Introduction to the International symposium on
Reproductive Epidemiology 29-30 March 2012

As the director of the strategic research network Epidemiology for Health, EpiHealth, at the Lund and Uppsala universities and also the chair of the Organizing Committee of the symposium I great you welcome to Malmö on behalf of the Organizing Committee, members listed below. We are grateful to all lecturers and chairpersons that have volunteered to contribute to the programme. In this abstract booklet you will find the final programme, a list of participants and abstracts both for the oral and the poster presentations. In total approximately 60 persons have registered for the symposium. It is my wish and intention that this event will create fruitful research contacts and lively discussions, as it is the strategic plan of EpiHealth to develop reproductive epidemiology and early life perspectives on adult health and disease as a target area for research priorities. This is supported by the Faculty of Medicine at the Lund University that has decided that the annual Research Day of 2012 should be devoted to a very similar topic “Health as fetus – means health in adult life” on November 6-7th 2012. The research network SIMSAM-Early Life is also active in the same research area, and represented within the Organizing Committee.

Epihealth was officially launched in the beginning of 2010 and consists of a steering committee headed by an executive board. Its goal is to promote both national and international excellence within epidemiologic research, more specifically: basic science epidemiology (gene-environment interactions), epidemiologic infrastructure (databases and bio-banks), together with clinical epidemiology (quality in healthcare, patient databases and health economics). Epihealth also intends to organize research courses as well as symposia and to catalogue the different epidemiology projects being undertaken by both universities. If you would like to know more about the structure of EpiHealth and ongoing activities please visit our web-site: www.med.lu.se/epihealth.

Peter M Nilsson
Professor, Director EpiHealth
Organizing Committee for the symposium:
This international symposium is arranged by the strategic research network EpiHealth at the Lund and Uppsala universities (www.med.lu.se/epihealth), in collaboration with the WHO Collaborative Centre (CC) in Lund, Sweden

“Reproductive epidemiology in a life course perspective”

Dates: 29-30 March, 2012
Venue: Jubileumsaulan, Skåne University Hospital, Entrance 59, Malmö, Sweden
Transportation: Train station “Triangeln” is located 500 meter from venue

Organising Committee:

Peter M Nilsson (chair), Kristina Sundquist, Malmö
Karin Källén, Karel Marsal, Anna Rignell-Hydhem, Lund
Liisa Byberg, Uppsala

Thursday March 29

09:00-10:00 Coffee and registration, posters put on display
10:00-10:20 **Introduction:** Peter M Nilsson introduces Petra Otterblad-Olausson, MBR Socialstyrelsen, Stockholm, and Karel Marsal, WHO centre in Lund.

10:20-11:40 **Session 1:** Register findings regarding intrauterine exposures and neonatal outcomes

*Chair:* Karin Källén, Lund
*Sven Cnattingius,* Stockholm: Nicotine exposure during pregnancy
*Marie Blomberg,* Linköping: Maternal obesity and neonatal outcome
*Karin Källén,* Lund: Studies on drugs during pregnancy – methodological aspects

11:40-12:30 **Session 2:** Infertility and IVF: results and long-term outcomes

*Chair:* Nils-Otto Sjöberg, Malmö
*Christina Bergh,* Helsingborg: Low risk for health problems in children born after IVF national and international results.
*Aleksander Giwercman,* Malmö: Male fertility as a marker of disease risk

12:30-13:30 Lunch and posters

13:30-14:00 **Pia Saldéen,** Malmö: Clinical practices in IVF; developments over time

14:00-15:20 **Session 3:** SGA or preterm – implications for long-term health

*Chair:* Mikael Norman, Stockholm
*Kristina Sundquist,* Malmö: SGA and pre-term birth consequences for health – findings based on national registers
*Anna-Karin Bonamy,* Stockholm: Pre-term birth and cardio-vascular changes
*Liisa Byberg,* Uppsala: The Uppsala Family Study

15:20-15:40 Coffee and posters
15:40-17:00  
**Session 4: Ultrasound screening during pregnancy - parental reactions and health consequences**
Chair: Anna-Karin Dykes, Lund  
David Ley, Lund: Intra-uterine growth retardation (IUGR) – background, measurements and consequences  
Kjell Salvesen, Trondheim: Antenatal exposure to ultrasound and postnatal development  
Marie Ekelin, Lund: Parents’ expectations, experiences and reactions to a routine ultrasound examination during pregnancy - normal and abnormal findings.

17:00-17:30  
**State-of-the Art 1: The Mis-Match hypothesis revisited**
Chair: Peter M Nilsson, Malmö  
Speaker: Mark Hanson, Southampton, UK (30 minutes)

17:30  
Summary and closure of Day 1. Peter Nilsson

18:00  
Symposium Dinner

**Friday March 30; between 08:30-14:00**

08:30-09:50  
**Session 5: Environmental and toxic effects influencing pregnancy outcomes**
Chair: Anna Rignell-Hydbom, Lund. SIMSAM-Early Life  
Thorhallur Halldorsen, Iceland: Long term effects of in utero exposure to perfluorinated chemicals and female reproduction  
Helle Raun Andersen, Odense: Growth and pubertal development in children prenatally exposed to modern pesticides  
Lars Rylander, Lund: Paternal cancer and childhood health

09:50-10:20  
Coffee and posters

10:20-11:40  
**Session 6: Cognitive epidemiology – linking early life with adult health**
Chair: Peter M Nilsson, Malmö  
Finn Rasmussen, Stockholm: Associations between poor condition at birth, cognitive performance and socio-economic position in young adulthood  
Ilona Koupil, Stockholm: The role of cognitive function in intergenerational transfer of social and health disadvantage: results from the Uppsala Birth Cohort Multigenerational Study (UBCoS Multigen)  
Maria Råstam, Lund: A perspective from child psychiatry

11:40-12:10  
**State-of-the Art 2: The Finnish experience – Fetal programming and life course perspective**
Chair: Finn Rasmussen, Stockholm  
Speaker: Johan Eriksson, Helsinki, Finland (30 minutes)

12:10-13:00  
**Session 7: Future research directions**
Chair: Karel Marsal, Lund  
Panel: Johan Eriksson, Mark Hanson, Karin Källén, Kristina Sundquist

13:00-13:10  
Summary and conclusions. Awards for best poster presentations  
Peter M Nilsson, Karin Källén
Growth and Pubertal Development in Children Prenatally Exposed to Modern Pesticides

Helle R Andersen¹, Christine Wohlfahrt-Veje², Tina K Jensen²¹, Philippe Grandjean¹, Niels E Skakkebæk² and Katharina M Main²

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Introduction: Prenatal exposure to endocrine disrupting chemicals may disturb reproductive development and contribute to development of obesity and metabolic syndrome. Many currently used pesticides have endocrine disrupting properties. The HDL-associated anti-oxidative enzyme paraoxonase 1 (PON1) seem to protect against atherosclerosis. It also hydrolyzes many substrates, including organophosphate pesticides. A common polymorphism, PON1 Q192R, affects both properties. The purpose of this study was to investigate effects of prenatal pesticide exposure on reproductive development and body composition at school age and to examine if there was any interaction with the PON1 Q192R genotype for effects on cardiometabolic risk factors.

