

Department of Women's and Children's
Health

ANNUAL REPORT
2010

Introduction

During 2010 there was a shift in chairmanship at the department, as I took over on July 1 after Ove Axelsson. It is a challenge and a privilege to head such an active and diversified department. 2010 was a successful year with respect both to research and education. The department has many devoted researchers within Pediatrics, Obstetrics/Gynecology and International Maternal and Child Health. Several collaborative projects with national and international research institutions are ongoing. The relocation of part of the research group of Medical Nutrition to the University Children's Hospital has enabled collaboration with several of our groups. The number of PhD students has steadily increased and reached 76 during 2010. During the year Lena Hellström-Westas was appointed professor in perinatal medicine and recruitments for several positions as professor or lecturer started.

All researchers are active in teaching and the department offers a number of educational programs including graduate courses for medical and nursing students, postgraduate programs for midwives and doctors in addition to several international courses including a master program in international health. During the major part of the year the number of medical students in pediatrics and obstetrics/gynecology was doubled since we had students both from the old and new educational program at the same time. This would not have been possible without extra efforts by our teachers and colleagues here in Uppsala and also at the affiliated county hospitals in the Uppsala region. I really want to thank all staff for their contributions during this period.

After the earlier application by the faculty to the National Agency for Higher Education the university regained the right to examine specialist nurses during 2010. This meant that our department could start the program for pediatric nursing again.

Since the department of Women's and Children's Health is a clinical research and educational institution it is important that there is a good cooperation with the University Children's Hospital and the Clinic of Obstetrics/Gynecology. The major part of our researchers and teachers have roles in health care as physicians, nurses or midwives. I am pleased to say that the relation with our clinical counterpart has continued to develop in a very positive way. This is a prerequisite for mutual success.

Finally, I want to thank all the staff at the department - teachers, researchers, administrators and laboratory technicians for their outstanding work during the past year. The research and education at our department is important for the physical and mental health as well as for the social well-being of women and children, both on a national and global level. The focus on this will continue in the coming years.

Uppsala in March 2011

Jan Gustafsson
Chairman of Women's and Children's Health

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Organization

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(from July 2008)

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Jan Gustafsson	teacher representative
Barbro Diderholm	teacher representative
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
Johanna Belachew	graduate student representative
Maria Stålhammar	graduate student representative, deputy
Johanna Rahmqvist, T6	student representative
Maria Sonmark, T6	student representative, deputy

Professor emeriti

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Yngve Hofvander

Elof Johansson

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Gudmar Lönnerholm

Gunnar Sedin

Torsten Tuvemo

Director of graduate studies

Inger Sundström Poromaa

Director of undergraduate studies

Tryggve Nevéus

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Obstetrical Research

Ove Axelsson, MD, PhD, Professor

Gynecological 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

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Pediatric Oncology

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Pediatric Neurology

Gunnar Ahlsten, MD, PhD, Associate Professor

Perinatal, Neonatal and Pediatric Cardiology Research

Anders Jonzon, MD, PhD, Associate Professor

General Pediatric Research Group

Lennart Nordvall, MD, PhD, Adjunct Professor

Pediatric Surgery and Pediatric Urology

Rolf Christofferson, MD, PhD, Associate Professor

Reproductive Health

Inger Sundström Poromaa, MD, PhD, Professor

Education at the Department of Women's and Children's Health

During 2010 an extra large number of students have participated in the broad range of programmes available at the Department of Women's and Children's Health. IMCH (International Maternal and Child Health) further has had more than 100 full-time students following the Master's Programme in International Health or single courses. We continuously educate medical and nursing students in pediatrics and gynecology/obstetrics during their pregraduate study programs. The number of medical students has been almost double the usual (that is approximately 200 instead of 120) during 2010 due to the fact that the Medical Study Program has been radically rearranged which resulted in double groups of students reaching the courses in paediatrics and gynaecology/obstetrics at the same time. The department also gives the Registered Midwife course and the postgraduate course in Specialist Paediatric Nursing.

The undergraduate/graduate courses given by the department

Obstetrics/Gynaecology and Paediatrics within the Registered Nurse Programme

The Registered Midwife Programme

Obstetrics and Gynaecology within the Medical Programme

Pediatrics within the Medical Programme

Global Medicine, an elective course for medical and nurse students which includes a 2-week study visit to hospitals and health centres in a low-income country

Postgraduate courses for nurses

Postgraduate Education in Pediatric Nursing

Child and Adolescent Health Care, Child and Adolescent Psychiatric care, 15 credit points (CP)

Nursing Care of Children and Adolescents with General Pediatric Conditions, 15 CP

Other postgraduate courses

Master's Programme in International Health (2-year programme)

International Training Programme focusing on global Child Survival issues

Separate courses

Global Reproductive Health 7 CP

Breastfeeding and Human Lactation, 7.5 CP

Pain in Children and Adolescents, 7.5 CP

Gynecological pain and analgesia 7 CP

Violence Against Women 7.5 CP

Mentorship for Midwives 7.5 CP

Independent Research Projects in Reproductive Health 10 CP

Global Nutrition 10 CP

Global Health Program Management 10 CP
Global Sexual and Reproductive Health and Rights 10 CP
Global Health in Humanitarian Action I + II 5 + 5 CP
Global Health 20 CP
Reproductive Health in a life-cycle perspective (also available within the Midwife Programme)
Global Health (also available within the Midwife Programme)
Qualitative Research Methods 10 CP
Quantitative Research Methods 10 CP
Information seeking 3 CP
Basic Biomedical Laboratory Science

The registered Midwife Programme

The registered Midwife Programme is a 90 ECTS degree program including practical training and a 30 ECTS examination. The cornerstone of the education is formal training in reproductive health and obstetrics but students are also prepared for independent work within the fields of maternal health, youth health (contraceptive advice), and infertility. Because of the available resources at the department particular emphasis on global reproductive health and violence against women is provided. Within the program it is possible to obtain a Master's degree, which in turn is a prerequisite for future PhD studies.

The Postgraduate Education in Paediatric Nursing

The postgraduate education in paediatric nursing has been extensively revised and restarted during 2010. The course is partly web-based and partly based on weekly seminars as well as practical education at paediatric in- and outpatient wards. As these programs are available on an advanced level, students are given the opportunity to obtain a Master's degree.

Obstetrics/Gynaecology and Paediatrics within the Registered Nurse Programme

The course in "Nursing and medical care in gynecological, obstetric and pediatric care", 12 CP, has now been running for 2 years. Both theoretical and practical teaching, as well as web-based seminars, and seminars using problem-based learning methods are available. Students are given the opportunity to write a minor independent scientific paper (C-thesis) during the course.

Obstetrics/Gynaecology and Paediatrics within the Medical Study programme

Medical students spend 15 weeks during their 9th and 10th semester at the department, studying pediatrics and gynecology/obstetrics. The studies are intense and comprise lectures, seminars (including problem-based learning) and auscultation at the hospital's various in- and outpatient wards. The department also cooperates with hospitals outside Uppsala (Eskilstuna, Västerås, Falun, Gävle, Hudiksvall, Mariehamn) for parts of the students' clinical education.

Education at IMCH

The Master's Programme in International Health is a 2-year programme that attracts physicians, nurses, midwives, nutritionists as well as students with a social sciences background. Most of the

participants come from low-income countries and are selected from several hundred applications. Core courses in international health and research methodology as well as elective courses and project planning, field work are followed by the compilation and defence of a Master's thesis. Many of the students return back to their home country for field work during the second year of the program. We notice that some PhD students are recruited among skilled and successful Masters students – and we have examples where the Masters thesis is the starting point for subsequent PhD research. The department is also involved in an European joint Master's Programme in Humanitarian Assistance, the NOHA programme. On behalf of SIDA and jointly with the University of Gothenburg and the Karolinska Institute the department is running an International Training Programme focusing on Global Child Survival issues. Senior colleagues with responsibilities for child health programmes from Ministries to non-Governmental programmes attend a one-month course in Uppsala and subsequent research/development work and follow-up workshop in their region.

Uppsala in March 2011

Tryggve Nevéus
Director of undergraduate studies

Research Education

The department has extensive PhD training within Pediatrics, Obstetrics/Gynecology and International Maternal and Child Health. The number of PhD-students increased to 76 during the year. The research students have varying backgrounds. Many are recruited among the pediatricians and obstetricians/gynecologists who perform their specialist training in the university hospital and the number of specialist nurses and midwives presenting theses is increasing.

At International Maternal and Child Health many of the PhD-students come from low-income countries, where the major part of their research is performed. Some PhD-students are recruited from the Masters program in international health. The projects are mostly carried out in collaboration with institutions in the different countries and the students regularly come to Uppsala for theoretical courses and contacts with their supervisors. Following dissertation many of the PhDs obtain positions within health care in their home countries and continue with research in collaboration with our department.

Scientific Reports

Reproductive biology

Matts Olovsson

Molecular mechanisms of implantation

Successful implantation depends on normal embryo development, communication between the embryo and maternal tract during the transport through the Fallopian tube and end normal development of the endometrium. Our studies show that although embryo development is tightly regulated (1), external factors such as IGF1 are of importance (2). The most optimal media for embryo culture is still not developed; we have shown that the media is of clinical importance for fertilization and thereby of success after fertility treatment (3). Our ongoing studies using proteomic pattern of embryo development in collaboration with Jonas Bergqvist, show that the growth factor gp130 seems to be important for embryo development. These studies will be included in Fredwell Hambiliki's thesis work.

Hormonal regulation of Fallopian tube function and communication between the embryo and fallopian tube is of interest in this group (4). Our previous studies on thyroid hormone in reproductive function (5,6) will be continued in Jesper Ekman's and Amani Rumman's thesis work.

Markers of endometrial receptivity is a main focus (7), most recently the distribution and regulation of aquaporin 1 (8) and HGP (9) has been shown. We are using human endometrial cell culture models to study hormonal regulation of the endometrium (10), most recently in collaboration with Linda Giudice in San Francisco.

Interactions between the embryo and endometrium are studied using our new approach is to use bioinformatic (11). For the future, studies on prostasomes and their interaction with endometrial cells will be a new approach to understand endometrial receptivity (12). Anneli Stavreus-Evers coordinates these studies.

