PI. Although statistically significant, the differences between the absolute values of ROC AUC were small, and the clinical importance could be questioned. For perinatal asphyxia or mortality, there was no difference between CPR, UA PI and MCA PI and all three had ROC AUC close to the line of identity, suggesting that none of the three parameters were useful in predicting acute hypoxia or deteriorating chronic hypoxia. For the outcome neonatal morbidity, CPR and MCA PI had better predictive ability among infants born SGA than among infants born AGA/LGA, and these Doppler measures were significantly better than UA PI. Our findings are in concordance with two large screening studies including 30 780 and 6178 pregnancies at 30-34 GW, respectively (57, 123). Significant association between CPR and SGA was reported, but both studies found the CPR to have poor predictive performance regarding adverse pregnancy outcome.

One issue of concern in studies of CPR are the heterogeneity of cut-off values reported. All the investigated Doppler parameters are also gestational-age specific. Since we included pregnancies from 32 GW to 41 GW, we chose to convert the values to z-scores based on the published gestational age specific reference values (119). Another strength was that the study investigated the performance of various Doppler measures by comparing the ROC AUCs, thereby evaluating the total predictive ability. Only few other studies have compared the performance of CPR with that of UA PI and MCA PI, respectively (124, 125).

Paper III

Results

From the quality register PRS, 14 030 live-born singleton infants born late preterm (GW 34-36) and 294 814 infants born at term (GW 37-41) were identified. The median GA among late preterm births was 36^{+0} and among term births 39^{+6} GW^{+days}. Mothers who gave birth late preterm were more often <20 years, ≥ 35 years, smokers, nulliparous, or suffering from underweight or obesity than mothers who gave birth at term. The infants born late preterm were more often born with malformations, were more often of male gender, more often small and large for gestational age and more often had Apgar scores <7 at 5 minutes compared to infants born at term. Infants born at term more often had UA pH <7.1 at birth. Nearly half (45.8%) of infants born late preterm were admitted to a neonatal unit, of which 32 % were admitted for more than one week. The corresponding numbers among infants born at term were 6.0% and 1.6%, respectively. The pregnancies resulting in a late preterm delivery were more often complicated by preeclampsia, diabetes (pregestational and gestational), poly- and oligohydramnios and amnionitis.

The emergency CS rate was 22.3% among late preterm births. At the beginning of the study period (1995-1999) the rate was 19.8%, increasing to 24.1% at the end of the period (2010-2013) ($p<0.001$). Simultaneously, the induction rate decreased with the corresponding amount. The elective cesarean section rate was stable over the study period (approximately 5%). The emergency CS rate was 6.5% among term births.

Overall, infants born late preterm had increased risks for all the investigated outcomes compared to infants born at term. The adjusted ORs ranged from 2.3 for infections to 13.1 for need of admission to neonatal unit. When analysing the impact of GA within late preterm births, the risk significantly decreased with increasing GA for the outcomes neonatal admission, respiratory disease, infections and respiratory support. For neonatal death and CNS complications the differences were not statistically significant. Frequencies and ORs are displayd in table 9.

Tabl 9. Impact of gestational age on neonatal outcome

	GW34		GW35		GW 36		GW 37-41		One GW increment, late preterm only		Late preterm versus term			
	n	%	n	%	n	%	n	%	aOR[a]	95%CI	OR	95%CI	aOR[a]	95%CI
Neonatal death	4	0.2	20	0.5	15	0.2	122	0.0	0.7	0.5-1.0	6.7	4.7-9.6	6.3	4.4-9.0
Survivors	2330	99.8	3925	99.5	7736	99.8	294692	100	1.0	reference	1.0	reference	1.0	reference
CNS complications	14	0.6	29	0.7	39	0.5	656	0.2	0.8	0.7-1.1	2.6	2.1-3.3	2.4	1.9-3.0
No CNS complications	2320	99.4	2916	99.3	7712	99.5	294158	99.8	1.0	reference	1.0	reference	1.0	reference
Respiratory disease	273	11.7	262	6.6	260	3.4	2462	0.8	0.5	0.4-0.5	7.6	7.0-8.2	7.7	7.1-8.3
No respiratory disease	2061	88.3	2683	93.	7491	96.6	292352	99.2	1.0	reference	1.0	reference	1.0	reference
Respiratory support	466	0.9	46	41.2	44	0.6	848	0.3	0.7	0.5-0.9	2.5	1.9-3.2	2.3	1.8-2.9
No respiratory support	1868	99.1	3899	98.8	7707	99.4	293966	99.7	1.0	reference	1.0	reference	1.0	reference
Infection	22	20.0	387	9.8	360	4.6	2657	0.9	0.4	0.4-0.5	10.4	9.7-11.1	9.9	9.2-10.7
No infection	2312	80.0	3558	90.2	7391	95.4	292157	99.1	1.0	reference	1.0	reference	1.0	reference
Neonatal admission	2102	90.1	2224	56.4	2105	27.2	17545	6.0	0.2	0.22-0.25	13.4	12.9-13.9	13.1	12.7-13.6
No neonatal admission	232	9.9	1721	43.6	5646	72.8	277269	94.0	1.0	reference	1.0	reference	1.0	reference