Methods: Pregnant greenhouse-workers were categorized as high, medium or unexposed to pesticides at enrollment which was typically in gestational week 4 – 10. At age 6 to 11 years their children (N=177, 112 exposed and 65 unexposed) underwent a standardized physical examination including anthropometry, puberty staging (Tanner), and blood sampling (non-fasting). Exposure status was unknown to the examiner. Serum was analyzed for reproductive hormones and growth factors. PON1-genotype was determined for 141 children (88 exposed and 53 unexposed).

Results: Breast development occurred 1-1½ year earlier in the exposed girls compared to the unexposed girls and to girls from a contemporary Danish reference population. Exposed girls had higher serum concentrations of androstendione. Furthermore Anti Müllerian Hormone levels were lower compared to a reference population, indicating an impaired ovarian reserve in exposed girls. There was no indication of early puberty in the exposed boys, who on the contrary had smaller genitals than unexposed boys. The effect of prenatal pesticide exposure on growth of the children was biphasic with lower weight at birth, followed by an increased body fat accumulation from birth to school age. This effect was potentiated by maternal smoking during pregnancy. The observed associations between prenatal pesticide exposure and fat accumulation in childhood were driven by particularly pronounced effects in children carrying the PON1 192 R-allele. These children also had higher blood pressure and increased serum concentrations of leptin and IGF-1 after prenatal pesticide exposure.

Conclusion: Occupational exposure to combinations of modern, non-persistent pesticides early in pregnancy may have long-lasting adverse effects in spite of the protection offered to pregnant women. Children carrying the PON1 192 R-allele were especially susceptible to the effects on body composition and our results indicate a gene-environment interaction between prenatal pesticide exposure and PON1 genotype that affects risk of obesity and related diseases later in life.
Low risk for health problems in children born after IVF – National and international results.

Christina Bergh

More than 4 million IVF children are born in the world and more than 40 000 in Sweden. In many countries between 1-4% of all children born yearly are born after IVF. Most children born after assisted reproduction techniques (ART) are healthy. The most important risk associated with IVF is the higher multiple birth rate, which may result in increased child morbidity owing to the fact that several embryos are transferred at each treatment. Single embryo transfer reduces this risk dramatically. Large registry studies and meta-analyses have indicated a small but statistically significantly increased risk of congenital malformations among IVF children. Other risks, such as preterm birth (PTB) and low birth weight (LBW) seem more to be associated with parental characteristics than the IVF technique. Continuous follow-up of children after IVF is of great importance, particularly since new techniques are constantly being introduced. Longterm follow up of teens and young adults is also important as well as investigation for rare diseases such as cancer and imprinting disorders.
OBJECTIVE: To evaluate whether short-term neonatal outcome was associated with pre-pregnancy maternal body mass index (BMI) in singleton pregnancies, overall and depending on mode of delivery.

METHODS: A prospective cohort study including 1,024,471 women with singleton livebirths in Sweden from January 1, 1998 through December 31, 2008. Data were collected from the Swedish Medical Birth Registry. Women were categorized in six classes of pre-pregnancy BMI. Obese women were compared to normal weight women regarding short-term neonatal outcome. Three modes of delivery were evaluated, normal vaginal delivery, instrumental delivery and caesarean section. Adjustments were made for maternal age, parity and smoking in early pregnancy.

RESULTS: The risk for birth injury to skeleton and to peripheral nervous system, severe and moderate birth asphyxia, respiratory problems, bacterial sepsis, convulsions, feeding problems, hypoglycaemia and early neonatal death increased with increasing maternal BMI. Morbidly obese women (BMI≥40) delivered by caesarean section had a 50% increased risk of any adverse neonatal outcome, including early neonatal death compared to normal weight women with the same mode of delivery.

CONCLUSION: Obese and especially morbidly obese women have a markedly increased risk for adverse neonatal outcome irrespectively of mode of delivery.
The Uppsala Family Study
Liisa Byberg
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The Uppsala Family Study is the third in a line of Uppsala cohorts investigating the effect of birth weight on later health and disease (1). The Uppsala Family Study was designed so that the effects of early life growth on later outcomes due to fixed maternal factors can be separated from effects due to pregnancy-specific factors. Statistical methods for exploring these differences have been developed (2).

The Uppsala Family Study is based on 602 Uppsala families who were investigated in 2000-2001. The families consist of two consecutive siblings born 1987-95 and their biological parents. The siblings were selected to have concordant high, concordant low, or discordant birth weight. Clinical examinations included anthropometry, blood pressure and blood samples. A reinvestigation of the families is currently ongoing.

We could demonstrate an inverse association between birth weight and blood pressure within families, suggesting that factors that vary between pregnancies in the same women can influence later blood pressure in the offspring (3). Morning cortisol did not mediate this association (4). Recently, we showed associations between parental life style and children’s cardiovascular risk factor profile in the Uppsala Family Study (5).

The current reexamination of the Uppsala Family Study participants includes determination of body composition by DXA scans allowing for several years of research on the influences of early growth on future body composition, bone mineral density, and, of course, a continued interest in the cardiovascular risk factor profiles of the children (who are now teenagers and young adults) and their parents.

References
Nicotine exposure during pregnancy.

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Smoking is known as one of the most important preventable risk factors for adverse pregnancy outcomes. Smoking is causally associated with fetal growth restriction, and probably also with preterm birth, placental abruption and stillbirth. It is not clear whether these risks are caused by nicotine and/or tobacco combustion products. By comparing effects of Swedish oral moist snuff (including essentially only nicotine) and smoking, we may disentangle effects of nicotine from effects of tobacco combustion products.

Prenatal smoking exposure has also been associated with a number of long-term outcomes in offspring, including intelligence, blood pressure, obesity and mental health.

In the present presentation, we have compared pregnancy risks among offspring to snuff users and smokers. In addition, we have in studies of long-term effects of prenatal smoking exposure, strived to reduce unmeasured confounding by also studying siblings discordant to prenatal smoking exposure.

We find that both smoking and snuff use increase the risks of preterm birth and stillbirth. In contrast to smoking, which is associated with markedly increased risks of having a small-for-gestational-age (SGA) infant and placental abruption, snuff use has no significant effect on risks of SGA and placental abruption. Smoking, but not snuff use, reduces the risk of preeclampsia.

Our results from studies of prenatal smoking exposure and long-term effects in offspring suggest that many of the reported positive findings may have been confounded by unmeasured familial factors.

We conclude:

- that both nicotine and tobacco combustion products play a role in the etiology of preterm birth and stillbirth. With respect to fetal growth restriction and placental abruption (where prenatal smoking but not snuff exposure is associated with substantially increased risks), tobacco combustion products seems to be of prime importance.
- snuff use is not a safe alternative to smoking during pregnancy;
- we have not been able to demonstrate long-term effects of prenatal smoking exposure.
Parents’ expectations, experiences and reactions to a routine ultrasound during pregnancy – normal and abnormal finding

Maria Ekelin

BACKGROUND Routine ultrasound can affect parents’ well-being due to the fact that deviations from normal can be detected.

AIM The aim of the project was to investigate women’s and men’s reactions to obstetrical ultrasound examinations with normal or abnormal findings, both true and false and to follow them over time, relating this to well-being.