Infertility diagnosis and treatment

For women with unexplained infertility, we lack good diagnostic tools, and the treatment could be more efficient. Our recent studies showed that HB-EGF, LIF receptor, Ghrelin, Calcitonin, Tissue factor and HABP2 is dysregulated in endometrium from women with unexplained infertility (13-18) and our array data show extensive gene expression in endometrium from fertile and infertile women (19). We can also show that fertility treatment has a negative influence on endometrial receptivity (manuscript). 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. Genetic variations might influence endometrial receptivity and infertility treatment. Our studies on genes involved in LIF pathway show that polymorphism in the gp130 gene is will reduce fertility (manuscript). We have also recently characterized the hormonal profile of women with unexplained infertility (20).

Low folate levels have been related to fertility problems (21), which can be due to genetic causes (22, 23). Studies on the importance of folate for pregnancy outcome will be included in Tiina Syvänen's thesis work. This study is performed in collaboration with Torbjörn Nilsson in Örebro and Andres Salumets, Tartu, Estonia. For the future, we will study epigenetic effects of folate on embryo development and placenta function

Miscarriage is also an infertility problem although most women with recurrent miscarriage usually will become pregnant. The cause of miscarriage is often aneuploidy but so far, there is no genetic cause found for recurrent miscarriage (24, 25). We have in collaboration with women's clinics in four hospitals 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.

Additional clinical studies from our group show that genetic background can influence outcome after fertility treatment (26) and that adrenomedullin might influence angiogenesis in women with menorrhagia (27). During fertility treatment we can show that luteal phase support with progesterone increase delivery rate (28) and that serum gp130 might predict pregnancy outcome after treatment (29). Furthermore, we found that it not an advantage to add hyaluronan during embryo transfer, it is not possible to force the embryo to stick to the endometrial lining (30).

In clinical practice, only one embryo is transferred at the time. For this, optimal freezing technique is of importance. The new freezing technique, vitrification, needs further evaluation. The best cryoprotectant is DMSO (31) although with the risk of toxicity. Initiated future studies will focus on epigenetic effects on different freezing methods. Julius Hreinsson and Kjell Wånggren are involved in these studies that are coordinated by Anneli Stavreus-Evers.

Breast cancer

Women with breast cancer have severe problems with dry vaginal mucosa affecting their quality of life (32), despite higher than expected estrogen levels (33). 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 Baumgardt in Örebro and Anneli Stavreus-Evers and Inger Sundström Poromaa in Uppsala, and the studies will be included in Theodora Kallak's doctorate thesis.

Preeclampsia

Pre-eclampsia (PE) 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 pathogenesis of PE and how to diagnose, predict and treat the disease. We have shown that there are differences between early and late onset PE concerning placental oxidative stress, angiogenic and anti-angiogenic markers and several inflammatory markers (34, 36, 38-41). Our data indicates that pathogenesis differs between early and late onset disease and they should most likely be predicted, diagnosed and treated differently. In cooperation with Stefan Hansson (Lund University) and my PhD-student Katja Junus we are studying the genomic profile differences between early- and late-onset PE where we can show that there are several differences in genes involved in the control of angiogenesis (40). In cooperation with Hella Hultin and Per Hellman we have shown an increased risk to develop PE in women with previous primary hyperparathyroidism (35) but there seem to be no association between vitamin-D receptor polymorphism and PE (41). 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 have a cooperation with Professor Graham Burton in Cambridge (UK) on placental/trophoblast metabolism, especially mitochondrial function. The studies are coordinated by Matts Olovsson.

Endometrium and endocrine disrupting chemicals (EDCs)

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 endometrial functions important for fertility. We are working with cell culture systems to screen for potential effects of these chemicals on endometrial functions. We have shown that several EDCs affects the expression of angiogenesis related genes in human endometrial endothelial cells (42-44) and that this effect depend on endometrial stromal cells (46, 47). We have also shown a colocalization of [3H]tamoxifen adducts, expression of GRP78, caspase 3, and tamoxifen-metabolizing enzymes in human glandular and surface epithelia suggesting a local bioactivation of tamoxifen at these sites and that epithelial cells are early target sites for tamoxifen-induced cell stress(45). We are also studying the control of

normal endometrial angiogenesis as a part of this project and we can show how vascular endothelial growth factor regulates the gene expression in HEEC (48). The studies are coordinated by Matts Olovsson.

Endometriosis

Endometriosis is a common gynaecological disease, occurring in about 10% of all women. The disease causes abdominal pain and reduced fertility. We are currently performing questionnaire studies on cost of illness and quality of life. We are also performing clinical studies on new non-surgical strategies to treat deep endometriotic lesions. There are also studies of endometrial factors associated with endometriosis related infertility (49). We also present case reports of more general interest (50). Our endometriosis research is done at our National Endometriosis Centre. The studies are coordinated by Matts Olovsson.

HPV testing and self-sampling in primary screening for cervical cancer

Cervical cancer is the second most frequent cancer among women worldwide and caused by persistent infection by oncogenic types of human papillomavirus (HPV). The organised gynaecological screening in Sweden has reduced the incidence of cervical cancer by 50%. A further reduction may be achieved by introducing HPV typing as a primary test and a screening system where women can take the samples at home at their own convenience and thereby increase the population coverage. We have shown that the use of self-sampling at home in combination with testing for high-risk HPV increases the participation rate of the organised screening and detects almost twice as many women with pre-malignant cell alterations (CIN 2-3) in comparison those with a single cytological smear (51, 52). At present there is however a lack of studies using repeat HPV testing and self-collected samples in primary screening. The purpose of this project is to fill this knowledge-gap by performing several studies such as on the efficiency of using repeat HPV testing based on self-collected cervicovaginal samples as compared to cytology screening, for identification of women at risk of developing cervical cancer. Further, what would the health-economic benefits be if using repeat HPV typing and self-collected samples in primary screening for cervical cancer, as compared to conventional cytology. A strategy based on self-collected samples and repeat HPV typing can reasonably provide very significant economic savings to the health care system. For instance, only by using longer intervals between screening of HPV negative women as compared to normal cytology would result in a saving of 200-250 MSEK per year. The studies are coordinated by a steering group consisting of Ulf Gyllensten, Erik Wilander, Ingrid Wikström, Karin Sanner and Matts Olovsson.

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 (53). 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 (54). Our latest data show that antral follicle count is strongly associated with live birth rates after ART (55). The studies are coordinated by Jan Holte, Thomas Brodin and Matts Olovsson.

Ovarian cancer

Prognostic factors for epithelial ovarian cancer in FIGO-stages I-II have been studied (56-59). We have studied the relevance of p53, bax, p21, p27, PUMA och c-MYC, EGFR, VEGF-R, VEGF and PTEN as prognostic factors. An ongoing project within genomics has generated interesting data that we still are working with. These studies are coordinated by Ingridur Skirnisdottir.

Members of the group

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Publications 2008-2010

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Research grants during 2010

- ALF, 1 192 325 SEK
- The Swedish Research Council: grants for position (forskarassistent) and project, 770 000 SEK plus 325 000 SEK
- European Union, 450 000 SEK
- Medical faculty, 165 510 SEK
- Vårdforskningsmedel, 195 000 SEK
- The Family Planning Fund in Uppsala, 110 000 SEK
- Other funds, 425 000 SEK
- Lions cancerforskningsfond, 150 000 SEK

Obstetrical Research

Ove Axelsson

During 2010 three of our research fellows presented their theses.

Hashem Amini's thesis focused on Fetal Diagnostics. In the first part he showed that ultrasound can give false positive diagnosis of fetal anomalies. In the second part he investigated the possibility to use magnetic resonance tomography (MRT) for fetal diagnosis in the second trimester as a complement to ultrasound. He concluded that MRT has a role, especially when the central nervous system is affected or when oligohydramnios or maternal obesity decreases the diagnostic power of ultrasound. Thus, MRT can be used as a tool to avoid false positive diagnosis of fetal anomalies. A continuation of this project is to investigate if 3-D ultrasound can improve Fetal Diagnostics even further.

Eva Bergman's thesis dealt with intrauterine growth restriction (IUGR). She could show that today's methods for antenatal identification of IUGR fetuses are poor. In cooperation with biostatisticians from Gothenburg she then tested a new way to diagnose IUGR during pregnancy with the help of frequent self-measurements of the symphysis-fundus distance. Data were used to construct a relative growth reference curve and subsequently analysed with a classical statistical method by Shiryayev-Roberts (SR) to investigate the capacity to detect IUGR fetuses. She concluded that with the data available the SR-method was not able to predict IUGR. Future studies will examine the concept of relative growth in other settings with focus on high-risk pregnancies.

Together with two other research groups at the department we are responsible for an ongoing collection of plasma and leucocyte samples from women pregnant at about 18 weeks. So far samples from almost 10,000 women have been collected. One of the aims is to identify factors predictive of pre-eclampsia and/or IUGR. Identification of better risk factors could be used to select women with increased risk for pre-eclampsia and/or IUGR. New methods for antenatal diagnosis of IUGR, e.g. relative growth, could then be applied on this subgroup of women.

Corrine Pedroletti presented a thesis where women operated upon for urine incontinence by the TVT-method were followed-up. She will continue her research in another research group.

During 2010 associate professor Helena Åkerud has joined our group. She has a preclinical background and her thesis dealt with angiogenesis. She is now a specialist in Obstetrics and Gynecology and focuses her research towards pre-eclampsia. She has set up a translational project to study defects in the implantation and placentation processes in an in vitro model. Such defects are often mentioned as underlying causes of pre-eclampsia. Another project, with Sarah Sohlberg as a research fellow, uses functional MRT to study placental metabolism in vivo with the aims to identify differences between pregnancies complicated by IUGR/pre-eclampsia and uncomplicated pregnancies. Still another project examines biochemical and biophysical markers to identify predictors of pre-eclampsia and to increase our knowledge on etiology and pathophysiology of this syndrome.

Anna-Karin Wikström has also joined the group in 2010. She defended her thesis on pre-eclampsia in 2007 and has just come back from a postdoc year at the Department of Clinical Epidemiology at the Karolinska Institute. She cooperates with Helena Åkerud in several projects and her new knowledge in epidemiology offers a most promising possibility to combine laboratory and epidemiological methods to set up projects which will help us to understand more about pre-eclampsia with the final aim to be able to prevent or treat this severe syndrome. Anna-Karin Wikström has published several papers on snuff and pregnancy complications during her stay at the Karolinska Institute. She has got good insight into the use of national registries for clinical research.

