

Department of Women's and Children's
Health

ANNUAL REPORT
2012

Introduction

It is a pleasure for me as a chairman to look back at the achievements at the Department of Women's and Children's Health during another successful year. Our department has dedicated researchers, teachers, administrators and laboratory technicians within Obstetrics/Gynecology, Pediatrics and International Maternal and Child Health (IMCH). As is evident from the research reports below there is ongoing collaboration with a great number of national and international research institutions on different projects related to health of women and children in Sweden and globally. The research includes experimental, clinical as well as epidemiological studies. The scientific production during the year has been most satisfactory since 281 articles have been published. The number of PhD students continues to increase and were 105 at the end of the year. Seventeen research students presented their doctoral theses during the year.

Our department has a proud tradition of research within social pediatrics and it is particularly exciting that a new research group, Social Pediatrics, was formed at the beginning of the year. The group, which is being headed by associate professor Anna Sarkadi, has several ongoing lines of research. One of the main projects is related to parenting support interventions. The project is supported by a major grant from FORMAS, FAS, VINNOVA and VR corresponding to 29.4 million SEK during a six years period.

During the year the research group "International Maternal and Reproductive Health" was divided into two new groups, that of "International Maternal and Reproductive Health and Migration", headed by associate professor Birgitta Essén and that of "International Sexual Reproductive Health" headed by associate professor Margareta Larsson. During the year the "National Centre for Knowledge on Men's Violence against Women (NCK) joined the group of "Gynecological Endocrinology" as far as research activities are concerned.

The teachers have made excellent contributions in education during 2012. Our department offers a variety of educational programs, which include graduate courses for medical and nursing students and courses in the laboratory science study program, postgraduate programs for midwives and doctors and several international courses, one of which is a master program in international health. The total number of students at the master program in international health has not decreased after the start of tuition and application fees for students, who are not citizens of the EU/EEA or Switzerland. However, the fees have resulted in a markedly decreased proportion of non-european students. It is certainly important that more scholarships become available for this group of students in the future.

During the year 2012 three appreciated teachers and researchers, Uwe Ewald, Lennart Nordvall and Gunilla Wallin retired. Uwe Ewald has been the head of neonatology at the Children's Hospital for several years and has combined clinical work with a position as an adjunct professor. Lennart Nordvall combined the position as a consultant in pediatric allergology with a position as an adjunct professor and Gunilla Wallin has been a skilled teacher for many years at the pediatric nursing program.

The appointment of a new professor and two senior lecturers during the year gives an important contribution to research and teaching at the department for the coming years. Stefan Swartling Peterson was appointed professor of global health during 2012. His appointment resulted in his return to Uppsala University after several years as a professor at Karolinska institute. Stefan Swartling Peterson, who presented his thesis on iodine deficiency at our department in 2000, was given the alumna of the year award 2012. The recruitment of Eva-Lotta Funkquist and Gunn Engvall as senior lecturers within the pediatric nursing programs will further strengthen the capacity for research and education within caring sciences.

The skilled administrative staff of our department provides high quality administrative support. This makes it possible for our researchers and teachers to concentrate on their most important tasks, research and education.

The department of Women's and Children's Health is closely linked to the University Children's Hospital and the Clinic of Obstetrics/Gynecology. Most of our researchers are also active in clinical work. A continued good cooperation with the clinical counterpart is essential for the mutual benefit of the university and the hospital. It is of particular importance that physicians, nurses and midwives, who are active in research, have the possibility to use research grants and scholarships by being out of clinical service during certain periods of time.

It is most inspiring to be the chairman of such a vital department as Women's and Children's Health. I want to thank all teachers, researchers, administrators and laboratory personnel for their committed work during 2012. Their accomplishments are of great importance for questions related to maternal and child health in Sweden as well as globally. We will continue this important work during the forthcoming years.

Uppsala in April 2013

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

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Organization

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Department board

(from July 2012)

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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
Johanna Belachew	graduate student representative, deputy
Cecilia Lundin	student representative
Ellinor Funegård Viberg	student representative
Johan Skogö	student representative, deputy
Fanny Sundin	student representative, deputy

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Elof Johansson

Gunilla Lindmark

Gudmar Lönnerholm

Gunnar Sedin

Torsten Tuvemo

Director of graduate studies

Lena Hellström Westas

Director of undergraduate studies

Tryggve Nevéus

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Susanne Thorell Löberg

Birgitta Olsson

Martin Selinus

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Kerstin Ståhlberg

Jenny Thor

Karin Törnblom

Computers/IT

Kristine Eklund

Hans Lindgren

Technicians

Eva Davey

Lena Moby

Elisabet Söderberg

Research Groups

Gynecological Endocrinology

Tord Naessén, MD, PhD, Professor

Obstetrical Research

Ulf Högberg, MD, PhD, Professor

Reproductive Biology

Matts Olovsson, MD, PhD, Professor

Reproductive Health

Inger Sundström Poromaa, MD, PhD, Professor

International Child Health and Nutrition

Lars-Åke Persson, MD, PhD, Professor

International Maternal and Reproductive Health and Migration

Birgitta Essén, MD, PhD, Associate Professor, Senior lecturer

International Sexual and Reproductive Health

Margareta Larsson, PhD, Associate professor, Senior lecturer

Pediatric Endocrinology

Jan Gustafsson, MD, PhD, Professor

Perinatal, Neonatal and Pediatric Cardiology Research

Lena Hellström Westas, MD, PhD, Professor

Pediatric Neurology

Gunnar Ahlsten, MD, PhD, Associate Professor

Pediatric Oncology

Susan Pfeifer, MD, PhD, Adjunct Professor

Pediatric Surgery and Pediatric Urology

Rolf Christofferson, MD, PhD, Associate Professor

Paediatric Inflammation

Tryggve Neveus MD, PhD, Associate professor, Senior lecturer

Social Pediatrics

Anna Sarkadi, MD, PhD, Associate professor, Adjunct senior lecture

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

Tryggve Neveus

During 2012, 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 180 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

Obstetrics and Gynaecology within the Medical Programme

Paediatrics within the Medical Programme

(The course in Global medicine, an elective course within the registered Nurse programme and within the Medical programme, is currently not given, due to restructuring of the Medical programme. It will start again in a few years)

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 was extensively revised and restarted in 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 4 years. Both theoretical and practical education, as well as web-based seminars, and seminars using problem-based learning methods are available.

The Laboratory Science Study Programme

The Department of Women's and Children's Health is now supervising the education of laboratory technicians/scientists. The students have courses at the Department during the first and last semester

of the program.

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, Karlstad) for parts of the students' clinical education. The students' rating of the courses have been steadily improving during recent years: the overall ratings of the courses are among the highest of the whole medical study programme.

Research Education

Lena Hellström Westas

The department has extensive PhD education within Paediatrics, Paediatric Surgery, Obstetrics/Gynecology and International Maternal and Child Health (IMCH). During the last two years there has been a continuous increase in the number of doctoral students at the department, and in the latter part of 2012 the number of students steadily remained above 100. Altogether 31 new doctoral students were registered. During 2012 there were 17 dissertations, and 10 half-time seminars as compared to the previous year 9 dissertations and 18 half-time seminars. At the end of the year, 105 doctoral students were registered at the Department of Women's and Children's Health.

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. International doctoral students constitute a substantial proportion of the doctoral students. 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.

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 the mechanisms for effects of environmental pollutants. We also study ovarian follicular fluid content of steroid hormones and proteins with regard outcome of in-vitro fertilization (IVF). We also suggest a new principle for non-invasive assessment of arterial aging/atherosclerosis, based on separate assessment of the artery wall layers, using non-invasive high-frequency ultrasound.

National Centre for Knowledge on Men´s Violence against Women (NCK)

Gun Heimer

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. Website: www.nck.uu.s

Current projects

I: Endogenous sex steroid concentrations in elderly in relations to; health, prevalent conditions (CVD brain volumes and cognition), prediction of CVD events/death and as mediators of negative health effects of environmental pollutants etc

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 etc.