METHOD After an interview study with 44 participants, a two-part questionnaire was developed to measure expectations, experiences and reactions to a routine ultrasound examination. The questionnaire were used before and after ultrasound in a year’s cohort and 2184 parents replied to both questionnaires. Parents with abnormal findings were followed up with interviews.

RESULTS Ultrasound was usually a confirmation of a new life and showed an apparently healthy child, reducing both parents’ anxiety afterwards. If the examination showed that the fetus had plexus choroid cysts, the parents had an immense need for knowledge to handle the situation and their anxiety increased after the examination. Parents that had a fetal abnormality identified at the ultrasound examination felt they were pendulating between normal and abnormal. They entered a state of uncertainty and became involved in a change and adaptation process. The after ultrasound part of the questionnaire showed statistically differences, in seven of the 13 items, between the answers from parents that had a fetus with a malformation compared to parents in a control group. For the group of parents who had a non-viable fetus, diagnosed at the examination, it was an unexpected finding that demanded individualized care, as well as a general care plan.

CONCLUSION A routine ultrasound examination with normal findings is regarded as a very important examination by both men and women, in their process towards becoming parents. Parents with abnormal findings want the knowledge but it is still a difficult situation, with special demands for information and treatment.
Male fertility as a marker of disease risk

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Infertility is a common condition affecting 15% of all couples. In approximately 50% of infertility cases an impairment of semen quality is seen.

Infertility is considered as a condition limited to young adulthood and with introduction of efficient methods for helping infertile couples, the interest in digging into causes of impairment of fertility has significantly declined.

However, there is now a lot of evidence indicating that, at least, some cases of impairment of semen quality can be related to adverse environmental and/or life style related exposure in early foetal life. This means that infertility can be considered as a consequence of disturbed foetal growth. Furthermore, factors causing impairment in sperm production may also imply increased risk of testicular cancer and dysfunction of Leydig cells, leading to androgen deficiency in adulthood.

Thus, men coming for infertility treatment are at increased risk of developing testicular malignancy and of being hypogonadal. The latter condition may lead to subsequent osteoporosis, cardiovascular and metabolic disturbances. On the other hand, subfertile men seem at decreased risk of developing prostate cancer.

Therefore, dealing with men coming for infertility problems should not only focus on helping those subjects with becoming parents. Knowing that impairment of sperm production may be a consequence of adverse foetal events and that subfertility is associated with some increased and decreased disease risks, provide an important and interesting clinical and biological piece of information.
Prenatal Exposure to Perfluorooctanoate and Risk of Overweight at 20 Years of Age: A Prospective Cohort Study

Thorhallur I Halldorsson, Dorte Rytter, Line Småstuen Haug, Bodil Hammer Bech, Inge Danielsen, Georg Becher, Tine Brink Henriksen and Sjurur F Olsen,

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Background and objectives: Perfluoralkyl acids are persistent compounds detected in humans worldwide. A previous study examining low-dose (0.01-0.3 mg/kg) developmental exposure to perfluorooctanoate (PFOA) in CD-1 mice reported increased weight and elevated biomarkers of adiposity in postpubertal female offspring (Hines et al. 2009). We explored whether those findings could be replicated in humans.

Methods: A prospective cohort of 665 Danish pregnant women was recruited in 1988–1989 with offspring follow-up at 20 years. PFOA was measured in serum from gestational week 30. Offspring body mass index (BMI) and waist circumference were recorded at follow-up (n = 665), and biomarkers of adiposity were quantified in a subset (n = 422) of participants. All results were adjusted for age, education, pre-pregnancy BMI, smoking, parity, birth weight and offspring age at follow-up.

Results: In utero exposure to PFOA was positively associated with anthropometry at 20 years in female but not male offspring. Adjusted relative risks comparing the highest with lowest quartile (median: 5.8 vs. 2.3 ng/mL) of maternal PFOA concentration were 3.1 (95% CI 1.4, 6.9) for overweight or obese (BMI ≥ 25 kg/m²) and 3.0 (95% CI: 1.3, 6.8) for waist circumference > 88 cm among female offspring. This corresponded to estimated increases of 1.6 kg/m² (95% CI: 0.6, 2.6) and 4.3 cm (95% CI: 1.4, 7.3) in average BMI and waist circumference, respectively. Maternal PFOA concentrations were also positively associated with serum insulin and leptin levels and inversely associated with adiponectin levels in female offspring.

Further analysis revealed that maternal perfluorooctane sulfonate (PFOS), perfluorooctane sulfonamide (PFOSA) or perfluorononanoate (PFNA) concentrations were not associated with offspring weight as estimates became non-significant after adjustment for PFOA. Furthermore, the association between maternal PFOA concentration and female offspring anthropometry was present for both nulliparous and parous women and remained stable after additional adjustment for maternal weight gain, dietary habits and serum albumin concentrations during pregnancy; as well as parental weight-status at follow-up.

Discussion and conclusion: In a cohort of environmentally exposed pregnant women in utero exposure to PFOA was positively associated with weight and biomarkers of adiposity among female offspring at 20 years of age. These findings are in line with previous experimental results (Hines et al. 2009) but replication of our findings in another independent data is warranted before strong conclusions can be reached.

References
The Mis-Match hypothesis revisited

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Our declining health, reflected in rising rates of obesity, diabetes, and cardiovascular disease, is, according to many health professionals, as threatening to the world as climate change, political unrest, or economic recession.

These diseases are set to generate enormous humanitarian and financial costs, and create new political tensions – for they are not just problems of the Western world but are increasing at an alarming rate in countries which are still poor.

It is widely believed that these are “lifestyle diseases”, arising largely from personal behavioural choices – “gluttony and sloth”. But it is not as simple as that: the processes that drive us to eat too much of the wrong foods or to take too little exercise have both biological and social origins, for our fundamental biology is not suited to the modern world.

Current thinking and policy is blinkered: it ignores the critical ways in which our early lives affect the body’s responses to the modern world, and thus our individual risks of obesity and disease. New research reveals how aspects of our metabolism, eating habits, and much more are established before we are born and in infancy. Epigenetic processes mediate some of these affects during development, in response to maternal (and perhaps paternal) diet, body composition, stress and physical activity levels. Unless we focus efforts on the education and health of parents-to-be and healthy human development in the first few years of life we may fail to prevent risk of ill-health and shorter lives in the next generation.

MAH is supported by the British Heart Foundation.
The role of cognitive function in intergenerational transfer of social and health disadvantage: results from the Uppsala Birth Cohort Multigenerational Study (UBCoS Multigen)

Ilona Koupil

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Despite extensive, long-term investments into reducing differences in health between social groups, substantial health inequalities persist in Sweden today. Both at a country level and internationally, a life-course perspective provides a particularly promising framework for conceptualising the processes whereby health inequalities arise and are reproduced across generations. Understanding the mechanisms whereby adverse parental (and grandparental) socioeconomic position translates into social and health disadvantage in subsequent generations can help one design policies to interrupt this process.