aOR, adjusted odds ratio; CI, confidence intervakl; CNS, central nervous system; GW, gestational week; OR, odds ratio. [a] aOR=adjusted for year, maternal age, parity, smoking, BMI,infant gender.

To explore the impact of underlying maternal medical conditions and pregnancy complications on neonatal morbidity, risk analysis within the group of infants born late preterm was performed. The previously described hierarchical classification system arranged by severity and probability as a cause of preterm birth was used. PPROM and hypertensive diseases were the most frequent underlying conditions among late preterm births, together occurring in 33%, but most preterm births had none of the conditions listed (53.4%, compared to 91.5% in the term control group) and composed the reference group (hierarchical group 7).

Table 10 shows that infants with malformations were at increased risk for morbidity, with adjusted OR (restricted model) between 1.5, for any respiratory support, to 4.1 (for any CNS complication). Exposure to antepartum hemorrhage increased the risk for any CNS complication, adjusted OR (restricted model) 4.6, and doubled the risk for respiratory disease and need of respiratory support. Infants to diabetic mothers also had substantially increased risk for morbidity with adjusted OR (restricted model) 3.1 for any CNS complication and adjusted OR (restricted model) 1.6 for respiratory support. Infants in the PPROM-group had lower risk for morbidity than any other group. Compared to the reference group "none of these", the adjusted ORs were 0.3, 0.7, and 0.8 for "any CNS complication", "any respiratory disease", and "respiratory support", respectively. Mortality was too infrequent to use as an outcome in this analysis.

A comparison between the low-risk PPROM group and infants born at term revealed that infants in the PPROM group had significantly increased risk for "respiratory disease" (adjusted OR 4.2; 95%CI 3.6-5.1) and need of "respiratory support" (adjusted OR 6.4; 95%CI 5.5-7.4). Within the PPROM group, the risk for these conditions decreased for each week of gestation (adjusted OR for one week GA increase 0.5; 95%CI 0.4-0.6, and adjusted OR 0.4; 95%CI 0.3-0.4, for "respiratory disease" and need of "respiratory support", respectively). No differences were found for the outcomes "any CNS complication" or "neonatal death" between infants born late preterm after PPROM and infants born at term ($p=0.38$ and $p=0.18$, respectively).

Table 10. Association between underlying causes of preterm birth according to a hierarchical system and selected neonatal outcomes. Late preterm infants only.

