

Department of Women's and Children's  
Health

**ANNUAL REPORT**

**2009**

## Introduction

This will be my last contribution to our Annual report as head of the department of Women's and Children's Health. I see it as a privilege to have had this important task during the last five years. The department is vital and expanding in education as well as in research. To be the head means that I have the advantage to meet ambitious teachers and researchers and loyal administrators. It hits me again and again that our department runs research projects covering all kind of topics within our specialities. We have researchers with excellent knowledge in qualitative as well as in quantitative research methods. This knowledge forms a basis for fruitful collaboration within and between our research groups. The department offers a wide variety of educational programs including graduate courses for medical and nursing students, postgraduate programs for midwives and doctors and several international courses, among them a master program in international health. During 2010 we expect to regain the right to examine specialist nurses in pediatric nursing. We are lucky to have devoted teachers, which is a prerequisite to succeed with our broad tapestry of educational tasks. We see it as important that all teachers are actively involved in research. Moreover, teachers in clinical programs should participate in the clinical work to be able to fulfil their teaching duties.

We have had the pleasure to welcome two senior lecturers during 2009. Tryggve Nevéus is a pediatrician with special interest in micturition disorders during childhood and Christine Rubertsson is a midwife with research merits in caring science. I am convinced that both will find their roles in the department and contribute with research, including tutorship, and teaching in a valuable way. I am also most satisfied that we finally have succeeded to create an adjunct position as senior lecturer in paediatric surgery for Rolf Christofferson.

2009 can be described as successful from an academic standpoint but disturbing from an administrative viewpoint. The new economical accounting system, which was introduced 2009 has created lots of confusion and loss of energy and time, which could have been used for better purposes.

I wrote last year that the cooperation with our clinical counterpart was most satisfying. I am very pleased to state that this spirit of mutual understanding in combination with a friendly atmosphere continues. We do need each other to succeed.

We have new exciting challenges to look forward to in the years to come. We are lucky to work within an important field with the aims to improve health for women and children, be it in Uppsala, Sweden, Europe or the world around.

Uppsala in March 2010

Ove Axelsson

Head of the department of Women's and Children's Health

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# Organization

## Chairman

Ove Axelsson

## Deputy Chairman

Jan Gustafsson

## Department board

(from July 2008)

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Jan Gustafsson	teacher representative
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Lars-Åke Persson	teacher representative
Inger Sundström Poromaa	teacher representative
Lennart Nordvall	teacher representative, deputy
Matts Olovsson	teacher representative, deputy
Karin Törnblom	representative for technical/adm. personnel
Lena Moby	representative for technical/adm. personnel, deputy

(from July 2008)

Elisabet Eriksson	graduate student representative
Elin Bannbers	graduate student representative
Tansim Akhter	graduate student representative, deputy
Filip Olsson, T9	student representative
Nadia Razmi, T9	student representative, deputy

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# Department of Women's and Children Health research groups

## Reproductive Biology

Matts Olovsson, MD, PhD, Associate Professor

## Obstetrical Research

Ove Axelsson, MD, PhD, Professor

## Gynaecological Endocrinology

Tord Naessén, MD, PhD, Associate Professor

## National Centre for Knowledge on Men's Violence against Women

Gun Heimer, MD, PhD, Professor

## International Maternal and Reproductive Health

Birgitta Essén, MD, PhD, Associate Professor

## International Child Health and Nutrition

Lars-Åke Persson, MD, PhD, Professor

## Paediatric Endocrinology

Jan Gustafsson, MD, PhD, Professor

## Paediatric Oncology

Susan Pfeifer, MD, PhD, Adjunct Professor

## Paediatric Neurology

Gunnar Ahlsten, MD, PhD, Associate Professor

## Perinatal, Neonatal and Pediatric Research

Anders Jonzon, MD, PhD, Associate Professor

## General Pediatric Research Group

Lennart Nordvall, MD, PhD, Associate Professor

## Pediatric Surgery and Pediatric Urology

Rolf Christofferson, MD, PhD, Associate Professor

## Reproductive Health

Inger Sundström Poromaa

# **Scientific Reports**

## **Reproductive biology**

**Matts Olovsson**

### **Research projects**

#### **1) Preeclampsia**

Pre-eclampsia is a complication that occurs in 3-5% of pregnancies. It is a potential threat against both mother and foetus. This project aims at a better understanding of the aetiology and pathogenesis of pre-eclampsia and how to predict the disease. We have shown that there are also several differences between early and late onset preeclampsia concerning placental oxidative stress, angiogenic and anti-angiogenic markers and several inflammatory markers. Our data indicates that pathogenesis differs between early and late onset disease and they should most likely be predicted, diagnosed and treated differently. Currently we are also studying potential markers such as angiopoietins to predict preeclampsia. In cooperation with Stefan Hansson (Lund University) and Katja Junus we are studying the genomic profile differences between early- and late-onset PE. In cooperation with Hella Hultin and Per Hellman we are studying the association between previous hyperparathyroidism (HPT) and an increased risk to develop PE, now focussing on vitamin-D receptor polymorphism. Together with Anna-Karin Wikström we have initiated a study where placental metabolism is studied *in situ* using MRS. Preliminary data clearly shows differences between women with preeclampsia and healthy pregnancies. Within the MRS-projects we are currently discussing some cooperation with Professor Graham Burton in Cambridge (UK) on placental/trophoblast metabolism, especially mitochondrial function. The studies are coordinated by Matts Olovsson. Publications no; 4, 6, 11, 14-16, 19.

#### **2) Endocrine disrupting chemicals and female reproductive health**

It has been shown that several environmental contaminants such as PCB and DDT have endocrine disrupting capacity, thus meaning that they may have effects on female reproductive functions. A lot of information can be achieved from animal experiments but this is expensive, time consuming and there is also an intension to reduce the number of laboratory animal use. This as a part of an EU project, ReProTect, within ECVAM. We are working with cell culture systems to screen for potential effects of these chemicals on female reproductive functions. We have used endometrial cells such as human endometrial endothelial cells in our test systems. The work is done in cooperation with several other European groups. We are currently preparing test systems where we test the effects of endocrine disrupting chemicals on the early implantation of human preembryos on an artificial *in vitro* endometrium. Techniques used include cell viability and mitosis assays, qRT-PCR and gene micro arrays. The studies are coordinated by Matts Olovsson. Publications no; 2, 3, 5, 7-9, 18, 21.

#### **3) Endometriosis and endometrial angiogenesis**

Endometriosis is a common gynaecological disease, occurring in about 10% of all women. The disease causes abdominal pain and reduced fertility. Together with a group from Moscow we are investigating the association between the proliferative activity in the lesions and the angiogenic activity. We have recently shown that serum and peritoneal fluid concentrations of several factors involved in the regulation of angiogenesis at least partly normalize within a week after surgical removal of the endometriotic lesions. We have also shown a relationship between a specific endometrial marker and whether the endometrium has normal functional properties, i.e. that the women become pregnant or not.

Angiogenesis is thought to play a pivotal role in the cycling endometrium and is regulated by a combination of systemic and local factors. Physiological angiogenesis is part of the endometrial repair and growth process following menstruation as well as at the time of embryo implantation. Endometrial pathologies such as endometriosis, hyperplasia and malignancy are all dependant on

angiogenesis. We have studied the transcript profile changes induced by VEGF-A and serum withdrawal in primary human endometrial endothelial cells using oligonucleotide microarray measurement, followed by analysis using Gene Ontology and pathway analysis databases. This work is done in cooperation with a group in Professor Steve Charnock-Jones in Cambridge (UK). We will continue this work by analysing existing data on several other exposure experiments. The studies are coordinated by Matts Olovsson. Publications no; 13 and 20.

#### **4) Improvement of organised cytological screening by self-sampling**

Women not attending organised cytological screening program are offered testing of vaginal smear obtained using a novel self-sampling device. We have shown that there is a high prevalence of oncogenic HPV in women not attending organised cytological screening and that about half of the women not attending the organised cytological screening program actually performs the self-sampling. The results have been presented in several publications (49-57), abstracts and presentations. We are currently starting a study where we will perform repeated (daily) HPV analysis during a menstrual cycle to determine changes in virus production and release. The studies are coordinated by Matts Olovsson.

#### **5) Prognostic factors in assisted reproduction techniques (ART)**

The importance and influence of ovarian reserve on treatment outcome in assisted reproduction techniques (ART) has been a matter of great scientific interest in the last decades. Different methods of estimating ovarian reserve have been described, such as measuring inhibin B or anti-Müllerian hormone, basal or clomiphene-stimulated serum levels of FSH, or estimating the ovarian volume or number of antral follicles.

We have shown that basal LH modifies and improves the information given by basal FSH alone. Low FSH level combined with high LH probably reflects a well-preserved ovarian reserve and is associated with the highest success rates at IVF/ICSI (Ref 28).

We have also shown that the mean menstrual cycle length is highly related to success rates in assisted reproduction, independently of age. A precise menstrual cycle history could be used as a simple marker of ovarian reserve (Ref 29). The studies are coordinated by Jan Holte and Matts Olovsson.

#### **6) Studies on the human embryo**

We have studied gene expression in human embryos, which was published in PlosOne 2009. These studies on gene expression is continuing with bioinformatics studies on the communication between the embryo and maternal side, and the gene expression specific the different cells related to implantation such as trophoblast cells and stem cells. These studies are performed in collaboration with Andres Salumets in Tartu, Estonia. The importance of media composition is ongoing, one manuscript has been published and one is submitted, which will be part of Fredwell Hambilikis thesis work. The studies are continuing using proteomic methodology, and are part of Kjell Wånggren's post doc work in collaboration with Jonas Bergqvist, Uppsala. Furthermore, an epigenetic project, initiated by Julius Hreinsson, focuses on epigenetic effects after freezing of embryos. IGF1 is involved in embryo development. Our first study on IGF1 receptor shows the importance for IGF1 receptor for embryo development was recently published. These studies are coordinated by Anneli Stavreus-Evers.

#### **7) Studies on the fallopian tube**

Hormonal regulation of fallopian tube function is included in our ongoing studies of embryo transport and communication with the maternal side. These studies will be included in Jesper

Ekman's and Amani Rumman's thesis work. Special emphasis is on the effect of thyroid hormones, which has resulted in one published and one submitted manuscript during 2009. These studies are coordinated by Kjell Wånggren and Anneli Stavreus-Evers.

### **8) Studies on the endometrium**

The development of the endometrium is crucial for embryo implantation. The development is regulated by steroid hormones. Our data show that not only the classical hormones, estrogen and progesterone is important, also thyroid hormone play a role in endometrial receptivity. Several studies on markers of endometrial receptivity such as ghrelin, aquaporins and tissue factor has lead to one accepted and one submitted manuscript. A study on aquaporins was summarized in Anna Nowosad's master thesis work. These studies are coordinated by Anneli Stavreus-Evers.

### **9) Studies on biochemical markers for diagnosis and treatment of infertility**

For women with unexplained infertility, there are reasons to believe that endometrial factors can be involved. Today, we lack good diagnostic tools for these women, and the treatment could be more efficient. Our studies showed that LIF and its receptors (LIFR and gp130) and inhibitor (SOCS1) in endometrium from fertile and infertile women is published. This study shows that it is more common with low LIFR expression concomitantly with high SOCS1 expression in endometrium from women with unexplained infertility compared to fertile controls. A similar study on HB-EGF and its receptors showing lower HB-EGF expression in endometrium from infertile women is accepted for publication in *Reproductive Sciences*. These studies are performed in collaboration with Lusine Aghajanova, San Francisco, USA.

Our array data showed extensive gene expression in endometrium from fertile and infertile women, which was recently published in *Molecular Human Reproduction*. We can also show that fertility treatment has a negative influence on endometrial receptivity. These studies are performed in collaboration with Carlos Simon and Jose Horcajadas in Valencia, Spain and will be part of Signe Altmäe's thesis work. These studies are coordinated by Anneli Stavreus-Evers.

### **10) Studies on genetic factors related to infertility**

Genetic variations might influence endometrial receptivity and infertility treatment. Our studies on genes involved in LIF pathway is ongoing, and has results in two student exams so far. We have shown that there is no relation between genes involved in the adrenomedullin pathway and infertility, submitted manuscript. However, there is clear evidence that HABP2 single nucleotide polymorphism in the regulatory region, gene and protein expression is related to unexplained infertility which has been summarized in a submitted manuscript. These studies will be part of Signe Altmäe's thesis work and are coordinated by Anneli Stavreus-Evers. Furthermore, in collaboration with women's clinics in four hospitals, we have been able to collect blood samples from 200 women with repeated miscarriage. These samples will now be used to study possible genetic factors related to repeated miscarriage.