Our results elucidate effects of endogenous steroid hormones (esp. estrogens) which might have implications for understanding parts of the aging process and for future directions and regimens with regard to hormone replacement in elderly.

II: We suggest 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 combined Common Carotid Artery – Intima media Thicknes (CCA-IMT). 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 conditions, including prevalent CVD. We currently evaluate the strength of this principle to predict CVD events in elderly, in monitoring effects of menopausal hormone therapy initiated soon after

menopause, to image effects of anti-estrogen therapy in women with breast cancer and possible differences in effects between aromatase inhibitors and receptor blockers and we study effects of 'ultra-low' vaginal estrogens on the artery wall. We also study possible changes in the artery wall layers during and after normal and pre-eclamptic pregnancies, pre-menopausal women with systemic lupus erythematosus (SLE), recurrent depressions pulmonary hypertension etc.

The suggested principle might be an alternative to the present 'gold-standard, Carotid-IMT (CCA-IMT), for non-invasive assessment of the artery wall with regard to arterial aging, stratification with regard to cardiovascular risk, prediction of CVD events and in monitoring effects of interventions against atherosclerosis/CVD, e.g. statins, menopausal hormone therapy and life-style changes.

III: 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).

The results might help 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.

IV: Pregnancy complications: effects on the artery wall image during and after pre-eclampsia and whether some pregnancy complication might in part be caused by preexisting systemic vascular effects.

Our recent data indicated that normal pregnancy is a 'stress' on the artery system, especially in women who in early pregnancy are older, have a higher BMI or a higher blood pressure. High-frequency ultrasound of the separate artery wall layers, but not CCA-IMT, clearly indicated the known increased risk of cardiovascular disease at diagnosis of preeclampsia as well as one year and more than 10 years after delivery, compared to normal pregnancies. Currently we study whether this method can predict occurrence or pregnancy complications, e.g. preeclampsia, intrauterine growth retardation etc.

The suggested method might become a mean to stratify women with regard to coming cardiovascular risk after e.g. preeclampsia.

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 stimulated ovarian follicular fluid with regard outcome of IVF treatment.

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.

VI (NCK):

A Ph.D. project focused on violence against women, with special reference to sexual violence.

Members of the group

Tord Naessen	Professor; research group leader
Gun Heimer	Professor (NCK)
Britta Nordström	Associate professor
Olle Eriksson	M.D, Ph.D
Gunilla Hallberg	M.D, Ph.D
Tansim Akhter	M.D, Doctoral student
Mariella Öberg	M.D, Doctoral student (NCK)
Jona Kristiansdóttir	MSc, Psychologist, Research student
Marita Larsson	Research nurse

Publications 2010 - 2012

1. Wide L, Naessén T, Eriksson K. Effects of 17 beta-oestradiol and norethisterone acetate on sulfonation and sialylation of gonadotrophins in post-menopausal women. *Upsala Journal of Medical Sciences*. 2010;115(2):97-106.
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Research grants 2012

ALF 634,000 SEK

Selanders foundation 200,000 SEK

Bröstcancerföreningens Riks Organisation (BRO), 200, 000 SEK

The Uppsala County Council research foundation 140,000 SEK

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. In process is establishment of the research database Uppsala Mother-Child Cohort, about 35,000 mother-child pairs, with clinical information from birth, neonatal and child health care linked to the national Swedish Health Registries.

Professor Ulf Högberg joined the group in 2011. His research profile is clinical and reproductive epidemiology. He is head supervisor of Susanne Hesselman and Anna Palm, co-supervisor within the research group, research group of International Maternal Health, KI and Umeå University. Ove Axelsson is senior professor. He is head supervisor for 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. Postdoc in her team is MD, PhD Karin Kårehed. Helena is head supervisor of: Lina Bergman, Lena Liljeström, Karin Lindgren, Evangelia Elenis, Sarah Nordqvist and co-supervisor of Michaela Granfors, Charlotte Hellgren (PhD defence May 2013), Johanna Gunnarsdottir and Helena Kaihola (licentiate examination 2012). She is also co-supervisor for Margit Endler (KI) studying placenta retention and obstetrical outcomes.

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, Johanna Gunnarsdottir 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 She has also started a forthcoming doctoral project with Maria Nelander addressing preeclampsia and the brain function evaluated short-term by MRI and longterm cognitive functions evaluated in the Twin Register.

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 and Susanne Hesselman. 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 who defended her thesis in 2012. 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.

Ph D Thesis 2012: 1) Maria Palm - Oxidative Stress, Angiogenesis and Inflammation in Normal Pregnancy and Postpartum; 2) Marie Bohlin – Pre-eclampsia Possible to Predict. A Biochemical and Epidemiological Study of Pre-eclampsia.

The eleven on-going PhD studies are:

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

Johanna Belachew: Evaluating diagnostic possibilities of 3-D ultrasound for placenta location after earlier cesarean delivery, and placental retention in the postpartum period. Half-time examination planned in 2013.

Michaela Granfors: Studies on epidemiologic and genetic aspects of thyroid disturbances and pregnancy outcome. Half-time examination planned in 2013

Karin Lindgren: Addressing infertility by focusing on causes, diagnosis and treatment. Distinct biological mechanisms that are affected in relation to assisted reproduction are investigated. Planned half-time examination in 2013.

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. Planned half-time examination in 2013.

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.

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.

Johanna Gunnarsdottir: Addressing placental dysfunction disorders addressing immunological and fetal origin aspects by epidemiological methods.

Susanne Hesselman: Cohort analysis of delivery complications to earlier cesarean delivery and surgical technique.

Anna Palm: Assessing a randomized intervention against violence exposure and alcohol abuse for Swedish youth, mixed-methods evaluation for evidence-based practice.

Members of the group during 2012

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
Marie Bolin	M.D, Ph.D
Maria Palm	M.D, Ph.D
Karin Kårehed	MD, Ph.D, postdoc
Helena Kaihola	Research fellow
Johanna Belachew	Research fellow
Michaela Granfors	Research fellow
Lena Liljeström	Research fellow
Karin Lindgren	Research fellow
Sarah Nordquist	Research fellow
Lina Bergman	Research fellow
Evangelia Elenis	Research fellow
Sara Sohlberg	Research fellow
Anna Palm	Research fellow
Susanne Hesselman	Research fellow

Publications 2010-2012

1. Granfors M, Karypidis H, Hosseini F, Skjöldebrand-Sparre L, Stavreus-Evers A, Bremme K, et al. Phosphodiesterase 8B gene polymorphism in women with recurrent miscarriage : A retrospective case control study.. *BMC Medical Genetics*. 2012;13:121-.
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Agencies that support the work (2012)

SLS	50000,00
FPF	70000,00
Gillbergska	50000,00
Allmänna BB	90000,00
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FoU Uppsala/Örebro	350000,00

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, external factors such as IGF1 and gp130 are of importance. 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.

Our ongoing studies using proteomic pattern of embryo development in collaboration with Jonas Bergqvist and Jörg Hanreider, show that the growth factor gp130 seem to be important for embryo development. These studies will be included in Fredwell Hambiliki's thesis work.

To find markers of endometrial receptivity is a main focus. We are using human endometrial cell culture models to study hormonal regulation of the endometrium, most recently in collaboration with Linda Giudice in San Francisco. An 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. For the future, studies on prostasomes and their interaction with endometrial cells will be a new approach to understand endometrial receptivity. Anneli Stavreus-Evers coordinates these studies.

Prostasomes are exosomes secreted from the prostate gland. They contain DNA, mRNA, miRNA and protein, and our studies show that they have the ability to enter both the sperm and somatic cell. It is likely that they are important for implantation, as they can induce processes important for implantation such as angiogenesis. Recently, we also showed that the prostasomes are capable for ATP production. These studies are performed in collaboration with Göran Ronquist, Gunnar Ronquist and Anders Larsson.