	n	OR[a]	95%CI	aOR[b]	95%CI
Any CNS complication N=82					
Malformations N=436	8	3.9	1.8-8.4	4.1	1.9-9.0
Antepartum hemorrhage N=496	10	4.3	2.1-8.6	4.6	2.2-9.3
Pregestational diabetes N=344	5	3.1	1.2-7.8	3.1	1.2-8.0
Hypertensive disease of pregnancy N=1344	12	1.9	1.0-3.6	1.9	1.0-3.6
SGA, other reason N=581	6	2.2	0.9-5.2	2.2	0.9-5.2
PPROM N=3331	5	0.3	0.1-0.8	0.3	0.1-0.9
None of these N=7498	36	1.0	reference	1.0	reference
Respiratory disease N=795					
Malformations N=436	40	2.	1.5-2.9	1.5	1.0-2.1
Antepartum hemorrhage N=496	85	4.3	3.3-5.5	2.0	1.5-2.6
Pregestational diabetes N=344	37	2.5	1.7-3.6	1.6	1.1-2.3
Hypertensive disease of pregnancy N=1344	115	1.9	1.6-2.4	1.2	1.0-1.6
SGA, other reason N=581	29	1.1	0.7-1.6	0.8	0.5-1.2
PPROM N=3331	142	0.9	0.7-1.1	0.7	0.6-0.9
None of these N=7498	347	1.0	reference	1.0	reference
Respiratory support N=1213					
Malformations N=436	96	3.6	2.9-4.6	2.8	2.1-3.6
Antepartum hemorrhage N=496	127	4.4	3.6	2.1	1.7-2.7
Pregestational diabetes N=344	51	2.2	1.6-3.1	1.6	1.2-2.3
Hypertensive disease of pregnancy N=1344	140	1.5	1.2-1.8	1.0	0.8-1.3
SGA, other reason N=581	51	1.2	0.9-1.7	0.8	0.6-1.1
PPROM N=3331	209	0.9	0.7-1.0	0.8	0.7-1.0
None of these N=7498	539	1.0	reference	1.0	reference
Any infection N=112					
Malformations N=436	12	3.6	1.9-6.8	3.2	1.7-6.1
Antepartum hemorrhage N=496	3	0.8	0.2-2.5	0.5	0.2-1.8
Pregestational diabetes N=344	4	1.5	0.5-4.2	1.2	0.4-3.5
Hypertensive disease of pregnancy N=1344	6	0.6	0.2-1.3	0.4	0.2-1.0
SGA, other reason N=581	4	0.9	0.3-2.5	0.7	0.3-2.0
PPROM N=3331	25	1.0	0.6-1.6	1.0	0.6-1.6
None of these N=7498	58	1.0	reference	1.0	reference
Neonatal admission N=6431					
Malformations N=436	278	2.8	2.2-3.4	2.5	2.0-3.1
Antepartum hemorrhage N=496	300	2.4	2.0-2.9	1.2	1.0-1.5
Pregestational diabetes N=344	235	3.4	2.7-4.2	3.7	2.9-4.8
Hypertensive disease of pregnancy N=1344	801	2.3	2.0-2.6	2.1	1.8-2.4
SGA, other reason N=581	481	7.5	6.0-9.4	8.5	6.7-11.0
PPROM N=3331	1407	1.1	1.0-1.2	0.9	0.8-1.0
None of these N=7498	2929	1.0	reference	1.0	reference

CNS, central nervous system; OR, odds ratio; PPROM, Preterm prelabour rupture of membranes; SGA, Small for gestational age. [a]Adjusted for gestational week. [b]Adjusted for variables with $p < 0.2$ in the first analysis. Any CNS: year of birth. Respiratory disease: gestational age, year of birth, smoking, maternal age, primipara, gender, elective and emergency Caesarean section (C-section). Respiratory support: gestational age, smoking, primipara, gender, elective and emergency C-section. Any infection: gestational, age year of birth, BMI, and emergency C-section. Neonatal admission: gestational age, year of birth, maternal age, primipara, gender, elective and emergency C-section

Comments

A large number of individuals are needed when studying rare outcome variables such as neonatal death and CNS complications, so a cohort study is an appropriate method to choose. We aimed to evaluate the impact of preterm birth per se and underlying conditions on neonatal morbidity. For this purpose, a hierarchical classification system, as previously described, was developed to estimate the impact of prematurity per se and impact of underlying conditions, respectively, on neonatal morbidity. The classification group with lowest risk within infants born late preterm was compared to infants born at term as a way of estimating the impact of preterm birth per se.

We found, in concordance with previous studies, that infants born late preterm had elevated risks for neonatal morbidity and mortality and the risk decreased for each GW increment within the late preterm period (80, 88, 93). Most Swedish neonatal units routinely admit all infants born before 35 GW, contributing to but only partly explaining the findings that nearly half (45.8%) of infants born late preterm were admitted, 32% for more than one week.

Analyses revealed that the probable underlying causes of the preterm birth according to the hierarchical classification system had a considerable impact on the neonatal morbidity outcomes. Infants born late preterm after PPROM with no other major complications were found to be the classification group of lowest risk. However, in comparison to infants born at term they had increased risks for respiratory disease and respiratory support.