### **11) Studies on the importance of folate for pregnancy outcome**

Low folate levels have been related to fertility problems. Data from Tiina Syvänen's and Cecilia Vanhainen's master thesis's show that it is more common with the polymorphism in the MTHFR 677 TT in women with unexplained infertility compared to the general population. These studies will be included in Tiina Syvänen's thesis work. The first study on infertility and folate pathway was published this year and a second manuscript is submitted. One review article was published in collaboration with Andres Salumets, Tartu, Estonia. These studies are coordinated by Anneli Stavreus-Evers.

## 12) Hormonal regulation in vaginal mucosa in women undergoing anti-hormonal treatment against breast cancer and in postmenopausal women

Women with breast cancer have severe problems with dry vaginal mucosa affecting their quality of life, which has been summarized in a first manuscript. Local treatment with estrogens is not available for these women. Our studies involve events in the vaginal mucosa related to hormonal regulation and the role of aquaporins. These studies are performed in collaboration with Kerstin Nilsson and Juliane Schlenstedt in Örebro and Anneli Stavreus-Evers and Inger Sundström Poromaa in Uppsala, and the studies will be included in Theodora Kallak's doctorate thesis.

## 13) Ovarian cancer

Prognostic factors for epithelial ovarian cancer in FIGO-stages I-II. We have studied the relevance of p53, bax, p21, p27, PUMA och c-MYC, EGFR, VEGF-R, VEGF and PTEN as prognostic factors. A future project within genomics has been planned. We have also published a paper about borderline ovarian tumours and ovarian cancer in Sweden in 1960-2005. These studies are coordinated by Ingridur Skirnisdottir. Publications no; 58-64.

### Publications 2007-2009

1. M. Lindahl, M. Olovsson, S. Nyberg, K. Thorsen, T. Olsson, I. Sundström Poromaa. Increased cortisol responsivity to adrenocorticotrophic hormone and low plasma levels of interleukin-1 receptor antagonist in women with functional hypothalamic amenorrhea. *Fertil Steril*. 2007 Jan;87(1):136-42. Epub 2006 Nov 13.
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12. Skalkidou A, Sylvén SM, Papadopoulos FC, Olovsson M, Larsson A, Sundström-Poromaa I. Risk of postpartum depression in association with serum leptin and interleukin-6 levels at delivery: a nested case-control study within the UPPSAT cohort. *Psychoneuroendocrinology.* 2009 Oct;34(9):1329-37.
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770 000 SEK plus 325 000 SEK

European Union, 450 000 SEK

FORMAS 600 000 SEK

Fakultetsmedel för inbjudan av forskare 165 510 SEK

Vårdforskningsmedel 195 000

#### **Dissertations 2009**

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## Obstetrical Research

### Ove Axelsson

In the spring 2009 Maria Jonsson defended her thesis entitled “Use of Misuse of Oxytocin During Delivery”. She was later awarded “Hwasserska Priset” for the best clinical thesis in Uppsala 2009. Maria Jonsson concluded in her thesis that misjudgement of CTG patterns and inappropriate use of oxytocine during delivery are strongly associated with acidemia at birth. Metabolic acidosis and related neonatal morbidity can probably be prevented in 40-50% of cases if guidelines are adhered to. Maria Jonsson was supervised by associated professors Solveig Lindeberg and Ulf Hanson.

In 2010 we will most probably see three research fellows, Hashem Amini, Eva Bergman and Corinne Pedroletti, present and defend their theses. Hashem Aminis’ research focuses on fetal anomalies. He has shown that fetal autopsies not always verify antenatal ultrasound diagnosis of fetal anomalies in connection with pregnancy terminations. He concludes that fetal autopsies are necessary to get the final diagnosis, so that the women and their partners will receive correct information concerning the significance for forthcoming pregnancies. He also advocates that at least two independent antenatal ultrasound examinations are performed before the final information is given to the woman to avoid false positive cases. Such cases might lead to a decision to terminate a pregnancy based on incorrect information. In Hashem Aminis’ thesis there is also a publication demonstrating that there is a substantial underreporting of fetal malformations to the Birth Defect Register from terminated pregnancies compared to the figures recorded for newborns. In his last two papers, Hashem Amini has investigated the role of magnetic resonance tomography (MRT) for diagnosis of fetal anomalies. MRT performed best concerning CNS and thoracic anomalies and when maternal obesity or oligohydramnios made ultrasound examinations inconclusive.

Eva Bergman takes an interest in antenatal identification of intrauterine growth retardation (IUGR). In her first paper she states that today’s methods, symfysis-fundus measurements or repeated ultrasound, are insufficient. She tries to improve screening methods in two ways. Firstly, she has tested self-measurements meaning that the pregnant women measure the symfysis-fundus distance on their own. She has found that there is no systematic difference between self-measurements and those done by midwives but the pregnant women’s measurements show greater variation. The advantage with self-measurements is that more measurement data are available for analyses, which should be useful when relative growth is tested for improvement of IUGR detection antenatally. Eva Bergman has worked together with biostatisticians from Gothenburg to see if relative growth in combination with a specific statistical method of Shiryaev-Roberts can improve antenatal detection of IUGR. This was found not to be the case when basic data originate from self-measurements of the symfysis-fundus distance. She was able to prove that neonatal morbidity is increased for newborns already when the birthweight is below the 10<sup>th</sup> percentile. The struggle to improve antenatal detection of IUGR must go on.

Corinne Pedroletti has done a follow-up study of women operated on by the TVT-method. Her main findings are that 85% of women with stress incontinence are free from symptoms eight years after surgery. The corresponding figure for women with mixed incontinence is 30%. In general, women state improved quality of life eight years after their operation irrespective of which type of incontinence they presented with before surgery. High age, parity and previous Caesarian sections are significant risk factors for development of urgency after a TVT-operation. Women over 75 years of age and obese women were free from symptoms to a minor degree than women below 75 years and women with normal weight.

Peter Lindgren is now engaged as an assistant supervisor in two projects focusing on information to pregnant women about fetal diagnosis. Associate professor Ulf Hanson has started up a randomized

multicentre study on treatment or no treatment of gestational diabetes. Karin Eurenus, Ajlana Lutvica and a new research fellow Johanna Belachew, have begun a project to see if 3-D ultrasound could improve diagnosis of placental remnants after delivery. Maria Palm continues to work with her biobank consisting of blood and urine samples from women with uncomplicated pregnancies. Her aims are to see if oxidative stress, inflammation and angiogenesis change during normal pregnancy.

### Members of the group during 2009

Ove Axelsson	Professor
Ulf Hanson	Associate professor
Solveig Lindeberg	Associate professor
Helle Kieler	Associate professor
Eva Gerdin	Associate professor
Dan Hellberg	Associate professor
Staffan Nilsson	Adjunct professor
Karin Eurenus	M.D, Ph.D
Peter Lindgren	M.D, Ph.D
Karin Zetterström	M.D, Ph.D
Ajlana Mulic-Lutvica	M.D, Ph.D
Karin Stålberg	M.D, Ph.D
Maria Jonsson	M.D, Ph.D
Hashem Amini	Research fellow
Maria Palm	Research fellow
Eva Bergman	Research fellow
Johanna Belachew	Research fellow
Corinne Pedroletti	Research fellow

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## **Dissertations 2009**

Maria Jonsson

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The regional research foundation Uppsala/Örebro 700 000 SEK

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The Uppsala county research foundation 200 000 SEK

Other research funds 500 000 SEK

## Gynecological Endocrinology

Tord Naessen

### Research projects

#### **a) Hormone replacement Therapy (HRT) and effects on postural balance function.**

We study effects of endogenous and exogenous sex hormones on bone mass and fracture risk. Over 50% of all fractures have normal bone density. Our results indicate that menopausal hormone replacement therapy (HRT) improve postural balance function, not by improved muscle strength, but most likely through a positive effect on the brain. *Significance:* If HRT can affect the brain and improve postural balance this might explain the rapid dynamic between HRT exposure and reduced fracture risk, the paradoxically stronger reduction in hip fracture risk when HRT is initiated soon, compared with late, after menopause and might also explain that it seems hard to show substantial effects on hip fracture risk after treatment with bisphosphonates.

#### **b) Effects of endogenous and exogenous sex steroids on the artery wall, prevalent cardiovascular disease (CVD), prediction of CVD / death events in women and men and effects on breast tissue in women.**

To our knowledge we were the first group to report systemic effects of real 'ultra-low' doses (7.5µg/24h) of estrogen given to elderly women, with systemic effects on bone markers, bone mass and serum lipid levels. We now evaluate the significance of subtle differences in endogenous steroid hormone levels with regard to artery wall aging (ultrasound), prevalent CVD and coming risk of CVD / death in elderly women and men. Endogenous steroid hormone levels are analyzed in samples from #1016 men and women at age 70, in the PIVUS study. We also study hormonal effects on human breast tissue. In 2009, we started a RPC-study on low-dose hormone replacement therapy, initiated soon after menopause, with regard to effects on the artery wall composition (arterial ageing).

*Significance:* There is a need to better understand effects of HRT with regard to age at start of therapy, especially when started soon after menopause, i.e. at ages when HRT is mostly needed and prescribed for treatment of climacteric symptoms. Effects of ultra-low hormone doses and endogenous steroid hormones give to elderly are so far a largely unexplored field or research.

#### **c) A new principle for non-invasive non-invasive assessment of the artery wall with regard to arterial aging and screening for cardiovascular disease (CVD), using high-frequency ultrasound.**

With increasing age and development of atherosclerosis the dimension of the artery wall intima layer increases whereas that of the media layer decreases. Thus, differential directions of changes in these two artery wall layers will reduce the usefulness of the present 'Gold-standard', the Carotid-IMT, assessing the combined intima+media thickness. We use separate assessment of the artery intima and media layers and use of the Intima/Media thickness ratio. We have completed the assessment of all #825 men and women 75 years old, in PIVUS-75. We will evaluate the strength of the method to predict coming incidence of CVD events and death.

We currently use this principle also in evaluations of effects on the artery system in women with SLE, young subjects with previous history of major depression and in studies on pre-eclampsia in pregnancy. *Significance:* In different settings we evaluate if our suggested principle is superior to present 'gold-standard', (Carotid-IMT) with regard to diagnosis of prevalent CVD, prediction (risk) of coming CVD events/death and in monitoring effects of interventions against atherosclerosis/CVD.

#### **d) Long term estrogen therapy and preservation of brain tissue and function.**

We study effects of long-term estrogen therapy on mental function, total and relative brain volumes (esp. hippocampal region) with MRI. By using Positron Emission Tomography (PET), we study whether HRT and higher endogenous steroid hormone levels can preserve the local estrogen synthesis in the brain (aromatase enzyme function) and reduce the normal age-related increase in amyloid deposits (PIB). *Significance:* If HRT, initiated soon after menopause, can preserve cognitive function, brain tissue, local estrogen production and reduce the normal age-related increase in amyloid deposits (PIB) this could generate ideas for preventive strategies against some forms of age-related cognitive decline / dementia.

#### **e) Premenstrual syndrome (PMS or PMDD).**

The normal variations sex steroids during the menstrual cycle give in some women a negative effect on mood and temper, with increased irritability and depressed mood (PMS). We study differences in the brain sensitivity to changes in sex hormone levels in women with and without a diagnosis of PMDD (PMS). The methods used include studies with Positron Emission Tomography (PET). *Significance:* to better understand the relation between hormones and symptoms in PMS, a disorder affecting many women with consequences for the individual, her family- and professional life.

#### **f) Steroid hormone concentrations and proteomics in ovarian follicular fluid.**

We investigate follicular fluid (FF) from women w and w/o a diagnosis of PCOS and after ovarian stimulation regimens during in vitro fertilization (IVF). We assess and compare concentrations of single FF hormones, the product/precursor ratios (illustrating specific enzyme activities) and results from analysis of proteomics. Methods used include Liquid Chromatography Tandem Mass Spectrometry (LS-MS/MS). *Significance:* the results are expected to have implications for a better understanding of anovulation in e.g. PCOS and for improvement of the success rate in IVF.

