

Department of Women's and Children's
Health

ANNUAL REPORT
2011

Introduction

It is a pleasure to note the accomplishments by the researchers, teachers, administrators and laboratory technicians at the Department of Women's and Children's Health during 2011. The department has devoted researchers within Obstetrics/Gynecology, Pediatrics and International Maternal and Child Health. A great number of collaborative projects with national and international research institutions are ongoing. The strong development of research within caring science is particularly satisfying. The scientific output at the department during the year has been notable since 246 scientific articles have been produced. Nine research students have presented their doctoral theses during the year. The number of PhD students continues to increase and reached 89 at the end of the year. This will lead to a marked increase of dissertations during coming years.

During the year 2011 Ove Axelsson retired from his position as professor of obstetrics and gynecology. He will however be active with research and education during the coming year as a senior professor. The appointment of three new professors of obstetrics and gynecology, Matts Olovsson, Tord Naessen and Ulf Högberg, is important for the forthcoming research and teaching at the department. The senior lecturer Kerstin Hedberg Nykvist also retired during the year. She has been a pioneer within neonatal care and has contributed extensively to our present knowledge on breast feeding and Kangaroo Mother Care.

The department further strengthened the capacity for research and education by recruitment of three senior lecturers during 2011, Eva-Lotta Ekström in global nutrition, Pia Olsson in global reproductive perinatal and sexual health and Ingemar Swenne in pediatrics.

At the department teaching is going on within a number of programs. These include graduate courses both for medical and nursing students, postgraduate programs for midwives and physicians as well as several international courses. It is satisfying that the total number of applications to the master program in international health has been essentially unchanged in spite of the new tuition and application fees for students, who are not citizens of the EU/EEA or Switzerland. However, for the coming years it is important that an increased number of scholarships are made available in order to make it possible for students outside EU/EEA to study at the program. The postgraduate education in pediatric nursing was restarted in 2010. In order to guarantee an adequate number of applicants a close collaboration with our clinical counterpart is necessary.

During 2011 the new KoF evaluation (quality and renewal 2011) of research at Uppsala University took place. The research within Reproductive Health received grade 1 (top quality). Also the research within the group of International Maternal and Reproductive Health and that of Gynaecological Endocrinology received fairly high grades (2-3). These areas of research have the potential to become even stronger within the next few years.

For a department like ours, which is active in clinical research and education, it is very important to have a good cooperation with the clinical counterparts, the University Children's Hospital and the Clinic of Obstetrics/Gynecology. As before, the majority of our researchers are active as physicians, nurses or midwives. The relation with our clinical counterparts has continued to be positive, which is necessary for

the development of the fields of Pediatrics and Obstetrics/Gynecology. It is of particular importance that doctors and nurses have the possibility to make use of scholarships and research grants by being out of clinical duty for certain periods of time.

To be chairman of the department of Women's and Children's Health is most inspiring. I want to thank all the staff - teachers, researchers, administrators and laboratory technicians for their excellent work during the previous year. The research and education at our department is important for the health and wellbeing of women and children both in Sweden and globally. We will continue this important work in the years to come.

Uppsala in April 2012

Jan Gustafsson

Chairman of Women's and Children's Health

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Margareta Larsson	teacher representative
Lars-Åke Persson	teacher representative
Inger Sundström Poromaa	teacher representative
Barbro Diderholm	teacher representative, deputy
Helena Åkerud	teacher representative, deputy
Karin Törnblom	representative for technical/adm. personnel
Lena Moby	representative for technical/adm. personnel, deputy
Charlotte Hellgren	graduate student representative
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Pauline Binder	graduate student representative, deputy
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Obstetrical Research

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Pediatric Oncology

Susan Pfeifer, MD, PhD, Adjunct Professor

Pediatric Surgery and Pediatric Urology

Rolf Christofferson, MD, PhD, Associate Professor

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

Tryggve Neveus

During 2011, as in previous years, a large number of students have participated in the broad range of programmes available at the Department of Women's and Children's Health. We continuously educate medical and nursing students in paediatrics and gynecology/obstetrics during their pregraduate study programs. The number of medical students is steadily increasing – presently around 140 students per year –. The department also gives the post graduate 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

Global medicine, an elective course within the registered Nurse programme and within the Medical programme

Obstetrics and Gynaecology within the Medical Programme

Paediatrics within the Medical Programme

The postgraduate Registered Midwife Programme

The registered Midwife Programme is a 90 ECTS degree program. The cornerstones of the education are reproductive health and obstetrics but students are also prepared for independent work within the fields of maternal health, youth health (contraceptive counselling), 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 Specialist Paediatric Nursing Programme

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 3 years. Both theoretical and practical education, as well as web-based seminars, and seminars using problem-based learning methods are available.

Obstetrics/Gynaecology and Paediatrics within the Medical Study programme

Medical students spend 15 weeks during their 9th and 10th semester at the department, studying paediatrics and gynaecology/obstetrics. The studies 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. The students' rating of the courses have been steadily improving during recent years: the evaluation results of the clinical education of

gynaecology/obstetrics course made it "climber of the year" during 2011, whereas the overall ratings of the paediatric course is among the highest of the whole medical study programme.

Education at International Maternal and Child health (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 background in the social sciences. Many of the participants come from low- and middle-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 Master's students – and we have examples where the Master's 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.

Research Education

Lena Hellström Westas

The department has extensive PhD training within Paediatrics, Paediatric Surgery, Obstetrics/Gynecology and International Maternal and Child Health (IMCH). At the beginning of 2011 there were 76 PhD student registered. During 2011 there were 9 dissertations, and 18 half-time seminars. Altogether 21 new doctoral students were registered. At the end of the year, 89 doctoral students were registered at the Department of Women's and Children's Health, 26 in Paediatrics, 3 in Paediatric Surgery, 35 in Obstetrics/Gynecology and 25 at the IMCH.

The doctoral students have varying backgrounds, a majority are recruited among paediatricians and obstetricians/gynecologists who perform their specialist training in the university hospital, or at local hospitals within the Uppsala region. The number of specialist nurses and midwives who register for doctoral studies is increasing. There were also 17 international doctoral students registered. Many of these 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 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.

It is obligatory to respond to the annual doctoral student reports, but in spite of this the reponse rate is varying. In 2011 the report was answered by around 70% of the PhD students who were not registered before 2011 and who did not finish their PhD studies during the year. Among the respondents >95% reported that their doctoral studies proceeded according to the individual syllabus, around 90% reported that the research education suited them good/excellent but some commented that they had problems in combining clinical service with the doctoral studies. More than 95% scored their supervision as good or excellent.

Scientific Reports

Gynecological Endocrinology

Tord Naessen

Our research group focus on effects of endogenous and exogenous steroid hormones with regard to e.g. fracture risk, the artery wall aging, cardiovascular disease (CVD), breast cancer, polycystic ovary syndrome (PCOS), premenstrual syndrome (PMS/PMDD) and pre-eclampsia, cognition / brain volumes and effects of environmental pollutants. We also study ovarian follicular fluid content of steroid hormones and proteins with regard outcome of in-vitro fertilization (IVF). Further, we suggest and evaluate a new principle for non-invasive assessment of arterial aging/atherosclerosis, based on separate assessment of the artery wall layers using high-frequency ultrasound.

I: Menopausal hormone replacement 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. Our results indicate that HRT rapidly reduces the risk of peripheral fractures, most likely via the brain with 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. It might also explain that it seems more difficult to show substantial effects on hip fracture risk from bisphosphonates, supposedly affecting bone mass only.

II: Endogenous sex steroids and effects on - the artery wall, prevalent cardiovascular disease (CVD), prediction of CVD events, cognition/brain volumes and effects of environmental pollutants etc.

To our knowledge we were the first group to report systemic effects of real 'ultra-low' doses of vaginal estrogen (7.5µg/24h) given to elderly women, with systemic effects on bone markers, bone mass and serum lipid levels. We analyze endogenous 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 the Internal Medicine Department, Uppsala, and ARUP laboratories in Salt Lake City, Utah, USA. Recently we found increased endogenous estrogen levels in both men and women with prevalent CVD and found associations to artery wall layer dimensions indicating an ‘unhealthy artery wall’ on ultrasound, which both most likely represents an endogenous attempt with estrogen synthesis to counteract an ongoing inflammatory/atherosclerotic process.

Currently we evaluate potential effects of subtle differences in endogenous steroid hormone concentrations in elderly with regard to artery wall aging (ultrasound), prevalent CVD, coming risk of CVD/death, cognition/brain volumes and associations to environmental pollutants in elderly women and men.

Significance: Our previous and current results elucidate effects of endogenous steroid hormones (esp. estrogens) which might have implications for future directions and regimens of hormone replacement in elderly.

III: We suggest and evaluate a new principle for non-invasive assessment of the artery wall with regard to arterial aging, based on 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. These differential changes in the intima and media layer dimensions reduces the usefulness of the present 'gold-standard', the Carotid-IMT (CCA-IMT), assessing the combined intima+media thickness. We suggest separate assessment of the artery intima and media layers and use of the Intima/Media thickness ratio.