Paper IV

Results

During the study period, 2 640 416 live-born singleton infants born in GW 34^{+0} to 41^{+6} were identified from the MBR. Children who died (=15 562) or emigrated (n=91 981) before completing compulsory school were excluded. Among the children who died 2 474 (2.2%) were born late preterm compared to 13 088 (0.5%) of children born at term. Another 61 342 children, of which 4286 born late preterm, were not enrolled in compulsory school, and were assumed to attend special school. We refer to this group as having "special educational needs". A cohort of 2 471 531 children enrolled in compulsory school was identified, of which 100 260 were born late preterm.

Compared to mothers of infants born at term, the mothers who gave birth late preterm were more often <20 years, ≥ 35 years, smokers, nulliparous, suffering from underweight or obesity, of lower educational level, and more often born outside the

Nordic countries (p <0.001). The prevalence of late preterm birth in this cohort of live-born children from GW 34 to 41was quite stable around 4% (between 3.5-4.7%) during the study period.

Over all children born late preterm had increased risks for poorer school performance and special educational needs compared to children born at term. For special educational needs fully aRR was 1.68 (95%CI 1.62-1.74), and with additional adjustment for birthweight z-scores, aRR 1.65 (95%CI 1.59-1.61). The risk of special educational needs decreased monotonously for each week until GW 40, p for linear trend<0.001, see figure 6.

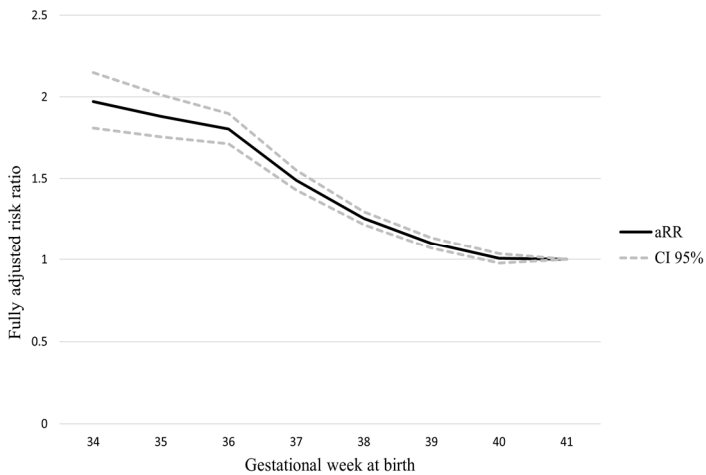

Figure 6. Fully adjusted risk ratios for Special educational needs. Gestational week 41 as reference.

Among children enrolled in compulsory school, no difference in risk of leaving school without grades between children born late preterm or term was detected in the fully adjusted models.

For all four school subjects investigated, the risk for grades below median were slightly, although statistically significant, higher in children born late preterm compared to children born at term (mathematics: aRR 1.02; 95% CI 1.02-1.03, Swedish and English: aRR 1.03; 95% CI 1.02-1.04, physical education: 1.04; 95%CI 1.04-1.06). See figure 7.

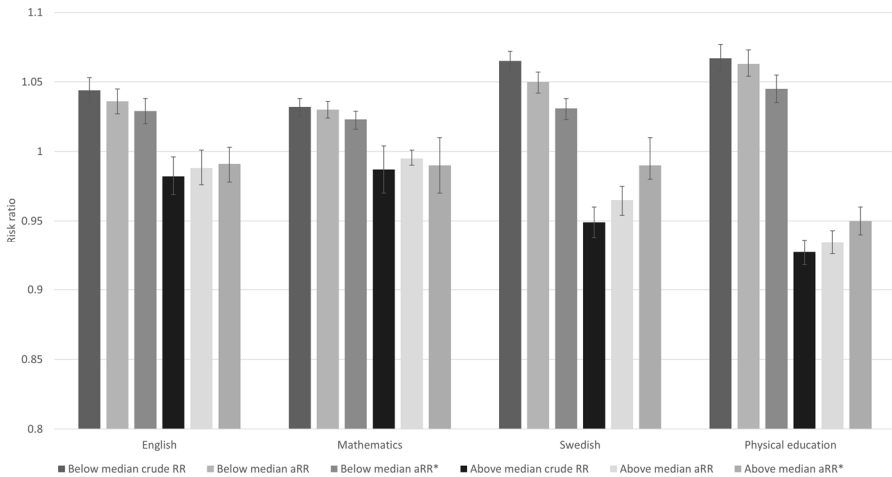

Figure 7 . Risk ratios and confidence intervals for grades below or above median for children born late preterm, compared to children born at term.