Other ongoing projects concern treatment of gestational diabetes (Ulf Hanson), 3-D ultrasound in the postpartum period (Karin Eurenus, Ajlana Lutvica and Johanna Belachew), asphyxia during labour

(Maria Jonsson and Lena Liljeström), thyroid disturbances and pregnancy outcome (Helena Åkerud, Anna-Karin Wikström and Michaela Granfors) and women's knowledge of methods to diagnose fetal chromosomal aberrations (Peter Lindgren).

Of our research fellows Maria Palm, Marie Bolin and Sarah Nordquist will present their halftime dissertations in 2011. Maria Palm uses a biobank of blood and urinary samples from healthy women with uncomplicated pregnancies with the aim to estimate oxidative stress, inflammation and angiogenesis during normal pregnancy. Marie Bolin is engaged in a project where biochemical and biophysical markers are evaluated concerning prediction of pre-eclampsia. A secondary aim is to increase our knowledge of the etiology and pathophysiology of pre-eclampsia. Sarah Nordquist's research field is IVF-pregnancies. Her project includes genetic expression analysis on placentas from IVF-pregnancies and, as controls, placentas from spontaneous pregnancies. The mechanisms behind unexplained infertility might be associated with the risk to develop pre-eclampsia.

Members of the group during 2010

Ove Axelsson	Professor
Ulf Hanson	Associate professor
Dan Hellberg	Associate professor
Helle Kieler	Associate professor
Solveig Lindeberg	Associate professor
Helena Åkerud	Associate professor
Staffan Nilsson	Adjunct professor
Hashem Amini	M.D, Ph.D
Eva Bergman	M.D, Ph.D
Karin Eurenus	M.D, Ph.D
Maria Jonsson	M.D, Ph.D
Peter Lindgren	M.D, Ph.D
Ajlana Mulic-Lutvica	M.D, Ph.D
Corinne Pedroletti	M.D, Ph.D
Karin Stålberg	M.D, Ph.D
Anna-Karin Wikström	M.D, Ph.D
Karin Kårehed	Ph.D, postdoc
Johanna Belachew	Research fellow
Marie Bolin	Research fellow
Michaela Granfors	Research fellow
Lena Liljeström	Research fellow
Sarah Nordquist	Research fellow
Maria Palm	Research fellow
Sara Sohlberg	Research fellow

Publications 2008-2010

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Dissertations 2010

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The Uppsala county research foundation 300 000 SEK

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Gynecological Endocrinology

Tord Naessen

In our research group we study effects and mechanisms of endogenous and exogenous steroid hormones with regard to e.g. fracture risk, the artery wall (atherosclerosis), cardiovascular disease (CVD), polycystic ovary syndrome (PCOS), premenstrual syndrome (PMS/PMDD), pre-eclampsia, cognition / brain volumes and ovarian follicular fluid content and IVF outcome. Further, we suggest and evaluate a new principle for non-invasive assessment of arterial aging/atherosclerosis, based on high-frequency ultrasound.

I: Menopausal hormone therapy (HRT) and fracture risk: ‘Peripheral ‘osteoporotic’ fractures – a brain disease or a bone disease?’

We study effects of endogenous and exogenous sex hormones on bone mass and fracture risk. Hip and distal forearm fractures (peripheral fractures) are strongly determined by a fall. Our results indicate HRT rapidly reduces the risk of peripheral fractures through effects via the brain and improved postural balance function, rather than effects on bone mass. *Significance:* An effect of HRT on the brain with improved postural balance, 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 more difficult to show substantial effects on hip fracture risk after treatment with bisphosphonates.

II: Endogenous and exogenous sex steroids and the artery wall, prevalent cardiovascular disease (CVD) and prediction of CVD event/death.

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. Currently we evaluate the significance of subtle differences in endogenous steroid hormone levels in elderly with regard to artery wall aging (ultrasound), prevalent CVD, coming risk of CVD / death and cognition/brain volumes in elderly women and men. We analyze 11 steroids and precursors within the cholesterol pathway in samples from #1016, 70 year old men and women (in PIVUS), using Liquid Chromatography Tandem Mass Spectrometry (LS-MS/MS) in collaboration with ARUP laboratories in Salt Lake City, Utah, USA.

We have found increased endogenous estrogen levels in both men and women with prevalent CVD and an ‘unhealthy artery wall’ on ultrasound, compared to those without CVD, which most likely represents an endogenous attempt to counteract an ongoing inflammatory/atherosclerotic process.

Significance: Our previous and current results indicate that smooth adjustment of serum estrogen levels, keeping them within ‘normal’ ranges for elderly, might be of benefit for organ function over time, e.g. the artery wall/atherosclerotic. i.e. a new field of research.

III: We suggest and evaluate a new principle for non-invasive assessment of the artery wall with regard to arterial aging, screening and prediction of cardiovascular disease (CVD), using high-frequency ultrasound (20MHz – 50MHz).

With increasing age and development of atherosclerosis the dimension of the artery wall intima layer increases whereas that of the media layer decreases. Thus, the differential changes in the intima and media layers will reduce the usefulness of the present 'gold-standard', the Carotid-IMT (CCA-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, and have found this principle to be superior to the conventional CCA-IMT. We have assessed all #825 men and women 75 years old, in PIVUS-75. They will be followed for occurrence of CVD events/death and thereby we evaluate the

strength of our suggested method/principle to predict coming incidence of CVD events/death. Currently we use this principle in a RCT study to monitor effects of HRT initiated early after menopause, as an alternative (preferable?) method to conventional carotid-IMT, which is used in the large ongoing US studies KEEPS and ELITE. Further, we evaluate effects on the artery wall in women with SLE, young subjects with a history of major depression, in pre-eclampsia, lipid-lowering therapy and in women with breast cancer. In the latter, to image effects of ‘anti-estrogen’ therapy as a group, and aromatase inhibition and receptor blocking (tamoxifen), respectively.

Significance: We believe that this principle/method might replace the present ‘gold-standard, Carotid-IMT, for non-invasive assessment of the artery wall with regard to subtle arterial aging in conditions/diseases, diagnosis of prevalent CVD, prediction of CVD events and in monitoring effects of interventions against atherosclerosis/CVD.

IV: Endogenous and exogenous estrogens and preservation of cognitive function, brain volumes and function.

We study effects of different levels of endogenous steroid hormones and of long-term estrogen therapy on cognitive function and total and relative brain volumes (esp. hippocampal region), assessed by MRI. By using MRI and Positron Emission Tomography (PET), we study whether HRT and higher endogenous steroid hormone levels can preserve brain volumes and reduce the normal age-related increase in amyloid deposits (PIB).

Significance: If HRT, initiated soon after menopause, can preserve cognitive function, brain tissue (volumes) 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.

V: 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 have found increased sensitivity in PMS/PMDD women to estrogen provocation and very strong association between worsening of PMS symptoms over the menstrual cycle and lower ‘serotonin’ signal in pre-defined brain regions. The methods used include studies with Positron Emission Tomography (PET).

Significance: to better understand the relation between hormones and mental symptoms in PMS, a disorder affecting many women with consequences for the individual, her family- and professional life.

VI: Steroid hormone concentrations and proteomics in ovarian follicular fluid in the normal menstrual cycles, in PCOS and after ovarian stimulation, IVF.

Steroid hormones and are analyzed using Liquid Chromatography Tandem Mass Spectrometry (LS-MS/MS). In PCOS we have found indications for a block in the aromatase enzyme function, which might be the background for the arrest in follicular development/anovulation in PCOS.

Significance: results might reveal underlying causes of anovulation. In IVF, we aim to develop methods that can help in choosing the ovum with the best chance to succeed in fertilization, implantation and born baby, methods that can be applied more broadly when mass spectrometry methods become easily available at university hospitals.

Members of the group

Tord Naessen	Senior Lecturer
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Tansim Akhter	Doctoral student
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Visual Sonic Inc., Toronto, Canada

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Selanders Stiftelse: 180,000 SEK

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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 positioned within Uppsala University as a centre for certain assignments, without faculty affiliation. NCK reports directly to the vice-chancellor and has its own Board.

NCK is commissioned by the Swedish Government to increase knowledge on men's violence against women, violence and oppression in the name of honour and violence in same-sex relationships. This is done by compiling research overviews, spreading knowledge and information, developing methods and conducting research within the centre's field. NCK also provides training for both students and professionals. The undergraduate courses for students are organized in cooperation with the Department of Women's and Children's Health.

NCK has been given several commissions from the Swedish government; three of them were completed in 2010.

NCK was in 2007 commissioned 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. A further assignment was the implementation of the sexual assault program and handbook as well as the revised *Assault Evidence Collection Kit*. The kit was revised in collaboration with the Swedish National Laboratory of Forensic Science (SKL) and is now implemented in the Swedish health care services and accessible in the majority of hospitals in Sweden. An application of the national program for sexual assault victims is planned in South Africa as a part of a larger SIDA-funded project dealing with the issues of sexual assault.

Secondly, NCK was assigned to develop methods for including issues relating to personal experience of violence into case histories in the health care service. The result was reported in the form of an anthology dealing with several aspects of inquiring about personal experience of violence within the health care service. Several nationally prominent researchers and experts within the centres field of research have contributed to the anthology, which also includes the results of four minor studies on i.e. the significance of cultural differences concerning the inquiring about personal experiences of violence. Also within the assignment was an instructional film for health care personnel, on how to inquire about personal experience of violence, completed.

The third assignment was to disseminate knowledge and information concerning violence and oppression in the name of honour and violence in same-sex relationships. Two research overviews were completed on violence and oppression in the name of honour and on female mutilation. NCK also initiated the production of a training film and a pedagogical manual on violence in same-sex relationships. Together with the research overview on violence in same-sex relationships that was completed in 2009, the film and manual constitutes parts of the training material used in the centres training.

In connection with the above mentioned assignments was an internet based Knowledge bank (Kunskapsbanken) on men's violence against women, violence and oppression in the name of honour and violence in same-sex relationships developed. The Knowledge bank contains subject overviews, research publications and information from both governmental and other organizations. The database also includes presentations of researchers and their field of research. The purpose of the Knowledge bank is to bridge the gap between research and practise and to present easy access to the field of men's violence against women, violence and oppression in the name of honour and violence in same-sex relationships.

Women subjected to violence are treated at the centre's outpatient clinic at Uppsala University Hospital. NCK also supports women exposed to violence on a national women's helpline (Kvinnofridslinjen). The national helpline was commissioned by the government in 2007 and is run by centre's clinical unit at Uppsala University Hospital. In 2010 the helpline received about 40 000 calls.