#### **Members of the group during 2009**

Tord Naessen	Senior Lecturer
Dmitrijus Kirilovas	MD, PhD
Kenny Rodriguez	MD, PhD
Olle Eriksson	MD, PhD
Gunilla Hallberg	Research fellow
Tansim Akhter	Research fellow
Jona Kristiansdottir	Postgraduate student
Ulrika Sjögren	Postgraduate student

#### **Publications 2007-2009**

1. Kirilovas D, Schedvins K, Naessen T, Von Schoultz B, Carlstrom K. Conversion of circulating estrone sulfate to 17beta-estradiol by ovarian tumor tissue: a possible mechanism behind elevated circulating concentrations of 17beta-estradiol in postmenopausal women with ovarian tumors. *Gynecol Endocrinol* 2007;23:25-8
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**Research grants > 100,000:-**

Hjärt- och Lungsjukas Förening': 100,000:-

Selander's Foundation: 100,000:-

Selander's Foundation: 180,000:-

# **National Centre for Knowledge on Men's Violence against Women**

## **Research and Education**

### **Introduction**

The National Centre for Knowledge on Men's Violence against Women (NCK) is a knowledge and resource centre at Uppsala University. NCK is commissioned by the Swedish Government to increase knowledge on men's violence against women, violence in the name of honour and violence in same-sex relationships. This is done by compiling and spreading knowledge, developing methods, conducting research and providing training. A further government assignment to NCK has been to draw up a national programme and develop methods for the Swedish health care system focusing on treatment and care to victims of sex crimes. For this purpose NCK has developed a *Handbook, National Action Programme for the Health Care and Medical Services' Reception and Care of Victims of Sexual Assault*. Included in the handbook is a guide with practical instructions.

Women subjected to violence are treated at the centre's outpatient clinic at Uppsala University Hospital. The Centre also supports women exposed to violence on a national women's helpline.

### **Scientific Reports**

#### **Violence against women in a medical perspective**

##### **Professor Gun Heimer**

The research at the NCK mainly focuses violence against women in a medical perspective. The studies are concerned with the physical, sexual and psychological aspects of violence alike. Violence against women is a major global problem representing a serious threat against women's health and therefore, regrettably, a research field of growing interest.

##### **Members of the research group**

Gun Heimer, Professor, MD, PhD  
Tommy Andersson, Ass. Professor, PhD  
Anna Berglund, MD, PhD  
Steven Lucas, MD, PhD  
Elisabeth Mattsson, CPM, PhD  
Kristina Stenson, CPM, PhD  
Mariella Öberg, MD

##### **List of the main research projects:**

Joint research project on violence, threat and sexual assault on young people is carried out by NCK, Umeå university and Sundsvall hospital. A national survey targeting young persons has been completed the data of which have been processed and analyzed.

Thesis project investigating how women with experience of sexual violence perceive the treatment and care that they receive from the health care system. Qualitative as well as quantitative methods are applied for processing the information.

Thesis project on gynaecological patient's with or without pms and these patient's exposure to violence. The project is carried out in cooperation by NCK, Uppsala university and Umeå university.

A joint research group from NCK and the Department of Social Work at Umeå university is developing a survey in order to investigate sexual assaults.

Monitoring of students and referee assignments are ongoing.

### **Publications 2007 – 2009**

1. Stenson, Kristina och Heimer, Gun; *Partner abuse experienced by female health staff: Relevance to awareness and action when meeting abused women patients*. Women's health issues December 2007.
2. Alander, Ture; Heimer, Gun; Svärdsudd, Kurt; Agrèus, Lars: *Abuse in Women and Men with and without Functional Gastrointestinal Disorders*. Digestive Diseases Scineces 2007.
3. Heimer, Gun; Stenson, Kristina: *Vården har en nyckelroll i att avslöja våld och hjälpa kvinnor*. Läkartidningen 2008:7
4. Heimer, Gun; Stenson, Kristina: *Prevalence of experiences of partner violence among female health staff: relevance to awareness and action when meting abused women patients*. Womens Health Issues March-April 2008
5. Heimer, Gun: *Handbook, National Action Programme for the Health Care and Medical Services' Reception and Care of Victims of Sexual Assault. Guide to care following sexual assaults*. NCK-rapport 2008:1
6. Heimer Gun: *Viktigt för sexualbrottsoffer att sjukvård och rättsväsende gör rätt*. Läkartidningen 2009:7

### **Undergraduate teaching**

The undergraduate courses on Men's Violence against Women organized by NCK in cooperation with the Department of Women's and Children's Health have an interdisciplinary content including medical perspectives. The courses address both students and professionals in different fields where women subjected to violence are likely to be found i.e. health professionals, social workers and police officers.

During 2009 NCK gave two courses on different levels for students: Violence against Women 7,5 points (spring and autumn) and Men's Violence against Women, advanced course 7,5 points (autumn). The advanced course was given for the first time.

Two distance education courses were organized for professionals: Violence against Women, 7,5 points for prosecutors and Violence against Women, 15 points for other professionals from different sectors who in their work meet with women subjected to violence.

Lectures were held in the programs for nurses, midwives and physicians at Uppsala University. NCK also gave classes in the programs for lawyers and psychologists as well as at the Center for Gender Research.

**Website**

[www.nck.uu.se](http://www.nck.uu.se)

## International Maternal and Reproductive Health

### Birgitta Essén

More than a third of the ill-health in women is related to their reproduction. Research must address both individual and structural factors contributing to these health problems, as well as the health interventions and programs that can be effective to alleviate the suffering, both in low- and high-income countries.

*Maternal health* care is a core component of health care. Studies address the quality of high-risk referrals in rural Tanzania and delivery care in Sri Lanka. Experiences of parents during the postpartum period are analyzed in Tanzania giving basis for improved support. In Bolivia, Sweden and Rwanda, cases of severe maternal morbidity (near miss) are compared to cases of maternal death in order to identify mechanisms due to delays in deciding to seek medical help, for reaching obstetric facility and receiving adequate care.

*Maternal mortality in a migration perspective* is another research topic. To explore public health issues in low-income countries and in what way these experience could be adopted among a migrant population in more high-income settings is a challenge. Not only medical factors, but socio-cultural factors and communication are thus explored. The research is linked to the Immigrant Well Woman Clinic, at the Department of Women's Health, Akademiska sjukhuset.

*Maternal nutrition* is essential for reproductive outcome. Studies in Bangladesh, Indonesia and South Africa focus on the effects of supplementation in pregnancy to increase birth-weight and protect against toxic effects of arsenic in water. A study in South Africa focuses on exclusive breastfeeding to improve child HIV-free survival.

*Gender-based violence* is a major health problem. The researchers at IMCH are collaborating with several universities for support to victims. In Nicaragua and Bangladesh the consequences for the newborn of violence during pregnancy are studied, in Tanzania attitudes to violence in all sectors of the community and the legal system. In Sweden, several projects focus on medical and socio-cultural factors related to honour violence, female genital cutting and surgery 'designer vaginas'.

*STI and HIV are threats to young people* when beginning their sexual life. IMCH studies behaviours and attitudes among adolescents in Uganda, Nicaragua, South Africa and Sweden as well as the access to contraception and abortions. The impact of information from the churches is studied in South Africa.

*Public Health in Humanitarian Assistance* is given attention at IMCH with research directed to experiences and training needs of health care workers.

*Information seeking training* is provided through the Inform program, a specialized program offered to collaborating partners.

The research is approached in an interdisciplinary way involving gynaecological and obstetrical issues, nursing, and epidemiology with public health aspects. These also include political, legal, social, and cultural aspects of medicine as well as theoretical frameworks in social anthropology.

### **Collaborating centres**

Department of Public Health, Lund and Umeå University

University of Donetsk, Ukraine

University of Sri Jayawardenepura, Colombo, Sri Lanka

Aadhar Research Institute, Jaipur Rajasthan, India

ICDDR,b Dhaka, Bangladesh

IPAS, New Delhi, India

London School of Hygiene and Tropical Medicine

Muhumbili University of Health and Allied Sciences (MUHAS) Dar-Es-Salaam, Tanzania

Makerere University, Kampala, Uganda

Malmö Högskola

National University of Rwanda (NUR)

Reproductive Health Research Unit, Johannesburg, South Africa

University Western Cape, South Africa

Medical Research Council, South Africa

Health Systems Trust, South Africa

UNAN, University of Leon, Nicaragua

### **Network collaboration**

- FOKO. Nordic Network for Research on Female Circumcision started in 2000, in order to bring scientific attention to female circumcision to health professionals and social workers.
- ROAM. A global epidemiological research group on reproductive health and migration, member since 2008.
- Women's Reproductive Health: Scientific network linking together the fields of global and migrant health. Initiated by IMCH in 2009, inviting Nordic researchers with different professional backgrounds.
- VAW. Global network for Research on Violence against Women.

*Key words: maternal health care, maternal nutrition, gender based violence, migration, STD and HIV/AIDS, contraception, abortions, youth health, public health in humanitarian assistance, information seeking*

### **Members of the group**

Birgitta Essén,

MD, Associate Professor, Senior Lecturer

Beth Maina Ahlberg

Adjunct Professor

Gunilla Aneblom

RNM, Ph.D.

Pia Axemo

M.D., Ph.D.

Anna Berglund	M.D., Ph.D.
Pauline Binder	Postgraduate student
Magdalena Bjerneld	Ph.D.
Kim Dickson	Postgraduate student
Eva-Charlotte Ekström	Ph.D. Associate Professor
Elisabet Eriksson	Postgraduate student
Annicka Esscher	Postgraduate student
Elisabeth Darj	M.D., Associate Professor, Adjunct Senior Lecturer
Martha Garrett	Ph.D.
Waheedul Hoque	Postgraduate student
Berit Höglund	Postgraduate student
Malin Jordal	Postgraduate student
Colomba Kokusiima Mbekenga	Postgraduate student
Margareta Larsson	RNM, Associate Professor, Senior Lecturer
Gunilla Lindmark	M.D., Professor emerita
Emma Lindström	Postgraduate student
Marlene Makenzius	Postgraduate student
Elisabeth Mattsson	Ph.D.
Magdalena Mattebo	Postgraduate student
Projesetine Muganyizi	Postgraduate student
Barni Nor	Postgraduate student
Viveca Odland	M.D., Adjunct Professor
Pia Olsson	RNM, Associate Professor
Andrea Pembe	Postgraduate student
Christine Rubertsson	RNM, Ph.D., Senior Lecturer
Mattias Rööst	Postgraduate student
Jill Trenholm	Postgraduate student
Karin Törnblom	Administrator
William Ugarte	Postgraduate student
Åsa Wahlberg	Postgraduate student

## **Publications 2007 – 2009**

### **2009**

Aarnio P, **Olsson P**, Chimbiri A, Kulmala T. Male involvement in antenatal HIV counselling and testing: exploring men's perceptions in rural Malawi. *AIDS Care* 2009;21(12):1537-46.

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#### **Agencies that support the work**

Swedish International Development Cooperation Agency (Sida)	4 246 000
Swedish Council for Working Life and Social Research (FAS)	1 150 000
The Swedish Programme for ICT in Developing Regions (Spider)	120 000
International Network for the Availability of Scientific Publications (INASP)	337 000
Vårdforskningsmedel	520 000
Sävstaholm Foundation	400 000
Family Planning Foundation	34 000
Allmänna BB	13 000

#### **PhD exam**

Magdalena Bjerneld: Images, Motives, and Challenges for Western Health Workers in Humanitarian Aid

## International Child Health and Nutrition

### Lars Åke Persson

The research programme International Child Health and Nutrition focuses on strategies for improved child survival, on interventions against child malnutrition and undernutrition, and on equity in child health and survival.

Global child survival chances have been considerably improved since the 1960s. Several low-income countries, especially in Asia and Africa, are on track to reach the Millennium Development Goal for Child Survival (MDG4). A persistent problem in many countries is a high neonatal mortality, and inequity in neonatal survival chances. This is addressed in a collaborative project in the entire Quang Ninh province in Vietnam, where a community-based cluster randomised trial is testing a facilitation approach for improved neonatal health and survival (the NeoKIP trial, Neonatal health Knowledge Into Practice, trial registration number ISRCTN44599712). A few of the baseline reports are already published and three PhD students are active in this ongoing project. Sida is the main funder of this project.

It is estimated that almost 15% of global under-five deaths could be prevented by exclusive breast feeding during the first six months of life. In a situation with high prevalence of HIV infection among pregnant women feeding options as well as an optimal provision of and use of health services remain a challenge. In a collaborative project in South Africa infant feeding is studied in the perspective of prevention of mother-to-child transmission of HIV (PMTCT). One PhD student defended his thesis along these research lines in 2008, and another one is active with fieldwork. Her studies are financed by a Links grant from the Swedish Research Council.