We have repeatedly found this principle superior to conventional CCA-IMT in a number of scenarios, including prevalent CVD. We currently evaluate the strength of this principle to predict CVD events in elderly, in monitoring effects of HRT initiated soon after menopause, to image possible effects of anti-estrogen therapy in women with breast cancer and effects of 'ultra-low' vaginal estrogens. We also study possible changes in the artery wall layers during normal pregnancy, in pre-eclampsia and in subjects with chronic pulmonary lung disease, pulmonary hypertension, sleep apnoea and recurrent depressions etc.

Significance: The suggested principle/method might be an alternative to the present 'gold-standard', Carotid-IMT (CCA-IMT) , for non-invasive assessment of the artery wall with regard to subtle artery wall changes, prevalent CVD, prediction of CVD events and in monitoring effects of interventions against atherosclerosis/CVD (medication or life-style changes).

IV: Premenstrual syndrome (PMS or PMDD).

The normal variations of 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, as assessed by Positron Emission Tomography (PET).

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

V: Steroid hormones and proteomics in ovarian follicular fluid during normal menstrual cycle, in PCOS and after ovarian stimulation during in-vitro fertilization (IVF).

Steroid hormones and proteins 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. Currently we study steroid hormones and proteins in the stimulated ovarian follicular fluid with regard outcome of IVF.

Significance: the results might elucidate underlying causes of anovulation/infertility. 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 becomes easily available at university hospitals.

Members of the group

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Jona Kristiansdottir	MSc, Psychologist, Research student
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Publications 2009 – 2011

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Dissertation during 2011

Gunilla Hallberg

Research grants 2011

ALF 371,000 SEK

Selanders foundation 180 SEK

The Uppsala County Council research foundation 140,000 SEK

Thuréus foundation 100,000 SEK

Elgqvists foundation 110,000 SEK

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.

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 field where women subjected to violence are likely to be found i.e. health care professionals, social workers and police officers.

During 2011 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 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 women subjected to violence. Secondly, a training for trainer course 7,5 hp part-time was given for professionals who work with education regarding men's violence against women.

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

Scientific Reports

Violence against women in a medical perspective

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.

Website

www.nck.uu.se

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Danielsson I, Blom H, Nilsson C, Heimer G, Högberg U. Gendered patterns of high violence exposure among Swedish youth. *Acta Obstet Gynecol Scand* 2009;88(5):528-535.

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Berglund A, Heimer G, Witkowski Å. Att fråga om våldutsatthet som en del i anamnesen – presentation av rapport från Nationellt centrum för kvinnofrid. *SFOG:s medlemsblad*, 2011:5.

”Handbok – nationellt handlingsprogram för hälso- och sjukvårdens omhändertagande av offer för sexuella övergrepp”, ISSN 1654-7195, NCK-rapport 2008:1, reviderad 2011.

”Lättare att söka hjälp – kvinnofridslinjens uppbyggnad och första år”, ISSN 1654-7195, NCK-rapport 2009:1.

”Våld i samkönade relationer – en kunskaps- och forskningsöversikt”, ISSN 1654-7195, 2009:2.

”Kartläggning av fristående universitets- och högskolekurser i ämnet mäns våld mot kvinnor”, NCK-rapport, februari 2009.

”Första helgen i juni”. NCK, serienovell, september 2009, ISBN 978-91-978448-0-2.

”Hedersrelaterat våld och förtryck – en kunskaps- och forskningsöversikt”, ISSN 1654-7195, NCK-rapport 2010:1.

”Antologi – sju perspektiv på våldtäkt”, ISSN 1654-7195, NCK-rapport 2010:2.

”Nationell kartläggning om hur mäns våld mot kvinnor, hedersrelaterat våld och förtryck samt våld i samkönade relationer beaktas i grundutbildningar vid universitet och högskolor”, ISSN 1654-7195, NCK-rapport 2010:3.

”Att fråga om våldsutsatthet som en del av anamnesen”, ISSN 1654-7195, NCK-rapport 2011:4.

”Världens sämsta sommar”. NCK, serienovell, juni 2010, ISBN 978-91-978448-1-9.

”Kvinnlig omskärelse/könsstympning i Sverige – en kunskaps- och forskningsöversikt”, ISSN 1654-7195, NCK-rapport 2011:1.

”Att möta patienter som söker för oro kring oskuld och heder”, ISSN 1654-7195, NCK-rapport 2011:2.

”Att fråga om våldsutsatthet som en del av anamnesen”, ISSN 1654-7195, NCK-rapport 2011:4.

Obstetrical Research

Ulf Högberg

The overall research theme is human reproduction from conception to birth adding knowledge about adverse outcomes why, how and then. The ultimate aim is to improve reproductive health. The research methods are translational, clinical and reproductive epidemiology. The research group is establishing an integrative approach with several other research groups at the department in a life course perspective from the womb to child and adolescent health. 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 about 80000 women have been collected. This unique blood bank is a research source for several on-going research projects and will be source for epigenetic studies. Preparation has been started to establish research databases of local clinical registries, covering birth, neonatal and child care, with this blood bank. National health registries are further a source for the research group.

Professor Ulf Högberg has joined the group in 2011. His research profile is clinical and reproductive epidemiology and has research collaboration with Umeå University, Karolinska Institutet (KI) and international network and is establishing research collaboration in the group. Ove Axelsson is now appointed as senior professor. He is head supervisor for Maria Palm and Johanna Belachew.

Associate professor Helena Åkerud has a broad translational research profile. She is presently focusing to investigate if there are distinct biological mechanisms that are affected in relation to assisted reproduction. Mechanisms that might explain why there seem to be increased risks related to assisted reproduction, such as pregnancy complications, adverse perinatal outcome, as well as an increased risk of birth defects and rare disorders where imprinted genes are affected will furthermore be investigated. She is head supervisor of Marie Bolin, Lina Bergman, Lena Liljeström, Karin Lindgren, Evangelia Elenis, Sarah Nordqvist and co-supervisor of Michaela Granfors, Charlotte Hellgren and Johanna Gunnarsdottir.

Anna-Karin Wikström became an associated professor in 2011. She has a focus on placental dysfunctional disorders, with preeclampsia as a main focus. During the last years she has had a close cooperation with the Clinical Epidemiological Unit at KI and has achieved excellent competence in reproductive epidemiology using national registries and has established collaboration with several national and international collaborators. She is head supervisor of Sara Solhberg, and Michaela Granfors and also co-supervisor of Marie Bolin, Lena Liljeström, Lina Bergman and Tansim Ather, and also co-supervisor for two PhD students at KI about placenta retention and obstetrical outcomes.

Associate professor Ulf Hanson has been continuing his studies on diabetes during pregnancy and has been supervisor for Helena Fadl, defending her thesis at Örebro University in 2012 and Martina Persson defending her thesis at Karolinska Institute in 2012. He is responsible a multicenter RCT regarding the value to threat IGT (impaired glucose tolerance) during pregnancy. He and associate professor Solveig Norden Lindeberg has ongoing register studies regarding preeclampsia and malformations.

PhD Maria Jonsson's research profile is asphyxia, metabolic acidosis and clinical epidemiology. She is co-supervisor for Lena Liljeström. PhD Peter Lindgren's research area is ultrasound and MR, evolving a comparative study on MR, ultrasound and MR for fetal malformation diagnostics. He is co-supervisor for Annika Åhman and Berit Höglund. PhD Ajlana Lutvica is involved in various project about ultrasound postpartum, MR and preeclampsia and maternal mortality audit. She is co-supervisor for Johanna Belachew and Sara Solhberg. PhD Eva Bergman is developing an epidemiologic project about neonatal complications for children born small for gestational age.

The nine on-going PhD studies are:

Maria Palm: Studying oxidative stress, inflammation and angiogenesis during normal pregnancy by using biobank of blood and urinary samples from healthy women with uncomplicated pregnancies. She had her halftime dissertation in 2011 and defends her thesis in 2012.

Marie Bolin: Analysis of biochemical and biophysical markers for prediction of pre-eclampsia. A secondary aim is to increase our knowledge of etiology and pathophysiology of pre-eclampsia, and

further studying the effect of hyperemesis gravidarum on adverse pregnancy outcomes. She had her half-time dissertation in 2011 and will defend her thesis in 2012.

Sarah Nordqvist: Exploring the mechanisms behind unexplained infertility and whether it might be possible to predict pregnancy outcome after *in vitro* fertilization (IVF). She will have her half-time dissertation in 2012.

Sara Sohlberg: Studies on preeclampsia by using MRT to study placental energy metabolism *in vivo* with the aim to identify differences between pregnancies complicated by IUGR/preeclampsia and uncomplicated pregnancies. Further, biochemical and biophysical markers will be analyzed to identify predictors of pre-eclampsia to increase knowledge on etiology and pathophysiology of this syndrome.

Evangelia Elenis: Portraying pregnancy through oocyte donor from a genetic, molecular and clinical perspective. A secondary aim is to perform genetic expression analysis on placentas from IVF pregnancies and placentas from spontaneous pregnancies to investigate if there are increased risks of placental dysfunction disorders based on specific molecular mechanisms in IVF pregnancies.