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, Ph
Elisabeth Mattsson, CPM, PhD
Mariella Öberg, MD, Research Fellow

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 patients'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 the prevalence of sexual assaults.

Monitoring of students and referee assignments are ongoing.

Publications 2008 – 2010

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2. 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

3. 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
4. Heimer Gun: *Viktigt för sexualbrottsoffer att sjukvård och rättsväsende gör rätt.* Läkartidningen 2009:7
5. Heimer, Gun; Ingela Danielsson; Helena Blom; Carin Nilsson; Ulf Högberg: *Tydliga könsskillnader i ungdomars utsatthet för våld* Läkartidningen nr 18, 2010 volym 107

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 care professionals, social workers and police officers.

During 2010 NCK gave four courses on different levels for students: Violence against Women, part-time, 7,5 hp (spring and autumn) and Men's Violence against Women, advanced course. Part-time 7,5 hp (spring and autumn).

Two distance courses were organized for professionals: Cross-professional distance learning, 15 hp: Men's violence against women, for professionals from different sectors who in their work meet with women subjected to violence. Secondly Violence in intimate relations, advanced course for prosecutors, 7,5 hp, in cooperation the Swedish Prosecution Authority.

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 Centre for Gender Research.

Website

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.

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.

Three Associate Professors have got new positions: Birgitta Essén received a position as Senior Researcher in Sexual and Reproductive Health, financed by the Swedish Research Council (VR forskartjänst). Pia Olsson received a position as Senior Lecturer in Global Sexual, Reproductive and Perinatal Health. Eva-Charlotte Ekström received a position as Senior Lecturer in Global Nutrition.

Doctoral student Helena Litorp has received a trainee research position from Akademiska sjukhuset (ST-forskartjänst).

Four doctoral students have defended their thesis successfully. Four new doctoral students have been registered during the year.

Ass Prof Birgitta Essén has been awarded by 1,6 miljonersklubbens forskningsstiftelse for her research on maternal mortality in a migration perspective. Doctoral student Barni Nor has been awarded by the British Institute for Strategic Dialogue for being one of the 10th most influential Muslim women in Europe.

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, and comprehensive abortion care in India. Too many caesarean deliveries as a challenge for Safe Motherhood is investigated in Tanzania and Nicaragua. 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 Women's Clinic, at the Department of Women's Health, Akademiska sjukhuset.

Maternal nutrition is essential for reproductive outcome. Studies in Bangladesh 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 Tanzania attitudes to violence in all sectors of the community and the legal system. Rape victims in Congo are studied in collaboration with the Centre

for Gender Research at Uppsala University. In Sweden, several projects focus on medical and socio-cultural factors related to refugees, honour violence and female genital cutting.

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. Pornography consumption among young women and men is studied.

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.

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. The fifth FOKO workshop was this year arranged in Uppsala with 25 international participants.
- 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. The yearly meeting 2010 had focus on caesarean section among immigrants in low income countries and gathered around 30 Nordic researchers.
- 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

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 University Western Cape, South Africa
 Medical Research Council, South Africa
 Health Systems Trust, South Africa
 UNAN, University of Leon, Nicaragua

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PhD exam

Mattias Rööst

Pre-hospital Barriers to Emergency Obstetric Care

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Promotion of Exclusive Infant Feeding in South Africa

Projestine Muganyizi

Rape against women in Tanzania. Studies of Social reactions and barriers to disclosure.

Andrea Pembe

Quality assessment of monitoring of maternal referrals in rural Tanzania

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, undernutrition and its consequences, and on equity in child health and survival. It has also contributed important new knowledge regarding the child health consequences of the ongoing environmental catastrophe with arsenic-contaminated tube well water in South Asia.

Child survival has improved considerably since 1990, and several poor countries 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 (35). 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). The project has already generated new knowledge on neonatal health (7,8,10,18,34,39,40), including a completed PhD thesis during 2010. Three more PhD students are active in the trial. Sida is the main funder of this project and additional funds have been provided by Swedish Research Council.

Exclusive breastfeeding during the first six months of life is considered one of the most important means of preventing child deaths in infections. We have recently shown that even in a poor community in Bangladesh this has no negative effects on iron and zinc status at 6 months (17). The dilemmas around exclusive infant feeding options when trying to prevent mother-to-child transmission of HIV are being studied by a series of PhD students in collaboration with University of Western Cape and MRC in South Africa (2). Swedish Research Council finances the ongoing studies to our group and Save the Children (US) provides support to our collaborating partners.

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 psychomotor development. Results so far show effects by combined food and multiple micronutrients on survival (submitted manuscript) and on development (46). Recently one PhD student defended her thesis where the consequences for micronutrient status were analysed (3,4,17). Currently the impact on child growth, blood pressure and metabolic markers are analysed by other PhD students in order to address research questions related to the DoHAD hypotheses (development origin of health and disease. Other research questions related to nutrition or social conditions and health have also been addressed in the MINIMat cohort (13,19,20,26,27,30,31,44,45,47). We collaborate with, among others, the research institution ICDDR 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. The Swedish Research Council and Sida have provided funding and the research partners have received funding from several agencies.

One research student from Bangladesh study the effect of stimulation (play therapy) in addition to food supplementation in the rehabilitation of severely malnourished children (21), while a PhD student from Ethiopia is setting up a study of the effectiveness of community-based rehabilitation of acute severely malnourished children. Sida has supported these studies.

The health consequences – also for children – of violence against women (VAW) have been studied in Nicaragua and Bangladesh (9,29,30,31,41,47). We have confirmed our earlier findings of

association between violence against mothers and higher mortality in offspring (47), and for the first time we have shown associations with child growth and morbidity (30,31). We have also shown that the earlier demonstrated association between VAW and size at birth partly is mediated over chronic stress as reflected in neuro-endocrine responses (29).

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 (11,12,15,22) and so far two PhD students from Bangladesh have defended their theses. We have also contributed to several other substudies dealing with the public health consequences of this environmental catastrophe (5,14,16,23,28,35,37,38,42,49). We collaborate with ICDDR, Bangladesh and with the department of Metals and Health, Karolinska Institutet.

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/>.

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Paediatric Endocrinology

Jan Gustafsson

Within pediatric endocrinology several lines of research have been ongoing during 2010.

1. Growth and metabolism during infancy and childhood

Jan Gustafsson, Barbro Diderholm, Fredrik Ahlsson, Inger Wahlström Johnson

Placental transfer of glucose is important for the development of the fetus. After birth the newborn infant must produce its own glucose until breastfeeding is established. Our research is directed on energy metabolism during pregnancy and in the newborn infant. In addition to neonatal hypoglycemia, infants who are born small or large for gestational age are at risk for developing metabolic disease later in life. We perform studies of glucose production and lipolysis by use of stable isotope labelled compounds and gas chromatography-mass spectrometry. Our results have pointed out important relationships between maternal metabolism and fetal weight. The central nervous system has a role in regulating hepatic glucose production and in the newborn infant the brain consumes the major part of the produced glucose. Perinatal asphyxia may influence neonatal glucose homeostasis and we presently investigate glucose metabolism and lipolysis during and after hypothermia in infants with perinatal asphyxia. In a collaborative project with the department of neurosurgery, the combination of microdialysis and stable isotope technique is used for the study of glucose metabolism in the brain.

2. Register based studies of fetal origin of adult disease

Maria Lundgren, Torsten Tuvemo, Inger Wahlström Johnson, Fredrik Ahlsson and Jan Gustafsson

Conditions during fetal life are important for development and morbidity during childhood and adult life. There are common mechanisms behind statural growth and the development of cognitive function. By use of different Swedish health registers we study effects of fetal conditions and birth characteristics on statural growth as well as adult intellectual performance and morbidity. Data on relationships between growth and intellectual performance in subjects born preterm have recently been published. Studies on long term consequences of being born large for gestational age are ongoing.

We have recently completed a study on mortality and causes of death in Down syndrome. The data show that mortality, particularly infant mortality, has decreased markedly during the last decades. Median age at death is increasing and is now almost 60 years.

3. Prematurity

Kerstin Hedberg-Nykvist, Uwe Ewald, Eva-Lotta Funkqvist, Katarian Strand-Brodd, Ylva Thernström

Prematurity is associated with a number of medical problems, including those related to poor growth. Several projects related to effects of feeding regimens on catch-up growth in infants born premature and/or small for gestational age are ongoing in the group. One project concerns the development of visual function in infants born very preterm (<32 w) 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.

4. Endocrine disease in children and young adults

Jan Gustafsson, Åsa Myrelid, Lemm Proos, Ingemar Swenne, Maria Halldin, Torsten Tuvemo, Anders Forslund

Down syndrome

We study growth and endocrine disturbances in Down syndrome in a long term project. During the year data on growth hormone secretion and effects of growth hormone therapy on growth and psychomotor performance in subjects with Down syndrome were published. Overweight and obesity is common in Down syndrome. Our results show a peripheral and hepatic insulin resistance in DS subjects. Presently studies of effects of adipokines in subjects with Down syndrome are ongoing.

Endocrine consequences of stem cell transplantation

Patients with hematologic malignancies, treated with bone marrow transplantation may develop late effects resembling those of the metabolic syndrome. After stem cell transplantation in childhood, survivors may develop disorders of glucose metabolism. In collaboration with pediatric oncology we have studied young adult patients who have undergone bone marrow transplantation median 18 years earlier and compared the data with those of matched healthy controls. The results show that the decreased insulin sensitivity found may primarily be explained by an adverse body composition, which in turn may owe to long-standing growth hormone deficiency. In another study the effect of childhood stem cell transplantation on bone mineralisation has been investigated.

Growth and endocrine function in eating disorders

Since energy supply is critical for growth and pubertal development, eating disorders may markedly influence the somatic development by effects on metabolism and the endocrine system. Models for prediction of growth, menarche and subsequent menstruations during the treatment of eating disorders have been created, and it has been possible to set somatic targets for treatment. Markers for bone accretion and breakdown are studied in relation to changes of weight and hormones. Concerning the relationship between somatic factors and psychiatric morbidity changes of thyroid hormones and essential fatty acids. predispose for depression and thus influence the expression of the eating disorder.