In an extensive prenatal intervention trial in Matlab, Bangladesh, effects of food and micronutrient supplements are investigated in a short- and long-term perspective. In this project, that has got the acronym MINIMat (Maternal and Infant Nutrition Interventions in Matlab, trial registration number ISRCTN16581394), effects are studied on infant mortality, foetal and child growth, micronutrient status, immune function, morbidity and psycho-motor development. Currently the cohort of children pass the age of 5 years and participate in a follow-up on body composition, blood pressure and metabolic markers in order to address research questions related to the DoHAD hypotheses (development origin of health and disease. The mothers are also being followed into the next pregnancy. We collaborate with, among others, the research institution ICDDRDB in Bangladesh, and research groups at London School of Hygiene and Tropical Medicine, Institute of Child Health, London, University of California at Davis and Cornell University in Ithaca, US. Currently 4 PhD students at our department use data from the cohort, and funding is provided from, among others, the Swedish Research Council and Sida.

One research student from Bangladesh study the effect of stimulation (play therapy) in addition to food supplementation in the rehabilitation of severely malnourished children, while a PhD student from Ethiopia is setting up a study of the effectiveness of community-based rehabilitation of acute severely malnourished children.

Equity in child health and survival is focused in studies in Vietnam and Nicaragua, where trends in child survival are analysed and reasons to differentials in child health between population groups. The health consequences – also for children – of violence against women have been studied in Nicaragua and Bangladesh. Health and living conditions of street children in Kenya are documented in another project. Grants have been provided by Sida for these studies.

We have contributed with epidemiological expertise in population-based studies on arsenic in tube wells in Bangladesh. Due to the newly discovered arsenic catastrophe in that country we took the initiative to epidemiological studies on health consequences of arsenic contamination of drinking water. The research activities are closely linked to mitigation activities for safe drinking water. We have provided evidence that prenatal arsenic exposure is associated with morbidity and mortality of the offspring in infancy. We collaborate with ICDDRDB and BRAC, Bangladesh and with the

department of Metals and Health, Karolinska Institutet. One PhD student defended his thesis in 2009, and another is planning to present his work in 2010.

We are coordinating a research network of Swedish researchers and their international collaborating partners, who focus research on global child health issues – especially research on knowledge implementation into practice for improved child survival. The network has the acronym RICH (Research on Improved Child Health). More on the website of the network <http://www.richnetwork.se/>.

### Publications 2007-2009

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#### **Research consortium reports**

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### **Dissertations**

Rahman Anisur. Prenatal Arsenic Exposure and Consequences for Pregnancy Outcome and Infant Health. *Epidemiological Studies in Bangladesh. Acta Universitatis Upsaliensis* 2009. (Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine ISSN 1651-6206; 450)

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## **Paediatric Endocrinology**

**Jan Gustafsson**

Within the pediatric endocrinology research group several lines of research have been ongoing during 2009.

### **Growth and metabolism during infancy and childhood**

Glucose is an important nutrient during fetal life. After birth the newborn infant must produce its own glucose particularly for the brain. Part of our research is directed on energy metabolism during pregnancy and in the newborn infant. Infants born both small as well as large for gestational age are at risk to develop metabolic disease later in life. Our group performs metabolic studies by use of stable isotope labelled compounds and gas chromatography-mass spectrometry. The results point out relationships between maternal metabolism and fetal weight. By a combination of microdialysis and stable isotope technique we also study glucose metabolism in the brain. Studies on energy substrate metabolism during hypothermia in newborn infants with perinatal asphyxia are ongoing.

By use of Swedish registers studies on growth and intellectual performance in subjects born preterm are ongoing. A recent study on relationships between growth and intellectual performance in subjects born preterm was awarded the Henning Andersen prize by the European Society of Pediatric Endocrinology. Prematurity is associated with several medical problems, one of which is development of visual function. In a longitudinal study visual function in infants born very preterm (<32 w) is studied and on a national level a 3 year cohort of infants born before 27 w are being followed up with respect to several aspects of development.

Within the group a number of projects related to growth and pubertal development are ongoing. A thesis on growth and endocrine disturbances in Down syndrome was presented during the year. Results from this indicate a beneficial effect of growth hormone therapy both on growth and psychomotor performance in subjects with Down syndrome.

### **Effects of care and nutrition on growth and development**

Two thesis projects related to effects of neonatal care and nutrition on growth and development are ongoing. The effect of kangaroo care on immature newborn infants is studied as well as motor performance in very preterm infants before and after implementation of the Newborn Individualized Developmental Care and Assessment Program. Further, studies on effects of feeding regimens on catch-up growth in infants born premature and full-term infants born small for gestational age have been performed.

An adequate supply of energy is critical for growth and puberty. Thus, eating disorders markedly influence somatic development. A longterm project on endocrine and metabolic consequences of anorexia nervosa is ongoing within the group. Recent results from these studies show the importance of IGF-1 and triiodothyronine as indicators of nutritional status and point out weight and growth requirements for menarche.

Overweight and obesity during childhood represents an increasing problem globally. In collaboration with the Pediatric Obesity Unit at the University Children's Hospital research on energy balance in children and adolescents with overweight/obesity is ongoing.

## **virus infections and relation to type 1 diabetes**

In vitro studies on relations between virus infections and type 1 diabetes have continued. Within the project effects of nicotinamide on virus replication and chemokine secretion have been studied in enterovirus-infected human islets. The question whether celiac disease may precede the development of type 1 diabetes represents another line of research within the project.

### **Members of the group during 2009**

Gustafsson, Jan Professor

Agrasada, Grace MD, PhD

Ahlsson, Fredrik MD, PhD

Diderholm, Barbro MD, PhD

Elmund, Anna PhD

Ewald, Uwe Adj professor

Flacking, Renée PhD

Forslund, Anders MD, PhD

Frisk, Gun Associate professor

Funkquist, Eva-Lotta Postgraduate student

Gebre-Medhin, Gennet MD, PhD

Gebre-Medhin, Mehari Professor em

Halldin-Stenlid, Maria MD, PhD

Hedberg Nykvist, Kerstin Associate professor, senior univ lecturer

Hodik, Monika Research student

Jonsson, Björn PhD

Kylberg, Elisabeth Associate professor

Lundgren, Maria MD, PhD

Myrelid, Åsa MD, PhD

Proos, Lemm MD, PhD

Skog, Oskar Postgraduate student

Strand-Brodd, Katarina Postgraduate student

Swenne, Ingemar Associate professor

Tuvemo, Torsten Professor em

Wahlström Jonsson, Inger MD

Söderberg, Elisabet Laboratory assistant

Westerberg, Barbro Laboratory assistant

## Prizes

Henning Andersson prize was awarded to Maria Lundgren, Torsten Tuvemo and Jan Gustafsson by the European Society of Pediatric Endocrinology at the LWPES/ESPE 8th Joint Meeting in New York in september 2009.

## Publications 2007-2009

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#### **Dissertations 2009**

Åsa Myrelid presented her thesis "Down syndrome – growth and endocrine impact".

#### **Agencies supporting the work**

SIDA/SAREC, Council of Sciences, Gillberg Foundation, Sävstaholmsföreningen, Swedish Society for Medical Research, The Foundation for Research in Pediatric Endocrinology, Throne-Holst Foundation, Landstingets FOU-medel, Regionala forskningsrådet i Uppsala-Örebro-regionen, Novo Nordisk, Strategiska ALF-medel.

## **Paediatric Oncology**

**Susan Pfeifer**

### **Leukemia – factors determining drug response**

**G. Lönnerholm, B-M. Frost, J. Palle**

We chair a study where all Nordic centres for pediatric oncology participate. Fresh bone marrow samples from children with newly diagnosed leukemia are sent by courier to Uppsala for test of *in vitro* sensitivity against a panel of clinically important anti-cancer drugs. Our results show that drug sensitivity at diagnosis can predict treatment failure in subsets of patients with ALL. Patients with well-defined genetic aberrations show characteristic patterns in drug sensitivity profiles. We collaborate closely with groups at Dept of Clinical Pharmacology (*in vitro* sensitivity test, gene expression profiling), Dept of Medical Sciences (genome wide analysis for identification of functional polymorphisms that affect drug response in acute leukemia) and Dept of Genetics and Pathology (sub-microscopic mutations in childhood acute leukemia).

Funding: Lions 100.000, ALF 200.000, Childhood Cancer Foundation 200.000 SEK.

### **Late effects after bone marrow transplantation**

**P. Frisk, J. Arvidson**

An increasing number of patients with hematologic malignancies are treated with bone marrow transplantation (BMT). The patients receive high doses of chemotherapy and often total body irradiation to eradicate their own bone marrow. This intensive treatment may cause a plethora of late effects, including cardiovascular complications. The therapy-related 'direct' cardiotoxicity has long been acknowledged. Recent data suggest that subjects who have undergone BMT may also be highly susceptible to development of the so called metabolic syndrome, which includes obesity, insulin resistance, hyperlipidemia, and hypertension, which may 'indirectly' lead to late cardiovascular morbidity.

We are currently investigating cardiac and metabolic status in a number of patients who underwent BMT more than 10 years ago and in an equal number of healthy controls.

In addition, these same patients will be offered a questionnaire regarding HRQoL and sexual functioning, and these data will be compared with data from a large cohort of survivors from childhood cancer.

Funding: Lions 100.000 SEK, Childhood Cancer Foundation, 75.000 SEK

### **Comparison of different regimens concerning intrathecal prophylaxis in children after allogeneic hematopoietic stem cell transplantation**

**Arvidson J, Frost B-M Uppsala in cooperation with Rubin J, Gustafsson B et al, Karolinska University Hospital – Huddinge.**

In a pilot study we compared outcome regarding CNS relapse of leukemia after bone marrow transplantation with or without post-SCT intrathecal therapy. We now follow up with a larger study, including many more patients from different centres, with the same endpoints.

### **Procedural pain and psychosocial issues in children and adolescents with cancer**

**G. Ljungman, L Hedén Uppsala**

The effects of midazolam, morphine, paracetamol and ibuprofen are examined in four separate double blind RCTs in parallel groups with intervention vs placebo. 50 children are included in each



of the 4 different studies. Children, parents, and nurses will report children's anxiety, distress, and pain on VAS.

Co-workers: Professor Louise von Essen, Dept of Public Health and Caring Sciences Uppsala University. Lena Högberg, RN, PhD student, Dept of Women's and Children's Health, Uppsala University.

Funding: The project started in 2005 and is since then funded by the Swedish Children's Cancer Foundation and the Swedish Cancer foundation. Total funding MSEK 2.8; 0,7 MSEK for 2008.

In addition to being a part of the Pediatric Oncology research group at the Department of Women's and Children's Health, Uppsala University, Gustaf Ljungman takes part in, and shares leadership of, the research group Psychosocial Oncology headed by Professor Louise von Essen. The title of the main projects are: 1 Cancer during adolescence. Psychosocial and health economic consequences and 2 Occurrence, development, and treatment of posttraumatic stress disorder among parents of children with cancer.

Funding: Lions 100.000 SEK

## **Functional and genetic aspects of neuroblastoma**

### **F. Hedborg**

1. Our main line of investigation deals with biological effects of hypoxia on neuroblastoma cells. By use of expression array analyses, xenograft models, hypoxic cell culture and verifying experiments on clinical tumors we have gained qualitatively new knowledge on neuroblastoma biology. Publications are under way and some of the data were presented at the biannual international conference on Neuroblastoma held in Chiba, Japan in May, 2008.
2. In a collaborative work with Teresita Diaz de Ståhl and Jan Dumanski at the Dept of Genetics and Pathology, Rudbecklaboratoriet the genetics of neuroblastoma is studied by whole genome CGH array technology. Data is still in the making. Preliminary results suggest a novel model for age-dependent differences in tumor genetics.
3. Two cases of neuroblastoma, with highly unusual tumor biology of principal interest, were presented at the international neuroblastoma meeting in Japan 2008.
4. Animal experiments have been performed to test the hypoxia-dependence of targeting neuroblastoma with meta-Iodo-benzoguanidin (mIBG)

Collaborators: Krister Karlsson, Cihan Cetikaya, PhD, Teresita Diaz de Ståhl.

Funding: 300.000:- from the Swedish Children's Cancer Foundation

## **Molecular characterization of pediatric brain tumors and their stem cells**

### **Susan Pfeifer**

Pediatric CNS tumors are the leading cause of death due to disease in children 1-15 years. A prerequisite for the development of targeting therapies and improved survival is knowledge of the biology of pediatric tumors, still poorly understood. Tumor specific genetic changes and changes in gene regulation in pediatric CNS tumors are studied in collaboration with Dept of Genetics and Pathology, Uppsala University. Using a clone-based array covering about 99% of the human genome, we have identified tumor specific chromosomal alterations, few of them novel and others previously known, that may be related to tumor initiation/progression. We are further characterizing gene regulation in tumorigenesis, by applying innovative assays that utilize massively parallel ultrahigh-throughput DNA sequencing. In a collaborative effort between the Karolinska Institute, and the Universities of Uppsala and Lund, we have recently started a project aiming at increasing our knowledge of pediatric brain tumor stem cells and their role in uncontrolled cell growth. Our ultimate goal is to use this knowledge to design new experimental treatments.