Children born late preterm more often chose a common course in mathematics and English compared to children born at term (mathematics: aRR 1.12; 95% CI 1.11-1.14, English: aRR 1.16; 95% CI 1.14-1.19).

In the evaluation of the mean grades or summary scores a dose-response association between GA and mean percentile for final grades or summary scores was found, ranging from mean percentile 46.2 (CI95% 45.7-46.7) in GW 34 to 50.5 (CI 95% 50.4-50.5) in GW 40. See figure 8.

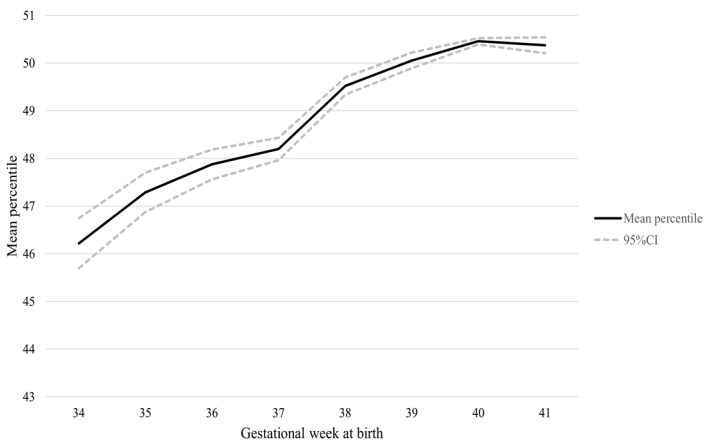

Figure 8. The mean percentile for the final mean grades or summary scoresfor each gestational week.

To investigate the impact of underlying maternal medical conditions and pregnancy complications on overall school performance and risk of special educational needs, analysis within the group of infants born late preterm was performed. The previously described hierarchical classification system arranged by severity and probability as a cause of preterm birth was used. For distribution of complications according to the classification system in the total study cohort see table 11.

Table 11. Distribution of complications according to hierarchical system, by gestational age.

	34GW N=16 349		35GW N=29 145		36GW N=59 052		37-41GW N=2 428 327	
	n	%	n	%	n	%	n	%
1.Malformations	763	4.7	1234	4.2	2295	3.9	56 965	2.4
2.Antepartum hemorrhage	881	5.4	1073	3.7	1498	2.5	13 777	0.6
3.Pregestational diabetes	116	0.7	237	0.8	402	0.7	4007	0.2
4.Hypertensive disease	1545	9.4	2171	7.4	3880	6.6	59 067	2.4
5.SGA, other	982	6.0	1495	5.1	2425	4.1	52 320	2.2
6.PPROM	2204	19.0	3111	10.7	3403	5.8	15 015	0.8
7.None of these	9858	60.3	19 824	68.0	45 149	76.5	2 223176	91.6

GW, gestational week; PPROM, preterm prelabor rupture of membranes; SGA: small for gestational age.

A majority of the children born late preterm had none of the complications listed, constituting the reference group (hierarchical group seven,"none of these"), 72.3% of children born late preterm and enrolled in compulsory school with mean grades or summary score $\leq 25^{th}$ percentile (n=28 649), and 56.9% of those born preterm with special educational needs (n=4286). PPROM and hypertensive diseases were the most frequent specified underlying conditions among children born late preterm and enrolled in compulsory school with mean grades $\leq 25^{th}$ percentile, together occurring in 14.3%.-For children born late preterm and not enrolled in compulsory school, a proxy for being educated in special schools, the pattern was different. The most frequent specified underlying condition was malformations followed by SGA (for other reason), occurring in 18.1% and 7.9%, respectively.