Johanna Belachew: Evaluating diagnostic possibilities of 3-D ultrasound for placenta location after earlier cesarean delivery, and placental retention in the postpartum period.

Michaela Granfors: Studies on epidemiologic and genetic aspects of thyroid disturbances and pregnancy outcome

Lina Bergman: Studies on cerebral dysfunction related to pregnancy and/or preeclampsia by analyzing circulating levels of S100B, a peripheral biomarker known to reflect injury in the central nervous system. The studies will also analyze cerebral oedema related to pregnancy and/or preeclampsia by MR spectroscopy.

Lena Liljeström: Addressing asphyxia during labour by analyzing the clinical importance of scalp sampling for fetal surveillance.

Karin Lindgren: Addressing infertility by focusing on causes, diagnosis and treatment. Distinct biological mechanisms that are affected in relation to assisted reproduction are investigated.

Johanna Gunnarsdottir: Study plan in preparation about placental dysfunction disorders addressing immunological and fetal origin aspects by epidemiological methods.

Members of the group during 2011

Ove Axelsson	Professor
Ulf Högberg	Professor
Ulf Hanson	Associate professor
Solveig Lindeberg	Associate professor
Helena Åkerud	Associate professor
Anna-Karin Wikström	Associate 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
Karin Kårehed	Ph.D, postdoc
Johanna Belachew	Research fellow
Marie Bolin	Research fellow
Michaela Granfors	Research fellow
Lena Liljeström	Research fellow
Karin Lindgren	Research fellow
Sarah Nordquist	Research fellow
Maria Palm	Research fellow
Lina Bergman	Research fellow

Evangelia Elenis
Sara Sohlberg

Research fellow
Research fellow

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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 seem to be important for embryo development. These studies will be included in Fredwell Hambiliki's thesis work.

We have a special interest in thyroid hormone function in relation to reproduction (4). Our studies on thyroid hormone in reproductive function (5, 6) will be continued in Jesper Ekman's and Amani Rumman's thesis work.

To find markers of endometrial receptivity is a main focus (7, 8). We are using human endometrial cell culture models to study hormonal regulation of the endometrium (9, 10), most recently in collaboration with Linda Giudice in San Francisco. A Eurostar project is financed to study endometrial markers of infertility and endometriosis

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, 13). 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 and Tissue factor is dysregulated in endometrium from women with unexplained infertility (14-19) and our array data show extensive gene expression in endometrium from fertile and infertile women (20). 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 (21).

Low folat levels have been related to fertility problems (22), which can be due to genetic causes (23, 24). 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 (25, 26). We have in collaboration with women's clinics in four hospitals and we have been able to collect blood samples from 200 women with repeated miscarriage. These samples will now be used to study possible genetic factors related to repeated miscarriage.

Additional clinical studies from our group show that genetic background can influence outcome after fertility treatment (27) and that adrenomedullin might influence angiogenesis in women with menorrhagia (28). During fertility treatment we can show that luteal phase support with progesterone increase delivery rate (29) and that serum gp130 might predict pregnancy outcome after treatment (30). 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 (31).

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. Julius Hreinsson and Kjell Wångren 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 (34-41). 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 (39). In cooperation with Hella Hultin and Per Hellman we have shown an increased risk to develop PE in women with previous primary hyperparathyroidism (34) but there seem to be no association between vitamin-D receptor polymorphism and PE (40). Within the PE-projects we have cooperation with Professor Graham Burton in Cambridge (UK) on placental/trophoblast metabolism, especially mitochondrial function. Recent evidence implicates placental endoplasmic reticulum (ER) stress in the pathophysiological characteristics of preeclampsia. We have investigated whether endothelin (ET)-1, which induces Ca²⁺ release from the ER, can induce placental ER stress. Our data show that ET-1 induced ER stress in trophoblasts via the ETBR and initiation of signaling through the PLC-IP3 pathway, with the potential for autocrine stimulation (41). We are currently studying the possible involvement of NT-proBNP in the pathogenesis of PE. These 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) and that this effect depend on endometrial stromal cells (43, 44). 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(43). 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 (46). 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 have done a questionnaire study on cost of illness and quality of life and we are currently working with the data that look very interesting. 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 (47). We also present case reports of more general interest (48). We have shown that the expression level of alphaB-crystallin before combined surgical and hormone treatment seems to have a great impact on post-treatment chances of becoming pregnant (49), data indicating that α BCr can be used as an endometrial receptivity biomarker. 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 (50, 51). 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. We have shown that self samples contained sufficient amounts of genomic DNA and the self-samples and that the Viba-brush and the FTA cartridge are suitable for self-sampling of vaginal cells and subsequent HR-HPV typing (52). It was also shown that offering self-sampling of vaginal fluid followed by a high-risk HPV test was considerably more effective for detection of histological CIN2-3 lesions in comparison with offering Pap-test in a midwife reception in women not regularly attending organized screening (53). We have shown that repeat testing for high-risk HPV using self-sampling of vaginal fluid can be used to increase the specificity in the screening for cervical cancer in women aged 30-65 years (54). From a very recent study we have concluded that self-sampling of vaginal fluid in combination with high-risk HPV testing appears to be an attractive method to improve screening coverage and decrease the prevalence of cervical cancer in women aged 50 years or older (55). The studies are coordinated by a

steering group consisting of Ulf Gyllensten, Erik Wilander, Ingrid Wikström, Karin Sanner, Riina Aarnio 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 (56). Our latest data show that antral follicle count is strongly associated with live birth rates after ART (57) and that antimüllerian hormone (AMH) serves not only as a marker of ovarian reserve but also as a prognostic factor of pregnancy and live birth rates (58). 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 (59-62). We have studied the relevance of p53, bax, p21, p27, PUMA och c-MYC, EGFR, VEGF-R, VEGF and PTEN as prognostic factors (59, 60). It seems as if p53 status divides ovarian carcinomas into 2 subgroups after prognosis, also in serous tumors. Presence of PTEN in p53-positive tumors seems to protect from bad prognosis and absence of PTEN seems to worsen prognosis in early stages (61). The objective of another study was to evaluate the prognostic effect of the apoptosis regulators p53, bax and PUMA for recurrent disease and disease-free survival (DFS) in a series of 105 patients in FIGO-stages I-II with epithelial ovarian cancer, all treated with post-surgical platinum-taxane chemotherapy. The results indicate that FIGO stage and p53 status alone were independent predictive factors for recurrence and prognostic factors for survival. Furthermore, p53 bax status was an independent prognostic factor for survival in this study (62). These studies are coordinated by Ingridur Skirnisdottir.

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Dissertations 2011

Signe Altmäe

Reproductive Health

Inger Sundström Poromaa

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 PADIA study included approximately 1500 women seeking induced abortion at five out-patient clinics. During the past year data from the study has been compiled and the first paper has been submitted. Results indicate that posttraumatic stress disorder is not more common among women seeking abortion than in the general population. Further data from the longitudinal assessments are awaited during next year.

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 first papers from the study was published in 2011.

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). The study has thus far included 1900 women and tissue sampling at delivery is obtained in more than 80% of cases. The first studies, using placenta samples

from BASIC are currently underway. Among the first aims is to establish placental gene expression pattern in women using serotonin reuptake inhibitors during pregnancy.

The neuroendocrinology of the female brain – focus on imaging

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. All these studies are concluded (altogether more than 160 fMRI scans have been performed) and data analyses are ongoing.

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. Our findings clearly indicate that urogenital atrophy is far more common than previously reported, and approximately 60% of women using aromatase inhibitors suffer from dyspareunia.¹⁻⁵⁶

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Regionforskningsmedel 200 000 SEK (ASS)
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Söderström Königska Foundation 200 000 SEK (AS)
Dissertations 2011

Birgitta Segeblad: Is it just the hormones?

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International Child Health and Nutrition

Lars Åke Persson

The research programme International Child Health and Nutrition focuses on health system strategies and interventions for improved child health and survival, on prevention and management of childhood malnutrition, and on equity in child health and survival.

Child health has improved considerably during the past few decades as reflected in Millennium Development Goal indicators. A persistent problem in many countries is a high neonatal mortality, and inequity in neonatal survival chances (22). 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 (16), Neonatal health Knowledge Into Practice, trial registration number ISRCTN44599712. The project has already generated new knowledge on neonatal health (4,8,12,20,22,29), 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.

In an extensive prenatal nutrition 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), we have shown that food supplementation early in pregnancy combined with multiple micronutrient supplementation substantially improves survival of the offspring (5). We have also evaluated the effects on child growth (10), micronutrient status in infancy (18), immune function (31), morbidity and psychomotor development. The cohort has also been used to study anaemia and micronutrient deficiencies in pregnancy (11), oxidative stress in pregnancy and birth weight (2), risk factors for infant anaemia (7), breast feeding and micronutrient status (28), maternal-infant interaction (1,30), household food security and child growth and development (24,37,38) and violence against women and child growth and morbidity (41,42). 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). A follow-up at age 10 years is planned for 2012-13. We collaborate with, among others, the research institution ICDDRb in Bangladesh, and research groups at London School of Hygiene and Tropical Medicine, 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.