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 and our array data show extensive gene expression in endometrium from fertile and infertile women. We can also show that fertility treatment has a negative influence on endometrial receptivity. We have also recently characterized the hormonal profile of women with unexplained infertility. Our studies on predictive factors related to pregnancy outcome show that age is still the best predictor of pregnancy outcome, but that gp130 is a promising candidate. These studies are performed in collaboration with Carlos Simon and Jose Horcajadas in Valencia, Spain and Signe Altmäe. 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.

Low folat levels have been related to fertility problems, our studies show that this can be due to genetic causes. Our studies show that folic acid intake is higher in women with unexplained infertility, and that infertile women with high folate levels have increased chance of becoming pregnant. The 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 Signe Altmäe, Granada Spain and Andres Salumets, Tartu, Estonia.

Recurrent miscarriage is regarded as an infertility problem although most women with recurrent miscarriage usually will become pregnant, which is also seen in our studies. The cause of miscarriage is often aneuploidy but so far, there is no genetic cause found for recurrent miscarriage. 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. In these samples we have shown that most genes are normal but some genes such as Phosphodiesterase 8B is differently regulated in women with recurrent miscarriage. These samples will now be used to study possible genetic factors related to repeated miscarriage. These studies are performed in collaboration with Helena Åkerud, Helena Kaypidis, Britt-Marie Landgren, Inger Sundström Poromaa, Helena Åkerud, Katarina Bremme and Lottie

Care after miscarriage is important as women tend to have more depression and grief after miscarriage. The best way to care for these couples will be included in Caroline Janssons thesis work and are performed in collaboration with Helena Volgsten, Agneta Skoog Svanberg and Kirsten Swanson, USA.

Additional clinical studies from our group show that genetic background can influence outcome after fertility treatment and that adrenomedullin might influence angiogenesis in women with menorrhagia. During fertility treatment we can show that luteal phase support with progesterone increase delivery rate. 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.

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, despite higher than expected estrogen levels. 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

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.

Within the PE-projects we have cooperation with Professor Graham Burton in Cambridge (UK) on placental/trophoblast metabolism. 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.

In a recent study we have tested whether placental pathology varies according to clinical presentation. A negative correlation was found between gestational age at delivery and activation of P-p38 kinase and ER stress markers, including phosphorylation of eukaryotic initiation factor 2 α (P-eIF2 α /eIF2 α), phosphorylation of inositol requiring protein kinase (P-IRE1 α /IRE1 α), activating transcription factor 6 (ATF6), glucose regulated protein 78 (GRP78), and splicing of X-box

transcription factor (XBP-1), with a clear cut-off around 32-34 wk. These findings provide molecular evidence that placental stress is highest in cases of early-onset pre-eclampsia. They support the concept that early-onset pre-eclampsia is predominantly due to placental pathology, while late-onset is likely the result of increased maternal sensitivity to pro-inflammatory factors of pregnancy.

We are currently studying the possible involvement of NT-proBNP in the pathogenesis of PE. Matts Olovsson is coordinating these studies.

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 (HEEC) and that this effect depend on endometrial stromal cells. We have also shown effects of EDCs on HEEC migration and tube formation. 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. Matts Olovsson is coordinating these studies.

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 can show that the quality of life is heavily affected by symptomatic endometriosis. It is also evident that women with symptomatic endometriosis cost about 70 000 SEK/year compared with about 20 000 SEK/year in a age and gender matched background population.

There are also studies of endometrial factors associated with endometriosis related infertility. 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. We have done similar studies on endometrial receptivity markers. Our endometriosis research is done at our National Endometriosis Centre. Matts Olovsson is coordinating these studies.

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). A further reduction in cervical cancer incidence 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, and that self sampling is a reliable sampling strategy compared with samples collected by health care personel.

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. 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. We are currently performing a randomized study to compare repeat HPV testing based on self-collected cervicovaginal samples with cytology screening.

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 studied; measuring anti-Müllerian hormone (AMH), LH and FSH, or estimating the ovarian volume or number of antral follicles. Our latest data show that AMH serves as the best marker of ovarian reserve and also as a prognostic factor of pregnancy and live birth rates. AMH is also a marker for oocyte quality. These studies are coordinated by Jan Holte, Thomas Brodin and Matts Olovsson.

Ovarian cancer

Prognostic factors for epithelial ovarian cancer have been studied. It has been shown that FIGO stage and p53 status alone were independent predictive factors for recurrence and prognostic factors for survival and that p53 bax status was an independent prognostic factor for survival. It has also been shown that a subgroup of patients with predominantly serous tumors with concomitant p21 negativity and p53 positivity had a poor survival. Another subgroup of with non-serous tumors with concomitant p21 and p27 positivity had excellent survival. These studies are coordinated by Ingridur Skirnisdottir.

Members of the group during 2012

Olovsson, Matts	Professor
Bourlev, Vladimir	Professor
Stavréus-Evers, Anneli	Associate professor
Edelstam, Greta	Associate professor
Rezapour, Masoumeh	Associate professor
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Hreinsson, Julius	MD, PhD
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Rumman, Amani	PhD-student
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Iliasova, Natalia	Research student
Norenhag, Johanna	Research student

Rauden, Anna	Research student
Davey, Eva	Biomedical laboratory scientist
Báth, Ann-Sofie	Study nurse
Victoria Engström	Study nurse
Ann Wettervik	Study nurse

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Dissertations 2012

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Research grants > 100 000 during 2012

- ALF, 1 625 000 SEK
- Vinnova/Eurostar 400 000 SEK
- The Family Planning Fund in Uppsala, 155 000 SEK
- Lions cancerforskningsfond, 100 000 SEK

Reproductive Health

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

The PADIA study: Prevalence of posttraumatic stress disorder among women undergoing induced abortion

PI Agneta Skoog Svanberg

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. The PADIA study included approximately 1500 women seeking induced abortion at five out-patient clinics. Results indicate that induced abortion is not associated with risk of developing posttraumatic stress disorder. During the past year data from the study has been compiled and the first paper has been submitted.

The Swedish multicenter study on gamete donation

PI Agneta Skoog Svanberg

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 to study short- and long-term psychosocial consequences of oocyte and sperm donation for the donors as well as the recipients. 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. Long-term follow-up of these subjects will start in January 2013. Nine papers from the study have thus far been published and additional manuscripts are under way.

The JUNO study: Internet-based psychological support following negative or traumatic experiences at delivery

PI Agneta Skoog Svanberg

In Sweden, approximately 100 000 women give birth every year. Obstetric interventions, obstetric complications, a sense of losing control during delivery and inadequate information may contribute to traumatic experiences and subsequent stress symptoms in laboring women. This projects is a longitudinal, randomized controlled trial on internet-based support to women with stress symptoms (anxiety, depression and posttraumatic stress symptoms) following delivery. Endpoints include propensity to request Caesarean section at next pregnancy. During the past year, extensive work has been put into the web-based platform that will be used for the intervention. Pilot study of the project is expected to start in 2013.

Obstetric care in India

PI Agneta Skoog Svanberg

Through a number of national programs, and with the aim of fulfilling the Millennium Development Goals, India has over the past years promoted institutionalized deliveries. By these measures, maternal mortality has been significantly reduced and 80 % of deliveries now take place in the clinic. Together with Indian collaborators this study evaluates quality of obstetric care in India, and women's satisfaction with given care. Qualitative and quantitative data will be collected from public delivery clinics in specific parts of Indian.

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

PI Alkistis Skalkidou

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. All women attending the routine ultrasound examination in gestational week 16 -17 are 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). Blood and tissue samples will be collected from all women at parturition, and a final assessment of all women will be made six months postpartum. The study has thus far included 2400 women and tissue sampling at delivery is obtained in more than 80% of cases. The first manuscript from BASIC has been submitted. Additional studies using placenta samples from BASIC are currently underway. Additional ethical approvals for sub-studies on PCOS, LGA and infertility have been obtained.

The neuroendocrinology of the female brain

PI Inger Sundström Poromaa

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. All women have been included and data analyses are ongoing. Thus far, three studies have been published.