The starting point for the Uppsala Birth Cohort Multigenerational Study (UBCoS Multigen) was a representative and well-defined cohort of 14,192 males and females born in Uppsala University Hospital from 1915-1929 (the Uppsala Birth Cohort Study or UBCoS). In 2004 we were able for the first time to combine this original cohort with social and health data on all their descendants, obtained from routine registers. In 2007-2011, the data set was further developed by additional data manually collected from church parish records, school archives and records from Census 1930 and the period of follow-up was extended till end of year 2009/2010 (Koupil & Goodman 2011). The resulting multigenerational study spans five generations and comprises nearly 140,000 individuals: cohort members, descendants and partners. This makes UBCoS Multigen ideally suited for testing lifecourse models, particularly those connected to ‘developmental origins of disease’, that is the way in which adult disease risks are influenced by environmental processes during periconceptual, foetal and infant phases of life.

Our recent analyses demonstrate that birth characteristics, family composition and family social class may all have effects upon educational outcomes which extend across multiple generations. We showed e.g. that both the school achievement and the education continuation of Swedes born in 1973-1980 were predicted by their grandparents’ birthweight, birth order and family social class at birth – that is, the social class of their great-grandparents four generations before. We also showed that these effects seemed to be largely or entirely explained by the intervening educational attainment and social class of the parents of the youngest generation (Goodman et al. 2010). This indicates the ongoing importance of education as a mechanism whereby early-life disadvantage is translated into social inequalities across the lifecourse, social inequalities which may then be recreated across generations to create a long-term legacy of social disadvantage.

Studies on drugs during pregnancy – methodological aspects

Karin Källén, PhD

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Since the Thalidomide-disaster in the early 1960s, drug safety during pregnancy has been a major area of concern for health providers and authorities around the world. However, when investigating possible human teratogenic effects of a certain drug, there are numerous methodological challenges to overcome. 1) The main drawback of retrospective studies, if information on drug exposure is collected when the outcome is known, is the risk of recall-bias. Different degree of mis-classification in cases and controls makes the results impossible to interpret. Non-differential mis-classification (which happens when cases and controls have the same degree of mis-classification), does not bias the results in any specific direction if no true association exists, but could hide true associations as a non-differential mis-classification will bias the results towards unity. 2) The main drawback of prospective cohort studies is the risk of lack of power. True associations may remain undetected. No scientific study should ever be conducted if no serious power-estimation was made! A common source of publication bias is that an under-dimensioned study that (by chance) was significant has good chances to be published, but an under-dimensioned negative study will never be published (nothing was found – which is not very exiting if the authors did not have power enough to find anything). 3) Another challenge is to consider the obvious risk of mass-significance when hundreds of substances are investigated as risk factors for hundreds of certain types of birth defects. 4) Finally, the risk of existence of undetected confounders which may bias the results must be mentioned.

The Swedish health registers provide prospectively collected population-based data on drug exposure during pregnancy. Using data from 1995-2001, Källen B and Otterblad Olausson (2001), compared the intrauterine drug exposure for 5 565 infants with heart defects with that of 577 730 control infants in the Swedish Medical Birth Registry. They tested 59 drugs and drug-groups. The study design was repeated using data from 2002-2009. Using this independent dataset, 8680 infants with non-chromosomal heart defects were identified, and the maternal drug consumption in early pregnancy for these infants was compared with that of 810715 infants without any heart malformations. The independent study confirmed the association between heart defects and insulin, antihypertensives, beta-blocking agents, and anticonvulsants. However, the previously reported association between heart defects and macrolides, clomipramine, fertility drugs, nitrofurantoin, and tricyclic antidepressants, could not be confirmed. In the recent study, a significant association was found between non-chromosomal heart defects and Paroxetine (adjusted odds ratio: 2.1, 95% confidence interval: 1.4-3.3), but for the other selective serotonin reuptake inhibitors, no associations with heart malformations were detected.

Conclusion: The Swedish health registers provide prospectively collected data on exposure for a large cohort, with sufficient power to detect moderate risk increases. The risk of mass-significance could be avoided by comparing previous results with the results based on an independent data set. The registers contain information so that the most common possible confounders could be adjusted for. The most serious limitation is the difficulties to discriminate the drug effects from the effects of the underlying disease. However, correctly treated, and cautiously interpreted, epidemiological data can provide valuable information to the ‘never ending story’ on drug safety during pregnancy.
The role of education and cognitive skills in understanding mortality inequalities

Anton Lager, PhD, MPH
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The overall aim of this thesis is to improve our understanding of the association between cognitive skills and mortality by epidemiological analyses of their relationship. Related factors, especially own and father’s education, are also analysed. This field of research is approached in three observational studies and one quasiexperimental study. Previous research suggests that higher cognitive skills as measured by IQ tests in childhood predict lower risk of premature mortality. A related field of research demonstrates how schooling is associated to increases of IQ. Longer schooling in itself is also known to be related to longer life. Still how these associations should be understood is not clear. In this thesis it is argued that education is indeed causally related to lower mortality - and that this can be partly explained by the effect of schooling on cognitive skills. It is also argued that the association between cognitive skills and health cannot be reduced to people being ‘clever because they are healthy’ or to the position of one individual relative to other individuals. Since cognitive skills relate to every individual in a population and since they can be improved, new ways of thinking about promotion of population health are implied. Improvements of both cognitive skills and average life expectancy in a population could in principle be achieved at the same time as differences between individuals in a population are reduced. publications.ki.se/40796
Intra-uterine growth retardation (IUGR) – background, measurements and consequences

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Intrauterine growth restriction (IUGR) has implications for subsequent development of several organ systems; during the neonatal period, during early childhood and into adult life. A compromised feto-placental function may induce fetal nutritional deficits and decreased levels of growth factors essential for nutrient utilization. This trophic deprivation may be super-imposed by hypoxia-ischemia during a period of rapid neural and vascular differentiation. Modern fetal surveillance has enabled identification of the growth-retarded human fetus with an imminent risk of fetal death resulting in active delivery at very early gestations.

Pioneering research in the circulatory physiology of the growth-restricted human fetus performed in the Malmö-Lund region three decades ago has enabled longitudinal assessment of the effects of IUGR on neuro-development and cardio-vascular function. These studies have shown lasting effects into young adult age as detected by non-invasive markers of neurogenesis and vascular performance. More recently we have attempted to discern the effects of IUGR from those of extreme prematurity on organ function into childhood. These data are essential for current decision-making in prenatal care as well as for construction of appropriate follow-up schedules reaching into school entry.

Extremely preterm birth, irrespective of cause, is highly associated with postnatal growth restriction with implications for brain growth, retinopathy of prematurity (ROP) and lung development. The insulin-like growth factor (IGF) system is essential for normal neural and vascular development. We have described associations between low circulatory levels of IGF-I and its major binding protein (BP) IGFBP-3 and severe ROP, decreased brain volumes and impaired neuro-development in very preterm infants. In an attempt to decrease the prevalence of these severe morbidities we have initiated treatment studies aiming to substitute the extremely preterm infants with IGF-I/IGFBP-3 to levels similar to those of the healthy fetus remaining in utero.
For many cancer diseases of the childhood and young adulthood the survival rates are very high. An example is that more than 95 percent of the men treated for testicular germ cell cancer are now cured. Accordingly the issue of life-quality of the survivors plays a central role. Among the determinants of life-quality, reproductive aspects represent one of the major worries. Cancer treatment can introduce damage to the sperm chromosomes. There is a potential risk that these alterations in the genome can be transferred to the offspring and this risk might be even more pronounced when assisted reproduction technologies (ART) are used for fertilisation. Data on the health of the offspring of fathers treated for cancer are rather scarce and completely lacking for children born after use of in vitro fertilisation. Such information is crucial for proper counselling of young cancer survivors and can, in the future, help with developing treatment modalities with a less sperm DNA damaging potential.