Exclusive breastfeeding during the first six months of life is considered one of the most important means of preventing child deaths by infections. 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 (15,17). Swedish Research Council finances the ongoing studies to our group and Save the Children (US) provides support to our collaborating partners.

The development of effective and feasible strategies for prevention and management of severely malnourished children are addressed in studies in Ethiopia and Bangladesh. One research student from Bangladesh studies the effect of stimulation (play therapy) in addition to food supplementation in the rehabilitation of severely malnourished children (3,32), 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 a series of studies (21,40,41,42). We have shown an association between VAW and size at birth, child growth and morbidity (40,41,42).

Due to the newly discovered arsenic catastrophe in Bangladesh we took the initiative to epidemiological studies on health consequences of arsenic contamination of drinking water. The research activities have been 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 (14,23,26) 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 (6,19,27,33,34,39). We collaborate with ICDDRB and BRAC, Bangladesh and with the department of Metals and Health, Karolinska Institutet.

In different studies in Uganda the diagnosis and management of children with fever are addressed (9,35,36).

The health-related Millennium Development Goals are in focus in studies in Nicaragua. In population-based studies in urban and rural areas the under-five mortality trends are analysed (13), and effects of community development work are studied with an equity lens.

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. Currently research is ongoing on assessing the health system context in relation to planning of services and analysis of effects on interventions. 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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Dissertation 2011

Hanna Eneroth: *Infant Anemia and Micronutrient Status. Studies of Early Determinants in Rural Bangladesh.* Acta Universitatis Upsaliensis 2011.urn:nbn:se:diva-143058

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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.

Two doctoral students have defended their thesis successfully. One new doctoral student has been registered during the year.

Ass Prof Birgitta Essén has received a government commission, which resulted in two reports: one in female genital cutting and one in the area of honoured related violence.

In the KoF evaluation 2011 the group was appointed the second best grade, 2-3, at the department.

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

- 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 2011 had focus on maternal Near Miss and gathered around 30 Nordic researchers.
- VAW. Global network for Research on Violence against Women had a meeting in Sri Lanka.

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*

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Agencies that support the work

Swedish International Development Cooperation Agency (Sida)	4 050 600
Vetenskapsrådet	1 849 300
Akademiska sjukhuset (ALF)	1 735 400
Vårdforskningsmedel	609 000
Sävstaholm Foundation	450 000
Family Planning Foundation	55 000
Spider, Stockholm University	120 000
Linnaeus Palme	173 000

PhD exam

Columba Kokusiima Mbekenga

Striving to Promote Family Health after Childbirth

Elisabet Eriksson

Christian Communities and Prevention of HIV among Youth in Kwa-Zulu-Natal, South Africa

General Pediatric Research Group

This group focuses 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.

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. Three different cohorts are being investigated and followed-up, the SPAIS, NOAK and MIDAS studies. Inclusion of patients in the MIDAS study cohort was recently finished.

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 (The MIDAS study). In a follow-up study of a community based cohort of school children (SPAIS) we found that elevated exhaled NO precedes the development of allergic rhinitis.

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 three projects:

1. Medical treatment of JIA (juvenile idiopathic arthritis) in Uppsala county during the last ten years.
2. Evidence of activated innate and adaptive immunity in JIA
3. Juvenile idiopathic arthritis in the nordic countries.
4. A regional, prospective population based study of children with rheumatic diseases. Den regionala, prospektiva, populationsbaserade studien kring barn med reumatisk sjukdom”,

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

Erik Normann

Measurement of gut perfusion and rectal microdialysis in early diagnosis of necrotizing enterocolitis in extremely preterm babies.

The urological research subgroup

Ongoing Clinical trials

Study on the treatment of therapy-resistant enuresis with desmopressin and reboxetine (EudraCT no 2008-002636-15).

A multicenter, open-label, single ascending dose study to evaluate pharmacokinetics, safety and tolerability of solifenacin succinate suspension in pediatric patients aged 5 to 17 years (inclusive) with Overactive Bladder (OAB) (EudraCT no 2009-017197-21)

Other ongoing research projects

Studies on therapy-resistant enuresis. PhD project by Dr Elisabet Lundmark under the supervision of TNe.

Studies on the treatment of enuresis with daytime urotherapy. PhD project by RN Maria Cederblad under the supervision of TNe.

Studies on vesico-ureteral reflux, in collaboration with Sverker Hansson, Gothenburg University.

Studies on orthodontic treatment of enuresis, in collaboration with Farhan Bazargani, Örebro University.

Studies on children below two years of age with first-time pyelonephritis. Pre-PhD project by junior physician Clara Patton under the supervision of TNe.

National and international collaboration

TNe is since 2006 Secretary General of the International Children's Continence Society (ICCS) – the only global organisation for researchers and clinicians involved in the paediatric lower urinary tract.

TNe is a delegate of the Swedish Enuresis Academy (SEA)

Birgitta Karanikas is a Board Member of European Society for Pediatric Urology (ESPU) nurses group since 2010

Invited lectures, international congresses

TNe has during 2011 been invited faculty, speaker and coorganiser of the following international courses:

ICCS workshop during the Brazilian Paediatric Congress in Salvador de Bahia, Brazil

ICCS course in Taipei, Taiwan

ICCS course in Moscow, Russia

INComb-TRUST-SEA conference in Stockholm, Sweden

Editorial Board tasks, referee activities etc

TNe is a Section Editor of Pediatric Nephrology, the only global periodical in that field. He is also a member of the editorial Board of Upsala Journal of Medical Science and Aust New Zealand Cont J.

TNe is a frequent referee for Acta Paediatrica, Pediatrics, Arch Dis Childh, Neurorol Urodyn, Aust New Zealand Cont J, Scand J Urol Nephrol, Urologia Internationalis, BJU Int and J Urol

Examination appointments (TNe)

Member of Examination Board at the at the PhD dissertation of Susanne Crambert at Karolinska Institute, Stockholm, Sweden

Opponent at the PhD dissertation of Ann de Guchteneare at the University of Ghent, Belgium

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*

Members of the group

Nordvall, Lennart	Adj professor
Alving, Kjell	Adj professor
Berntsson, Lillemor	MD Ph.D.
Cederblad, Maria	RN, Ph.D stud
Dahlbom, Ingrid	Ph.D. Researcher
Engstrand, Malin	Research student
Engsheden, Nathalie	Research assistant ?
Fredin, Kerstin	Nurse ?
Hansson, Tony	Associate prof
Heijkenskjöld, Charlotte	M.D.
Hjelm, Fredrik Ph.D.?	
Hollsing, Annika	Ph.D.
Johnson, Jennifer	M.D.
Kalm Stephens, Pia	Research nurse
Kalliopi, Kazamia	M.D doctoral stud
Karanikas, Birgitta	Research nurse
Kollberg, Hans	Professor em
Lettesjö, Helene	Researcher
Lundmark, Elisabet	M.D., doctoral stud
Neuman, Åsa	M.D., doctoral stud
Nevéus, Tryggve	Associate professor, senior lecturer
Normann, Erik	Ph.D.
Nyberg, Britt-Inger	Research assist
Näs, Elisabet	Research nurse Pedroletti, Christophe
Stålhammar, Jenny	Dietician
Krantz, Christina	M.D.

Publications 2009-2011

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Presentations at international conferences

1. Customisation, fidelity or both? Experiences from implementing Triple P in Sweden. Helping Families Change conference Birrsbane, Australia, 2010

Pediatric Endocrinology

Jan Gustafsson

Several lines of research are ongoing within pediatric endocrinology

1. Energy substrate metabolism during infancy and childhood

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

After birth the newborn infant has to produce its own glucose particularly for the need of the brain until nutrition by breastfeeding is established. Both infants who are born small and large for gestational age are at risk for neonatal hypoglycaemia as well as metabolic disease later in life. One of our lines of research is directed on energy metabolism during pregnancy and in the newborn infant by use of stable isotope labelled compounds and gas chromatography-mass spectrometry. By a combination of microdialysis and stable isotope technique studies of glucose metabolism in the brain under basal conditions and following injury are also performed. Since perinatal asphyxia may influence neonatal glucose homeostasis and cerebral glucose consumption, we investigate glucose metabolism and lipolysis during and after hypothermia in infants with perinatal asphyxia.

2. Register based studies on fetal origin of adult disease

Maria Lundgren, Inger Wahlström Johnson, Fredrik Ahlsson and Jan Gustafson

Fetal conditions may influence development and morbidity during childhood and adult life. By use of the Swedish health registers we study effects of conditions during fetal life and birth characteristics on statural growth, intellectual performance and morbidity in young adults. Data on relationships between growth and intellectual performance in subjects born preterm have recently been published and a study on school performance of subjects born preterm is ongoing. In a cohort study of all term, single births in Sweden, 1973-1982, we aim to investigate relationships between a high birth weight and adult metabolic disease. The registers used are the Medical Birth Register, the Inpatient Care Register, the Drug Register and the Causes of Death Register.

3. Growth and development of newborn infants

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

Prematurity is associated with a number of medical problems, including those related to poor growth. Projects related to effects of feeding regimens on growth of infants born premature and/or small for gestational age are ongoing. 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 followed up with regard to several aspects of development. A thesis project related to the effect of Kangaroo Mother Care is ongoing.