Adverse mood effects on combined oral contraceptives

PI Inger Sundström Poromaa

Adverse mood symptom and sexual dysfunction are common complaints in oral contraceptive users, but no placebo-controlled trials have been performed in this area to establish drug-related causality. We have recently been granted to perform a randomized controlled trial of oral contraceptives and it is expected to start in 2013.

Urogenital symptoms in breast cancer patients on adjuvant endocrine therapy

PI Inger Sundström Poromaa

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.

Cervical cancer

PI Dan Hellberg

In 2012, Professor Dan Hellberg in Falun joined the research group. Professor Hellberg has several research projects ranging from long-term health in participants of the Vasa cross-country skiing race to odontology. However, of importance for the research group, he has extensive experience in the field of cervical dysplasia and cervical cancer. In collaboration with the Human Protein Atlas in Uppsala, new biomarkers for progression of cervical dysplasia are evaluated.

U-CAN Gynecologic cancer

In the beginning of 2012 gynecological cancer was included as a new diagnosis in the U-CAN project in Uppsala. Gynecological cancer includes the diagnoses cervix, endometrial and ovarian cancer. During the first year samples from more than 100 patients have been collected. Samples taken in this diagnosis area include tumor tissues at surgery and blood samples. Tissue samples are biobanked at the pathology unit according to U-CAN routines. Blood samples are collected as research samples and in Cosmic. Clinical data and patient information is stored as quality registry forms from gynecology and pathology, and heredity and health protocols. In addition, detailed information on reproductive history is stored. Karin Stålberg is chairman of the U-CAN gynecology research team.

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Dissertations 2012

Fatimah Dabo: Genetics and Labor Pain Behavior

Sara Sylven: Biological and Psychological Aspects of Postpartum Depression

Elin Bannbers: The Effect of Steroid Hormones in the Female Brain During Different Reproductive States

Research grants > 100 000 SEK

The Swedish Research Council 500 000 SEK (ISP)

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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.

Reducing neonatal mortality

A persistent problem in many countries is a high neonatal mortality, and inequity in neonatal survival chances (5,14,17,28,53). This has been addressed in a collaborative project in the entire Quang Ninh province in Vietnam, where a community-based cluster randomised trial has tested a facilitation approach for improved neonatal health and survival; the NeoKIP trial (57), Neonatal health Knowledge Into Practice, trial registration number ISRCTN44599712. The main outcome of the trial was a reduction in neonatal mortality by half in the intervention clusters (PLOS Medicine, in press, 2013). This project has generated several papers on neonatal health (14,17,27,40,49,53,57,61,63), including three completed PhD theses (Mats Målqvist 2010, Leif Eriksson 2012 and Nguyen T Nga in early 2013). One more PhD student has ongoing studies related to the trial. Sida is the main funder of this project and Swedish Research Council has provided additional funds.

Newborn health care and survival has also been the focus of a just concluded cluster randomized trial, the Uganda Newborn Study (UNEST). Initial publications of protocol (45) and Community Health Worker capacity to recognize Newborn illness have been published (4) and a series of articles are being prepared for a supplement. A further study on scaling up newborn care in seven hospitals in Eastern Uganda has received funding for its pilot from the Einhorn Family Foundation.

In Rwanda an evaluation of the “Helping Babies Breathe” (HBB) training program was performed, showing that such training substantially increased knowledge but that refresher training was needed to sustain skills in the management of newborns with breathing difficulties (34). Studies are ongoing on perinatal audit and risk factors for early neonatal death.

In Nepal there is an ongoing trial on the evaluation of the same simplified neonatal resuscitation protocol (HBB) to improve the perinatal mortality in a tertiary hospital since July 2012 (9). The baseline of the study has been completed. A total of 9575 live births were registered during baseline period with a stillbirth rate of 21/1000 deliveries and an early neonatal mortality rate of 9/1000 live births. The intervention period began in early 2013. The intervention consists of training all health care providers attending births on HBB, development of continuous improvement cycle to implement the HBB protocol and a weekly review of the progress and challenges in implementing HBB. A total of 558 health care providers (doctors, nurses, midwives and nursing students) have been trained on HBB. A quality improvement cycle model was applied to reinforce the training and to improve quality of care.

Short- and long-term effects of improved prenatal nutrition

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 (42). We have also evaluated the effects on child growth (51), micronutrient status in infancy (59), morbidity and psychomotor development. Emma Lindström completed her PhD thesis 2012 based on this cohort studying anaemia and micronutrient deficiencies in pregnancy (52), oxidative stress in pregnancy and birth weight (26) and metabolic markers at 4.5 years. The publications from MINIMat also include risk factors for infant anaemia (48), breastfeeding and

micronutrient status, maternal-infant interaction (13), household food security and child growth and development (65) and violence against women and child growth and morbidity. Ashraful Khan completed his thesis in 2012 studying the impact by the interventions on child growth (51) and body composition (23,24). This also represents research questions related to the DoHAD hypotheses (development origin of health and disease). A follow-up at age 10 years is ongoing 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 and HIV

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 (12,19,20,56,57). Swedish Research Council finances the ongoing studies to our group and Save the Children (US) provides support to our collaborating partners.

Children with fever

In different studies in Uganda the diagnosis and management of children with fever are addressed. During the year we have added to the evidence base, and co-edited a special issue in the American Journal of Tropical Medicine and Hygiene (10,15,29,31). A research prioritization process with worldwide participants (so called CHNRI) is now the next step where we are core members. We have previously contributed to changing WHO/UNICEF and Uganda policy to integrated community case management (iCCM) of Malaria, Pneumonia and Diarrhoea by means of Community Health Workers, which is now expanding through Africa supported by UNICEF, USAID and others. This year we have shown that iCCM may also work in private sector drug shops in Uganda (10), where many sick Ugandan children get treated. This is of immediate policy relevance to, for example, the Global Fund's Affordable Medicine Facility Malaria, a major private sector initiative in nine countries. Together with Makerere University we have acquired funding for further trials from Swedish Research Council and the (WHO affiliated) Alliance for Health Policy and Systems Research.

The "know-do gap" refers to the fact that 2 out of 3 children in the world die unnecessarily – we have the knowledge and resources to prevent or cure them, but it is not translated to action. We have two projects evaluating various forms of "implementation bottleneck analysis" and quality improvement as strategies to improve access to and quality of care. Funded by the European Union and Gates Foundation, respectively, these studies are implemented in Uganda and Tanzania in collaboration with Makerere University, Ifakara Health Institute, Karolinska Institutet and London School of Hygiene and Tropical Medicine. Several publications are foreseen with process and results from these studies in the coming years.

Assessing the context of the health system

We have together with international partners been involved in developing a questionnaire-based tool for assessment of the health system context and the individual health worker's perceptions of aspects regarding different building blocks of the system (11). This Context Assessment for Community Health (COACH) tool was developed in Bangladesh, Vietnam, South Africa, Uganda and Nicaragua and the tool will be finally evaluated and made available in the near future.

Management of severe malnutrition

The development of effective and feasible strategies for prevention and management of severely malnourished children are addressed in studies in Ethiopia and Bangladesh. Baitun Nahar from Bangladesh completed her PhD studies during 2012 analysing the effect of stimulation (play therapy) in addition to food supplementation in the rehabilitation of severely malnourished children (38,39). A PhD student from Ethiopia has completed fieldwork of a qualitative study and an observational study of the effectiveness of community-based rehabilitation of acute severely malnourished children. Sida has supported these studies.

Inequity in health is a major challenge to the global health community and a research priority getting more and more attention. Since 2011 the EPI-4 project has worked for increased capacity to make evidence-informed decisions on policies and implementation for health for disadvantaged groups in relation to MDGs 4, 5 and 6 in China, India, Indonesia and Vietnam. The Vietnam team, consisting of researchers from the National Pediatric Hospital, Uppsala University, and Karolinska Institutet, has been successful in engaging the EPI-4 Vietnam network in applying research to policy for the promotion of equitable health policies. They have several publications in international journals (5,7,8,27,28,44) and have been asked by WHO in Vietnam and the MOH to conduct an intervention study to attempt to reduce inequities in health in disadvantaged populations.