Analyses within the group of children born late preterm revealed a significant ($p<0.001$) heterogeneity of the magnitude of the risk increase for special educational needs, or mean grades or summary scores <25th percentile, respectively, by the underlying conditions related to the preterm birth in the hierarchical classification model. For both outcomes, compared to children with none of the specified conditions (reference group), the highest aRRs were detected for children born with any malformation, and for children born SGA for other reasons than the prioritized conditions specified in the hierarchical system. The corresponding lowest aRRs were detected for children born after PPROM. Table 12 displays the crude and adjusted RR. A comparison between the PPROM group among children born late preterm and children born at term revealed that children in the PPROM group were at significantly increased risk of special educational needs compared to children born at term, crude RR 1.34 (95%CI 1.19-1.40), aRR 1.27 (95%CI 1.13-1.43) and

fully adjusted RR 1.23 (95%CI 1.10-1.38). The risk of having mean grades or summary score, respectively, below the 25th percentile did not differ between children born late preterm after PPROM compared to children born at term (crude RR 1.02, 95%CI 0.98-1.06; aRR 1.03, 95%CI 1.03-1.07; fully adjusted RR 1.01, 95%CI 0.98-1.05).

Table 12. Association between underlying causes of preterm birth, according to a hierarchical system, and mean grades or special educational needs. Children born late preterm only.

	n	RR[a]	95% CI	aRR[b]	95% CI	aRR[c]	95% CI
Mean grades ≤25th percentile[d], n=28 649							
Malformations N=3463	1169	1.16	1.11-1.21	1.17	1.12-1.23	1.16	1.10-1.20
Antepartum hemorrhage N=3251	907	0.95	0.90-1.01	0.97	0.92-1.02	0.96	0.91-1.01
Pregestational diabetes N=708	225	1.10	0.98-1.22	1.12	1.01-1.24	1.10	1.0-1.22
Hypertensive disease N=7238	1932	0.92	0.88-0.95	1.03	0.99-1.01	1.08	1.03-1.12
SGA, other reasons N=4510	1559	1.19	1.14-1.24	1.25	1.20-1.30	1.21	1.15-1.28
PPROM N=8347	2148	0.88	0.84-0.91	0.94	0.90-0.98	0.95	0.91-0.98
None of these N=71 567	20 709	1.0	reference	1.0	reference	1.0	refernce
Special educational needs[e], n=4286							
Malformations N=4292	775	5.52	5.12-5.95	5.51	5.1-5.9	5.6	5.1-6.1
Antepartum hemorrhage N=3452	152	1.34	1.14-1.57	1.24	1.05-1.46	1.22	1.04-1.4
Pregestational diabetes N=7596	33	1.34	0.96-1.87	1.29	0.92-1.81	1.22	0.87-1.71
Hypertensive disease N=7596	276	1.11	0.98-1.25	1.14	1.01-1.29	1.16	1.02-1.32
SGA, other reasons N=4902	339	2.11	1.89-2.36	2.14	1.9-2.4	2.2	1.9-2.5
PPROM N=8718	274	0.95	0.84-1.08	0.92	0.81-1.04	0.92	0.81-1.05
None of these N=74 831	2437	1.0	reference	1.0	Reference	1.0	reference

PPROM, preterm prelabor rupture of membranes; RR, risk ratio; SGA, small for gestational age. aAdjusted for gestational age. b Adjusted forgestational age, year, schoolgrade system period, infant gender, maternal age, parity, mother´s educational level, mother´s country of birth. cAnalyses of infants born from 1983, adjustments for variables listed above with addition of BMI and smoking. [d]Analysis within the group of children born late preterm with mean grade percentile >0, N=99 084. [e]Analysis within all children born late preterm, N=104 546.

Comments

The last decade several investigators have reported on a linear association between GA and school performance or special educational needs until full term gestation. (76, 100, 103). The results of the current study are in concordance with this. In analysis of the specific school subjects (mathematics, Swedish, English and physical education) the risk for grades below median were slightly, although statistically significant, higher among children born late preterm compared to children born at term.

We also explored the impact of underlying conditions and the prematurity per se on outcome, respectively. To our knowledge, this is the first study investigating the impact of pregnancy-related complications, except for fetal growth, on school performance among children born late preterm (35, 126). As commented for the third study we believe that the hierarchical classification system developed for this purpose has advantages compared to other methods. We found the highest relative risks for mean grades below the 25th percentile and special educational needs among children born preterm with congenital malformations and for children born SGA for other reasons than the prioritized conditions specified in the hierarchical system.

