

## Summary

The thesis consists of three subprojects:

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### First subproject

The first subproject aimed to analyze the association between growth in first half of pregnancy and the risk of adverse outcome in a cohort of 8215 pregnant women. Data was obtained from the Copenhagen First Trimester Study conducted in 1998-2001. Two papers were published.

The objective of the first paper was to relate growth rate of the biparietal diameter (BPD) between the first and second trimesters to the risk of perinatal death, intrauterine growth restriction, macrosomia, preterm/post-term delivery and preeclampsia. We analyzed sonographic BPD measurements at 11-14 and 17-21 weeks, and defined growth rate as millimetres of growth per day between the two measurements. Growth rate was dichotomized into growth rates  $< 2.5^{\text{th}}$  and  $> 97.5^{\text{th}}$  vs.  $2.5^{\text{th}}$ - $97.5^{\text{th}}$  centiles. Odds ratios and 95% confidence intervals for adverse outcome were calculated. We found a significant relationship between the growth rate of BPD from the first to the second trimester and adverse pregnancy outcome. Low growth rates were associated with increased odds ratios for perinatal death and intrauterine growth restriction, while high growth rates were associated with increased odds ratios for macrosomia and preterm delivery.

The second paper was written in collaboration with Dr. Francesc Figueras and Professor Jason Gardosi from West Midlands Perinatal Institute, Birmingham, UK. In this collaboration data was analyzed using conditional centiles and customized fetal growth charts. Conditional centiles are an acknowledged statistical method, used to estimate growth longitudinally, and customized fetal growth charts are growth charts that are individually adjusted / "customized" for physiological factors known to affect birth weight and growth. The objective of the second paper was to determine the association between fetal size and growth between the first and second trimesters and subsequent adverse pregnancy outcome using conditional centiles and customized fetal growth charts for statistical analyzes. The cohort was the same as in the first paper: 8215 pregnant women that had fetal size estimated by ultrasound at 11-14 weeks (CRL and BPD) and again at 17-21 weeks (BPD). With the use of conditional centiles and customized fetal growth charts we found a strong association between early fetal growth rate and perinatal death before 34 weeks (OR 16.0, CI 2.9-88.7).

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### Second subproject

The second subproject was done in collaboration with Professor Anders Juul, Department of Growth and Reproduction, Rigshospitalet and Dr Michael Christiansen, Department of Clinical Biochemistry, Statens Serum Institute. In this project we wished to analyze the association between growth factors in maternal blood and fetal growth rate in first half of pregnancy. We investigated if maternal levels of human Placental Lactogen (hPL), Placental Growth Hormone (PGH) and Insulin Growth Factor I (IGF-I) are associated with growth rate of the biparietal diameter (BPD) between week 11-14 and week 17-21. Again data from 8215 singleton pregnancies from the Copenhagen First Trimester Study were analyzed, and growth rate was defined the same way as in our first paper. Fetuses with growth rate of the BPD below the  $2.5^{\text{th}}$  centile (low growth

rate) and fetuses with growth rate above the 97.5<sup>th</sup> centile (high growth rate) were identified. As a reference group a similar number of fetuses with growth rate around the median were identified (intermediate growth rate). The maternal blood serum concentration of hPL, PGH and IGF-I was determined in the three different growth rate groups. We found that when adjusted for maternal weight and crown rump length (CRL), maternal PGH levels were 12% higher in women carrying fetuses with high first trimester growth rates compared to controls. Thus, PGH may be involved in fetal growth regulation already in early human pregnancy.

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### **Third subproject**

The third subproject is a prospective study conducted in collaboration with Dr Lene Sperling, Department of Obstetrics and Gynaecology, Herlev Hospital. In this study we looked at fetuses with a discrepancy in gestational age determined by crown rump length (CRL) and last menstrual period, and used a “smaller than expected CRL” as an indicator of first trimester growth restriction.

We wished to investigate if fetuses with a smaller than expected CRL have impaired perfusion of the placenta, measured by ultrasound Doppler of the uterine and umbilical arteries compared to a control group, and to investigate if a smaller than expected CRL in combination with abnormal flow in the uterine and umbilical arteries can be used to predict adverse neonatal outcome.

We included 182 singleton pregnancies with a gestational age set by CRL that was seven days or more smaller than the gestational age set by last menstrual period and 230 controls with a gestational age set by CRL that was equal to the gestational age set by last menstrual period. The study entailed the routine scans (nuchal translucency scan in first trimester and anomaly scan in second trimester), a growth scan in gestational week 23-24 and a questionnaire. At the anomaly scan and growth scan umbilical and uterine artery Doppler flows were measured.

We were not able to demonstrate a link between poor placental perfusion and first trimester growth restriction, and therefore, based on the result from this study, do not recommend measurements of uterine or umbilical artery flow specifically for fetuses with at smaller than expected CRL.

## Dansk resume

### Afhandlingen består af tre delprojekter

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#### Første delprojekt

Formålet var at analysere associationen mellem føtal vækst i første halvdel af graviditeten og risikoen for dårligt graviditetsudkomme i en kohorte på 8215 gravide kvinder. Data kom fra "Copenhagen First Trimester Study 1998-2001". To artikler er publiceret i første delprojekt.