Collaborators: Teresita Diaz de Ståhl, Jan Dumanski, Pelle Nilsson, Karin Forsberg-Nilsson, Uppsala University; Monica Nister, Urban Lendahl, Jonas Muhr, Johan Holmberg, Mikael

Lindström, Stefan Holm, Bengt Gustafsson, Karolinska Institute; Peter Siesjö, Xialong Fan, Lunds University.

Funding: Barncancerfonden 150.000, Lions 130.000, Barncancerfonden 800.000 SEK(collab)

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## **Paediatric Neurology**

### **Gunnar Ahlsten**

The research of the Paediatric Neurology research group deals with clinical neurological diseases and neurological dysfunctions. The researchers come from many different professions and their research comprise a wide range of scientific questions.

### **Epilepsy**

Rolandic epilepsy, the most common type of childhood epilepsies, has been studied in several aspects. A follow-up study with magnetic resonance spectroscopy of the hippocampus is ongoing to assess whether or not abnormalities has normalized.

There is also an ongoing follow-up study of children previously treated for epilepsy.

### **Spina bifida**

Research on this group of children has been carried out for at least 15 years. Different medical factors especially the Chiari II-malformation and early puberty has been in focus in follow-up studies.

The global function of these children and adults is studied and its implications for what type and extent of support these individuals need at different ages has generated valuable new knowledge. A new study deals with children with spinal malformations who have an intact skin above the lesion.

### **Follow-up studies of prematurely born infants**

Together with the Departments of Psychology, Ophthalmology, Neuroscience and Neonatology a longitudinal study of the development of visual perception in infants born before 32 weeks of gestation and its relation to periventricular leucomalacia or other perinatal brain damage has been going on for 3 years. 113 children are included and the results are under evaluation for publication. The study will provide much new information in this field.

We also participate in a national prospective study on neurological, ophthalmological and psychological development of infants born after less than 27 weeks of gestation. 497 children have survived and have been followed-up to 2½ years corrected age. The results are now evaluated and will be published in international journal when ready for publication. A new follow-up of the cohort at 6½ years are under planning. The results of the study may have great importance for future perinatal care.

### **Perinatal brain injury and early prediction of outcome**

Perinatally acquired brain damage is associated with life-long suffering and significant costs for society. We have previously shown that amplitude-integrated EEG (aEEG) and limited-channel EEG can be used for continuous evaluation of brain function in high-risk infants. The project investigates mechanisms for perinatal brain damage, and methods for very early diagnosis of brain injury and prediction of outcome. The specific aims are:

- To evaluate neurophysiological methods, especially EEG and aEEG, for early evaluation of brain function and cerebral maturation, and for prediction of neurocognitive outcome.
- To investigate perinatal mechanisms for adverse neurodevelopment in relation to neonatal illness, medical treatment, pain and stress, and infant gender.

The project contains several lines of work and includes clinical as well as epidemiological studies, and international collaboration within three large EU-funded projects.

1. The relation between timing of umbilical cord clamping, iron deficiency and neurodevelopment is investigated in 400 normal full-term singleton pregnancies randomised to immediate or delayed cord clamping at Halmstad county hospital, May 2008-Sept 2009 (Ola Andersson PhD project).
2. Factors affecting EEG continuity and spectral power in extremely preterm infants who had aEEG/EEG recorded during the first 72 hours of life. Factors that are evaluated in relation to EEG and long-term outcome include brain injury, carbon dioxide, glucose, and medications (Sverre Wikström PhD project).
3. NEOBRAIN (Neonatal Estimation of Brain Damage Risk and Identification of Neuroprotectants) is an EU-funded translational project under the lead of Prof Olaf Dammann (Hannover/Boston). The focus of the project is prevention of hypoxic-ischemic and inflammatory-associated brain damage in preterm newborns by identifying early damage markers and novel pathways for interventional neuroprotection. Lena Hellström-Westas is workpackage (WP) leader for neurophysiology and aEEG/EEG analysis.
4. NeoOpioid is an EU funded multicenter project under the lead of Prof Hugo Lagercrantz (Karolinska). During a 4-year period the project will perform a European survey on neonatal pain management, a clinical study of morphine and fentanyl (pharmacokinetics/ pharmacodynamics/ pharmacogenetics/ catechol-amines/NIRS/EEG) and develop opioid preparations especially adapted for newborn infants. Lena Hellström-Westas is WP leader for the clinical study.
5. NEMO- treatment of NEonatal seizures with Medication Off-patent: Evaluation of safety and efficacy of bumetanide – is an funded collaborative project coordinated by Dr Ronit Pressler at University College London. The aim of the project is to systematically evaluate antiepileptic treatment in term newborn infants with NE, starting with bumetanide, a diuretic drug with promising antiepileptic effects in experimental settings.

## **Evaluation of motor function**

Different studies with different techniques are used to study children with cerebral palsy and spina bifida regarding balance, posture and muscle tone. Other research deals with energy consumption in different movement disorders.

The development of the motion analysis laboratory of the University Hospital is an important resource for some of these studies.

A follow-up-study of children who were operated on with selected devised rhizotomy is under progress.

## **Arthrogryposis**

Arthrogryposis (Arthrogryposis Multiplex Congenita, AMC) is a descriptive term for conditions with multiple congenital contractures. The cause is varying, and background pathology may be in muscle, CNS, peripheral nerve, connective tissue or other. There are approximately 200 conditions with AMC. The most commonly occurring forms are Amyoplasia and Distal Arthrogryposis (DA) syndromes. Ongoing research projects are on further clinical and genetic investigation of DA syndromes with mutations in sarcomeric protein genes, DA with mutations in connective tissue genes, and investigation of children with arthrogryposis, mental retardation and dysmorphic signs with arrayCGH. Further follow-up studies of children with amyoplasia is planned. The results are of importance for diagnosis and classification of types of arthrogryposis, understanding of pathological mechanisms and for treatment and habilitation for this group of children.

## Members of the group

Alhsten Gunnar	Associate professor
Bratteby-Tollerz, Linda	Magister
Dahl, Margareta	Associate professor
Eeg-Olofsson Orvar	Associate professor
Ehrstedt Christoffer	Research student
Hellström-Westas Lena	Associate professor
Höglund Anette	Magister
Jonsson, Pysse	Research student
Kimber Eva	Ph.D
Kristiansen Ingela	Research student
Larsson Katrin	Research student
Lidström Helene	Postgraduate student
Lidström Åsa	Magister
Liminga Gunnar	Ph.D
Lundberg Staffan	Ph.D
Norrlin Simone	Ph.D
Strömberg Bo	Associate professor
Tjäder Cecilia	Medical doctor
Wester Ulrika	Medical doctor
Ölund A-C	Medical doctor

## List of publications 2007-2009

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### **Agencies that support the work**

ALF, Regional research council, Norrbacka-Eugenia foundation and other funds.

- NEOBRAIN (partner and WP leader for Neurophysiology) 2006-2010 (€ 167 000)
- NeoOpioid (partner and WP leader for Clinical study) 2008-2012 (€ 226 665)
- NEMO (partner and WP leader for European survey) 2009-2014 (€ 242,880)

## **Perinatal, Neonatal and Pediatric Research**

**Anders Jonzon**

### **Projects**

#### **1. Clinical studies concerning inflammatory substances and their migration in neonatal lung tissue.**

Inflammatory reactions are involved in the development of bronchopulmonary disease in prematurely born infants. The studies hope to clarify what kind of white cells that are involved and which substances they respond to. The results might give possibilities to limit the harmful effects on lung tissue.

Researchers: Richard Sindelar, MD PhD, Uppsala,  
Maria Stålhammar PhD, Uppsala,  
Lena Douhan Håkansson, MD, PhD, Uppsala  
Cecilia Ewald, specialist nurse  
Anders Jonzon, MD PhD, Uppsala

#### **2. Studies of ventilatory support in small children**

Ventilatory support in prematurely born children is a cornerstone in neonatal care. Barotaruma is thought to be a major contributor to lung damage. Intermittent ventilation, various patient-triggered modes and resistive and elastic unloading are investigated. The effects on airway pressure, patient response in various aspects are measured. In addition measurements are made concerning pulmonary vascular flow and water content.

Researchers: Linda Wallström, MD, Uppsala  
Josanne Munsters, MD, Nijmegen  
Karl Wilhelm Olsson, MK, Uppsala  
Richard Sindelar, MD PhD, Uppsala  
Anders Jonzon, MD PhD, Uppsala  
Johan Ågren, MD PhD  
Torgny Norsted, MD PhD  
Onnen Mörer, MD, Göttingen  
Göran Hedenstierna, prof, Uppsala

#### **3. Exchange of heat between child and mother during skin-to skin care.**

Prematurely born children lose great amount of water and heat from the skin. Investigations are made to measure the losses during skin-to-skin treatment and consequent needs to compensate fluid losses. Better understanding of this form of care may diminish the need for incubator care a further enhance parental involvement.

Researchers: Johan Ågren, MD PhD  
Ann-Britt Heinemann, specialist nurse  
Jenny Puranen, MK  
Kerstin Hedberg Nyqvist, specialist nurse, PhD

#### **4. Fluid balance at different infusion rates in extremely premature infants.**

There is little knowledge concerning amounts of fluids needed to best support the smallest population of prematurely born infants. Studies are made both retrospectively and prospectively.

Researchers: Johan Ågren, MD PhD

Dimitrios Kritikos, MD

#### **5. Markers for development of lungdisease and pulmonary hypertension in extremely prematurely born infants.**

In order to prevent pulmonary hypertension, a potentially serious condition, we are investigating possible preventive measures to preclude increases in pulmonary vascular resistance.

Researchers: Erik Norman, MD, PhD

Johan Ågren, MD, PhD

Uwe Ewald, MD, PhD professor

Anders Jonzon, MD, PhD

Dimitrios Kritikos, MD

#### **6. Investigations on cardiac rhythm in small children**

a. Congenital heart block is a disease mostly connected to maternal rheumatic disease. We are collecting blood specimens from all patients in Sweden, their parents and siblings in order to find markers where the risk for a fetus to establish heart block is high. We are also trying to find if there are specific genotypes that are more sensitive to an attack of maternal antibodies.

Researchers: Marie Wahren-Herlenius, MD, PhD, professor, Stockholm

Stina Salomonsson, PhD, Stockholm

Sven-Erik Sonesson, MD, PhD, Stockholm

Håkan Eliasson, MD, Stockholm

Annika Öhman, MD, Uppsala

Anders Jonzon, MD, PhD, Uppsala

b. Clinical application of mobile-phone transmission of EKG in diagnosing heart rhythm disturbances in children. Effects of antiarrhythmic drugs on heart rhythm variability in small children.

Elinor Bärnevåg, bio-med.tech, Uppsala

Annika Öhman, MD, Uppsala

Anders Jonzon, MD PhD, Uppsala

#### **7. Quality of life in children and young adults in need of ventilatory support. We are particularly interested in the use of phrenic nerve stimulation as a way to mimic spontaneous respiration.**

Researchers: Richard Sindelar, MD PhD, Uppsala

Anders Jonzon, MD PhD, Uppsala

Gunnar Sedin, MD, PhD, prof.

#### **8. Follow up studies concerning motor development, speech development in infants born to early.**

Researchers: Kristina Persson, physiother. PhD

Margareta Jennische, PhD

Gunnar Sedin, MD, PhD, prof.

## **9. Early clinical predictors for failure of pharmacological ductus arteriosus treatment in extremely preterm infants**

Researchers: Karl Wilhelm Olsson, MS  
Richard Sindelar, MD PhD  
Anders Jonzon, MD PhD

## **10. Studies of a family with long QT syndrome. A new genetic trait.**

Researchers: Susanna Gröndal, MS  
Marie Louise Bondesson, PhD  
Anders Jonzon, MD PhD

### **Publications 2007-2009**

2007

#### **Full Papers**

Farooqi A, Hägglöf B, Sedin G, Gothefors L and Serenius S. Mental Health and social competencies in 10- to 12-year-old children born at 23-25 weeks' gestation in the 1990s: A Swedish national prospective follow-up study. Pediatr 120(1),118-133, 2007.