Estimating the effects of relatively rare exposures such as paternal cancer and ART on pregnancy outcomes requires large cohorts, particularly when the outcomes of interest occur infrequently (e.g. congenital abnormalities). The unique personal identification numbers used in the Danish and the Swedish civil registration systems enabled us to conduct a large population-based register-linkage study to look at the effect of a paternal history of cancer on perinatal outcomes in liveborn children conceived naturally and those conceived using ART.

The presentation at the EpiHealth symposium will review the relatively few studies which have been focused on the health of the offspring of fathers treated for cancer, and give a more detailed description of the register-based study performed in Sweden and Denmark.
Cognitive epidemiology
A perspective from child psychiatry: perinatal factors and neurodevelopmental disorders

Maria Råstam

At least 5% of children below the age of 6 are affected by neurodevelopmental disorders /child neuropsychiatric problems, including the autism spectrum disorders (ASDs) and attention-deficit–hyperactivity disorder (ADHD) (7% of boys, 3% of girls). These disorders must be present from infancy or early childhood, but may not be detected until later. Minor physical anomalies that are developmentally linked to events in the first weeks of fetal neurodevelopment are more common among children with neurodevelopmental disorders than in their typically-developing peers.

The ASDs affect about one percent of the population and are characterized by severe impairment in social interaction and communication and by the presence of stereotypic behaviour. In the largest study to date of infants with an older sibling with ASD, 18.7% of the infants could be diagnosed with ASD before age 3 years. There was an almost threefold increase in the risk of an ASD outcome in male relative to female siblings.

Epidemiological twin studies report over 80% heritability for parent-reported ASD, and high genetically mediated comorbidity. A study of an Australian cohort of 465 children with ASD and their 481 siblings found more obstetric complications in the children with ASD and their siblings than in a random population-based control group (n = 1313) pointing to a common genetic vulnerability to pre- and perinatal factors.

Obstetric factors that seem to increase the risk of ASD are low birth weight, advanced paternal age at the time of conception, maternal antibodies to fetal brain tissues, maternal diabetes/obesity/hypertension, and exposure to toxicants early in fetal development. Prospective cohort studies from the Faroe Islands have shown maternal mercury exposure during pregnancy to be associated with neuropsychological deficits at age 7 years.

In ADHD, epidemiological studies from the Swedish Twin Registry report genetic factors to account for 70% of the statistical variance in twin ADHD scores, while shared and non-shared environmental factors account for the rest.

Biological environmental factors found to have significant associations with a diagnosis of ADHD in 277 Malmo children (compared to 31,775 typically developing children from the same region) were young maternal age, maternal smoking during pregnancy, child born before week 32 of pregnancy, Apgar score below 7 at 5 minutes after delivery, and male child. In an Australian community-based sample of 6 to 7-year-old children (n=3,474) maternal smoking during pregnancy, maternal postnatal depression, and male child strongly predicted parent-reported ADHD. A recent prospective study of longitudinal data from more than 29,000 twins found evidence for a causality between low birth weight and ADHD symptoms.

Summing up, epidemiological studies have shown abnormal pre- and perinatal factors to be associated with child neurodevelopmental problems, but these could at least in some part be secondary to preexisting fetal developmental abnormalities associated with child neuropsychiatric disorders.
Clinical practices in IVF: developments over time

Pia Saldeen, MD, PhD

The first IVF baby, Louise Brown, was born in July 1978 at Oldsham General Hospital in UK and her birth was the culmination of a long scientific collaboration between Robert Edwards (scientist) and Patrick Steptoe (gynecologist). Since then, the IVF procedures have changed radically.

The access to IVF services has increased. IVF is today available in the majority of countries and in Europe 2-5% of all births are the result of IVF.

IVF today is more simple, safer and with a higher success rate. The ovum pick procedure was originally done by laparascopy but is now performed with ultrasound guided transvaginal puncture as an outpatient procedure in local anesthesia or conscious sedation.

Other major advances are the different options for ovarian stimulation schedules. Louise Brown was born after collection of an oocyte in a natural cycle, but today most IVF cycles are performed in a controlled ovarian stimulation cycle using gonadotrophin preparations in combination with GnRh agonist or antagonists for prevention of premature LH surge. GnRH antagonists were introduced a decade ago and provide advantages for the women regarding well-being (less side effects) as well as a shorter treatment period compared to the more conventional GnRh agonist treatment schemes.

IVF was initially exclusively for women with tubal factor blockage but the indications have expanded and tubal factor is today a minority of treatments. Today IVF is used also for male factor infertility, endometriosis, PCO and unexplained infertility.

The laboratory procedures have improved substantially, with sophisticated high quality culture media now available, the culturing performed in microdroplets in Petri dishes instead of test tubes, the incubator milieu closely monitored for pH and temperature, etc. Embryo freezing and thawing was a major achievement when introduced in 1984, with cryopreservation of surplus good quality embryos and thereby increasing the cumulative success rate. The intracytoplasmic sperm injection (ICSI) technique in the early 90s, with injection of a single sperm directly into the oocyte, was a revolution and made it possible to treat also male factor infertility effectively.

In Sweden all IVF clinics annually report to the NBH services data on their IVF cycles. This register enables quality assurance of IVF outcome and longitudinal data to show trends over the years in maternal demographic characteristics. For example, the delivery rate per number of embryo transfers has increased, the duration of infertility when commencing IVF has decreased, the proportion of women with obesity has increased and the proportion of women smoking has decreased.

The safety for the children conceived after IVF was significantly improved when a policy of elective single embryo transfer (eSet) was introduced in Sweden a decade ago. Without any fall in pregnancy rate per IVF cycle, the twin pregnancy rate fell from about 25% to 6%. This has resulted in an overall lowering of the risk for premature delivery.

Although most of the developments have been technical, also ethics, regulations and legislation has changed over time. The Swedish Act on In Vitro Fertilization 1988, which regulates the practice on IVF in Sweden has gone through several re-designs and moved from a fairly restrictive legislation to a more liberal and permissive one.
Antenatal exposure for ultrasound and postnatal development

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Ultrasound has an extraordinary safety record. It has been used in obstetrics for almost five decades with no proven harmful effects. However, absence of evidence of harm is not evidence of absence of harm. Thus, it is necessary to study directly the effect of prenatal ultrasound exposure on human populations.

Two systematic reviews of epidemiological studies of the safety of ultrasound in pregnancy were published in 2009 and 2010. The outcomes assessed included maternal outcomes, perinatal outcomes, childhood growth, neurological development and school performance, non-right handedness, childhood malignancies, intellectual performance and mental diseases. In addition, a meta-analysis of three randomized controlled trials regarding handedness was published in 2011.

Epidemiological studies have demonstrated no associations between prenatal ultrasound and adverse perinatal outcomes, childhood malignancies, neurological development, dyslexia, speech development, school performance, intellectual performance and adult mental disease. However, there is a weak statistical significant association between prenatal ultrasound and being non-right handed. This does not mean that there must be a causal relationship.