Childhood obesity

Overweight and obesity during childhood represents an increasing global problem. The prevalence of type 2 diabetes mellitus (T2DM) and obesity among children is increasing. In recent years several loci connected with obesity and T2DM have been discovered. A majority of these susceptibility loci are connected with beta-cell function. In collaboration with professor Peter Bergsten at the Department of Medical Cell Biology we study underlying mechanisms of altered beta-cell function during development of obesity and T2DM. Knowledge about mechanisms of how insulin secretion develops over time in obese individuals is important as there may be a window when there is a possibility to restore an altered insulin secretory pattern.

Members of the group

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Collaboration

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Dissertations 2010

Eva-Lotta Funkqvist defended her thesis ” Policies and Practice in Neonatal Nursing Related to Nutrition”

Agencies supporting the work during 2010

Council of Sciences

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Novo Nordisk

ALF

Pediatric Oncology

Susan Pfeifer

Intensive international research focus on pediatric oncology has resulted in a dramatic increase in overall survival of pediatric cancer diseases - yet these rare diseases still today account for the main medical cause of death in children aged 1-15 years. Increased understanding of the biology, molecular basis and treatment of leukemia, the main cancer disease in children, now results in 80% cure of the disease. Research interest is now focusing on pediatric neural tumors, the second largest group of pediatric malignancies, accounting for the highest mortality and morbidity in children with cancer, and at present the main challenge in pediatric oncology.

The research of the Pediatric Oncology research group deals with clinical cancer diseases of children, their biology, treatment, and consequences. The research of the group comprises a wide range of scientific questions.

Childhood leukemia: biology, treatment, and consequences

Targets and function of DNA methylation in acute childhood leukemia (Lönnerholm, Syvönen, Gustafsson, Frost, Palle et al).

Multidisciplinary study using patient leukemia cell specimens in the Scandinavian NOPHO biobank. The primary objective is to identify the most important genes or genomic loci that display variations in CpG methylation patterns and thus may be used as biomarkers for classification of childhood ALL and AML and for prognosis of the disease progression and response to treatment in individual patients. As DNA methylation is reversible, genes with methylated CpG sites are potential targets for novel therapies.

In vitro cytostatic drug resistance in childhood AML (Palle et al).

AML has a worse prognosis than ALL. The aim is to study in vitro resistance to chemotherapeutic drugs in AML and correlate the results to treatment outcome in patients. Samples from all Nordic children with AML collected in a common biobank at Uppsala University in collaboration with the Nordic Society for Pediatric Hematology and Oncology (NOPHO) are analyzed by a fluorometric in vitro cytotoxicity assay, and have shown increased sensitivity for AML chemotherapy in patients with Down syndrome or t(9;11).

Chimerism analysis after hematopoietic stem cell transplantation, HSCT (Arvidson et al).

The aim is to better understand the significance of increased chimerism of blood cells of children treated with allogeneic stem cell transplantation and to identify in what situations interventions aimed to enhance the immune recovery are indicated. Chimerism data as well as outcome data from 266 transplantations performed in 222 paediatric patients transplanted at Uppsala, Huddinge, Lund and Göteborg during 2000-2007 have been collected in a common database and analyses are ongoing.

Insulinresistance and bone health in young adults who underwent stem cell transplantation of childhood (Frisk et al).

The aim of this cross-sectional study is to investigate the prevalence of insulin resistance in young adults who underwent stem cell transplantation in childhood and to investigate their bone health. The patient group includes all those > 18 years of age who underwent stem cell transplantation in childhood (< 18 years) in Uppsala or Huddinge, Stockholm.

Childhood cancer and complications

Hodkin's lymphoma- ethiological factors in children and adolescents (Ljungman et al).

Study of pediatric patients with Hodgkins lymphoma at two institutions, Stockholm and Uppsala. The aim is to 1) analyse differences in inflammatory microenvironment in HL in children, adolescents and adults, 2) identify the cells responsible for FDG uptake in PET analyses, and 3) investigate the proportion of EBV-positive HL in children and adolescents in a western population and determine if HL can be a consequence of a primary EBV infection in children.

Interventions for oral mucositis in children with cancer (Ljungman et al).

Mucositis is one of the worst experiences during cancer treatment of children. Specific pharmacological interventions that can reduce oral mucositis symptoms are evaluated.

The studies will be carried out on a national level at the different pediatric HSCT centers (hematopoietic stem cell centers) in Sweden.

Procedural pain in children and adolescents with cancer (Ljungman et al).

Study of pain, a major problem in pediatric cancer patients. The effects of pharmacological intervention is evaluated at the Department of pediatric Oncology Uppsala.

Development, evaluation and cost effectiveness of a treatment program with a behavioural medicine approach for adolescents with persistent pain is evaluated at a national level.

At the intersection of curative and palliative treatment in pediatric oncology (Frost et al)

The aim is to examine to what extent there is a distinctive focus on palliative treatment in departments of pediatric oncology in Sweden, and how children in terminal care and their families perceive the meaning and importance of palliative care.

Psychosocial studies in children with cancer and their families

Psychosocial issues in children and adolescents with cancer (Ljungman et al)

Multi-institutional collaboration, part of a new strategic research proposal from Uppsala University, the U-Care program. The aim is to analyze psychosocial aspects of cancer during adolescence, health economic consequences, and the occurrence, development, and treatment of posttraumatic stress disorder among parents of children with cancer.

Psychosocial functioning 20 years after hematological stem cell transplantation (Arvidson et al).

Follow up program of BMT in Uppsala, where all survivors of haematological bone marrow transplantation since 1985 are followed both somatically and psychologically. Focus is on quality of life as well as organ function.

Experiences and ethics of sibling donors (Frost et al)

Uppsala collaborative study between the medical and philosophical faculty, which will in a later phase collaborate with international colleges. The study will concentrate on the impact of being used as a donor during childhood. Emphasis is put on psychological, social and ethical questions.

Biology of pediatric neural tumors: brain tumors and neuroblastoma

Functional and genetic studies on neuroblastoma (Hedborg et al).

Collaborative study with the Dept of Genetics and Pathology, Uppsala University, where neuroblastoma patient biopsies are studied using a variety of modern cell biological and molecular genetical methods. Research focus is on the significance of tumor hypoxia, long non-coding RNA, and of gene amplification on chromosomes 11 and 12 tumorigenesis.

Neuroblastoma: somatostatin receptors as prognostic markers (Georgantzy et al).

The aim of this study is to study the expression of somatostatin receptor subtypes and other neuroendocrine markers and proteins in neuroblastoma cell lines and in a large clinical material, with correlation to tumor stadium, and prognosis. The goal is to identify neuroendocrine markers as targets for new therapeutic strategies in neuroblastoma.

Functional and genetic studies of pediatric brain tumors and their stem cells (Pfeifer et al).

Tumor specific genetic changes have been identified in several brain tumor types in children using array CGH and expression arrays, in a joint project with the Rudbeck laboratory. Global array and sequencing-based analyses, as well as studies of the role of noncoding RNA in brain tumors is planned. A translational project between the Karolinska Institute, Uppsala University, and the University of Lund, aims at isolating and characterizing brain tumor stem cells in pediatric brain tumors. The goal is to eventually develop new therapies for children with brain tumors.

National biobank for pediatric neural tumors (coordinator Susan Pfeifer).

A collaborative effort since 2009 between the six universities in Sweden and the Childrens Cancer Foundation and its neural network NBCNS (neuroblastoma CNS tumors in children) with the goal of establishing a well functioning national biobank of pediatric neural tumors, ie brain tumors and neuroblastoma. The purpose of the biobank is to facilitate research leading to improved diagnostics, and the development of new therapeutic strategies.

Prizes 2010

Dr Catarina Trager and Fredrik Hedborg: shared best poster prize on neuroblastoma at annual SIOP conference in Boston 2010

[http://\(www.nbglobe.com/2010/1107/siop-2010-neuroblastoma-poster-winners](http://(www.nbglobe.com/2010/1107/siop-2010-neuroblastoma-poster-winners)

Funding

VR coapplicants together with Louise von Essen.

SSF coapplication (Lonnerholm et al - DNA metylation in childhood leukemia)

BCF/NBCNS coapplication (Nister et al. - stem cells)

BCF 750.000/year, 3 years (Ljungman et al- oral mucositis)

BCF 600.000/2years. NovoNordisk 200.000 (Frisk et al- insulinresistance)

BCF 400.000/year, 3 years (Frost et al- intersection of curative /palliative treatment)

BCF 300.000/year, 2 years (Hedborg, Pfeifer - noncoding RNA in neural tumors)

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Professor Jan Hirsch, dental surgeon, Lena Blomstrand, dentist, PhD student Ann-Carin Svanberg, representatives of the HSCT centers (oral mucositis)

Professor Louise von Essen, professor Anne Söderlund, Västerås, professor Steven Linton, Örebro, professor Ulf Persson, Lund (psychosocial issues , pediatric cancer)

Professor Mats G Hanson (curative/palliative treatment)

Professor Per Kogner, KI, assoc professor Tommy Martinsson, Göteborg (neuroblastoma)

Professor Chandrasekhar Kanduri, Uppsala (noncoding RNA, neural tumors)

Professor Monica Nister ,PI, professor Karin Forsberg-Nilsson ,Urban Lendahl, Jonas Muhr, Johan Holmberg, Mikael Lindström, Stefan Holm, Bengt Gustafsson, Karolinska Institute; Peter Siesjö, Xialong Fan, Lunds University (bartin tumor stem cells)

Neurosurgery, Pediatric Surgery, Neuropathology, Pediatric Neurology, Pediatric Oncology.

Departments of Uppsala University, Karolinska Institute, University of Lund, Linöping and Göteborg, Norrlands University (national biobank of neural tumors)

Publications 2008-2010

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Pediatric Neurology

The research of the 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

In a population based study of childhood epilepsy a subgroup of children has been investigated and published with the title '10-year follow-up of childhood epilepsy in well-functioning children and adolescents'. This group is now investigated with respect to social and psychological factors. Rolandic epilepsy, the most common type of childhood epilepsies, has been studied from several aspects. A follow-up study to describe oromotor difficulties in this electroclinical syndrome is ongoing. So is also a follow-up study with magnetic resonance imaging including spectroscopy.

In collaboration with epileptologists from London University, the genetic background to childhood absence epilepsy is studied.

A new method for quantification and assessment of epileptiform activity in EEG also using electric source imaging has been published and investigated further for clinical application in collaboration with clinical neuropsychologists from Oslo University.

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.