Sindelar R, Rieger-Fackeldey E, Sedin G and Jonzon A. A pressure increase due to hydrostatic pressure of perflouorocarbon is not obvious as sensed by pulmonary stretch receptors. Am J Respir Crit Care Med, 175(3):290, Author reply 290-291, 2007.

Wall K, Oddsson H, Ternstedt BM, Jonzon A, Nylander E, Schollin J. Thirty-year electrocardiographic follow-up after repair of tetralogy of Fallot or atrial septal defect. J Electrocardiol 40(2):214-7, 2007.

Nagase, H., Ågren, J., Saito, A., Liu, K., Agre, P., Hazama, A., Yasui, M. Molecular cloning and characterization of mouse aquaporin 6. Biochem Bioph Res Co 352, 12-16, 2007.

Hemgren E and Persson K. Associations of motor co-ordination and attention with motor-perceptual development in 3-year-old preterm and full-term children who needed neonatal intensive care. Child Care Health Dev 33(1):11-21, 2007.

2008

#### **Full Papers**

Rieger-Fackeldey, E., Sindelar, R., Sedin,G., Jonzon, A. Bronchopulmonary C-fibers modulate the breathing pattern in surfactant-depleted juvenile cats. Respir Physiol Neurobiol 160, 341-349, 2008.

Matsson, H., Eason, J., Bookwalter, CS., Klar, J., Gustavsson, P.,Sunnegardh. J., Enell, H., Jonzon, A., Vikkula, M., Gutierrez, I., Granados Riveron, J., Pope, M., Bu'Lock, F., Cox, J., Robinson, TE., Song, F., David Brook, J., Marston, S., Trybus, KM., Dahl, N. Alpha-cardiac actin mutations produce atrial septal defects. Hum Mol Genet 17, 256-265, 2008.

Hemgren, E and Persson K. Deficits in motor co-ordination and attention at 3 years of age predict motor deviations in 6.5-year-old children who needed neonatal intensive care. Child Care Health Dev 35(1):120-129, 2008.

### **Book Chapters**

Sedin G and Ågren J. Kuvösvård. Nyföddhetsboken, Studentlitteratur, eds H Lagercrantz, Lena Hellström-Westas, M Norman, 2008.

Ågren J and Sedin G. Vätskebalans. Nyföddhetsboken, Studentlitteratur, eds H Lagercrantz, Lena Hellström-Westas, M Norman, 2008.

2009

### **Book Chapters**

Rehncrona S, Sedin G and Fodstad H. Apnea: Phrenic nerve stimulation. In: Textbook of Stereotactic and Functional Neurosurgery Eds: Springer-Verlag Berlin/Heidelberg, 2009.

### **Agencies that support the work**

Anders Jonzon Hjärt- Lungfonden	400.000 SEK
Anders Jonzon Stiftelsen Samariten	100.000 SEK
Richard Sindelar Externa Medel	185.000 SEK
Richard Sindelar Externa Medel	100.000 SEK

## **General Pediatric Research Group**

The "General Paediatric Research Group" is a heterogeneous group made up of one entity with focus on Paediatric inflammatory diseases and in addition to that other general paediatric research areas i.e Paediatric pulmonary diseases with focus on cystic fibrosis and other pulmonary diseases, Paediatric nephrology and Neonatal infectious diseases. Another very research active entity within the group is the Child Public Health Unit with focus on child health care and preventive medicine.

## **Centre for Paediatric Inflammation Research**

A "Centre for Paediatric Inflammation Research" has been established within the research group. Research focus is put on improved clinical phenotyping of childhood inflammatory diseases and improved characterization of inflammatory characteristics of diseases in collaboration between clinical and preclinical scientists. The purpose of these efforts is to be able to improve diagnosis and to tailor and optimize anti-inflammatory treatment in patients. Minimally-invasive sampling methods suitable for use in paediatric patients are being developed. A large Vinnova grant has been received for the purpose. Participants in the center are Professor Kjell Alving, PhD, Professor Lennart Nordvall, MD, PhD, Dr Tony Hansson, PhD, Dr Lillemor Berntson, MD, PhD, Dr Ingrid Dahlbom, PhD, Dr Andrei Malinovski, MD, PhD, Ms Britt-Inger Nyberg, BSc, Ms Pia Kalm-Stephens, BSc

## **Airway Inflammation**

In asthma focus is put on airway inflammation by measuring exhaled nitric oxide, a surrogate marker of allergic inflammation. A research prototype NIOX Flex is being evaluated and enables monitoring of nitric oxide (NO) in various compartments of the airways (bronchi, alveoli) of which the therapeutic implication is to be able to tailor treatment. In patients with very low levels of NO emphasis is put on differential diagnosis in childhood asthma. Here focus is on differential diagnosis versus ciliary dysfunction and chronic infection. Characterisation of a large cross-sectional cohort of children and young adults with asthma and controls is under way in order also to further investigate phenotypes of asthma.

## **Gastrointestinal Inflammation**

We are developing concepts for characterising individual patients with gastrointestinal inflammations based on disease specific antibodies and panels of inflammatory molecules. Our research main focus is on the possibilities to improve the use of disease related antibodies and inflammatory molecules for early diagnosis and non-invasive follow up of celiac disease and other symptom-sharing gastrointestinal diseases. Furthermore, we are investigating the association between celiac disease and other chronic inflammatory diseases, and whether undiagnosed inflammation that disturbs the intestinal barrier may lead to the development of other diseases e.g. type 1 diabetes. Another area of interest is gastrointestinal inflammation in IgE and non-IgE mediated food allergies.

The research and development projects at the clinical section for gastroenterology and nutrition have focused on IBD, celiac disease and clinical nutrition.

A new collaborative project between the Dpt of Clin Genetics and Pathology (Prof. U Gyllensten, Assoc Prof. Alkwin Wanders) and the Dept of Woman and Child Health and CMM Karolinska Institutet, Assoc Prof. Jonas Fuxe aims to study the effects of enterotopic virus on tight junction proteins in the stomach and small and large intestine. This presumed effect could be a starting point for the inflammatory response in IBD. This project is timely in the context of present research frontiers in IBD.

A nationwide inventory of endoscopy resources for paediatric clinical and scientific purposes was carried out to be published in collaboration with colleagues from Great Britain.

## **Rheumatic Inflammation**

The pediatric rheumatology research involves four projects:

The study of JIA (juvenile idiopathic arthritis) in the Nordic countries has continued. Different variables for disease activity has been part of the project. One important result is the paper on HLA-B27 and its influence on the clinical signs and symptoms in boys with JIA. Anders Öman has been introduced into the project during 2008 and data has been prepared for coming publications.

Anders Öman and Lillemor Berntson have continued a project with Sandra Kleinau (BMC) in which complement receptors in juvenile idiopathic arthritis are studied. Preliminary results are available but some more samples are needed to complete the study.

Collection of data in the regional, prospective, population based study in children with JIA and celiac disease has continued. The project is part of the regional collaboration in children with JIA and gives possibility for future research within the field.

The national registry for children with JIA, receiving biological drugs, is now prepared to be implemented.

## **Major grants**

*The Centre for paediatric inflammation research* in collaboration with other groups at Uppsala University and three industrial partners recently received a SEK 20 milj grant over four years from The Swedish Governmental Agency for Innovation Systems (VINNOVA Sambio 2007-00084) in collaboration with Phadia AB, Aerocrine AB and Alimenta Medical AB. One of the purposes of this grant is to strengthen collaboration between academic researchers and industry. Funding has also been received from the Gillbergska Foundation, Samverkansfonden, the Swedish Heart-Lung foundation 200 000 and Stiftelsen Astma- och Allergiförbundets forskningsfond. 300 0000.

## **Paediatric Neonatal Infections.**

Two projects were finished by Erik Normann during a second and last year as a post-doc working at the University of Alberta, Edmonton, Canada. One project was about the importance of intra-uterine infections on the foetal lung and brain development. For this project a mouse model was developed. Also, the combined effect of antenatal inflammation and postnatal exposure to high levels of oxygen was studied. The second project was to develop a simple method for monocyte isolation from umbilical cord blood.

## **Pediatric Nephrology.**

During 2008 the nephrological research has been focussed on the paediatric urinary tract. Dr Nevéus is Secretary General of the International Children's Continence Society (ICCS), the relevant global research organisation. In this position he has had a central role in organising the ICCS biennial conference in Boston, October 2008. He has also lectured in several locations nationally and internationally.

There are several ongoing research projects regarding therapy-resistant enuresis. Specific therapies that are under investigation are reboxetin and sleep modification via orthodontic procedures.

Dr Nevéus is principal local investigator in the National Reflux Study – a randomised trial of antibiotic prophylaxis, endoscopic treatment and watchful waiting in children with dilated vesicoureteral reflux. Data collection has been concluded december 2008 and will be presented at an international conference in Gothenburg in 2009. Uppsala will participate in the evaluation of outcome vis-a-vis renal damage, urinary tract infections and the reflux *per se*.



## **Major Grants**

2006 and 2007; approximately 200 000 SEK from Pfizer 2008; approximately 110 000 SEK from Ferring Pharmaceuticals.

Smaller funds and contributions.

## **STUDIES ONGOING AT THE UPPSALA CF CENTER**

### **Treatment study of Azitromax in patients with cystic fibrosis in the Nordic countries**

Monitoring of energy and body composition in patients with cystic fibrosis through different methods

Monitoring of different factors in the immune system in patients with cystic fibrosis

Examining blood and mucosa samples from patients with cystic fibrosis and trying to find proteins to explain differences in disease severity, an EU study

Genotypes, phenotypes and colonization of *Pseudomonas aeruginosa* in patients with cystic fibrosis in all Nordic countries

Scandinavian nutritional multicenter study of cystic fibrosis patients in the Nordic countries

Screening of depression and life quality in patients with cystic fibrosis, a combined study in Europe and the US

Treatment study with specific immunoglobulin Y in patients with cystic fibrosis to try inhibiting growth of mucoid *Pseudomonas aeruginosa*

## **GENERAL PAEDIATRICS – SOCIAL PEDIATRICS 2009**

The Child Health Unit in Uppsala carries a strong tradition of social paediatric research. Prevention & screening, child health surveillance, and translational research are the main focus areas dealt with in our work. In 2008 we assisted Government with scientific data to support their development of a national parenting support strategy. In 2009 we received a major research grant for a cluster-randomised controlled study of Triple P in Uppsala county. The Triple P trial had its baseline measurement in October and comprises the first Swedish data on parenting practices and child behaviour in a general Swedish sample. The study also includes implementation processes and aims to answer the question whether or not preschools are a suitable arena for parenting support from the perspective of different stakeholders: parents, preschool teachers, preschool heads and local government officials. The research group is interdisciplinary and has research assistants, doctoral students, and postdocs as well as assistant professors. We have both national and international collaboration and receive many students who do their masters theses with us. They participate in any one of the parallel research projects at the unit that have to do with our main research areas.

## **Publications 2007-2009**

### **International peer-reviewed publications**

1. Holmbäck U, Fridman J, Gustafsson J, Proos L, Sundelin C, Forslund A. Overweight more prevalent among children than among adolescents. ; *Acta Paediatrica*. 2007;96(4):577-81.
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14. Bisgaard H, Pedersen S, Anhøj J, Agertoft L, Hedlin G, Gulsvik A, et al. Determinants of lung function and airway hyperresponsiveness in asthmatic children.. *Respir Med*. 2007;101(7):1477-82.
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17. Neveus T. *Terapicompedium i Pediatrik*. : Inst. för kvinnors och barns hälsa; 2007.
18. Stenhammar C, Sarkadi A, Edlund B. The role of parents' educational background in healthy lifestyle practices and attitudes of their 6-year-old children.. *Public Health Nutrition*. 2007;10(11):1305-1313.
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35. Nevéus T, Tullus K. Tolterodine and imipramine in refractory enuresis; a placebo-controlled crossover study. *Pediatric nephrology (Berlin, West)*. 2008;23(2):263-267.
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### Reports

Sarkadi A (red). Föräldrastöd i Sverige idag: när, vad och hur? Underlagsrapport. (Parenting support in Sweden today: When, what, and how? Report). Statens Folkhälsoinstitut, 2008.