Gender-based violence and child health

The health consequences – also for children – of violence against women (VAW) have been studied in a series of studies. We have shown an association between VAW and size at birth, child growth and morbidity (43,46,62).

The MDGs in local settings

The health-related Millennium Development Goals in Nicaragua were in focus in the thesis by Wilton Pérez, which he defended in 2012. In population-based studies in urban and rural areas the under-five mortality trends were analysed. Community development work were studied with an equity lens showing that the fourth Millennium Development Goal will be met and the social inequalities in survival has decreased in the studied areas. A reduction of poverty with increasing equity was also seen among those receiving rural development interventions (41,54).

Arsenic in drinking water

Due to the discovery of the 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 and we have also contributed to several other substudies dealing with the public health consequences of this environmental catastrophe (16,25,47,55,60,64,66,67,68). We collaborate with ICDDR, Bangladesh and with the department of Metals and Health, Karolinska Institutet.

We are coordinating a research network of Swedish researchers and their international collaborating partners, who focus research on global child health issues – especially research on knowledge implementation into practice for improved child survival. 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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Leif Eriksson. Knowledge translation in Vietnam: Evaluating facilitation as a tool for improved neonatal health and survival. Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 785. Uppsala: Acta Universitatis Upsaliensis 2012.

Baitun Nahar. Effects of Food Supplementation and Psychosocial Stimulation of Growth and Development of Severely Malnourished Children: Intervention Studies in Bangladesh. Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 786. Uppsala: Acta Universitatis Upsaliensis 2012.

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Ashraful Isalm Khan. Effect of Pre- and Postnatal Nutrition Interventions on Child Growth and Body Composition: The MINIMat Trial in Rural Bangladesh. Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 811. Uppsala: Acta Universitatis Upsaliensis 2012.

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Agencies that support the work/Funding

Currently the research program is supported by grants from Swedish Research Council (Vetenskapsrådet), Sida, and Uppsala University. In addition, several international funding agencies support the joint research studies directly to our collaborating partners in low- and middle-income countries.

International Maternal and Reproductive Health and Migration

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.

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

Maternal mortality and severe obstetric morbidity in a globalized world

Maternal mortality is a well-known quality indicator of obstetric care, and maternal near miss is fast gaining interest as a complementary indicator, particularly among vulnerable groups with a lack of social networks in situations of general instability or poverty in low-income settings (Rwanda and Tanzania), or after migration to high resource settings (Sweden, UK). Our current research activities include analyses of maternal and perinatal ill-health in low-, middle- and high-income settings from a migration perspective. Partner's role in the provision of support during antenatal and obstetric decision-making is also explored as an influence on birth outcome barriers. The overall aim is to develop tools for comprehensive maternal health services to women living in underprivileged situations. The research program is interdisciplinary and uses multiple mixed methods, including epidemiological, audit, as well as anthropological methods to define the social and cultural aspects of these medical phenomena.

The significance of these findings yields improved medical and culturally relevant ways to understand and prevent the tragic incidence of maternal or perinatal loss of life. The multidisciplinary group has previously shown effects of ethnic background, suboptimal care and [socio-cultural factors](#), such as [female circumcision](#), on the risk of perinatal mortality and maternal morbidity and results have been implemented in health care practices among ethnic groups in [Latin America](#) and in [Sweden](#). The findings have contributed to theoretical knowledge, but have also been implemented through guidelines in order to reduce health inequalities in an ethnic perspective.

Too many caesarean deliveries challenge Safe Motherhood

There is a global trend of increasing rates of caesarean delivery due to such reasons as medicalization, economic incitements and parental autonomy, whilst from an equity and priority perspective, safe motherhood is not implied. Hospital caesarean section rates of 24 - 75% are reported from Latin America, Asia and Africa. This project is focused on Iran, Nicaragua and Tanzania.

The study designs are hospital based: audits, demographic health surveillance site, interviews of mothers at hospital delivery and follow-up; maternal and child outcomes, including Robson 10-group classification; and sampling of parents and doctors for anthropological interviews to explore decision making, attitudes, birth experiences and health economic analysis.

Genitals, gender and ethnicity: The Politics of Genital Modifications

This study, conducted by an anthropologist and a gynaecologist, aims at reaching an understanding of societal views of the relation between 'sex', 'gender' and genitals, through analysing the political positions that have given rise to decisions to advocate, accept or criminalise certain surgical genital modifications. The phenomena analysed are male and female circumcision, cosmetic genital surgery, hymenoplasty and operations on transsexual adults/intersexual infants. Society's views of these procedures have their own social, medical and political history, and as yet there is no systematic analysis juxtaposing them. The theoretical approach is social constructivist, inspired by gender theory and critical medical anthropology. Empirical data include legislative texts and qualitative interviews with professionals in medicine and with key activists. Through discourse analysis we will explore the social values about 'sex' and 'gender' that are conveyed in legal decisions and medical practice in this field, and in alternative discourses. The study adds to our research about female genital cutting and cosmetic genital surgery. Procedures involving the genitals provide an arena where medicine and culture converge. Understandings of 'sex' are interwoven with politicised socio-cultural constructions of 'gender'. What is 'given by nature' can be modified through surgery, but medical practice itself develops within a norm structure that is time- and culture-bound.

Increased access to comprehensive abortion care – A Partner Driven Cooperation between Uppsala University and Ipas India, 2010-2013

Maternal mortality has decreased in India over the past decade and huge efforts have been put into promoting delivery in the hospital. However, less focus has been put on the deaths from abortions, estimated to account for 20% of the maternal deaths. The purpose of the Partner driven cooperation between the NGO Ipas India and Department of Women's and Children's Health, Uppsala University is to increase access to comprehensive abortion care in the public health system in the states of Maharashtra, Madhya Pradesh and Assam through strengthened partnership between India and Sweden.

The group has several on-going and completed community- and hospital-based projects but all have in common the use of interdisciplinary and mixed methods to define the complexity of reproductive ill-health covering biomedical, social, cultural, gender equality and legal aspects. Studies in the project are; exploring future physician's attitudes and perceptions towards abortion and contraception, health care providers' perceptions on pregnancy and comprehensive abortion care, women's and men's views and perceptions on sexual and reproductive health issues.

Outcomes are sharing of knowledge and experience by the faculty members of the two countries, which will help in enhancing the knowledge base and implementing best practices into the teaching systems. The joint research activities on evaluating attitudes can help to build on the on-going policy work made by Ipas within the country and developing a pool of advocates to influence policy on mid-level providers in abortion services.

Daily life and wellbeing for irregular immigrants in detention centres in three EU countries

Sweden receives a major share group of asylum seekers in the world. In year 2007 the EU member states had together about 3,8 million irregular migrants from countries outside EU. Most of the European countries use detention centres in order to facilitate deportation of irregular migrants who have been captured.

The time spent in the detention unit is important for a detainee as it affects his/her life at present and in the future. The health situation of the detainees, which is already deteriorated, is worsened when they are detained at the detention centres. They need support to handle the stressful situation in the detention. In order to provide this support, an understanding of the detainee's daily life is required.

Most of the EU states use a comparatively similar system for handling irregular immigrants. In this project the system in Sweden, France and the Netherlands will be analysed and compared.

The overall aim of the project is to create a knowledge base for the development of the care of detainees in three EU countries with a focus on the Swedish detention system. The objectives are to: describe how the detainees experience the daily life, well-being and received care; describe the staff's and the volunteer's perspectives on the care of provided for the detainees; compare the experiences of detainees from the three countries; identify factors which support or prevent the well-being of the detainees; develop a model for promoting the well-being for detainees. Qualitative methods are used for the data collection in the project, which is run as a PhD project in the area of International health with the PhD student Soorej Jose Puthooppambal.