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:

- 1 To evaluate neurophysiological methods, especially EEG and aEEG, for early evaluation of brain function and cerebral maturation, and for prediction of neurocognitive outcome.
- 2 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 two 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). The first publications from this project are in progress.
2. Factors affecting EEG continuity and spectral power in extremely preterm infants who had aEEG/EEG recorded during the first 72 hours of life and long-term follow up. We have shown that the early aEEG/EEG background is affected by brain injury, blood levels of carbon dioxide

- and glucose, and morphine (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. 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.

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 and its relation to periventricular leucomalacia or other perinatal brain damages in infants born before 32 weeks of gestation has been going on since 2004. 113 children are included and three papers are accepted for publication during 2011. These papers are included in a thesis that will be defended during the autumn this year.

We also participate in a national prospective longitudinal study on the neurological, ophthalmological and psychological development of infants born after less than 27 weeks of gestation between 2004 - 2007 in Sweden. 497 children survived until 1 year of age and these children have been followed - up at 2½ years corrected age. The results from the 2½ year examinations will be published during 2011. The study is going on and the follow-up investigations of the cohort at the age of 6½ years started in October 2010 and will continue until 2013. The results from this study will have great importance for the future perinatal care.

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.

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

Brain tumors in children

Together with the Department of Paediatric Oncology at the Karolinska Institute in Stockholm we have started a follow-up project of the Neurocognitive, Psychosocial and Medical long-term outcome of children diagnosed with braintumors in the Stockholm and Uppsala - Örebro healthregions in Sweden. This project started October 2010 and will continue until 2013.

Arthrogryposis

Arthrogryposis multiplex congenita (AMC) is a descriptive term for conditions with multiple congenital contractures.

Ongoing research projects are on further clinical and genetic investigations of different distal arthrogryposis syndromes. Other projects in this field are also planned.

Members of the group

Ahlsten, Gunnar	Associate professor
Borgestig, Maria	Postgraduate student
Bratteby-Tollerz, Linda	Physiotherapists
Dahl, Margareta	Associate professor
Eeg-Olofsson, Orvar	Associate professor
Ehrstedt, Christoffer	Research student
Ek, Ingalill	Speech therapist
Hellström-Westas, Lena	Professor
Höglund, Anette	Physiotherapists
Jonsson, Pysse	Research student
Kimber, Eva	Ph.D
Kristiansen, Ingela	Research student
Larsson, Katrin	Research student
Lidström, Helene	Doctoral student
Lidström, Åsa	Physiotherapists
Liminga, Gunnar	Ph.D
Lundberg, Staffan	Ph.D
Norrlin, Simone	Ph.D
Stenninger, Eric	Ph.D
Strinnholm, Margareta	Psychologist
Strömberg, Bo	Associate professor
Söderström, Helena	Research student
Wester, Ulrika	M.D.
Wikström, Sverre	Doctoral student

List of publications 2008-2010 – original articles

1/ Bajic D, Wang C, Kumlien E, Mattsson P, Lundberg S, Eeg-Olofsson O, Raininko R: Incomplete inversion of the hippocampus - a common developmental anomaly. *Eur Radiol* 18:138-42, 2008.

2/ Everett KV, Chioza B, Aicardi J, Aschauer H, Brouwer O, Callenbach P, Covanis A, Dulac O, Eeg-Olofsson O, Feucht M, Friis M, Goutieres F, Guerrini R, Heils A, Kjeldsen M, Lehesjoki AE, Makoff A, Nababout R, Olsson I, Sander T, Sirén A, McKeigue P, Robinson R, Taske N, Rees M, Gardiner M. Linkage and association analysis of CACNG3 in childhood absence epilepsy. *Eur J Hum Genet* 2008;16:659-60.

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- 16/ Mattsson S, Dahl M, Olsson I, Wendelius M, Westbom L, Astrom E. A Swedish follow-up programme for children with myelomeningocele. *Cerebrospinal Fluid Research* 2009 (suppl 2): P32.
- 17/ Vanhatalo S, Hellström-Westas L, de Vries LS. Bumetanide for neonatal seizures: Based on evidence or enthusiasm? *Epilepsia* 2009 May;50(5):1292-3.
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- 26/ The EXPRESS Group. Incidence of and risk factors for neonatal morbidity after active perinatal care: extremely preterm infants study in Sweden (EXPRESS). *Acta Pædiatrica* 2010, 99:978-992.
- 27/ Christersson S., Strömberg B. Childhood stroke in Sweden I: incidence, symptoms, risk factors and short-term outcome. *Acta Pædiatrica* 2010; 99:1641-9.
- 28/ Christersson S., Strömberg B. Stroke in Swedish children II: long-term outcome. *Acta Pædiatrica* 2010; 99:1650-6.
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- 35/ Hansen Pupp I, Hövel H, Hellström A, Hellström-Westas L, Löfqvist C, Larsson EM, Lazeyras F, Fellman V, Hüppi P, Ley D. Postnatal decrease in circulating insulin-like growth factor-I and low brain volumes in very preterm infants. *J Clin Endocr Metab*, 2011 in press
- 36/ Wikström S, Lundin F, Ley D, Hansen Pupp I, Fellman V, Rosén I, Hellström-Westas L. Carbon dioxide and glucose effects on EEG background in extremely preterm infants. *Pediatrics*, 2011 in press

Reviews/book chapters

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- 2/ Lidström H, Borgestig M. Assistive technology devices in computer activities. In: Eliasson A, Burtner P eds. *Improving hand function in cerebral palsy*. London: Mac Keith Press, 2008.
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- 4/ Lagercrantz H, Hellström-Westas L, Norman M (Eds). Neonatologi. *Studentlitteratur* Lund, 2008, pp 1-539.
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- 9/ Hellström-Westas L. Amplitude-integrated EEG - useful for early outcome prediction after birth asphyxia? *Nat Clin Pract Neurol* 2008;4(2):74-75.
- 10/ Shah DK, de Vries LS, Hellström-Westas L, Toet MC, Inder TE. Amplitude-integrated electroencephalography in the newborn: a valuable tool. *Pediatrics* 2008;122(4):863-865.
- 11/ Hemmingsson H, Lidström H, Nygård L eds: Assistive technology devices in educational settings: Students' perspective. 2009 (Vol 25). Florence, Italy: IOS Press.
- 12/ Eklund C, Kristiansen I. Metodhandbok – svårigheter och möjligheter i skolarbetet efter förvärvad hjärnskada. Folke Bernadotte regionhabilitering, Barncancerfonden och Hjärnskadeförbundet Hjärnkraft 2009.
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- 15/ Butler A, Strinnholm M. Elever med ryggmärgsbräck – neuropsykologiska och pedagogiska aspekter. Folke Bernadotter regionhabilitering 2009
- 16/ Eeg-Olofsson O. Kroppsliga orsaker och utredning av återkommande huvudvärk. I: Migrän och spänningshuvudvärk hos barn och tonåringar. Ed: Bo Larsson. *Studentlitteratur* 2009
- 17/ Hellström-Westas L. The need for more research on seizures in preterm infants. *J Pediatr* 2010;157(5):700-701.

Agencies that support the work

ALF, research support to the University Hospital

Regional research council

Gillberg foundation

Barncancerfonden

Norrbacka-Eugenia foundation

NEOBRAIN (partner and WP leader for Neurophysiology) 2006-2010 (€ 167 000)

NEMO (partner and WP leader for European survey) 2009-2014 (€ 242,880)

Perinatal, Neonatal and Pediatric Cardiology Research

Anders Jonzon

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

Clinical studies concerning inflammatory substances and their migration in neonatal lung tissue. Lung-injury is common among infants born before full gestation. The underlying mechanisms are probably manifold. Airway pressures, oxygen toxicity and inflammation are important candidates. This study focuses on the migration of inflammatory cells in normal lungs and lungs from neonates. 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. Ways to minimize airway pressure while maintaining adequate ventilation are explored. 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 loose 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. Effects on comfort, metabolic rate and growth are investigated. 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.

Fluid balance at different infusion rates in premature infants. These infants lose large amounts of fluid through their skin, more early after birth and then successively less. Optimal support results in maintaining weight, supporting circulatory, respiratory and metabolic adaptation. . Studies are made both retrospectively and prospectively. Researchers: Johan Ågren, MD PhD Dimitrios Kritikos, MD

5. Regulation of pulmonary vascular resistance

Pulmonary vascular resistance is a dominant factor in the circulatory adaptation of the newborn child irrespective if born premature or in time. Reduction of pulmonary resistance occurs rapidly in the healthy newborn. If this does not occur properly severe symptoms may develop and can reflect pulmonary mal-adaptation and cardiac disease. Production of endogenous NO from the lungs and nasal sinuses are probably involved in this process. Collection of reference values is currently under way. No-production in the nose and lungs is affected by various lung/airway diseases. Nothing is known of nasal NO-production and its role in the adaptation of pulmonary resistance. The method might be of great importance in early detection of neonatal disease. Researchers: Hugo Olsson MD, Johan Ågren, MD PhD

6. 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

7. Investigations on cardiac rhythm in small children

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. Genetical mapping has now been made, Fetal flow/Doppler markers indicating progress from a low degree AV-block to complete block has investigated. Other etiologies than immunological are investigated. Researchers: Marie Wahren-Herlenius, MD, PhD, professor, Stockholm Stina Salomonsson, PhD, Stockholm Sven-Erik Sonesson, MD, PhD, Stockholm, Gunnar Bergman MD PhD, Håkan Eliasson, MD, Stockholm Annika Öhman, MD, Uppsala Anders Jonzon, MD, PhD, Uppsala, and others.

8. Heart rate variability in children treated with anti-arrhythmica

Analysis of Holter recordings before, during and after treatment with antiarrhythmic drugs. Elinor Bärnevåg, bio-med.tech, Uppsala Anders Jonzon, MD PhD, Uppsala

9. Phrenic nerve stimulation as an alternative to respirator treatment.

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: Mikaela Winderud Med.stud, Richard Sindelar, MD PhD, Uppsala Anders Jonzon, MD PhD, Pelle Nilsson MD PhD, Uppsala Gunnar Sedin, MD, PhD, prof.