For the four school subjects investigated, children born late preterm had a slightly higher but statistically significant risk for grades below median when compared to children born at term.

The size of the risk estimates differs considerably between studies investigating the effect of late preterm birth on academic performance (103). This could be due to the variety of reported outcome measures (school grades, teachers and parents' reports, IQ-scores) and the disparity in age at follow-up. An important confounder to consider in studies of cognitive ability after preterm birth is socioeconomic status and parental educational level, variables associated both with preterm birth and poor academic performance. In two Swedish cohort studies the impact of socioeconomic and genetic factors on intellectual performance were found to be considerable (84, 109). In their register study of cognitive competence among young men during military service conscription, Ekeus et al estimated that one third of the association between preterm birth and test scores could be explained by socioeconomic factors (84). In our study, adjustments for infant and maternal characteristics, including maternal age, parity, smoking, BMI, maternal highest final educational level, and maternal country of birth only lowered the relative risk estimates marginally. In another Swedish cohort study, using information from the school grade register, Ahlsson et al. conclude that the negative effects of preterm delivery after 31 GW on final grades in compulsory school was attributable to other factors than the preterm birth itself since the negative effect of prematurity vanished when comparing siblings (109).

In our study, after exclusion of children who died or emigrated before graduation, we used the lack of registration in the school grade register as a proxy for being

enrolled in special school for children with cognitive disabilities. It is possible that the number of children with special educational needs are overestimated since some children may be missing in the school grade system for other reasons than education in special schools. We consider it unlikely that this will seriously bias the results as it is not related to the prospectively collected information on GA at birth.

General discussion

Detection and optimal timing of delivery of fetuses suspected of growth restriction is a clinical challenge. The main goal for detection is to reduce the risk of stillbirth and serious adverse events. With current knowledge, there is a lack of evidence-based protocols of surveillance and guidance for optimal timing of delivery of late-onset FGR. Detection of suspected growth restriction is often equal to interventions leading to termination of the pregnancy by induction of labor or elective cesarean section. In a number of studies, antenatally detected growth restriction was associated with 10-14 days shorter gestation (10, 14, 127). The risk of stillbirth, when an expectative approach is chosen, must be weighed against neonatal and long-term consequences of shortening gestation, both in the late preterm and in the early term period. The clinical decision will be even more challenging since methods for detection and surveillance of late-onset FGR are imperfect leading to a substantial number of false positive individuals with no benefit and possible harm from the interventions. As much as half of the fetuses suspected of growth restriction before birth were normally grown when born (128, 129).

The first study of this thesis showed no convincing improvement of clinical outcome when pregnant women were offered screening for SGA with ultrasound and measure of fetal growth, even though screening ultrasound improved detection of SGA at birth compared to selective ultrasound. This is in concordance with several other studies (8, 9, 130).

The second study showed that in a cohort of high-risk pregnancies, 32-41 GW, mostly with suspicion of FGR but still having positive end-diastolic velocity in the UA, Doppler CPR z-score did not predict perinatal mortality or asphyxia.

There are ongoing trials of surveillance and timing of delivery in pregnancies complicated by suspected late-onset FGR. Time will show if the investigated surveillance methods have the capacity of meeting the clinical need for effective detection and intervention of fetuses with late FGR.

During the last 15 years there has been growing evidence that children born late preterm have elevated risks both short and long term (75, 76, 80, 86, 88, 89). In study three and four of this thesis we explored the proportion of the increased risks for adverse outcomes both during the neonatal period and in school that could be attributed to underlying maternal and pregnancy related conditions and evaluated the effect of preterm birth per se on the outcomes. A challenge in studies of the

effect of preterm birth on morbidity risk is the fact that the severity of a condition or complication present at lower GA is not equivalent to the effect of a similar condition occurring at term. It is reasonable to assume that each condition, e.g., preeclampsia, present at lower GA age is likely to be more severe than the corresponding condition at term, and therefore will affect the risk for adverse outcome to a higher extent.