Unaccompanied Somali refugee girls in Sweden – a follow-up study

Sweden has received unaccompanied children since the end of 1980ths. During the period 1980 - 2010 around 11000 unaccompanied children arrived in Sweden. The tendency is that this group of children will increase in the future. In the beginning of 1990th the Somali children was the largest group and they still are, together with children from Afghanistan. The majority is boys but one third is girls. The majority of the children have received asylum and have therefore lived their first years as young adults in Sweden. During 1998-1999 we performed a study in Sweden where unaccompanied girls from Somalia were interviewed. They experienced great cultural differences concerning the expectations on girls. They had difficulties to learn Swedish and lack of trust in new people.

The overall aim with this study is to document and to analyse how a group of unaccompanied girls from Somalia look back on their first years in Sweden as young adults. The objectives are to document how they have experienced the reception of the authorities, how they have been received by the Swedish health care system, how they self-rate their own health and how they have developed their social network in Sweden. Their experiences will identify factors important for a good reception and integration. This knowledge can be useful for authorities and caretakers when they plan for other groups of unaccompanied children today and in the future.

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 2012 had focus on culture and SRHR, and gathered around 30 Nordic researchers.

Key words: maternal health care, gender based violence, migration, STD and HIV/AIDS, contraception, abortions, youth health, FGC

Members of the group

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Anna Arvidsson	Doctoral student
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Magdalena Bjerneld	PhD
Ulrika Byrskog	Doctoral student
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Karolinska institutet
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Uppsala universitet, Inst. for folkhälso- och vårdvetenskap
All India Institute of Medical Science and the WHO - collaborating centre in New Delhi
Ipas – Indien
Muhimbili National Hospital, Dar es Salaam, Tanzania
Läkare utan gränser – MSF
National University of Rwanda (NUR)
Umeå University, Public Health and Clinical Medicine
Universidad Nacional Autónoma de Nicaragua UNAN - Leon, Nicaragua
Shahid Beheshti University of Medical Sciences/ Infertility Reproductive Health Research Center

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PhD exam 2012

Pauline Binder

The Maternal Migration Effect. Exploring Maternal Healthcare in Diaspora Using Qualitative Proxies for Medical Anthropology

Agencies that support the work

Swedish International Development Cooperation Agency (Sida)	4 050 600
Vetenskapsrådet	1 849 300
Akademiska sjukhuset (ALF)	1 735 400
Family Planning Foundation	55 000
FAS	1 300 000

International Sexual and Reproductive Health

Margareta Larsson

Sexual and reproductive health and rights (SRHR) are important public health issues and concern women, men and their children throughout the entire life cycle. It is a prioritized area within Swedish bilateral cooperation. This new research group was created during 2012 and studies nutrition, youth health, women's health, as well as care and support related to pregnancy, birth, breast-feeding and parenthood in Sweden and internationally in collaborative projects with researchers in other countries. Many projects are interdisciplinary and have a gender perspective. Four PhD students defended their thesis during 2012 and new doctoral students have been registered.

Reproductive Health and Healthcare are addressed in a number of studies, with a particular focus on quality throughout the continuum of care from home, through the community and on to health services and referral hospitals. An intervention study in Tanzania investigates home based life saving skill education within maternal and new-born care. Other studies in Tanzania are related to the quality of high-risk referrals in rural areas, to dysfunctional labor during childbirth and to the experiences of postpartum care. All studies have the ultimate aim to provide a knowledge base for improved care and support. One project investigates reproductive health risks, gender and women's internal migration in Sri Lanka. Reproductive health in Sweden has been addressed by introducing and evaluating a Reproductive Life Plan. Another study focused on care and prevention in relation to unintended pregnancy and abortion and one study investigated pregnancy childbirth and midwifery care among women with intellectual disability. Fear of childbirth and the relation to caesarean section on maternal request has been investigated among women in Australia and Sweden. Parents' capacity, willingness and experiences of providing Kangaroo Mother Care to their preterm infant was studied in two university hospitals in Sweden. Fetal movements during pregnancy, decision related to foetal diagnostics and the language and communication during the birth process are other aspects under investigation.

Sexual Health and Rights among young people are studied in different contexts. Teenagers' views on contraception and abortion as well as associations between pornography consumption and physical and mental health are studied in Sweden. STI and HIV are threats to sexual health and knowledge, attitudes, behaviors, and prevention were investigated among adolescents in Uganda and among immigrants from countries in sub-Saharan Africa. Gender-based violence is yet another sexual health problem and war rape has been studied in Democratic Republic of Congo in collaboration with the Centre for Gender Research at Uppsala University. Another study investigates health seeking behavior and care of survivors of child sexual abuse and rape in Tanzania.

Nutrition and Women's Health is another focus of the group. Maternal nutrition is essential for reproductive outcome. Randomized trials in Bangladesh are evaluating effects of nutrition interventions in early life on maternal and child health over time, currently pre-puberty. Exclusive breastfeeding promotion in South Africa focus and importance of women's empowerment in infant and young child health and nutrition are studied in Nicaragua and Ethiopia. Another project investigates Jigger infestation; an invisible and neglected public health problem in the East African Region. The use of skin-lightening cosmetics among immigrant women in Sweden is also studied.

Key words: sexual health, youth health, reproduction, pregnancy, childbirth, postpartum, breast-feeding, kangaroo mother care, quality of care, maternal nutrition, gender based violence, STI, HIV/AIDS, contraception, abortion

Members of the group during 2012

Abeid Muzdalifat; Doctoral student
Ahlberg Beth Maina; PhD, Adjunct Professor
Furaha August; Doctoral student
Axemo Pia; PhD
Berglund Anna; PhD
Contreras, Mariela; Doctoral student
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Haines Helen; PhD
Hildingsson Ingegerd; PhD, Professor
Hoque Waheedul; Doctoral student
Höglund Berit; PhD
Jordal Malin; Doctoral student
Kaime-Atterhög Wanjiku; PhD
Kidanto Hussein; PhD
Larsson Margareta; PhD, Associate Professor, Senior Lecturer
Lindmark Gunilla; PhD, Professor emerita
Makenzius Marlene; PhD
Malm Mari-Cristin; Doctoral student
Mattebo Magdalena; Doctoral student
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Dissertations 2012

1. Marlene Makenzius
2. Berit Höglund
3. Wanjiku Kaime Atterhög
4. Emma Lindström

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Pediatric Endocrinology

Jan Gustafsson

In the pediatric endocrinology research group several lines of research are ongoing

Energy substrate metabolism during infancy and childhood

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

Until nutrition by breastfeeding is established the newborn infant has to produce its own glucose particularly to supply the brain with energy. Both infants with high or low birth weight are at risk for neonatal hypoglycaemia as well as metabolic disease later in life. One line of research is directed on energy metabolism in the pregnant woman and the newborn infant by use of stable isotope labelled compounds and gas chromatography-mass spectrometry. By use of a combination of microdialysis and stable isotope technique studies of cerebral glucose metabolism are also performed. Since perinatal asphyxia may influence glucose homeostasis and cerebral glucose consumption in the newborn infant, we investigate glucose production and lipolysis during and following hypothermia in infants with perinatal asphyxia.

Register based studies on fetal origin of adult disease

Maria Lundgren, Inger Wahlström Johnson, Fredrik Ahlsson, Jan Gustafsson

Conditions during fetal life may influence development and morbidity during childhood and adult life. By use of Swedish health registers we study effects of conditions during fetal life and childhood on statural growth, development of obesity, morbidity and intellectual performance. A recently finished study points out an association between overweight/obesity and impaired intellectual performance in young adults, particularly those with a low birth weight. In addition a study on school performance of subjects born preterm is ongoing. A recently published work demonstrates that women treated with mood stabilisers for bipolar disorder has an increased risk of adverse pregnancy and birth outcomes. In a study of term, single births in Sweden, 1973-1982, we investigate long term effects of high birth weight and adult metabolic disease. The registers used are the Medical Birth Register, the Conscript register, the Inpatient Care Register, the Drug Register and the Causes of Death Register.

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 nutrition and growth. Projects related to effects of feeding regimens on growth of infants born premature and/or small for gestational age have been ongoing. During the year a doctoral thesis on the effect of Kangaroo Mother Care has been presented. In another project the development of visual function in very preterm infants (<32 w) is studied.