4. Endocrine and metabolic disease in children and young adults

Jan Gustafsson, Åsa Myrelid, Lemm Proos, Ingemar Swenne, Maria Halldin, Anders Forslund, Johan Staaf

Down syndrome

We have studied growth and endocrine disturbances in Down syndrome for several years. Previously, data on secretion of growth hormone and the effects of growth hormone therapy on

growth and psychomotor performance in subjects with Down syndrome have been published. Overweight and obesity is common in Down syndrome and presently studies on effects of adipokines in subjects with Down syndrome are ongoing. By use of Swedish registers we have completed a study on mortality and causes of death in Down syndrome. The data shows that infant mortality in DS has decreased markedly. Median age at death is still increasing and is now close to 60 years.

Endocrine consequences of stem cell transplantation

Patients suffering from hematologic malignancies, who are treated with stem cell transplantation (SCT) may develop late effects similar to those of the metabolic syndrome including disorders of glucose metabolism. We have studied young adult patients who have undergone bone marrow transplantation during childhood 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

Supply of energy is critical for growth and pubertal development. Eating disorders influence somatic development by effects on metabolism and hormone balance. Models for prediction of growth, menarche and subsequent menstruations during the treatment of eating disorders have been created. As far as the relationship between somatic factors and psychiatric morbidity is concerned changes of levels of thyroid hormones and essential fatty acids predispose for depression and thus influence the expression of the eating disorder. The results show that low circulating levels of thyroxine may provide a link between starvation and depression in adolescent girls with eating disorders. The data also suggests a lower dietary intake of ω 3 PUFA in those with depression.

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. Studies of altered beta-cell function resulting in hypersecretion of insulin as a mechanism behind childhood obesity is ongoing in collaboration with professor Peter Bergsten at the Department of Medical Cell Biology. Knowledge about how insulin secretion develops over time in obese individuals is important as there may be a window during which there is a possibility to restore an altered insulin secretory pattern.

Energy homeostasis in fatty acid oxidations defects

This project represents collaboration between our department and the Karolinska Institute. Fatty acid oxidation disorders are inherited diseases affecting the energy production from oxidation of fatty acids. This results in shortage of energy in situations when fatty acids are preferred as energy source. In these situations there is a risk of hypoglycemia and brain damage. The most common disorder is Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD). Our first study is on LCHAD deficiency. It aims at characterization of the energy balance in different situations such as resting, physical activity, fasting and during meals. We also want to study body composition, neurocognitive outcome and long term complications.

Another study shows that patients with LCHAD deficiency have chorioretinopathy. ERG was pathologic in seven of ten patients. Early diagnosis and proper treatment seemed to delay, but not prevent ophthalmologic changes. In another study statural growth was analysed. Four of the ten

studied patients had reached final height, two within target height. The children developed overweight to a higher extent than children without LCHADD.

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Dissertations

Katarina Strand-Brodd defended her thesis “Delayed Development of Visuomotor Capacity in Very Preterm Infants” during the year.

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Novo Nordisk
ALF

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 fenotype/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

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List of publications

Original publications

EXPRESS Group (incl Ewald U), Fellman V, Hellström-Westas L, Norman M, Westgren M, Källén K, Lagercrantz H, Lindgren A, Marsál K, Serenius F, Wennergren M. One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA* 2009;301(21):2225-33.

Funkquist EL, Tuvemo T, Jonsson B, Serenius F, Nyqvist KH. Preterm appropriate for gestational age infants: size at birth explains subsequent growth. *Acta Paediatr* 2010;99(12):1828-33.

van Kaam AH, Rimensberger PC, Borensztajn D, De Jaegere AP; Neovent Study Group (incl R. Sindelar). Ventilation practices in the neonatal intensive care unit: a cross-sectional study. *J Pediatr* 2010;157(5):767-71.e1-3

Funkquist EL, Tuvemo T, Jonsson B, Serenius F, Nyqvist KH. Influence of test weighing before/after nursing on breastfeeding in preterm infants. *Adv Neonatal Care* 2010;10(1):33-9.

Salomonsson S, Dzikaite V, Zeffer E, et al (incl Jonzon A). A population-based investigation of the autoantibody profile in mothers of children with atrioventricular block. *Scand J Immunol* 2011;74(5):511-7.

EXPRESS Group (incl Hellström-Westas L, Ewald E, Sjörs G, Serenius F). Incidence of and risk factors for neonatal morbidity after active perinatal care: extremely preterm infants study in Sweden (EXPRESS). *Acta Paediatr* 2010;99(7):978-92.

Ågren J, Zelenin S, Svensson LB, Nejsum LN, Nielsen S, Aperia A, Sedin G. Antenatal corticosteroids and postnatal fluid restriction produce differential effects on AQP3 expression, water handling, and barrier function in perinatal rat epidermis. *Dermatol Res Pract* 2010; 789729.

Farooqi A, Hägglöf B, Sedin G, Serenius F. Impact at age 11 years of major neonatal morbidities in children born extremely preterm. *Pediatrics* 2011;127(5):e1247-57.

Kjallstrom B, Sedin G, Ågren J. Clothing reduces evaporative water and heat loss in preterm infants. *Journal of Neonatal-Perinatal Medicine* 2011; 4:89-92.

Feltes TF, Sondheimer HM, Tulloh RM, et al (incl Jonzon A). A randomized controlled trial of motavizumab versus palivizumab for the prophylaxis of serious respiratory syncytial virus disease in children with hemodynamically significant congenital heart disease. *Pediatr Res* 2011;70(2):186-91.

Ambrosi A, Salomonsson S, Eliasson H, et al (incl Jonzon A). Development of heart block in children of SSA/SSB-autoantibody-positive women is associated with maternal age and displays a season-of-birth pattern. *Ann Rheum Dis* 2012;71(3):334-40.

Munsters J, Wallström L, Ågren J, Norsted T, Sindelar R. Skin conductance measurements as pain assessment in newborn infants born at 22-27 weeks gestational age at different postnatal age. *Early Hum Dev* 2012;88(1):21-6.

Karlsson V, Heinemann AB, Sjörs G, HedbergNykvist K, Ågren J. Early skin-to-skin care in extremely preterm infants: Thermal balance and care environment. *J Pediatr* 2012, in press

Reviews and invited commentaries

Ågren J. Monitoring fluid balance in the neonate. *Acta Paediatr* 2012 Feb 28. doi: 10.1111/j.1651-2227.2012.02653.x. [Epub ahead of print]

Bonamy AK, Stjernqvist K, Serenius F. [Extremely premature infants could be a new risk group in adult care]. *Lakartidningen* 2010;107(42):2548-52 (Swedish).

Letters

Sjörs G. Treatment decisions for extremely preterm newborns: beyond gestational age. *Acta Paediatr*. 2010 Aug 17. [Epub ahead of print] No abstract available

Sjörs G. Fluid and Electrolytes in Pediatrics - a Comprehensive Handbook. *Acta Paediatr*. 2012 Feb 20. doi: 10.1111/j.1651-2227.2012.02639.x. [Epub ahead of print] No abstract available.

Examensarbeten

Susanna Gröndal:, Bondesson. M-L., Jonzon,A.

Congenital long QT syndrome. KNCQ1 and a novel KCNH2 variant associated with a complex form of long QT syndrome. Godkänt examensarbete. Manuskript föreligger för vetenskaplig publicering.

Mikaela Winderud, Nilsson,P., Jonzon,A., Sindelar,R., Mattsson,E.

1. Diaphragm pacing in Congenital hypoventilation Syndrome. The Swedish experience.
2. Living with diaphragm pacing – A multinational quality of life study of children with Congenital Central Hypoventilation Syndrome.

2 abstracts presenterade på international 4th International Conference on Primary Central Hypoventilation Warsaw 12-14 april 2012

Agencies that support the work

Hjärt- Lungfonden
Stiftelsen Samariten
ALF

Pediatric Neurology research group

Gunnar Ahlsten

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.

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

Perinatally acquired brain damage is associated with life-long suffering and significant costs for society. The project investigates mechanisms for perinatally acquired brain damage, e.g. from complications related to pregnancy/delivery, and neurophysiological methods for very early evaluation of brain injury, prediction of long-term outcome, and treatment of seizures. Some of the projects are performed in international collaboration, funded by EU grants (NEOBRAIN and NEMO). These studies resulted in a PhD dissertation by Sverre Wikström (2011) on various aspects of amplitude-integrated EEG monitoring in very preterm infants in relation to long-term outcome.

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. These studies resulted in a PhD dissertation (Katarina Strand Brodd) 2011.

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 are analysed and a manuscript will be submitted for publication during 2012. The

study is still going on and follow-up investigations of the cohort at the age of 6½ years which 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 tumours in children

Together with the Department of Paediatric Oncology at the Karolinska Institute in Stockholm a follow-up project of the Neurocognitive, Psychosocial and Medical long-term outcome of children diagnosed with brain tumours in the Stockholm and Uppsala - Örebro healthcare regions in Sweden are going on. The project started October 2010 and will continue until 2013.