### National peer-reviewed publications

1. Runestam K, Sarkadi, A. Inget informerat samtycke inför rutinmässigt ultraljud heller. Debattinlägg. (No informed consent before routine ultrasound [in pregnancy] either. Debate article). *Läkartidningen* 2007; 104(39): 2823

### Presentations at international conferences

1. Lecture: The Potential of the Internet as a source of social support in parenting. European Society of Social Paediatrics Annual Meeting. Cardiff, UK, 2006.
2. Poster: Local failure in BCG vaccination coverage of at-risk children in Uppsala, Sweden - and what we did about it. European Society of Social Paediatrics Annual Meeting. Trieste, Italy, 2007.
3. Workshop: Evidence-based preventive work in action. 55th International Commission on Couple and Family Relations. Helsingfors, Finland, 2008.
4. Customisation, fidelity or both? Experiences from implementing Triple P in Sweden. Helping Families Change conference Birsbane, Australia, 2010

### Major research grants

**2008** National Institute of Public Health. 3.1 million SEK for preparing a background report to the Swedish government's special investigator on parenting support. *Parenting support in Sweden today: When, what, and how?*

**2009-** National Institute of Public Health/Uppsala community Preschools as arena for parenting support: a randomised controlled study of Triple P in Uppsala. 3,5 million SEK.

## **Pediatric Surgery and Pediatric Urology**

**Rolf Christofferson**

### **Metabolic balance in children with home parental nutrition**

**Gertrud Angsten**

Long chain polyunsaturated fatty acids (LCPUFA) are contained in breast milk and participate in the postnatal development of the nervous system. LCPUFA can be synthesized from essential fatty acids, but this endogenous synthesis may not meet pediatric requirements. Children of varying ages with home-parental nutrition, due to complete or partial intestinal failure, are worked-up regarding metabolic balance, based on 3-day collection of blood, urinary and fecal samples. Analyses are made of hematologic and biochemic parameters, vitamins, trace elements and nitrogen losses. Furthermore, the basal metabolism is determined by indirect calorimetry, body composition by bioimpedance analysis, and bone density by dual energy x-ray absorptiometry (DEXA). The n-3 LCPUFA docosahexaenoic acid (DHA) is an important component of the cell membrane, including myelination of neurons. DHA can be labeled with the stable isotope  $^{13}\text{C}$ . A non-hazardous dose of labeled DHA is given to the child, and the DHA metabolism is assayed in blood samples and exhaled air from the child, and correlated to the child's basal metabolism and DHA concentrations in the maternal breast milk. The project will give new information on the metabolic balance in children with home parental nutrition due to intestinal failure, specifically the metabolism of DHA, which information will help in composing the optimal parental nutrition.

### **Antegrade continence enemas in children with anal incontinence**

**Rolf Christofferson, Ann-Marie Kassa**

Anal incontinence is socially handicapping, and reduces the quality of life and self-esteem. Anal incontinence is reported to be cured in more than 90% of cases by antegrade continence enemas (ACE), and an ACE is also reported to increase the patient's autonomy. The ACE principle is that an empty colorectum can not leak fecal matter. An ACE is constructed on either the right or the left side of the colon, with or without a catheterizable channel (conduit) made of the appendix, a colonic flap, or a small intestinal tube. The ACE can be catheterized intermittently or have an indwelling catheter. Through the ACE, the patient typically self-administer 500-1500 ml tap water causing antegrade emptying of the colon within 30-45 min. In this register-based study, we retrospectively analyze clinical data from the 67 children that received an ACE in Uppsala between 1993-2008. Several parameters are included in the analysis, e.g. diagnosis, location, conduit, type of catheterization, complications, and anal continence. This project will give information on how to construct the most efficient ACE and how to select the patients that will benefit from the procedure.

### **The enteral bacterial flora in pretermatures with and without necrotizing enterocolitis**

**Helene Engstrand Lilja**

Necrotizing enterocolitis (NEC) is a severe intestinal disease mainly in premature infants, causing septicemia and bowel perforation with a ~30% mortality. There is a hypothesis that the enteral bacterial flora in babies that develop necrotizing enterocolitis (NEC) differs from that of premature babies that do not. In this prospective investigation, we collect stool samples from infants born before 29 weeks of gestation with a birth weight under 1,500 g. The expected incidence of NEC in this group is 10-15%. Bacterial-specific DNA in stool samples will be retrieved by 454-pyrosequencing. The project will characterize the enteral bacterial flora in premature infants with and without NEC, and will help in developing new strategies in preventing NEC.

## **Risk factors and long-term quality of life following gastroschisis**

**Helene Engstrand Lilja**

Gastroschisis is a congenital abdominal wall defect in which the intestines and sometimes other organs herniate outside the abdominal cavity through the opening in the abdominal wall. There is limited data on the long-term bowel function in children operated for gastroschisis. In this retrospective study, we follow up children operated for gastroschisis in Uppsala between 1990-2009. Gestation age, delivery mode, extent of intestinal edema, the interval from birth to surgical hernia reduction and closure of the defect, postoperative abdominal pressure, are correlated to the time before full enteral feeding. Also co-morbidity (e.g. septicemia and intestinal resections), and mortality are registered. To objectively follow up the long-term bowel function and quality of life, we apply an internationally validated Gastrointestinal Quality of Life Index protocol, which has been adapted for children. The study will identify risk factors in and long-term quality of life following gastroschisis repair.

## **Isolation and transplantation of human hepatocytes**

**Elisabet Gustafson**

In liver failure, regardless of cause, there is a clinical need for hepatocyte transplantation. We have established a method for isolation and culture of human hepatocytes from liver biopsies. Our isolated hepatocytes have been used for analyses of the "innate immunity" (the un-specific defense against infections), but also for assaying hepatotoxic effects of oncolytic adenoviral vectors. The early "innate" immune reaction generates considerable loss of transplanted hepatocytes by activating cytokines, the coagulation and complement systems, and leukocytes. We are now using isolated human hepatocytes in culture to dissect details of the acute "innate" immune reaction when the hepatocytes are exposed to AB0-incompatible blood. In vitro, we can now pharmacologically quench this immune reaction. The aim of this project is to develop better protocols for hepatocyte transplantation, protocols that improve the short- and long-term survival of transplanted hepatocytes. In the future, we hope to establish a national collaboration for hepatocyte transplantations in patients with liver failure.

## **Long-term follow-up following endoscopic Deflux-therapy due to vesicoureteral reflux**

**Göran Läckgren, Arne Stenberg, Anders Stenbäck, Erik Sköldenberg, Gillian Barker**

The treatment of vesicoureteral reflux (VUR) with febrile infections has been controversial. A safe, efficient and minimally invasive therapy is endoscopic injections of Deflux® (dextranomer/hyaluronic acid) submucosally under the ureteric orifice in the bladder. Deflux injections offers short-term cure rates similar to that of open surgery, but there is limited information on the long-term results. In this longitudinal study, we follow up patients that were subjected to Deflux injections due to VUR 10-17 years ago. The follow-up protocol involves episodes of urinary tract infections, self-reported voiding function, clinical examination, renal function by scintigraphy, uroflowmetry, and post-void residual volume. The study will give new and clinically important information on the long-term outcome of Deflux therapy in VUR.

## **Early detection of necrotizing enterocolitis**

**Anders Stenbäck, Niclas Högberg**

Necrotizing enterocolitis (NEC) is a sometimes lethal intestinal disease in premature infants, causing septicemia, bowel perforation, and strictures. As a consequence, intestinal failure may develop due to extensive bowel resections. The early symptoms of NEC are non-specific and ambiguous. Currently there is no diagnostic tool specific for NEC. Therefore, we are studying the potential role of intestinal intraluminal microdialysis (assaying glucose, lactate, pyruvate, glycerol, and hydrogen ions) in an animal model of NEC. Hopefully we will be able to detect early changes in intraluminal metabolites that will be helpful in making the diagnosis.

## Members of the group

Gertrud Angsten	M.D., Ph.D., consultant
Gillian Barker	M.D., Ph.D., consultant
Rolf Christofferson	Associate professor, lecturer, M.D., Ph.D., consultant
Johan Danielson	M.D., Ph.D.-student, resident
Helene Engstrand Lilja	M.D., Ph.D., consultant
Ammar Farman	M.D., resident
Elisabet Gustafson	M.D., Ph.D.-student, consultant
Kajsa Gustafsson	M.D., resident
Niclas Högberg	M.D., Ph.D.-student, resident
Ann-Marie Kassa	RN, research nurse
Göran Läckgren	Professor, M.D., Ph.D., consultant
Hussein Naji	M.D., resident
Erik Sköldenberg	M.D., Ph.D., resident
Arne Stenberg	Surgeon-in-Chief, associate professor, M.D., Ph.D., consultant
Anders Stenbäck	M.D., Ph.D., resident

## Publications 2007-2009

1. Bäckman U, Svensson A, Christofferson RH, Azarbayjani F (2008) The bisphosphonate, zoledronic acid reduces experimental neuroblastoma growth by interfering with tumor angiogenesis. *Anticancer Res.* May-Jun; 28(3A): 1551-7.
2. Engstrand Lilja H, Finkel Y, Wester T. Serial transverse enteroplasty (STEP) är en ny kirurgisk teknik för behandling av korta tarmens syndrom. *Läkartidningen.* 2008 Jun 11-24;105(24-25):1849-51.
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15. Sköldenberg EG, Larsson A, Jakobson A, Hedborg F, Kogner P, Christofferson RH, Azarbayjani F (2009) The angiogenic growth factors HGF and VEGF in serum and plasma from neuroblastoma patients. *Anticancer Res*. Aug; 29(8): 3311-9.
16. Stenberg A, Läckgren G. Treatment of vesicoureteral reflux in children using stabilized non-animal hyaluronic acid/dextranomer gel (NASHA/DX): a long-term observational study. *J Pediatr Urol*. 2007 Apr; 3(2): 80-5. Epub 2006 Nov 1.
17. Svensson A, Bäckman U, Fuchs D, Christofferson R, Azarbayjani F (2007) Angiogenesis can be reduced without significant reduction of tumor growth. *Anticancer Res*. Nov-Dec; 27(6B): 3883-9.
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## **Reproductive Health**

### **Inger Sundström Poromaa**

The research of my group focuses on all aspects of reproductive health, with an aim of improving the life and mental well-being of women in childbearing ages. The research presented ranges from clinical studies whose results immediately may be implemented into clinical practice to preclinical studies aiming at understanding pathophysiological processes, which in turn may be valuable for early recognition and improved treatment.

### **Prevalence of depression, anxiety and posttraumatic stress disorder among women undergoing induced abortion (the PADIA study).**

**Agneta Skoog Svanberg, Inger Sundström Poromaa, Ulf Högberg and Sigrid Nyberg, Umeå University, Ingrid Östlund, Örebro University, Lottie Helström, Karolinska Institute, Gunilla Sydsjö, Linköping University and Örjan Frans, Department of Psychology, Uppsala University, Erika Schytt, Karolinska Institute.**

Although most women cope well with having an abortion, there is an increasing awareness that the abortion as such may deteriorate a pre-existing depressive and/or anxiety disorder or trigger the onset of a depressive episode. Targeted efforts are needed to aid these women through the abortion process.

The objectives of the proposed study are: 1) to assess the prevalence of post-traumatic stress disorder (PTSD), depressive symptoms and anxiety among women with unwanted pregnancies, 2) to assess the prevalence of PTSD symptoms such as intrusive thoughts, avoidance behavior and arousal following induced abortion, 3) to assess risk factors for development of PTSD and deterioration of depressive symptoms following induced abortion, such as personality and genetic vulnerability traits, pre-existing depression and/or anxiety and abortion method (medical or surgical abortion).

The design is a cross-sectional multi-center hospital-based study. Women will be recruited from five participating out-patient clinics (Uppsala, Örebro, Falun, Umeå, Södersjukhuset). All women asking for abortion with a gestational length less than 12 pregnancy weeks will be approached for participation in the study at their first visit at the clinic.

At baseline, the following data are collected: The Swedish universities Scales of Personality (SSP), Hospital Anxiety and Depression scale (HAD), Screen Questionnaire - Post traumatic Stress Disorder (SQ-PTSD), Socio-demographic data. Blood sample for analyses of a number of functional polymorphisms (VNTRs and SNPs) in candidate genes for affective disorders will be genotyped by Erika Comasco and Lars Oreland, Department of Neuroscience, Uppsala University. Candidate genes include SLC6A4 (5HTT), BDNF, MAOA, COMT, GABRA6, CRHR1, PER2, and OPRM1.

Patients will be followed by additional questionnaires after 3 months and 6 months, including the HAD, SQ-PTSD, and KUPP (Quality from the Patient Perspective) questionnaires.

Project status: The study started in September 2009 and thus far more than 900 patients have been included. Response rate is more than 65 %. We expect to include approximately 2500 women to reach the estimated target of 1500 women with complete data on follow-up.