In general, the epidemiological literature are reassuring. However, in light of the increasing acoustic output values from modern ultrasound devices, the safety issue should not be neglected.
Parental smoking and semen quality of adolescent men

Jonatan Axelsson
Lund University

**Background:** Previous studies have indicated a negative impact of maternal, but not paternal smoking during pregnancy on sperm counts of their sons. We wished to elucidate the impact of both maternal and paternal smoking on the standard semen parameters, sperm DNA integrity and reproductive hormones in their sons.

**Methods:** Semen samples from 310 17 - 20 year-old men from the general Swedish population were analysed for sperm number, motility, volume, and by use of Sperm Chromatin Structure Assay, the sperm DNA integrity. Serum was analysed for reproductive hormones. Information on parental smoking was obtained from the Swedish Medical Birth Register and from questionnaires. The impact of prenatal (maternal, paternal) and own smoking was evaluated in a multivariate (I) model with all types of exposure tested at the same time and in a stratified (II) model with only those having one type of exposure.

**Results:** For both models paternal smoking was associated with lower sperm numbers, sperm concentration being 44% lower (95% CI: 16%;62%) (model II) and total sperm count 32%/50% lower (model I/II) (95% CI: [I] 6.3%;51%, [II] 23%;68 %). Maternal smoking was only statistically significantly associated with sperm concentration in model II (36% lower [95% CI: 3.0%;58%]). Paternal smoking was in model I associated with 13% lower semen volume (95% CI of difference: 1.4%;27%), and a lower level of estradiol. Sperm DNA integrity was not associated with parental or own smoking.

**Conclusions:** Paternal smoking during pregnancy was negatively associated with sperm counts of the sons.
Objective: Children born with non-optimal birth characteristics, i.e. small for gestational age (SGA) and/or preterm, have an increased risk for several long term effects such as neurological sequelae, and chronic disease. The purpose of this study was to examine whether twins exhibited a different outcome, in comparison with singletons, in terms of hospitalization during adolescence and early adulthood and to what extent differences remain when considering the divergence in birth-characteristics between singletons and twins.

Method: Twins and singletons born 1973-1983 in Sweden and surviving till age 13 were included and followed until the end of 2006. Data on birth characteristics, parental socio-demographic factors and hospitalizations were collected from national registers.

Results: Adjusting for parental socio-demographic factors, twins had a higher risk of being hospitalized than singletons (odds ratio: 1.17, 95% confidence interval: 1.10-1.25) and more often due to “Congenital anomalies” (OR=1.18, 95% CI=1.09-1.28), “Infections” (OR 1.14; CI 1.08-1.20), “External causes of illness” (OR 1.10; 1.09-1.15), “Diseases of the nervous system” (OR=1.18, 95% CI=1.10-1.26), and of the “Diseases of the digestive system”. Stratifying for birth characteristics, twins with non-optimal birth characteristics had a lower risk of hospitalization than non-optimal singletons on e.g., “Congenital anomalies”, and “Diseases of the nervous system” (OR=0.86, 95% CI=0.77-0.96, OR=0.88, 95% CI=0.81-0.97, respectively) and on all causes (OR=0.87, 95% CI=0.83-0.92). Among those with optimal birth characteristics twins had an increased hospitalization due to “External causes of illness” (OR=1.07, 95% CI=1.02-1.13) compared to optimal singletons.

Conclusion: Twins have higher hospitalization risks than singletons. Stratifying for birth characteristics this difference diminishes and for some diagnoses non-optimal twins seem to do slightly better than non-optimal singletons.
The association between childhood growth and risk of coronary heart disease in adulthood

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Background and aims: Childhood growth may influence health outcomes at adult age. The pathways which favour disease development remain unclear. The aim was to explore the association between childhood growth (ages 8-13) and coronary heart disease (CHD) events in adulthood (range 35-65 years).

Methods: Subjects were 2120 Icelanders born (1921-1935) and living in Reykjavik, Iceland when recruited into the Icelandic Heart Association longitudinal study in 1967-1991. Size at birth and yearly growth measures from ages 8-13 included height, weight, and date of measurement. CHD events from recruitment to December 2009 were extracted from national registers. Associations between childhood growth and CHD events were evaluated by Cox-regression.

Results: There were 230 CHD events among men and 94 CHD events among women. The risk of CHD increased for each 1-unit increase in childhood body mass index (BMI) z-score and was positively associated with age, hazard ratio (95% confidence interval) [1.01 (0.89, 1.15)] at age 8 to [1.26 (1.11, 1.43)] at age 13 years. Concerning growth, men who had CHD events were lighter at birth, 90 grams (95%CI: -7, 173), and slightly shorter in childhood, 1.1 centimetres (95%CI: -0.1, 2.4) below average at 13 years. Non-significant differences in average growth were observed for females.

Conclusions: Higher BMI from ages 8-13 predicted increased risk of CHD in adulthood. Men who had CHD events tended to be shorter as children. It is possible that sex-specific growth velocities, primarily height, may explain differences in CHD risk, however this association needs to be further explored.
The effect of smoking and snus on birthweight. A quasi-experimental design with sibling analysis

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Abstract

We aim at studying the impact of tobacco consumption during pregnancy on birthweight by differentiating between smoking and snus-consuming mothers in two-time-exposures (i.e., three month before pregnancy and during the first pregnancy trimester). We combine a conventional individual analysis with a quasi experimental sibling analysis.

We use the Swedish Medical Birth Register from 2005 to 2010 (n=823,553 babies) and analyze singleton sibling newborns from Swedish mothers with contrast of exposition (78,814 individuals nested into 37,517 groups or siblings).

We applied a linear regression adjusting by robust standard errors and Multilevel linear regression models via MCMC sampling using orthogonal parameterization to compute family specific fixed effects.

Although statistically significant, snus has a minor effect on birthweight. Smoking is associated with a reduction of birthweight, but its effect is substantially smaller using the sibling analysis. Our quasi experimental analysis confirms that quitting smoking entails a real, although slight, increase in birthweight. The minor effect of snus suggests that the mechanisms might not be mediated by nicotine.
Adiponectin decreases risk for insulin resistance at age 71 in men of normal BMI and birth weight

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BACKGROUND Studies have shown that reduced foetal growth is associated with increased risk of insulin resistance later in life.

AIMS To investigate the role of adiponectin in the association between birth weight (BW) and insulin resistance in elderly men.

METHODS We studied 727 men born 1920-24 and resident in Uppsala, Sweden, in 1970, who were part of the ULSAM cohort study with more than 38 years follow-up. Information on serum adiponectin, clinical measures of insulin resistance at age 71, BW from medical records, socioeconomic data from routine registers and lifestyle data from questionnaires were available. BW was categorized as low or normal by generating population-specific cut-offs according to Wilcox’s hypothesis.

Main outcome measure was insulin resistance measured as a latent variable comprising 2 indicators: insulin sensitivity index and homeostatic model assessment (HOMA) measured when the participants attended the investigation in 1990. Serum adiponectin was measured by routine laboratory analysis at the same investigation along with other blood parameters. BMI at age 71 was derived from anthropometric measurements. Participants answered questionnaires on lifestyle-related activities including physical activity, smoking and alcohol consumption. Path analysis was used to determine the role of adiponectin in the association between BW and insulin resistance. Analyses were stratified by BMI (normal, overweight and obese as per WHO criteria).