10. Early clinical predictors for failure of pharmacological ductus arteriosus treatment in extremely preterm infants

Closure of ductus arteriosus in the premature infant. Influence of fluid regimes, ventilator settings, timing of COX treatment, and relation to pulmonary vascular resistance/systemic resistance. Retrospective and prospective studies. Doppler/flow measurements indicative for success of COX-treatment. The Retrospective study is finished and the prospective is accepted by the ethical comitee. Oxygen, flow velocity (dependent of systemic/pulmonary resistance), release of prostanoids are measured. Timing of intervention and outcome is studied. We are seeking collaboration to set up an experimental model. Researchers: Karl Wilhelm Olsson, MS Richard Sindelar, MD PhD Anders Jonzon, MD PhD

11. Follow up of infants born extremely early

Express study: Nationwide follow up of extremely premature infants. Increasing survival of these infants. There is a considerable morbidity in this group of infants but there does not seem to be an increase in children with severe functional problems at an age of 30 months (corrected age). Few children have severe handicap. Compared with infants born at time this group of children is vulnerable and deserves sincere follow-up. Researchers: Fredrik Serenius prof and others.

12. Studies of a family with long QT syndrome. A new genetic trait.

Genetic study concerning new possible gene resulting in LQTS (Long Q-T syndrome). The index case show a severe form of this inherited disease and historical and familiar investigations of

phenotype/genotype are made. Researchers: Susanna Gröndal, MS Marie Louise Bondesson, PhD Anders Jonzon, MD PhD

13. Radiation exposure to children undergoing catheterablation for tachycardia.

Researchers: Lina Norén, MS, Per-Erik Åslund, PhD. Anders Jonzon, MD PhD

Members of the group

Bergman, Gunnar	Ph.D.
Farooqi, Aijaz	Ph.D.
Gröndal, Sanna	Research student
Jennische, Margareta	Ph.D.
Johansson, Anders	
Jonzon, Anders	Adj senior lecturer
Naumburg, Estelle	Ph.D.
Norén, Lina	Research student
Norsted, Torgny	Ph.D.
Persson, Kristina	Associate professor
Rieger-Fackeldey, Esther	Ph.D.
Schermann, Ligia	
Schulze, Andreas	
Sedin, Gunnar	Prof em
Serenius, Fredrik	Visiting prof
Sindelar, Richard	Ph.D.
Sjörs, Gunnar	Ph.D.
Stålhammar, Maria	Doctoral student
Wallström, Linda	Doctoral student
Ågren, Johan	Ph.D.
Öhman, Annika	Research student

Publications 2008-2011

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.

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.

2010

1. Pre-treatment Low Ductal Peak Flow Velocity Associated With Failure of Early Pharmacological Patent Ductus Arteriosus Treatment. Karl Wilhelm Olsson, Anders Jonzon, MD, PhD, Richard Sindelar¹ MD, PhD (submitted)
2. Under agarose migration assay - A method to study graded chemotactic activity of leucocytes in newborn infants. M. Stålhammar¹, L. Douhan Håkansson², R. Sindelar¹
3. Clinical trial of premature newborn infants with ventilatory assistance and different levels of PEEP measured by FOT (forced oscillatory ventilation). Linda Wallström, Richard Sindelar
4. Munsters JMA^{1,2}, Simonsson Wallström L¹, Ågren J¹, and R Sindelar¹. Skin Conductance (SC) Measurements as Pain Assessment in Newborn Infants Born at 22-27 weeks gestational age (GA) and at different postnatal age (PNA).
5. Aurelie Ambrosi¹, Stina Salomonsson¹, Elisabeth Zeffler¹, Vijole Dzikaite¹, Håkan Eliasson¹, Gunnar Bergman¹, Eva Fernlund², Elke Theander³, Annika Ryberg⁴, Thomas Skogh⁵, Solbritt Rantapää⁴, Michael Fored¹, Paul Blomqvist¹, Anders Ekbohm¹, Mats Melander⁶, Annika Öhman⁷, Ola Winqvist¹, Fredrik Gadler¹, Anders Jonzon⁷, Sven-Erik Sonesson¹, Marie Wahren-Herlenius¹. Influence of season of birth and maternal age in the development of congenital heart block in anti-Ro-SSA/La-SSB positive pregnancies 2010
6. Herlenius Eric¹, Park Jeosoong¹, Ambrosi Aureli², Dzikaite, Vijolee, Strandberg L², Kuchroo Vijay³, Wahren-Herlenius Marie² RO52 AUTOANTIBODIES SPECIFIC FOR AMINO ACID 200-239 MEDIATE CALCIUM DYSREGULATION IN CARDIOMYOCYTES 2010
7. Therese Östberg¹, Stina Salomonsson¹, Bo Ding², Håkan Eliasson³, Åse Elfving¹, Lars Alfredsson², Lars Klareskog¹, Anders Hamsten¹, Tomas Olsson⁴, Leonid Padukov¹, Tomas Axelsson⁵, Swedish Congenital Heart Block Study Group¹, Fredrik Gadler¹, Anders Jonzon⁶, Sven-Erik Sonesson³, Ingrid Kockum⁴, Marie Wahren-Herlenius¹. HLA-DRB1*04 is a novel fetal susceptibility genic variant in congenital heart block 2010

2011

Susanna Gröndal, MS Marie Louise Bondesson, PhD Anders Jonzon, MD PhD. Genetic study concerning new possible gene resulting in LQTS (Long Q-T syndrome). Examensarbete 2011

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 Paediatric 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 . Three different cohorts are being investigated and followed-up, the SPAIS, NOAK and MIDAS studies.

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 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 is under way. 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. Dr Niklas Nyström aims to accomplish a thesis on this project and two publications are under way.

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.

The nephrological research has been focused 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 and the study was presented at an

international conference in Gothenburg in 2009. Uppsala has participated 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* and *Staphylococcus aureus* 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 2010

The Child Health Unit in Uppsala carries a strong tradition of social paediatric research. Prevention & screening, child health surveillance, outcome studies and translational research are the main focus areas dealt with in our work. Since 2008 we have increasingly focused our research on parenting support. We have assisted the Government with scientific data to support the development of a national parenting support strategy. We are currently involved in five community-based studies on parenting support, mainly including parents of preschool-aged children in the general population. We are concluding the first Triple P trial in Sweden where we have shown that the program is effective in decreasing behavioural problems in children when it is offered to parents as part of the preschool's services. In another study we have identified circumstances under which effective co-production of family services with the voluntary sector might occur. The research group is interdisciplinary and has staff ranging from research assistant to assistant professor. We have both national and international collaborations 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.

Members of the group

Nordvall, Lennart	Adj professor
Alving, Kjell	Adj professor
Berntsson, Lillemor	Ph.D.
Bokström, Pär	Research assistant

Cederblad, Fredrik	M.D.
Dahlbom, Ingrid	Researcher
Dannaeus, Anders	Associate professor
Engstrand, Malin	Research student
Engsheden, Nathalie	Research assistant
Fjaertoft, Gustav	Ph.D.
Fredin, Kerstin	Nurse
Frid, Christina	Ph.D.
Hagelin, Elisabet	Ph.D.
Hansson, Tony	Associate professor
Hedov, Gerth	Ph.D.
Heijkenskjöld, Charlotte	M.D.
Hjelm, Fredrik	Ph.D.
Hjern, Anders	Associate professor
Hollsing, Annika	Ph.D.
Holmberg, Kirsten	Ph.D.
Holmberg, Lars	Ph.D.
Kalm Stephens, Pia	Research nurse
Karanikas, Birgitta	Research nurse
Kollberg, Hans	Professor em
Lagerberg, Dagmar	Associate professor
Lettesjö, Helene	Researcher
Lucas, Steven	Ph.D.
Magnusson, Margaretha	Ph.D.
Nayeb, Laleh	
Neuman, Åsa	M.D., doctoral student
Nevéus, Tryggve	Associate professor, senior lecturer
Normann, Erik	Ph.D.
Nyberg, Britt-IngeR	Research assistant
Näs, Elisabet	Research nurse
Pedroletti, Christopher	Ph.D.
Salari, Raziye	Ph.D.
Sarkadi, Anna	Associate professor
Shebani, Eyman	Ph.D.
Stenhammar, Christina	Doctoral student
Stålhammar, Jenny	Dietitian
Sundelin, Claes	Professor em
Terreros, Cathrine	Research assistant
Thunström, Malena	Ph.D.
Varga, Gabriella	Research assistant
Wallby, Thomas	Doctoral student
Wenngren, Eva	Physiotherapist
Westerlund, Monica	Associate professor
Williams, Maria	M.D.
Zetterlind, Liselott	Research student
Åhman, Annika	M.D.
Åhs, Stina	M.D.
Östberg, Monica	Ph.D.

Publications 2008-2010

International peer-reviewed publications

1. Holmberg K, Sundelin C, Hjern A. Routine developmental screening at 5.5 and 7 years of age is not an efficient predictor of attention-deficit / hyperactivity disorder at age 10. *Acta Paediatrica*. 2010;99(1):112-120.
2. Lindblad F, Hjern A. ADHD after fetal exposure to maternal smoking. *Nicotine & tobacco research*. 2010;12(4):408-415.