Formålet med den første artikel var at relatere vækstrate af biparietal diameteren (BPD) mellem første og andet trimester af graviditeten til risikoen for perinatal død, intrauterin væksthæmning, macrosomi, præterm/postterm fødsel og præeclampsi. Vi anvendte ultralydsmålt af BPD målt i uge 11-14 og 17-21 af graviditeten. Føtal vækstrate definerede vi som millimeter vækst pr. dag mellem de to målinger. Materialet blev dichotomiseret i grupper med vækstrate  $< 2.5^{\text{th}}$  vs.  $2.5^{\text{th}}-97.5^{\text{th}}$  percentil samt  $> 97.5^{\text{th}}$  vs.  $2.5^{\text{th}}-97.5^{\text{th}}$  percentil og odds ratio og 95% confidence interval for dårligt graviditetsudkomme blev beregnet.

Vi fandt signifikante sammenhæng mellem BPD-vækstraten fra første til andet trimester og risikoen for dårligt graviditetsudkomme. Lav vækstrate var associeret med en øget odds ratio for perinatal død og intrauterin væksthæmning og høj vækstrate var associeret med øget odds ratio for macrosomi og præterm fødsel.

Den anden artikel blev skrevet i samarbejde med Dr. Francesc Figueras og Professor Jason Gardosi fra West Midlands Perinatal Institute, Birmingham, UK. I dette samarbejde analyserede vi data ved brug af "conditional centiles" og "customized fetal growth charts". "Conditional centiles" er en anerkendt statistisk metode, der anvendes til at estimere vækst målt longitudinelt og "customized fetal growth charts" er vækstdiagrammer som er individuelt justeret/"customized" for fysiologiske faktorer, som påvirker fødselsvægten og væksten.

Formålet med artikel nummer to var at beskrive associationen mellem føtal størrelse og vækst mellem første og andet trimester og efterfølgende graviditetsudkomme ved anvendelsen af "conditional centiles" og "customized fetal growth charts" til de statistiske analyser.

Kohorten var den same som i den første artikel: 8215 gravide kvinder, som havde fået foretaget ultralydsmålinger i uge 11-14 (CRL, BPD) og igen i uge 17-21 (BPD). Ved anvendelsen af "conditional centiles" og "customized fetal growth charts" fandt vi en stærk association mellem vækst i den tidlige graviditet og perinatal død før uge 34 (OR 16.0, CI 2.9-88.7).

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#### Andet delprojekt

Andet delprojekt blev skrevet i samarbejde med Professor Anders Juul, klinik for vækst og reproduktion, Rigshospitalet og overlæge Michael Christiansen, klinisk biokemisk afdeling, Statens Serum Institut. I dette projekt ønskede vi at analysere associationen mellem vækstfaktorer i maternelt blod og fosterets vækstrate mellem første og andet trimester. Vi undersøgte om maternelle serum niveauer af human Placental Lactogen (hPL), Placental Growth Hormone (PGH) og Insuline Growth Factor I (IGF-I) er associerede med vækstraten af biparietal diameteren mellem uge 11-14 og uge 17-21. Vi anvendte den samme kohorte fra "Copenhagen First Trimester Study" som i første delprojekt, ligesom vækstraten blev defineret på samme måde som i den første

artikel. Fostre med BPD-vækstrate under 2.5 percentilen (lav vækstrate) og fostre med vækstrate over 97.5 percentilen (høj vækstrate) blev identificeret. Et tilsvarende antal fostre med vækstrate omkring medianen (intermediær vækstrate) blev anvendt som referencegruppe.

Maternelle serum koncentrationer af hPL, PGH og IGF-I blev målt i de tre forskellige vækstrate grupper. Vi fandt at efter justering for crown rump length (CRL) og maternel vægt er det materielle serum niveau for PGH 12% højere hos gravide med fostre, der har en høj vækstrate sammenlignet med den intermediære kontrol gruppe og konkluderede derfor at PGH er involveret i føtal vækstregulering allerede tidligt i graviditeten.

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### **Tredie delprojekt**

Det tredie delprojekt er et prospektivt studie udført i samarbejde med overlæge Lene Sperling, Obstetrisk/Gynækologisk afdeling, Herlev Hospital. I dette studie fokuserede vi på fostre, hvor der var en forskel i gestationsalderen fastsat ved crown rump length (CRL) og gestationsalderen fastsat ved sidste menstruation. Vi anvendte "mindre end forventet CRL" som en indikator for første trimester vækstretardering. Vi ønskede at undersøge om disse små fostre har dårligere perfusion af placenta målt ved ultralyd Doppler i aa. Uterinae og a. Umbilicalis sammenlignet med en kontrol gruppe, samt at undersøge om dårligt flow i aa. Uterinae og a. Umbilicalis kan anvendes til at forudsige dårligt neonatal udkomme. Vi inkluderede 182 singleton graviditeter, hvor gestationsalderen estimeret ved CRL i første trimester var syv dage eller mere mindre end gestationsalderen estimeret ved sidste menstruation og 230 kontroller hvor gestationsalderen estimeret ved CRL og sidste menstruation var den samme. Studiet omfattede rutine skanningerne (nakkefoldsskanningen i første trimester og anomaliskanningen i andet trimester) samt en tilvækstskanning i uge 23-24 og et spørgeskema. Ved gennemskanningen og tilvækstskanningen blev blodgennemstrømningen i aa.uterinae og a.umbilicalis målt med ultralyd Doppler. Vi fandt ikke en association mellem dårlig perfusion af placenta og første trimester vækstretardering, og kan på baggrund af dettes studie derfor ikke anbefale uterin eller umbilical arterie flow målinger specielt til fostre med en mindre end forventet CRL.