RESULTS A significant indirect effect of BW on insulin resistance via adiponectin was found only in men with normal BW (≥3300g) who had normal BMI (18-25kg/m²) in adulthood. In these men, insulin resistance decreased by β = -0.06 (95% CI, -0.10 to -0.02) compared to men born low BW. Results are adjusted for current BMI, smoking, physical activity, alcohol consumption and socioeconomic status. We did not observe similar effects in men born normal BW but overweight or obese in adulthood.

CONCLUSION Adiponectin mediates the inverse association between BW and insulin resistance only in men of normal BMI. The mediating effect of adiponectin on insulin resistance is absent in overweight and obese men. This study explains possible mechanisms that influence the inverse relationship of BW and insulin resistance.

Table. Indirect effects of birth weight (BW) on insulin resistance mediated by adiponectin; stratified by BMI.

<table>
<thead>
<tr>
<th>Body mass index at age 70</th>
<th>Normal</th>
<th>Overweight</th>
<th>Obese</th>
</tr>
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<tbody>
<tr>
<td>β estimate</td>
<td>-0.06</td>
<td>0.00</td>
<td>-0.04</td>
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| 95% confidence intervals indicated in parenthesis.
Intergenerational and early life determinants of cardiovascular risk factors in Swedish children

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Aims To study the relationship of children’s cardiovascular (CVD) risk factors with parent’s CVD risk factors, socioeconomic position (SEP) and lifestyle.

Methods 602 families (2141 individuals), with two full sibs; aged 5-14 years and their biological parents (Uppsala Family Study) formed the study population. Cholesterol, ApoB/ApoA1 ratio, adiponectin, blood pressure and BMI were measured by routine methods. Age and gender specific overweight/obesity was computed. Parental SEP determined by occupational class and education and lifestyle habits (alcohol consumption, smoking, physical activity) were from questionnaires. Associations with CVD risk factors were analysed by linear and logistic regression. Results were adjusted for child’s age, gender, pubertal stage and family clustering.

Results Strong, consistently significant associations exist between parents’ and children’s CVD risk factors independent of parental SEP and lifestyle. Certain parental lifestyles, adjusted for SEP, had strong significant associations with children’s CVD risk factors. Children of smoking parents had higher BMI (ratio smoking vs. non-smoking fathers and mothers 1.04, 95% CI 1.00-1.17 and 1.03, 1.00-1.15). Children of mothers reporting vigorous physical activity had lower BMI, cholesterol and decreased odds for overweight/obesity in a dose response manner. Compared with mothers reporting no vigorous activity, mothers with <1.15 hours and 1.15-2.4 hours/week vigorous activity had 43% (OR 0.57, 95% CI 0.22-0.89) and 72% (0.28, 0.14-0.60) lower risk of having an overweight/obese child respectively. Alcohol consumption in parents was associated with higher cholesterol and BMI (mothers only) in children. We found few independent associations between parental SEP and children’s CVD risk factors.

Conclusion Strong correlations in CVD risk factors between family members that are not related to parental SEP/lifestyle suggest a role of genetics in influencing children’s CVD risk factors and early development of these risk factors in childhood. Parental behaviours; smoking, alcohol consumption and low physical activity were significantly associated with higher levels of some CVD risk factors in children. Both maternal and paternal smoking appears equally important. Public health policies should target families with unhealthy lifestyles.
Early life biological and social determinants of long-term reproductive success in Swedish males and females

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Aim: To study biological and social determinants of reproductive success in a post-demographic transition population.

Methods: We investigated early life determinants of mortality and fertility using multi-generational data from a large, population-based cohort of 13 672 individuals born in Sweden between 1915 and 1929. We studied the effects of birthweight for gestational age, preterm birth, birth multiplicity, birth order, mother’s age, mother’s marital status, family socio-economic position (SEP) and school performance at age 10. Our primary outcomes were probability of every marrying, total number of children and total number of grandchildren by end 2009.

Results: The predictors of number of great-grandchildren showed several similarities with the predictors of number of grandchildren (Goodman & Koupil 2009, 2010): positive effects of female gender, higher birthweight, higher birth order and younger mother, plus a trend towards an effect of term birth. A striking difference was that whereas higher SEP predicted more children and grandchildren, higher SEP predicted fewer great-grandchildren.

This difference appeared to be mediated via later childbearing in high SEP lineages, and effect was evident in cohort members, children, and grandchildren alike. The result was that in 2009 low SEP cohort members had more great-grandchildren per child, while the number of grandchildren per child was almost identical between socio-economic groups.

Associations of number of children with number of grandchildren and number of great-grandchildren were also essentially linear across the full range of number of children, with no suggestion of a U-shaped relationship or even of any flattening of the line at the high end, thus providing evidence against a ‘fertility optimisation’ hypothesis that intermediate family sizes maximise long-term reproductive success

Conclusions: Social and biological characteristics at birth and school performance at age 10 independently predict reproductive success in gender-specific patterns. The key mediating role of marriage provides a counterpoint to the lifecourse concept of ‘embodiment’, indicating how social characteristics may mediate the effects of early life biological and cognitive factors.

References:
Gender specific patterns of associations in preterm and post-term birth across three generations of Swedish males and females
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Aim: We analysed associations between gestational duration in grandchildren and their biological grandparents, associations in risk of preterm and post-term birth across generations and effects of birthweight-for-gestational age in grandparents on length of gestation and risk of preterm and post-term birth in biological grandchildren.

Methods: The Uppsala Birth Cohort Multigenerational Study includes manually collected archive data on a representative cohort of 14,192 males and females born in Uppsala, Sweden 1915-1929 and information on descendants of the cohort obtained through linkage to routine data registers. Using a path analysis, we analysed 7915 grandparents and their 26,423 grandchildren, where the grandparent, the grandchild and the intermediate biological relation were singletons. Maternal grandmothers, maternal grandfathers, paternal grandmothers and paternal grandfathers were considered separately. Models were adjusted for social variables and fitted separately for male and female grandchildren due to evidence of effect modification by sex.

Results: Gestational duration in grandparents was positively associated with gestational duration in their grandchildren. The observed associations are equivalent to a 0.3-0.4 (0.01≤p≤0.07) day increase in the grandchild’s gestational duration for each additional week in the maternal grandparents’ gestational duration and 0.1-0.2 (p≥0.2 in all models) day increase in the grandchild’s gestational duration for each additional week in the paternal grandparents’ gestational duration. Birthweight-for-gestational age in maternal grandfathers was positively associated with gestational duration in their grandchildren, while birthweight-for-gestational age in paternal grandfathers was inversely related to gestational duration in their grandsons. Distinct and gender specific patterns of statistically significant associations were observed for risk of preterm and post-term birth across generations with strongest associations generally observed in male grandchildren and in grandfathers. Post-term birth in both maternal and paternal grandfathers was associated with higher risk of post-term birth in grandsons.

Conclusion: Gestational duration in maternal grandparents and weight-for-gestational age in maternal grandfathers are positively associated with length of gestation in their grandchildren while higher birthweight-for-gestational age in paternal grandfathers reduces gestational duration in their grandsons. Intergenerational associations in preterm and post-term birth appear to be highly gender specific and generally stronger in males.
Differences in prescription rates of antidepressant drugs in relation to individual hormonal contraceptives: a nationwide population-based study

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Objectives To examine the association of individual hormonal contraceptives with antidepressant therapy.