Mechanisms behind precocious puberty

Lemm Proos, Maria Halldin, Jan Gustafsson

Precocious puberty occurs more frequently in girls than in boys. Girls with myelomeningocele are particularly prone to develop early or precocious puberty. This may lead to practical and psychological problems in addition to those caused by the myelomeningocele. The project aims to identify predictors for development of precocious puberty in case of myelomeningocele as well as other conditions.

Down syndrome

Jan Gustafsson, Åsa Myrelid, Ulrika Wester Oxelgren

In the group we have studied growth and endocrine disease in Down syndrome for several years together with professor Göran Annéren at Department of Immunology, Genetics and Pathology. Data on secretion of growth hormone and effects of growth hormone therapy on growth and psychomotor performance in subjects with Down syndrome have been published earlier. Overweight and obesity are 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 studied mortality and causes of death in Down syndrome. The data shows that infant mortality in Down syndrome has decreased markedly. Median age at death is still increasing and is now close to 60 years. In a doctoral thesis project the association between Down syndrome and ADHD is investigated.

Endocrine consequences of stem cell transplantation

Jan Gustafsson, Per Frisk, Andes Öberg

Children suffering from hematologic malignancies, who undergo stem cell transplantation (SCT), may develop metabolic disease later in life. We have earlier demonstrated that young adult patients who have undergone bone marrow transplantation during childhood have a decreased insulin sensitivity which may be due to an adverse body composition, in turn caused by long-standing growth hormone deficiency. In a recent study on bone mineralisation we found decreased BMD in SCT survivors, which may in part be caused by 25-(OH) vitamin D deficiency.

Growth and endocrine function in eating disorders

Ingemar Swenne

Adequate energy supply is necessary for growth and pubertal development. Eating disorders influence development by effects on metabolism and hormone balance. Models which predict growth and menarche during the treatment of eating disorders have been created. Levels of thyroid hormone and essential fatty acids may influence the expression of the eating disorder. By use of fMRI the arousal response to food stimuli in adolescents with anorexia nervosa is presently being studied in collaboration with professor Helgi Schiöth, Department of Neuroscience.

Childhood obesity

Anders Forslund, Johan Staaf, Jan Gustafsson

Overweight and obesity during childhood represents a major global problem. Several loci connected with obesity and T2DM have been discovered. A majority of these susceptibility loci are connected with pancreatic beta-cell function. Studies of hypersecretion of insulin as a mechanism behind childhood obesity is ongoing together with professor Peter Bergsten at the Department of Medical Cell Biology. Knowledge about how insulin secretion develops over time in individuals who become obese, is essential since a window may exist, during which it is possible to change the insulin secretory pattern.

Energy homeostasis in fatty acid oxidations defects

Maria Halldin, Jan Gustafsson

This project is a collaboration between our department and the department of Clinical Science, Intervention and Technology, Division of Pediatrics, Karolinska Institute. Fatty acid oxidation disorders are inherited diseases, which affect energy production from oxidation of fatty acids. The patients have a risk of hypoglycemia and brain damage. The most common disorder is Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHAD). Within the project growth, energy balance, neurocognitive outcome and long term complications are studied children with LCHAD.

Diabetes

Charlotte Nylander, Ylva Tindberg and Jan Gustafsson

Knowledge about factors which influence treatment adherence is essential in the care of chronically ill adolescents. The association between risk- and protective factors for development of risk behaviour is of particular importance. Detection of concomitant “invisible” disabilities, such as neurodevelopmental problems like ADHD is also essential, since these problems can influence treatment adherence. Within the project the relation between neurodevelopmental problems and disease control is being investigated in patients with type 1 diabetes. The project is performed together with professor Elisabeth Fernell, University of Gothenburg.

Members of the group during 2012

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Pediatric endocrinology publications 2010 - 2012

2012

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Dissertation

Ylva Thernström Blomkvist defended her thesis: Kangaroo Mother Care: Parents' experiences and patterns of application in two Swedish neonatal intensive care units

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Perinatal, Neonatal and Pediatric Cardiology Research

Lena Hellström-Westas

1. Inflammation and neonatal lung injury

Richard Sindelar, Lena Douhan Håkansson, Maria Stålhammar

Acute and chronic lung injury is common in very preterm infants. The underlying mechanisms are only partly understood and include inflammation, oxygen toxicity, and barotrauma from mechanical ventilation. This study investigates migration of inflammatory cells in newborn infants under agarose (simulating tissue migration), migratory influence on respiratory burst, and the receptor expression for adherence, inflammatory state, phagocytosis and migration in response to different inflammatory stimulators encountered in preterm newborn infants with evolving bronchopulmonary dysplasia (BPD).

2. Mechanical ventilation and pulmonary function

Richard Sindelar, Anders Jonzon, Raffaele Dellaca, Chiara Veneroni, Liisa Lehtonen, Hanna Soukka, Linda Wallström

Barotrauma is considered to be a major cause of preterm lung injury. This clinical project investigates effects of different modes of assisted ventilation (intermittent mandatory ventilation, patient-triggered ventilation, proportional assisted ventilation, and neurally adjusted ventilatory assistance [NAVA]) to minimize airway pressure while maintaining adequate ventilation. The effect of end-expiratory pressure on lung mechanics and regulation of breathing during invasive and non-invasive assisted ventilation is studied with forced oscillatory technique and with electrical activity of the diaphragm. A randomized multi center clinical study (Uppsala and Åbo) has received ethical approval and will investigate the early effect on breathing activity and the early ventilatory outcome during nCPAP and non-invasive NAVA in newborn infants born at less than 32 gestational weeks.

3. Early clinical predictors of response to pharmacological treatment of persistent ductus arteriosus in extremely preterm infants

Richard Sindelar, Anders Jonzon, Anders Larsson, Karl Wilhelm Olsson

Newborn infants born before 28 gestational weeks have a high incidence of patent ductus arteriosus (PDA). The postnatal presence of a haemodynamically significant left to right shunt through the duct is associated with a lower survival rate and an increased incidence of intraventricular haemorrhage (IVH), necrotizing enterocolitis, and BPD. We have previously shown that a high maximal flow in ductus arteriosus is associated with successful pharmacological closure of PDA in 22-27 gestational weeks. The present study investigates early haemodynamical effects of PDA in extremely preterm infants by assessing early sequential echochardiographic examinations and biochemical markers for pulmonary circulation and cardiac load. The aim is to elucidate prognostic factors for successful pharmacological treatment with cyclooxygenase inhibitors, and to evaluate new therapeutical approaches for the closure of PDA.

4. Pain assessment of extremely preterm infants during stressful interventions and specifically during eye examination for ROP

Richard Sindelar, Johan Ågren, Josanne Munsters

To assess pain or stress in newborn infants submitted to intensive care is important in view of organ function and specifically brain development. Visual pain assessments are uncertain in newborn infants and therefore new techniques have been developed to continuously monitor pain or stress such as skin conductance measurements (SCM; sweating induced by sympathetic activity), and

tissue saturation by near-infrared spectroscopy. SCM is studied during daily care procedures in an intensive care environment and during potential painful interventions in extremely preterm infants at different postnatal ages, as well as during eye examination for retinopathy of prematurity (ROP). These studies include visual pain assessments (N-PASS), vital organ monitoring, NIRS and skin evaporation. The pain reducing effect of nitrous oxide during ROP examination will also be studied.

5. Heat exchange and fluid balance in extremely preterm infants

Johan Ågren, Laszlo Markasz

These investigations measure heat exchange and fluid balance in extremely preterm infants cared for during different clinical conditions (skin-to skin with parent, incubator, surgery). The aim is to better understand the dynamics of heat and fluid balance in very low birth-weight infants and to better support postnatal circulatory, respiratory and metabolic adaptation. The studies also include assessments of both parental and infant comfort and stress.