### **The Swedish multicenter study on gamete donation: follow-up focusing on variables predicting negative psychosocial outcomes for donors, heterosexual and lesbian recipients and offspring**

**Agneta Skoog Svanberg, Professor Gunilla Sydsjö, Linköping University and Associate Professor Claudia Lampic, Karolinska Institute.**

To improve the readiness of the general population to act as gamete donors, more research on the psychosocial consequences for donors and recipients is needed.

The aims of the study are: 1) To identify variables predicting negative long-term psychosocial outcomes among families following OD/SD, using two matched comparison groups (couples using IVF, and couples with a spontaneous pregnancy) 2) To investigate the predictive value of oocyte and

sperm donors' personality characteristics, motives and ambivalence before the donation for their long-term emotional distress and dissatisfaction with the donation 3) To investigate OD/SD couples' intention/behavior to disclose information about genetic origin to offspring 4) To study the influence of OD/SD couples' general openness/secretcy regarding the donation, and their specific intention/behavior with regard to disclosure of information about genetic origin to offspring on couple relationship, emotional distress, parental stress and child development 5) To explore experiences of parenthood following gamete donation among heterosexual and lesbian OD/SD couples.

The multi-center study includes all infertility clinics performing gamete donation in Sweden, at the University hospitals in Stockholm, Gothenburg, Uppsala, Umeå, Linköping, Örebro, and Malmö. Donors, recipients, and control subject individually completed three questionnaires: at the start of treatment, 2 months after treatment, and 2-3 years after treatment. The long-term follow-up questionnaires, including the instruments Hospital Anxiety and Depression Scale (HADS), ENRICH (measuring satisfaction with family relations), The Swedish Parenthood Stress Questionnaire (SPSQ), The Toddler Behavior Questionnaire (TBQ), Openness/secretcy, and Disclosure intention/behavior are currently being sent out.

Project status: Between 2006-01-01 and 2008-03-31 all couples starting donation treatment and all gamete donors were approached regarding participation, and about 80% accepted participation. The present multi-center study will show whether participation in oocyte or sperm donation involves any long-term negative consequences for donors, recipient couples and their children. This project has already provided important, theory-driven knowledge about how the intentions of the Swedish legislation are enacted by patients and health care professionals.

## **BASIC - Biology, Affect, Stress, Imaging and Cognition in Pregnancy and the Puerperium.**

**PhD students Sara Sylven and Charlotte Hellgren, Malin Gingnell, Alkistis Skalkidou, Fotios Papadopoulos, Lisa Ekselius, Mimmie Willebrandt, Department of Neuroscience, Konstantinos Frangkakis, Johns Hopkins University, USA.**

We have previously conducted a population-based study on postpartum depression and the outlined study is an attempt to further extend our knowledge on the pathophysiological processes underlying the disorder but also to find predictors of the disease to improve early recognition.

These are some of the aims of the study; 1) Which biological markers in blood, saliva, spinal fluid or amniotic fluid can be used to identify women at increased risk of developing PPD? 2) Which genetic factors, personality factors and gene-environment interactions predispose to development of PPD? 3) May increased fear-potentiated startle response, decreased prepulse inhibition, cognitive deficits or attentional bias be used as predicting factors of PPD? 4) Do women with PPD exhibit a greater amygdala response in comparison with healthy controls?

The study design is complex, involving numerous psychiatric evaluations and psychological tests as well as the collection of blood samples, spinal fluid, umbilical cord blood and placenta tissue. In brief, all women attending the routine ultrasound examination in gestational week 16 -17 will be asked to participate in this study. During the pregnancy women are followed by web-based questionnaires. A randomized sample (n = 250) will be invited to an extensive psychological test at term pregnancy (gestational weeks 36 – 40). Blood and tissue samples will be collected from all women at parturition, and a final assessment of all women will be made six weeks postpartum. All women fulfilling the criteria for PPD (according to EPDS and a structured psychiatric interview (MINI)) will be invited to psychological testing and functional magnetic resonance imaging (fMRI). A randomized sample of healthy women at this time-point will also be invited as healthy controls.

Project status: Thus far, more than 400 women have been included and the first woman who gave birth within the BASIC cohort did so during the last week of January. Collection of blood and tissue samples at delivery has been successful in more than 90 % of subjects.

## **Do women with severe premenstrual symptoms have increased objective anxiety during the luteal phase and how does this relate to neurosteroid levels and symptom severity?**

PhD students Malin Gingnell and Elin Bannbers, post doc Kristiina Kask, Inger Sundström Poromaa, Professor Torbjörn Bäckström, Umeå Neurosteroid Research Center, Professor Bryndis Birnir, Department of Neuroscience, Associate Professor Johan Wikström, Department of Radiology, Professor Mats Fredrikson, Department of Psychology, Professor Mark Geyer and Associate Professor Victoria Risbrough, Department of Psychiatry, University of California, San Diego.

We have previously shown that patients with PMDD have an increased startle response during the late luteal phase of the menstrual cycle. As the startle response may be used as a proxy of amygdala activation, the next step is to use functional magnetic resonance imaging (fMRI) to explore the relation between PMDD diagnosis, menstrual cycle phase and the response of the amygdala to fearful stimuli.

50 women with PMDD and 50 healthy controls have been recruited for the study, among which 20 in each group have participated in the fMRI study. PMDD diagnosis was made according to international scientific standards, including two months of prospective symptom ratings on the previously validated Cyclicity Diagnoser (CD) scale and evaluation of ongoing psychiatric disorders by use of the M.I.N.I. interview, MADRS, STAI. Subjects were tested in the follicular phase and late luteal phase of the menstrual cycle. At each menstrual cycle testing, fear-potentiated startle response, fMRI and blood samples for genetic analyses and GABA<sub>A</sub>-receptors are made. The following fMRI paradigms are used:

1. A simple perceptual task involving the processing of facial expressions that has been developed by Hariri and colleagues. This paradigm has repeatedly been shown to effectively and consistently engage the amygdala.
2. A paradigm consisting of colour-coded emotionally salient pictures with positive or negative valence, which gives the opportunity to study affective processing and inhibitory control of emotions, similar to the startle response paradigm
3. A response inhibition paradigm (Go-NoGo) developed by Garavan and colleagues that will be used to examine differences in inhibition modulation and error-processing.

Project status. All PMDD patients and healthy controls have been included in the study. Preprocessing of data has been done during summer 2009 and preliminary data are available.

## **How is sensorimotor gating affected by reproductive events?**

Post doc Kristiina Kask, Associate Professor Maria Gulinello, Dominick P Purpura Department of Neuroscience, Albert Einstein College of Medicine, NY, USA

Patients with disrupted sensorimotor gating are typically characterized by difficulties in concentrating and deficient gating has been reported in subjects with PMDD, panic disorder, posttraumatic stress disorder, and obsessive compulsive disorder. Sensorimotor gating can be assessed by measuring prepulse inhibition (PPI) of the startle response.

I. Effects of ovarian steroids on PPI can be evaluated in women devoid of their endogenous ovarian steroids. 30 postmenopausal women without hormone replacement therapy, 30 postmenopausal women with continuous combined low dose estradiol/progestin treatment and 30 healthy cycling women have been included for the evaluation of prepulse inhibition of startle response across the menopausal transition and during postmenopausal hormone treatment.

II. 30 pregnant women, undergoing treatment for fear of child birth will be studied in a separate sub-study. These subjects will be measured twice, once during the third trimester of pregnancy and once during the first week after parturition. As startle response and PPI of startle response are known to be deteriorated in anxiety disorders, the joint effect of anxiety and ovarian steroids can be studied in this group of women. Inclusion of subjects is ongoing.

Preliminary data: In accordance with our hypothesis, postmenopausal women display increased PPI in comparison with cycling women. Also, PPI levels vary according to serum concentrations of estradiol levels in postmenopausal women, with lower levels present among women with estradiol levels in the fertile range.

## **Adverse mood effects from combined oral contraceptives – myth or reality?**

**Inger Sundström Poromaa, Malin Gingnell, Kristiina Kask.**

Although the majority of women report unchanged or improved mood while on COCs, mood-related side effects, such as irritability, mood swings and depressive symptoms have always, in spite of decreasing hormone concentrations over time, been one of the major reasons for discontinuing treatment. However, as no placebo-controlled, randomized clinical trials have been performed in healthy women, the true estimates of COC-related adverse mood symptoms are largely unknown. In order to elucidate the true prevalence of drug-related adverse mood symptoms and the underlying pathophysiology of COC-induced depression two studies are planned.

The primary aim of the study is to explore if reinsertion of oral contraceptives to women who previously have responded with adverse mood effects will induce aversive symptoms *de novo*. A secondary aim is to explore whether symptom deterioration, induced by combined oral contraceptives or by placebo, is correlated with increased amygdala activation.

40 women, with retrospective reports of aversive mood symptoms during prior use of COC, will be recruited for the study. They will be randomly assigned to receive either an oral contraceptive (30 µg ethinyl estradiol in combination with 150 mg levonorgestrel) or placebo for one treatment cycle. The study is double-blinded. One month before reinsertion and during treatment subjects will keep daily diaries of mood symptoms to measure symptom changes throughout the study course (CD-scale). Symptom changes will also be monitored by STAI and MADRS scores. To examine amygdala activation and response inhibition we will use functional magnetic resonance imaging (fMRI) using the same paradigms as previously described.

Project status: 12 patients have been randomized. Inclusion will continue until end of 2010.

## **Towards individually tailored labor analgesia**

**PhD student Fatimah Dabo, Helena Åkerud, Inger Sundström Poromaa, Fred Nyberg, Department of Pharmaceutical Biosciences, Uppsala University.**

The aim of these studies is to elucidate the roles of endogenous endorphins, genetic disposition, personality traits and psychiatric morbidity on pain perception, analgesia utilization, and effect of labour analgesia. The ultimate goal of our studies is to improve and tailor labour analgesia for delivering women.

Study I. 53 pregnant women have been followed with five repeated blood samples throughout pregnancy, with the aim of studying how levels of  $\beta$ -endorphin vary during pregnancy and to investigate whether preterm levels of  $\beta$ -endorphin are related to use of analgesia during labour. Plasma levels of  $\beta$ -endorphin were determined by RIA.

Study II. A population-based sample of 814 women have given a blood sample for analyses of genetic polymorphisms (opioid m-receptor SNP: A118G, Nitric Oxide Synthase, NOS1 SNP: AAT VNTR, Interleukin 6 SNP: G174C, Serotonin transporter SNP: 5HTTLPR, Bradykinin receptor 2 SNP: C58T, GTP cyclohydrolase SNP: five different pain protective haplotypes). All women who subsequently delivered in Uppsala and had a vaginal delivery (n = 728) filled out a pain questionnaire within 24 hours of delivery. Data on utilization of labour analgesia and obstetric variables have been collected from their medical records. The Magstration 12GC system (Precision System Science (PSS), Chiba, Japan) was used for the total genomic DNA preparation, followed by amplification and hybridization using Handy BioStrand with Cy5 labeled probes for the SNPs typing analysis.

Study III. 100 pregnant women, between gestational weeks 38-40, are currently being included in a study where genetic analyses,  $\beta$ -endorphin levels, personality traits, ongoing depression and anxiety, fear-potentiated startle response and pain sensitivity are being assessed in relation to labor pain and labor analgesia usage. Pain sensitivity was assessed by the cold-pressor test using skin-conductance as objective outcome measure.

Project status: All patients have been included in all sub-studies. Preliminary data indicate that low  $\beta$ -endorphin levels at term pregnancy and GTP cyclohydrolase pain protective haplotypes are associated with increased need for labor analgesia.

### **Psychiatric disorders, risk factors and personality in infertile women and men undergoing *in vitro* fertilization treatment**

**PhD student Helena Volgsten, Agneta Skoog Svanberg, Lisa Ekselius, Department of Neuroscience, Uppsala, Pia Olsson, Department of Women's and Children's Health, Uppsala.**

Between 2005 -2007, all couples scheduled for IVF treatment at the Reproductive Center, UAS, have been asked to participate in this study. After informed consent subjects fill out the screening form of the Primary Care Evaluation of Mental Disorders (PRIME-MD), which we previously have used in several studies. The PRIME-MD system evaluates the presence of major and minor depressive disorder, dysthymia, partial remission of major depressive disorder, generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, social phobia and bulimia nervosa.

In a third study, 10 female and 10 male subjects with unsuccessful treatment after completed IVF have been interviewed in a qualitative approach to assess the life impact of infertility, infertility treatment and failing treatment in these subjects. The females and males were interviewed separately.

Project status. Helena Volgsten defended her thesis in November 2009. The last manuscript is currently being submitted.

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