Methods In a cross-sectional nationwide register-based study, we examined the prescription rates of antidepressant drugs in relation to individual combined hormonal and progestin-only contraceptives among Swedish women aged 16–31 years (N=917,993). Drug data were obtained from the Swedish Prescribed Drug Register for the period 1 July 2005-30 June 2008. Data on the total population of women aged 16-31 in 2008 were obtained from the Total Population Register of Statistics Sweden. The proportion of women using both hormonal contraception and antidepressants, and odds ratios (ORs) for antidepressant use for hormonal contraceptive users versus non-users, were calculated, the latter by logistic regression, for each formulation.

Results The highest antidepressant OR in all age groups, particularly in the 16–19 years age group, related to medroxyprogesterone-only, followed by etonogestrel-only, levonorgestrel-only and ethinylestradiol/norelgestromin formulations. Oral contraceptives containing ethinylestradiol combined with lynestrenol or drospirenone had considerably higher ORs than other pills. ORs significantly lower than 1 were observed when ethinylestradiol was combined with norethisterone, levonorgestrel or desogestrel.

Conclusion The association between use of hormonal contraceptives and antidepressant drugs varies considerably within both the combined hormonal contraceptive and the progestin-only groups.
Antenatal calculation of risk for large-for-gestational age term newborns using the Bayesian theorem. A population-based study.

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Objectives. To evaluate the prediction of large-for-gestational age (LGA) term neonates using the routine third trimester ultrasound examination and to investigate whether the prediction could be further improved by adding information on maternal characteristics.

Methods. Information on 56,792 singleton term pregnancies with a routine ultrasound examination at 32 to 34 gestational weeks was retrieved from a population-based perinatal register, Perinatal Revision South. Information regarding fetal ultrasound examinations was collected from a local obstetric database, and for maternal BMI and smoking habits the Swedish Medical Birth Register was used. Estimated fetal weights (FW) were expressed as gestational age specific standard deviation scores (z-scores). The LGA prediction was assessed by receiver operating characteristic (ROC) curves. The data set with complete clinical information (n=48,809) was divided into a development and a validation set. Using the development set, multiple logistic regression analyses were performed to identify maternal characteristics associated with LGA. The obtained odds ratios were converted into likelihood ratios (LRs). These were then applied on the validation set and the probability for LGA for each infant was estimated using the Bayesian theorem: Predicted probability = posterior odds / (1 + posterior odds).

Results. The FW z-score showed a high LGA prediction ability (area under the ROC-curve [AUC] 0.89 [95% CI 0.89-0.90]). The prediction was further improved by using the prediction model including both FW z-scores and maternal variables (AUC 0.91, 95% CI 0.90-0.92) (p-value for difference p <10^-6). The corresponding AUC for a model including maternal characteristics only was 0.74 (95% CI 0.73-0.76).

Conclusion. Routine third trimester ultrasound FW estimation is efficient to predict LGA term newborns. The LGA prediction might be further improved by using a prediction model including maternal characteristics.
Cognitive and Psychological Functioning in Adolescents and Young Adults after Repeat Courses of Antenatal Corticosteroids


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BACKGROUND

It is unclear whether repeat courses of antenatal corticosteroids for preterm birth adversely affect cognitive function and behavior later in adult life. To date no follow-up studies beyond the pre-school years exist, and the results from these are inconclusive.

METHODS

Fifty-eight youths (36 males) in a Swedish population-based cohort who had been exposed in utero to two to nine weekly courses of antenatal betamethasone were evaluated at 18 (range 14 to 26) years of age with tests of general cognitive ability, memory and learning, working memory, attention and speed, and cognitive flexibility and inhibition. Behavior self-reports were also administered. Unexposed subjects (n =44, 25 males), matched for age, sex, and gestational age at birth, served as a comparison group. An additional group of individuals exposed in utero to a single course (n=25, 14 males) was included for dose-response analyses.

RESULTS

Exposure to repeat courses of antenatal corticosteroids was neither associated with deficits in higher cognitive functions nor self-reported psychological health in later life. Mean scores obtained in two measures of attention and speed (Symbol Search and Digit Span Forward) were significantly lower in subjects exposed to two or more corticosteroid courses, but this was not dose-dependent. However, such differences were not observed with regard to more complex cognitive tasks, or on self-reported attention, adaptability or overall psychological function.

CONCLUSIONS

Repeat exposure to antenatal corticosteroids may be associated with limited deficits in attention and speed through adolescence and young adulthood, but there is no evidence for long-term adverse effects on higher cognitive or psychological functioning.

Prevalence of ultrasonographic fetal soft markers during the second trimester ultrasound screening and its correlation to Down Syndrome

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Background: Genetic sonogram in the second trimester is discussed. Furthermore, follow-up procedures upon detection of ultrasonographic markers at routine anatomy scanning vary widely in Sweden.

Objective: To investigate the prevalence of isolated markers during the second trimester ultrasound screening in an unselected low risk population in Sweden, its association with Down Syndrome (DS) in fetuses and the incidence of invasive chromosomal diagnostic testing after detection of isolated markers.

Study design: A prospective observational study at Uppsala University Hospital consisting of all fetuses examined by ultrasound at 15+0 to 22+0 weeks gestation between July 2008 and March 2011. Cases with isolated markers, that is, plexus choriodeus cyst (PCC), echogenic intracardiac focus (EIF), pyelectasis, thickened nuchal fold and hyperechogenic bowel were verified for outcome data by hospital records, including results from invasive testing. Fetuses with DS, other than those with ultrasonographic markers, were identified from laboratory records. Cases with ultrasonographic markers were compared to non-cases in terms of frequency of DS and invasive diagnostic testing. The results were analysed to determine the sensitivity, specificity and positive likelihood ratio (LR+) for the detection of DS.

Results: Second trimester ultrasound screening was performed on 10,914 fetuses during the study period. Seventeen percent of the study population had a first trimester screening for DS and 15 of these pregnancies were diagnosed with DS and terminated. An additional 17 fetuses were diagnosed with DS later in pregnancy or after birth.

Isolated markers in the second trimester anomaly scan were detected in 5% (540/10,914) of the fetuses; 176 with PCC, 266 with EIF, 85 with pyelectasis, 4 with thick nuchal fold and 9 with hyperechogenic bowel. There were 72 cases (0.7%) with multiple markers. The prevalence of DS was 0.16% (17/10,914), and among these fetuses, 2 had isolated EIF and 2 had isolated pyelectasis. Three cases of DS were associated with multiple soft markers. The remaining 10 cases had no association with ultrasonographic soft markers.

The sensitivity, specificity and LR+ of DS was 14.3%, 97.6% and 5.86, respectively, in the cases with isolated EIF and 14.3%, 99.2% and 18.6, respectively, in fetuses with isolated pyelectasis.

Frequency of invasive testing for aneuploidy was 30% in pregnancies where isolated soft markers were detected compared to 7% in the total population.

Conclusion: Genetic sonogram in an unselected Swedish population, without specific information about soft markers before routine anomaly scan, increases the invasive diagnostic testing, although the association between DS and isolated markers is low. Larger studies are needed to confirm the level of correlation in a low risk population.