The third and fourth study in this thesis showed that the underlying condition that was the probable cause of the preterm birth had a considerable impact on the neonatal morbidity and on the risk of special educational needs or lower mean grades when graduating from high school. To estimate the risk of the prematurity per se on adverse outcome among children born late preterm we identified the group of late preterm infants at lowest risk and compared them to those born at term. Both regarding neonatal morbidity and school performance the group at lowest risk within late preterm births were normally grown infants born without malformations, to non-diabetic normotensive mothers after PPROM. These infants still had increased risks for respiratory disease (aOR 4.2, 95%CI 3.6-5.1) and respiratory support (aOR 6.4, 95%CI 5.5-7.4). When comparing the late preterm PPROM group to infants born at term there were no difference between the outcomes CNS complications and neonatal death. Corresponding comparisons were made regarding having mean grades or summary score when graduating compulsory school $\leq 25^{th}$ percentile and not being enrolled in compulsory school (proxy for being educated in special schools for children with disabilities). No difference was found in the risk of receiving mean grades $\leq 25^{th}$ percentile between children born late preterm after PPROM and children born at term, but the risk for special educational needs was elevated, fully aRR 1.23 (95%CI 1.10-1.38). This result indicates that the preterm birth per se increases the risk of special educational needs.

Study three and four found that underlying maternal and pregnancy-related conditions had a substantial impact on the outcome of the children, both as neonates and as adolescents in school. Efforts should be made to prevent preterm birth in general, including late preterm birth, and obstetricians have a responsibility to avoid iatrogenic late preterm birth when feasible.

Conclusions

Routine ultrasound in GW32-34 improves detection of SGA compared to ultrasound on indication, but no convincing improvement of perinatal outcome was found even if a higher proportion of SGA fetuses was identified antenatally. These findings emphasize the need for clinical guidelines and secondary tools to identify the infants at risk of adverse outcome when growth restriction is suspected.

The Doppler parameters CPR, UA PI and MCA PI were not found to be useful in predicting perinatal mortality or asphyxia among high-risk pregnancies after GW 32. CPR z-score was found to have a high predictive value of SGA at birth, significantly better than UA PI and MCA PI z-scores. CPR and MCA PI performed equally good in predicting neonatal morbidity.

Late preterm infants have increased risk for neonatal mortality and morbidity and need for special education compared to infants born at term. The risk estimates decreased for each added GW. A linear association was also found between GA at birth (GW 34-41) and mean grades or summary scores. The underlying medical conditions accounted for a substantial proportion of the perinatal morbidity and the risk for poorer school performance.

Within the group of children born late preterm, those born after PPROM without any other major pregnancy complication were found to be a group of low risk. However, in comparison to children born at term they had increased risks for respiratory problems. Among late preterm infants, respiratory problem seemed to be specifically related to the preterm birth per se, regardless of its cause.

The underlying maternal conditions and pregnancy complications were found to significantly contribute to the association between late preterm birth and special educational needs, but late preterm birth per se also increased the risk for special educational needs.

Among children born preterm who attended compulsory school, the difference in school performance compared to children born at term was less pronounced. Children born late preterm had modest, but statistically significant, elevated risks for grades below the median and lower mean grade percentiles, respectively.

Future perspectives

Effective screening methods and guidance for intervention in late-onset FGR is still an unresolved issue in obstetrical practice. Part of the explanation could be that current definitions are too imprecise. Methods separating the true growth restricted fetuses from those constitutionally small could improve detection and outcome. Different strategies are being or could be investigated, such as more individualized growth reference curves, addition of biochemical markers, serial ultrasound measurements and Doppler parameters.

It would be of interest to study academic performance in relation to birth weight and suspected growth restriction at all gestational ages.

Regarding late preterm births, further analyses could be done in the group of infants born late preterm with no major pregnancy complication. Were the deliveries iatrogenic or spontaneous in this group? In the fourth study of this thesis, we found that 2.2% of infants born late preterm died before completing compulsory school, compared to 0.5% among children born at term. Studies of the causes of death among children born late preterm could be important.

In this project we explored the impact of underlying maternal and pregnancy-related conditions on neonatal morbidity risk and school performance at the age of 16 among children born late preterm. An increasing number of obstetric guidelines recommend delivery at early term for several maternal conditions and pregnancy complications. Investigation of the impact of underlying conditions on risk of adverse short and long-term outcome after early term birth could provide important knowledge.

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