During 2011 two different doctoral projects were started dealing primarily with different follow-up studies of children with brain tumors treated in Uppsala and the surrounding regions

Arthrogyrosis

Arthrogyrosis 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 arthrogyrosis syndromes. Other projects in this field are also planned.

Members of the group

Ahlsten, Gunnar	Associate professor
Andersson, Ola	Research student
Borgestig, Maria	Postgraduate student
Bratteby-Tollerz, Linda	Magister
Dahl, Margareta	Associate professor
Eeg-Olofsson, Orvar	Associate professor
Ehrstedt, Christoffer	Postgraduate student
Ek, Ingalill	Magister
Hellström-Westas, Lena	Professor
Höglund, Anette	Magister
Jonsson, Pysse	Postgraduate student
Kimber, Eva	Ph.D
Kristiansen, Ingela	Postgraduate student
Larsson, Katrin	Research student
Lidström, Helene	Ph.D
Lidström, Åsa	Magister
Liminga, Gunnar	Ph.D
Lundberg, Staffan	Ph.D
Norrlin, Simone	Ph.D
Strinnholm, Margareta	Magister

Strömberg, Bo	Associate professor
Söderström, Helena	Research student
Wester, Ulrika	Postgraduate student
Wikström, Sverre	Ph.D

List of publications 2009-2011 – original articles

- 1/ Lundqvist P, Källén K, Hallström I, Hellström-Westas L. Trends in outcomes for very preterm infants in the southern region of Sweden over a 10-year period. *Acta Paediatr* 2009; 98(4):648-653.
- 2/ Bengtsson J, Ederoth P, Ley D, Hansson S, Amer-Wählin I, Hellström-Westas L, Marsál K, Nordström CH, Hammarlund-Udenaes M. The influence of age on the distribution of morphine and morphine-3-glucuronide across the blood-brain barrier in sheep. *Br J Pharmacol* 2009; 157(6):1085-1096.
- 3/ Larsson PG, Wilson J, Eeg-Olofsson O. A new method for quantification and assessment of epileptiform activity in EEG with special reference to focal nocturnal epileptiform activity. *Brain Topography* 2009; 22,52-9.
- 4/ Barry A, Chioza, Jean Aicardi, Harald Aschauer, Oebele Brouwer, Petra Callenbach, Athanasios Covanis, Joseph M. Dooley, Olivier Dulac, Martina Durner, Orvar Eeg-Olofsson, Martha Feucht, Mogens Laue Friis, Renzo Guerrine, Marianne Juel Kjeldsen, Rima Nabbout, Lina Nashef, Thomas Sander, Auli Sirén, Elaine Wirrel, Paul McKeigue, Robert Robinsson, R. Mark Gardiner, Kate V. Everett. Genome wide high density SNP-based linkage analysis of childhood absence epilepsy identifies a susceptibility locus on chromosome 3p23-p14. *Epilepsy Res* 2009;87:247-55.
- 5/ Jemtå L, Fugl-Meyer KS, Oberg K, Dahl M. Self-esteem in children and adolescents with mobility impairment: impact on well-being and coping strategies. *Acta Paediatr* 2009; 98: 567-72.
- 6/ 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.
- 7/ Vanhatalo S, Hellström-Westas L, de Vries LS. Bumetanide for neonatal seizures: Based on evidence or enthusiasm? *Epilepsia* 2009 May;50(5):1292-3.
- 8/ Lidström Å, Ahlsten G, Hirschfeld H, Norrlin S. Intrarater and interrater reliability of myotonometer measurements of muscle tone in children. *J Child Neurol* 2009;24(3):267-74.
- 9/ Höglund A, Norrlin S. Influence of dual tasks on sitting postural sway in children and adolescents with myelomeningocele. *Gait & Posture* 2009;30:424-30.
- 10/ Nyström, A.-M., Ekvall, S., Strömberg, B., Holmström, G., Thuresson, A.-C., Annerén, G. and Bondeson, M.-L. A Severe Form of Noonan Syndrome and Autosomal Dominant Café-au-lait Spots – Evidence for Different Genetic Origins. *Acta Paediatrica* 2009; 98:693-98.
- 11/ Lannering, B., Sandström, P.-E., Holm, S., Lundgren, J., Pfeifer, S., Samuelsson, U., Strömberg, B and Gustafsson, G. Classification, Incidence and Survival Analyses of Children with CNS Tumors diagnosed in Sweden 1984-2005. Accepted for publication in *Acta Paediatrica* 2009.
- 12/ The EXPRESS Group Fellman V et al. One-year survival of extremely preterm infants after active perinatal care in Sweden. *JAMA* 2009; 301:2225-2233.
- 13/ Bajic D, Kumlien E, Mattsson P, Lundberg S, Wang C, Raininko R. Incomplete hippocampal inversion – is there a relation to epilepsy? *Eur Radiol* 2009;19:2544-50
- 14/ Larsson PG, Michel CM, Seeck M, Eeg-Olofsson O, Lantz G. Decrease in propagation of interictal epileptiform activity after introduction of levetiracetam visualized with electric source imaging. *Brain Topography* 2010; 23:269-78.

- 15/ Larsson PG, Brockmeier F, Evsiukova T, Ramm-Pettersen A, Eeg-Olofsson O. Does sleep deprived EEG recordings reflect spike index as found in full-night EEG recordings? *Epilepsy Behav* 2010;19:348-51.
- 16/ 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.
- 17/ Christersson S., Strömberg B. Childhood stroke in Sweden I: incidence, symptoms, risk factors and short-term outcome. *Acta Pædiatrica* 2010; 99:1641-9.
- 18/ Christersson S., Strömberg B. Stroke in Swedish children II: long-term outcome. *Acta Pædiatrica* 2010; 99:1650-6.
19. Stalberg K., Haglund B., Stromberg B and Kieler H. Prenatal exposure to medicines and the risk of childhood brain tumor. *Cancer Epidemiology* 2010; 34:400-4.
- 20/ Hallin AL, Hellström-Westas L, Stjernqvist K. Follow-up of adolescents born extremely preterm: cognitive function and health at 18 years of age. *Acta Paediatr* 2010; 99(9):1401-1406.
- 21/ Thoresen M, Hellström-Westas L, Liu X, de Vries LS. Effect of hypothermia treatment on the predictive value of amplitude integrated electroencephalograph in infants with moderate and severe perinatal asphyxia. *Pediatrics* 2010; 126(1):e131-139.
- 22/ Palmu K, Wikström S, Hippeläinen E, Boylan G, Hellström-Westas L, Vanhatalo S. Detection of 'EEG bursts' in the early preterm EEG: visual versus automated detection. *Clin Neurophysiol* 2010; 121(7):1015-1022.
- 23/ Palmu K, Stevenson N, Wikström S, Hellström-Westas L, Vanhatalo S, Palva M. Automated detection of spontaneous activity transients in early preterm EEG: Optimization of an NLEO-based algorithm. *Physiol Measurement* 2010; 31(11):N85-93.
- 24/ Lidström H, Ahlsten G, Hemmingsson H. The use of Information and Communication Technology (ICT) outside of school for boys and girls with motor disabilities. *J of Child Health Dev* 2011
- 25/ 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;96(4):1129-35.
- 26/ 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;127(4): 1628-34.
- 27/ Brodd Strand K, Ewald U, Grönqvist H, Holmström G, Strömberg B, Grönqvist E, von Hofsten C, Rosander K. Development of smooth pursuit eye movements in very preterm infants 1. General aspects. *Acta Pædiatrica* 2011; 100:983-991.
- 28/ Nord H, Pfeifer S, Nilsson P, Popova S, Sandgren J, Strömberg B, Alafuzoff I, Nistér M, Diaz de Ståhl T. Novel amplifications in pediatric medulloblastoma identified by genome-wide copy number profiling. *J Neurooncol* 2011; doi 10.1007/s11060-011-0716-0.
- 29/ Bratteby Tollerz L, Olsson RM, Forslund A, Norrlin S. Reliability of energy cost calculations in children with cerebral palsy, cystic fibrosis and healthy controls. *Acta Paediatrica* 2011;100(12):1616-20.
- 30/ Proos L, Tuvemo T, Ahlsten G, Gustafsson J, Dahl M. Increased perinatal intracranial pressure and brainstem dysfunction predict early puberty in boys with myelomeningocele. *Acta Paediatrica* 2011;100(10):1368-72.
- 31/ Jonsson P, Eeg-Olofsson O. 10-year outcome of childhood epilepsy in well-functioning children and adolescents. *Eur J Paediatr Neurol* 2011;15(4):331-7.

32/ Mefford HC, Yendle SC, Hsu C, Cook J, Geraghty E, McMahon JM, Eeg-Olofsson O et al. Rare copy number variants are an important cause of epileptic encephalopathies. *Ann Neurol* 2011;70(6):974-85.

33/ Bakke KA, Larsson PG, Eriksson AS, Eeg-Olofsson O. Levetiracetam reduces the frequency of interictal epileptiform discharges during NREM sleep in children with ADHD. *Eur J Paediatr Neurol* 2011;15(6):532-8.