3. Normann E, Lacaze-Masmonteil T, Winkler-Lowen B, Guilbert J. Isolation of Non-Activated Monocytes from Human Umbilical Cord Blood. *American Journal of Reproductive Immunology*. 2010;63(1):66-72.
4. Frisk P, Arvidson J, Neveus T. Glomerular and tubular function in young adults treated with stem-cell transplantation in childhood. *Pediatric nephrology (Berlin, West)*. 2010;25(7):1337-1342.
5. Aro P, Ronkainen J, Storskrubb T, Vieth M, Engstrand L, Johansson S, et al. Use of tobacco products and gastrointestinal morbidity : an endoscopic population-based study (the Kalixanda study). *European Journal of Epidemiology*. 2010;25(10):741-750.
6. Åhman A, Runestam K, Sarkadi A. Did I really want to know this? : Pregnant women's reaction to detection of a soft marker during ultrasound screening. *Patient Education and Counseling*. 2010;81(1):87-93.
7. Neveus T, Eggert P, Evans J, Macedo A, Rittig S, Tekgül S, et al. Evaluation of and treatment for monosymptomatic enuresis : a standardization document from the International Children's Continence Society. *Journal of Urology*. 2010;183(2):441-447.
8. Böhme M, Kull I, Bergström A, Wickman M, Nordvall L, Pershagen G, et al. Parental smoking increases the risk for eczema with sensitization in 4-year-old children. *Journal of Allergy and Clinical Immunology*. 2010;125(4):941-943.
9. Holmberg K, Sundelin C, Hjern A. RE: Routine developmental screening at 5.5 and 7 years of age is not an efficient predictor of attention-deficit/hyperactivity disorder : a critical comment: author's reply. *Acta Paediatrica*. 2010;99(9):1280-1280.
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11. Eriksson M, Westerlund M, Miniscalco C. Problems and limitations in studies on screening for language delay. *Journal of Research in Developmental Disabilities*. 2010;31(5):943-950.
12. Holmberg L, Hellberg D. Sexually abused children. Characterization of these girls when adolescents.. *International journal of adolescent medicine and health*. 2010;22(2):291-300.
13. Kristjánsdóttir J, Olsson G, Sundelin C, Naessen T. Could SF-36 be used as a screening instrument for depression in a Swedish youth population?. *Scandinavian Journal of Caring Sciences*. 2010;
14. Gingnell M, Dahlbom I, Lindholm A, Hudecova M, Arnadóttir R, Hansson T, et al. Patients with polycystic ovary syndrome have lower levels of IgM anti-phosphorylcholine antibodies than healthy women.. *Gynecological Endocrinology*. 2010;
15. Bröms K, Norbäck D, Eriksson M, Sundelin C, Svärdsudd K. Effect of degree of urbanisation on age and sex-specific asthma prevalence in Swedish preschool children. *BMC Public Health*. 2009;9:303-.
16. Stenhammar C, Olsson G, Bahmanyar S, Hulting A, Wettergren B, Edlund B, et al. Family stress and BMI in young children. *Acta Paediatrica*. 2010;99(8):1205-1212.
17. Wallby T, Hjern A. Parental region of birth, socio-economic status and infants' exposure to second-hand smoke. *Acta Paediatrica*. 2008;97(11):1542-1545.
18. Kristjánsdóttir J, Sundelin C, Naessen T. Health-related self-assessed quality of life in young people at a Youth Centre in Sweden. *Scandinavian Journal of Caring Sciences*. 2009;23(3):465-472.
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20. Korponay-Szabó I, Vecsei Z, Király R, Dahlbom I, Chirido F, Nemes E, et al. Deamidated gliadin peptides form epitopes that transglutaminase antibodies recognize. *Journal of Pediatric Gastroenterology and Nutrition - JPGN*. 2008;46(3):253-261.
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23. Blennow M, Carlsson R, Hanson L, Lindberg A, Lindquist L, Magnusson M, et al. Vacciner till barn - skyddseffekt och biverkningar : En systematisk litteraturöversikt. Stockholm: SBU; 2009. SBU:s rapporter, 191.
24. Nevéus T. Editorial Comment : Inconsistent lower urinary tract symptoms in children with enuresis. *The Journal of Urology* Sept; 180(3):1085-9; Discussion 1089-90. *Journal of Urology*. 2008;180(3):1090-.
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26. Jablonska B, Lindberg L, Lindblad F, Rasmussen F, Östberg V, Hjern A. School performance and hospital admissions due to self-inflicted injury : a Swedish national cohort study. *International Journal of Epidemiology*. 2009;38(5):1334-1341.
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28. Lundmark E, Nevéus T. Reboxetine in therapy-resistant enuresis : a retrospective evaluation. *Scandinavian Journal of Urology and Nephrology*. 2009;43(5):365-368.
29. Neveus T. Nocturnal enuresis. In: *Pediatric Urology*. 2 Philadelphia/London: Saunders; 2009. p. 380-385.
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36. Westerlund M, Lagerberg D. Expressive vocabulary in 18-month-old children in relation to demographic factors, mother and child characteristics, communication style and shared reading. *Child Care Health and Development*. 2008;34(2):257-266.
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46. Knudsen P, Olesen H, Høiby N, Johannesson M, Karpati F, Laerum B, et al. Differences in prevalence and treatment of *Pseudomonas aeruginosa* in cystic fibrosis centres in Denmark, Norway and Sweden. *Journal of Cystic Fibrosis*. 2009;8(2):135-142.
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50. Pedroletti C, Lundahl J, Alving K, and Hedlin G, Effect of nasal steroid treatment on airway inflammation determined by exhaled nitric oxide in allergic schoolchildren with perennial rhinitis and asthma. *Pediatr Allergy Immunol*, 2008. 19(3): p. 219-26.
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52. Malinovski A, Janson C, Holm L, Nordvall L, and Alving K, Basal and induced NO formation in the pharyngo-oral tract influences estimates of alveolar NO levels. *J Appl Physiol*, 2009. 106(2): p. 513-9.
53. Syk J, Uden AL, and Alving K, Relationship between exhaled nitric oxide and IgE sensitisation in patients with asthma: influence of steroid treatment. *Clin Respir J*, 2009. 3(3): p. 143-51.
54. Nilsson MC, Hambræus-Jonzon K, Lattuada M, Chen L, Li R, Alving K, Wiklund P, Hedenstierna G, and Freden F, Distant effects of nitric oxide inhalation in endotoxemic pigs. *Crit Care Med*, 2010. 38(1): p. 242-8.
55. Malinovski A, Henrohn D, Eriksson A, Lundberg JO, Alving K, and Wikström G, Increased plasma and salivary nitrite and decreased bronchial contribution to exhaled NO in pulmonary arterial hypertension. *Eur J Clin Invest*, 2011: p. (in press).
56. Montella S, Alving K, Maniscalco M, Sofia M, De Stefano S, Raia V, and Santamaria F, Measurement of nasal nitric oxide by hand-held and stationary devices. *Eur J Clin Invest*, 2011: p. (in press).

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}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 prematures 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 MD, PhD
Gillian Barker MD, PhD
Rolf Christofferson Associate professor, MD, PhD
Johan Danielson M.D, PhD-student
Helene Engstrand Lilja MD, PhD
Ammar Farman M.D., resident
Fanny Fredriksson MD
Elisabet Gustafson MD, PhD-student
Niclas Högberg MD, PhD-student
Ann-Marie Kassa RN, research nurse
Göran Läckgren, Professor, MD, PhD
Hussein Naji MD
Erik Sköldenberg MD, PhD
Arne Stenberg Associate professor, MD, PhD
Anders Stenbäck MD, PhD

Publications 2008-2010

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.
3. Fuchs D, Christofferson R, Stridsberg M, Lindhagen E, Azarbayjani F (2009) Regression of orthotopic neuroblastoma in mice by targeting the endothelial and tumor cell compartments. *J Transl Med.* Mar 12; 7(1): 16.
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Reproductive Health

The Reproductive Health research group focuses on all aspects of reproductive health, with an aim of improving mental and sexual well-being of women at all ages. These projects are on-going:

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

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 (including post-traumatic stress 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, involving five out-patient clinics. At baseline, a series of questionnaires investigating depressive and anxiety symptoms, personality traits and PTSD are collected. Blood sample for analyses of a number of functional polymorphisms (VNTRs and SNPs) in candidate genes for affective disorders will be genotyped. Patients have been followed by additional questionnaires after 3 months and 6 months.

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

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 oocyte donation (OD)/ sperm donation (SD), 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 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. 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.

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

This study is an attempt to further extend our knowledge on the pathophysiological processes underlying antenatal depression and postpartum depression (PPD) and also to find predictors of the diseases to improve early recognition.

In brief, all women attending the routine ultrasound examination in gestational week 16 -17 will be asked to participate in this study. During pregnancy women are followed by web-based questionnaires (depression rating scales, personality inventory, early life stress, sleep disorders). All women with antenatal depression and a random sample of healthy pregnant women (n = 250) will be invited to extensive psychological tests (cognitive tests, attentional bias, prepulse inhibition, blood samples, morning awakening saliva samples) at term pregnancy. 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 (similar to the tests at term pregnancy test). All women fulfilling the criteria for PPD and a random sample of healthy controls at this time-point (n = 250) will be invited to psychological testing (similar as during pregnancy), and a subset also for functional magnetic resonance imaging (fMRI).

The neuroendocrinology of the female brain – focus on imaging

From a neuroendocrine/reproductive imaging perspective, the female brain is immensely understudied. Given the female preponderance for depression and anxiety disorders, further studies on the interaction between ovarian steroids and the neuro circuits involved in depression/anxiety are greatly needed. We are currently running three different functional magnetic resonance imaging (fMRI) studies at the department of Women's and Children's Health. Three different groups of women are included: 1) Women with and without premenstrual dysphoric disorder, evaluated in the follicular and luteal phases of the menstrual cycle, 2) Newly delivered mothers, examined twice in the postpartum period (within 48 hours of normal delivery and six weeks postpartum), 3) women, with retrospective reports of aversive mood symptoms during prior use of combined oral contraceptives, before and during double-blinded randomized allocation to an oral contraceptive (30µg ethinyl estradiol in combination with 150 mg levonorgestrel) or placebo.

Following psychiatric evaluation, blood samples for hormones and relevant genotypes, these women are subjected to three different paradigms in the scanner: 1) A simple perceptual task involving the processing of facial expressions, designed to engage the amygdala, 2) A paradigm consisting of colour-coded emotionally salient pictures with positive or negative valence, targeting anxious anticipation and relevant neurocircuits in the amygdala, insula and prefrontal lobes, 3) A response inhibition paradigm (Go-NoGo), targeting impulse control and predominantly the prefrontal lobes.

Urogenital symptoms in breast cancer patients on adjuvant endocrine therapy

In developed countries approximately 75 % of all breast cancers occur in postmenopausal women, and 80 % of these cancers are hormone receptor positive. Adjuvant endocrine treatments are all primarily directed to induce estrogen deprivation, either at the estrogen receptor level (tamoxifen), or by inhibiting estrogen biosynthesis (aromatase inhibitors (AI)). The use of both tamoxifen and AI has, however, been associated with gynecological side effects and worsening of menopausal symptoms. With more women receiving adjuvant endocrine therapy after primary therapy for breast cancer, and more women surviving breast cancer, any increase in the frequency of urogenital symptoms represent a clinical challenge especially since there is now a lack of effective treatment options. The aim of the present study was to investigate the prevalence and degree of urogenital symptoms, sexual dysfunction, and vaginal atrophy, morphology and functionality in postmenopausal breast cancer patients on adjuvant endocrine therapy with tamoxifen or AI compared to age-matched women with or without estrogen therapy.

Members of the group

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Publications 2008-2010

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Regionforskningsmedel 200 000 SEK (ASS)

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Dissertations 2010

Åsa Lindholm: Metabolic aspects in the polycystic ovary syndrome.

Miriam Hudcová: Reproductive and metabolic consequences of the polycystic ovarian syndrome.