34/ Wiberg-Itzel E, Åkerud H, Andolf E, Hellström-Westas L, Winbladh B, Wennerholm U-B. Association between adverse neonatal outcome and lactate concentration in amniotic fluid. *Obstet & Gynecol* 2011;118(1):135-42.

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Reviews/book chapter

1/ Hemmingsson H, Lidström H, Nygård L eds: Assistive technology devices in educational settings: Students' perspective. 2009 (Vol 25). Florence, Italy: IOS Press.

2/ Eklund C, Kristiansen I. Metodhandbok – svårigheter och möjligheter i skolarbetet efter förvärvad hjärnskada. Folke Bernadotte regionhabilitering, Barncancerfonden och Hjärnskadeförbundet Hjärnkraft 2009.

3/ **Hellström-Westas L**, de Vries LS. Diagnosing seizures with amplitude integrated EEG. *J Pediatr Neurol* 2009;19:19-23.

4/ **Hellström-Westas L**, de Vries LS. Electroencephalography and evoked potentials. In: Fetal and Neonatal Neurology and Neurosurgery, 4th ed. Eds: MI Levene & FA Chervenak. *Churchill Livingstone Elsevier*, Edinburgh, 2009, pp 192-221.

5/ Butler A, Strinnholm M. Elever med ryggmärgsbräck – neuropsykologiska och pedagogiska aspekter. Folke Bernadotter regionhabilitering 2009

6/ Eeg-Olofsson O. Kroppsliga orsaker och utredning av återkommande huvudvärk. I: Migrän och spänningshuvudvärk hos barn och tonåringar. Ed: Bo Larsson. Studentlitteratur 2009

7/ **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

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Pediatric Oncology

Susan Pfeifer and Gustaf Ljungman

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 and immunosuppressive therapy after allogeneic SCT in childhood (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.

A national study. Collaboration with K Mellgren, Göteborg, and the Swedish SCT group.

The impact of conditioning regimen on outcome after allogeneic SCT for childhood ALL- a Nordic study (Arvidson et al)

A retrospective evaluation of different conditioning regimens utilized prior to allogeneic stem cell transplantation of children with acute lymphoblastic leukemia .

Insulinresistance and bone health in young adults who underwent stem cell transplantation for childhood leukemia (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.

Treatment-related complications of childhood cancer and epidemiology of solid tumors

Hodgkin lymphoma in children and adolescents – ethiological factors, epidemiology and late-effects of treatment (Ljungman, Englund, et al).

This is a study of pediatric patients with Hodgkins lymphoma (HL). The aims are to: 1) Study if HL in children, adolescents and adults differ with respect to inflammatory micro-environment (eosinophils, macrophages, mast cells, regulatory T-cells and CD20-positive cells) and if the microenvironment has any implications for clinical outcome in children and adolescents (collaboration between Uppsala, Stockholm and Umeå). 2) Present a population-based epidemiological survey of all children and adolescents with HL in Sweden for a time period of 25 years (1985-2009). 3) Study late effects of HL treatment comparing being treated in childhood (<18 years) with being treated as an adult (collaboration between Uppsala and Umeå).

Interventions for procedural pain in children and adolescents with cancer (Ljungman, Hedén, et al).

Pain is a major problem for children with cancer. Pain can be procedure-related, treatment-related pain (side-effects of treatments such as chemotherapy and radiotherapy), and cancer-related. In this project, we study procedure-related pain and it's treatment. Needle insertion in a subcutaneous port can be regarded as a model where children's fear, distress, and pain in connection to procedures can be studied in a reasonably standardized way. Using this model we can learn about the effects of different pharmacological and psychological interventions in different randomized controlled trials.

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

Oral mucositis is a painful condition with inflammation and ulceration of the mucous membranes in the mouth, caused by chemo- and radiotherapy and is particularly frequent in hematopoietic stem cell transplantation (HSCT). Pain intensity varies, but the pain is often so severe that the patient is unable to eat solid food (grade 3) or even to consume liquids (grade4). In very severe cases the patient cannot talk, nor swallow saliva. Oral mucositis is reported by patients to be one of the most painful and debilitating side effects of cancer treatment.

Specific pharmacological and psychological interventions that can reduce oral mucositis symptoms are evaluated in randomized controlled trials. The studies will be carried out on a national level at the different pediatric HSCT centers in Sweden.

Psychosocial studies in children with cancer and their families

Psychosocial issues in children and adolescents with cancer and their parents (Ljungman, Engvall, et al).

In addition to being a part of the Pediatric Oncology research group at the Department of Women's and Children's Health, Uppsala University, Ljungman takes part in, and shares leadership of, the Psychosocial Oncology research group headed by Professor Louise von Essen. The projects have resulted in a number of publications and they can be categorized in either one of the two following main groups: 1. Cancer during adolescence - Psychosocial and health economic consequences and 2. Occurrence, development, and treatment of posttraumatic stress disorder (PTSD) among parents of children with cancer. Presently this has moved on to a multi-institutional collaboration in one part of a new strategic research proposal from Uppsala University, the U-Care program. The aim is to provide, and with scientific rigour evaluate, internet-based stepped-care treatment for parents of children with cancer with PTSD and for adolescents with cancer with psychosocial problems.

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.

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, one of the most malignant tumors of childhood.

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 laoratory. 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 isolataing 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.

Difficult decisions and ethical aspects in pediatric oncology

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.

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.

Research group

Pfeifer Susan	Professor in pediatric oncology, coopted
Arvidson Johan	MD, PhD
Englund, Annika	MD, PhD student
Engvall, Gunn	RN, PhD
Frisk, Per	MD, PhD
Frost, Britt-Marie	MD, PhD
Georgantzi, Clary	MD, PhD student
Hedborg, Fredrik	Associate professor
Hedén, Lena	RN, PhD student
Jalmsell, Li	MD, PhD student
Ljungman, Gustaf	Associate professor
Lönnerholm, Gudmar	Professor emeritus
Palle Josefine	MD, PhD
Stenmarker, Margareta	MD, PhD
Thorsell, Jenny	MS, PhD student
Öberg, Anders	MD PhD student

Funding

VR coapplication 40 milj SEK (von Essen et al; Ljungman - U-CARE)

SSF coapplication 20 milj SEK (Syvönen et al; Lönnerholm - DNA metylation in childhood leukemia)

BCF/NBCNS 7.5 milj SEK/3years (Nister et al; Pfeifer - stem cells)

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

BCF 300.000/year, 2 years; 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)

Publications

2011

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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. LCFUPA 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 hematological and biochemical 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.

Studies on anorectal malformations and anal incontinence

Johan Danielson, Wilhelm Graf, Urban Karlbom, Tomas Wester

This project addresses the long term outcome of anorectal function and quality of life (QoL) in adult patients operated for anorectal malformations (ARM) in childhood. It also evaluates different strategies to reduce persistent anal incontinence after primary ARM surgery. The first study is of all ARM patients that have undergone primary surgical repair at the section of pediatric surgery between 1961 and 1993. The follow-up includes e.g. a validated QoL questionnaire, which also is answered by sex- and age-matched controls. A second study compares the functional outcome of ARM patients operated with the modern Peña procedure (posterior sagittal anorectoplasty) with that of patients operated with older types of surgery. The third study evaluates anorectal function and QoL in ARM patients subjected to dynamic graciloplasty due to anal incontinence in adulthood. The fourth study evaluates the effect on anorectal function and QoL two years after treatment with a new method against anal incontinence; anorectal submucosal injections of dextranomer particles suspended in non-animal hyaluronic acid (Solesta).

Intestinal microbial profiles of infants with short bowel syndrome using 454-pyrosequencing technique

Helene Engstrand Lilja, Niklas Nyström, Yigael Finkel och Lars Engstrand

This project compares the enteral bacterial flora in infants with short bowel syndrome (SBS) and healthy infants. Bacterial overgrowth (BO) is a common problem in these infants but specific diagnostic methods of BO is missing. In this study we investigate which bacteria are involved with bacterial overgrowth in infants with SBS by analysing bacterial-specific DNA in stool samples with the 454-pyrosequencing technique. Pyrosequencing is the method of choice to demonstrate bacterial diversity, but is not quantitative. Low bacterial diversity has previously been associated with IgE-associated eczema in children. Low bacterial diversity in infants with SBS may result in less stimulation of the immune system, that could cause BO. In this study we also want to investigate if a low and altered bacterial diversity in infants with SBS can be corrected with fecal transplantation from a healthy relative. Fecal transplantation has successfully been used in adults with e.g. refractory bacterial enteritis, but never in children with SBS.

Is it possible to prevent postoperative peritoneal adhesions in infants?

Fanny Fredriksson, Rolf Christofferson, Helene Engstrand Lilja

Postoperative adhesions are a leading cause of abdominal pain, bowel obstruction and infertility. These complications represent a heavy burden to both patients and healthcare providers. The knowledge on postoperative adhesions in children is limited, and due to a long expected lifespan, infants would benefit the most from reduction of adhesion formation. This project comprises four parts: (1) A retrospective study of infants that have undergone laparotomy during the first year of life (1976-2011, n=1067) with a questionnaire follow-up. The study will define the proportions of the problem and the time-scale for developing complications. (2) Establishing a relevant and reproducible experimental model (rat) for intra-abdominal adhesions. The model will elucidate adhesion formation development from the initial peritoneal trauma and which mediators that are involved. (3) Prevention of adhesion formation in the experimental model, using e.g. barriers, anti-inflammatory agents and inhibitors of cytokine signalling. The number and extent of adhesions as well as the bursting strength of a constructed intestinal anastomosis will be quantified. (4) A prospective study, examining RNA expression profiles in blood samples from patients with bowel obstruction and compare them to those of healthy children. We hypothesise that genes that mediate inflammation, coagulation and matrix formation are up-regulated, while fibrinolytic genes are down-regulated in children with bowel obstruction. Hopefully, children at high risk of adhesion-related complications can be identified and be offered reductive therapy in the future.

Isolation and transplantation of hepatocytes

Elisabet Gustafson

In liver failure, regardless of cause, there is a clinical need for alternatives to liver transplantation. Hepatocyte transplantation is one option that has been held promising for a long time. The method has however been hampered by an early clearance of the transplanted cells by the innate immune system. We have established a method for isolation and culture of human hepatocytes from liver biopsies. The cells have been used for *in vitro* experiments analyzing the different aspects of innate immunity when the cells come in contact with ABO-compatible blood. Besides the inflammatory reactions from neutrophils and the complement system, there is also activation of several steps in the blood coagulation system.

The study has also included attempts to control the adverse effects from the innate immune system by use of different inhibitors. We have now turned the experiments to *in vivo*. In our animal model (pig) can also the effects of the resident cells (i.e. endothelial and Kupffer cells) be studied. Pigs were used both as donors and recipients in the transplantation experiments.

The aim of this project is to gain knowledge that may improve the short- and long-term survival of transplanted hepatocytes. In the future, we hope to establish a national collaboration for hepatocyte transplantation in patients with liver failure.

Local delivery of bupivacaine in the wound reduces opioid complementation after intestinal and bladder procedures in children

Olga Hermansson, Tomas Wester, Rolf Christofferson, Mary George

This is a blinded, prospective, randomized study of the need for opioid complementation for postoperative pain relief in children. A catheter was placed on the fascia in the wound, and connected to a pump that delivered a defined volume of bupivacaine or saline (control group) over time. After informed parental consent, children undergoing elective surgery for enterostomy closure, open gastrostomy, or ureteral reimplantation, at age 6 month to <13 years were randomized to receive bupivacaine (n=17) or saline (n=15) in their wound catheters. Exclusion criteria were severe chronic disease or active infection. All patients were operated under general anesthesia with similar

ventilation and pharmacological administration. In the surgical pediatric ward, pain was assessed every third hour using FLACC for children 0-3 years, FPS-R from 4 to 6 years, and VAS from 7 years of age. All patients received 20 mg/kg acetaminophen p.o. or p.r. every 6 hours. In case of breakthrough pain or VAS>3, morphine, 0.05 mg/kg, was given i.v. If several (>3) bolus doses of morphine were necessary for VAS<3, a continuous morphine infusion was started. Outcome measures were morphine use, length of hospital stay and return to full oral intake. The manuscript is in preparation, but doses of morphine (0.05 mg/kg) complementation were significantly higher in the saline group compared to the bupivacaine group ($p<0.05$) on the first postoperative day. No adverse reactions were seen, neither significant difference in length of stay or return to full oral intake.

Microdialysis studies in experimental and clinical necrotizing enterocolitis

Niclas Högberg, Anders Stenbäck och Helene Engstrand Lilja

Necrotizing enterocolitis (NEC) is the most serious gastrointestinal disorder in newborn infants with an incidence of 10 to 15% in those with very low birth weight (VLBW <1500 g). More than 90% of the infants who develop NEC are born prematurely. The risk of NEC is inversely related to gestational age and birth weight. The disease is characterized by inflammation of the bowel that can progress to bowel necrosis and multiple organ failure. Despite extensive research, NEC remains a major cause of death in neonates, with mortality rates approaching 40 % in VLBW infants. Intestinal ischemia is thought to be an important component of the pathogenesis of NEC, causing variable degrees of ischemia of the small and large intestine, ranging from mild ischemia of the intestinal mucosa to transmural necrosis of the gut wall. There is a need for a new, sensitive and specific diagnostic method for early identification of NEC in order to attenuate its course. We have recently shown that rectal intraluminal microdialysis in an animal model of NEC is a reproducible, sensitive and specific, non-invasive early diagnostic method to detect intestinal hypoxia. At present we are investigating if rectal intraluminal microdialysis is a useful early diagnostic method of intestinal hypoxia in infants suspected of suffering from NEC.

High blood pressure in children with hydronephrosis

Ammar Al-Mashhadi, Arne Stenberg

Arterial hypertension is a growing health problem in the Western world, leading to e.g. myocardial infarction and stroke. Hypertension can be caused by renal dysfunction. Hydronephrosis is a relatively common (1%) condition after birth, and is characterized by dilation of the renal pelvis. Hydronephrosis is usually due to a partial ureteropelvic junction obstruction. Hydronephrosis may lead to progressive renal dysfunction. Although hydronephrosis is common, its pathophysiology is poorly understood and its clinical management is debated. Non-operative management of neonatal hydronephrosis is currently advocated, since the renal function can be rather well preserved for years. However, the long-term consequences of this new strategy are not known. We have recently discovered a strong connection between hydronephrosis (experimental and congenital) and obstructive nephropathy and hypertension in later life. Increased oxidative stress and reduced nitric oxide (NO) bioavailability in the affected kidney(s) are thought to drive this process. In experimental hydronephrosis, we intend to determine if increased oxidative stress and reduced NO bioavailability in the macula densa cells can explain the arterial hypertension and the reduction of kidney function. The relative role of the systems can be determined by anti-oxidative therapy and/or NO-stimulatory therapy. We will also determine if relief of the obstruction, by either nephrectomy or pyeloplasty, reduces hypertension and salt-sensitivity in hydronephrosis. Also the roles of the renin-angiotensin system, reactive oxygen species, the renal sympathetic nerve activity, inflammatory molecules and infectious agents in hydronephrosis during early and adult age will be addressed. In children with hydronephrosis, we intend to determine if they have increased oxidative stress and/or decreased NO bioavailability and if they develop hypertension and renal disease in later life.

National, prospective studies of children with disorders of sexual development (DSD)

Gillian Barker, Maria Halldin, Agneta Nordenskjöld et al.

Every year, approximately 40 children are born in Sweden with external genitalia that are neither typically masculine nor feminine. The situation is called disorders of sexual development (DSD), and can be caused by a variety of alterations on the chromosomal, gonadal, or phenotypic levels. In this national, multicenter project, the parents of all children born in Sweden with DSD are asked to take part of a prospective study which will follow the treatment and development of the child. The four DSD centers in Sweden (Uppsala, Stockholm, Göteborg, and Lund) are involved in the study. This work has led to collaborative work between the centers including preparation of national clinical guidelines. One collaborative project that has been submitted to ethical committee is a randomized, controlled trial of a free buccal mucosal graft in hypospadias repair.

Long-term effects of endoscopic treatment of high-grade vesicoureteral reflux

Göran Läckgren, Anders Stenbäck, Erik Sköldenberg

Approximately 1% of all children have vesicoureteral reflux (VUR; back-flow of urine from the bladder to the ureter), and half of them develop clinical symptoms of urinary tract infections (UTI) of varying severity. The reflux is graded I-V. In 1993, endoscopic treatment of VUR with dextranomer particles in non-animal hyaluronic acid (Deflux), was introduced. Submucosal injection of Deflux below the ureteral orifice in the bladder reduces VUR and can be done on an out-patient basis. This project addresses the long-term effects of Deflux therapy in children with advanced VUR (grade IV-V) in two cohorts, 1993-1998, and 1998-2003. In the first study, the hospital records (in Uppsala and at their local hospital) of patients treated 1993-2003 (n=222) are reviewed, and parameters such as documented UTI, findings on cystometry, micturition cystograms, and renal scintigraphies, as well as morbidity and intercurrent diseases, are extracted. In the second study, a questionnaire is filled in by, and a telephone interview is performed with the parents or patients with focus on UTI and signs of bladder dysfunction. In the third study, a clinical assessment of the patients is performed at the local hospital, combined with MAG-3 renal scintigraphy to detect residual VUR, and ultrasonography of the kidneys and bladder. In the fourth study, the 54 patients that had residual, symptomatic VUR despite Deflux therapy, and subsequently were subjected to open reimplantation of the ureter(s), will be reviewed and worked-up as the other 222, thereby permitting a head-to-head comparison of Deflux therapy vs. open surgery for the first time. In the fifth study, all the micturition cystograms of all the patients will be reviewed to determine whether the type of VUR or the bladder volume affects Deflux outcome or not. In the sixth and final study, a cost-benefit analysis will compare endoscopic Deflux therapy vs. open surgical reimplantation of ureters. The project will reveal the long-term effects of Deflux against VUR and will identify risk factors for severe UTI, and thereby the possibility to avoid them. The rationale for comparing two cohorts regarding outcome and kidney function is to distinguish between children that need early, active treatment and children that may not need treatment for their VUR at all.

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