6. Maternal, neonatal and long-term effects of delayed versus early cord clamping in healthy preterm infants

Lena Hellström-Westas, Ola Andersson

In this project, 400 healthy women with normal pregnancies were randomized to delayed or early cord clamping after delivery. Infants subjected to delayed cord clamping had higher neonatal haemoglobin, and at four months they had higher ferritin and lower risk for iron deficiency. There was no difference in neonatal bilirubin levels between the groups. Long-term follow up is in progress. There were no effects on maternal haemorrhage from time to cord clamping.

7. Prediction of outcome from early electrocortical activity in very preterm infants

Lena Hellström-Westas, Sverre Wikström

Very preterm infants are at increased risk for developing neurodevelopmental handicaps with life-long consequences. Mechanisms for such brain injury are multifactorial, but a significant proportion of brain injury probably occurs around birth. We continuously record early brain function with amplitude-integrated EEG monitoring and limited channel EEG (aEEG/EEG). Several factors affect early electrocortical activity such as brain injury, carbon dioxide levels, glucose levels and blood pressure. Subclinical seizures are common but their relation to long-term outcomes is not established.

8. Epidemiological research

Fredrik Serenius, Lena Hellström-Westas, Johan Ågren, Annika Öhman, Elisabet Mattsson, Margareta Jennische, Kristina Persson, Gunnar Sedin

This project includes long-term follow up of three cohorts of extremely preterm infants: the national Express study group (infants born 2004-2007), the “1000 gram study” (infants born 1992-93), a regional cohort of infants born in the south of Sweden in 1985-86, and a regional Uppsala cohort of infants born 1986-89, who required neonatal intensive care. This project also includes follow up of high-risk infants, including infants with severe cardiac malformations, and register-based research on neonatal seizures, and effects on mortality and neonatal morbidity of fetal/newborn gender.

Members of the group

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Publications

2012

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Pediatric Neurology

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

Epilepsy

In a population based study of childhood epilepsy a subgroup of children has been investigated and published with the title '10-year follow-up of childhood epilepsy in well-functioning children and adolescents'. This group is now investigated with respect to social and psychological factors. Rolandic epilepsy, the most common type of childhood epilepsies, has been studied from several aspects. A follow-up study to describe oromotor difficulties and dichotic listening test 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.

Follow-up studies of prematurely born infants

We 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 the results will be presented in an article accepted for publication in 2013. The study is still going on and the follow-up investigations of the cohort at the age of 6½ years which started in october 2010 will end december 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 underwent 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 with brain tumours in children and adolescents treated in Uppsala and surrounding regions. One part of both projects is to give a broad description of the initial presentation, clinical course and late effects for all children treated for brain tumours 1995-2006. In the other parts two different kind of low-malignant tumours. neuroglial tumours and low-grade astrocytomas in the posterior fossa. are studied with an emphasis on cognitive late effects and possible methods for intervention

Arthrogryposis

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

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

Rehabilitation

Children with brain tumours, traumatic brain injuries or epilepsy nowadays, to a large extent, survive the injury or illness. Many children, however, demonstrate long-lasting difficulties affecting motor function, cognition and/or behaviour. The aim of the present project is to investigate incidence and prevalence, rehabilitation received, functioning level, as well as activities and limitations in daily life of children with acquired brain injury. Another aim is to create and evaluate a new model of rehabilitation focusing on the needs of children and families in a long perspective.

Members of the group

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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

Lönnérholm, Syvänen, 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.

DNA methylation in pediatric acute myeloid leukemia.

Palle, Nordlund, Bäcklin, Syvänen.

AML has a worse prognosis than ALL. The aim is to study the epigenetics in childhood AML with the Illumina 450 K analyses which gives information of the methylation status in 450.000 CpG sites over the AML cell genome. This data will be analysed comparing the methylation status in different subgroups of AML to outcome and we will also compare AML with ALL. These samples have before been analysed with in vitro drug resistance and the methylation status will also be correlated to this. All samples have been collected in collaboration with the Nordic Society for Pediatric Hematology and Oncology (NOPHO).

Late complications after treatment for childhood cancer

Johan Arvidson, assoc prof. Co-workers: Kay Sundberg, Lena Wettergren, Per Frisk, Anders Öberg, Jan Gustafsson, Jacek Winiarski, Huddinge, Jacek Toporski, Lund, Karin Mellgren, Göteborg, Anders Glomstein Oslo, Marianne Ifversen and Carsten Heilmann Köpenhman, Päivi Lähteenmääki, Turkku, Kim Vettenranta Helsingfors, Cecilia Follin and Eva-Marie Ehrfurt, Lund, Britt Edén Engström, Gustaf Ljungman and Tove Kamsvåg Magnusson, Uppsala.

A longstanding topic has been long term complications in a special cohort of survivors of autologous bone marrow transplantation for haematological malignancies. Studied complications have included both somatic function and quality of life.

Ongoing studies: 1) Psychosocial functioning including sexual functioning 20 years after treatment with autologousbone marrow transplantation for lymphoid malignancies versus first line treatment

without transplantation. 2) Insulin resistance in long-term survivors of allogeneic stem cell transplantation in childhood. 3) Retrospective study of interventions due to decreasing donor chimerism in patients after pediatric allogeneic SCT 4) Retrospective study on outcome after different conditioning regimens used in children with ALL who undergo HSCT. A Nordic study.5) Oral mucositis in children treated with chemotherapy and/or radiation therapy.

Future project: Late complications after treatment with cranial radiation therapy in children with ALL.

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

Per Frisk MD, PhD, assoc professor, Anders Öberg, MD, PhD student

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 patients > 18 years of age who underwent stem cell transplantation in childhood (< 18 years) in Uppsala or Huddinge, Stockholm. Hitherto, 29 patients have been enrolled into the study and 10 patients have completed their investigations.

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, Kamsvåg-Magnusson 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 (grade 4). 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 are 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.

Design and evaluation of care environment and technical tools in pediatric radiotherapy

Engvall et al. Umeå University, Karolinska Institutet Stockholm, and Uppsala University are included in a multicenter study. The Institute of Design, Umeå and Skandion Clinic are co-workers.

The project started 2012, focusing on design and evaluation of care environment and technical tools in Pediatric radiotherapy. The aims are to develop methods and material for pre-treatment information and preparation, develop methods that enable contact between child and parents during treatment, and finally to evaluate these methods to identify which methods that should be implemented in the Skandion clinic.

Implementing a Pediatric Early Warning Score for increased patient safety

Engvall et al.

In order to increase patient safety, a pediatric early warning score (PEWS) is introduced in the daily routine at the medical, surgery, and orthopaedic wards, excluding neonatology, at the University Hospital of Pediatrics in Uppsala (Målqvist&Engvall). The aim is to determine the effect of the implementation of PEWS at the different wards at the hospital. The focus is on both process and outcome variables. The used implementation method is based on a participatory approach. The impact of PEWS on health outcomes among children admitted to the University Hospital of Pediatrics in Uppsala will be investigated.

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 different neuroendocrine markers and proteins in a big clinical material of neuroblastoma and to examine how these proteins are correlated to the tumor stadium, biological markers, prognosis and outcome.

1. The tumors are immunostained for diverse neuroendocrine markers and hormones.

If neuroblastomas express neuroendocrine markers and proteins, it will be able to find new therapy strategies in the future. 2. Blod/serum CgA, CgB och NSE was analyzed in 80 neuroblastoma patients stage I-IV and correlated to stage, prognosis och biological markers. If chromogranin is correlated to stadium, biological markers and outcome it will be possible to use chromogranin as a predictor of outcome and as an early marker in relapse. 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 neural tumors

Pfeifer with collaborators Diaz deStåhl, Johanna Sandgren, Chandrasekhar Kanduri .

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 Karolinska Institute. Using global array and genome-wide sequencing-based analyses, we have found individual tumor-specific aberrations in many pediatric medulloblastomas, necessitating possible individualized therapy in the future.

Studies on the role of noncoding RNA in neural tumors are ongoing, and suggest that nc RNA, originating from the large bulk of nontranscribed DNA, may have key regulatory functions in neuroblastoma and possibly other pediatric neural tumors.

National biobank for pediatric neural tumors

Susan Pfeifer, coordinator.

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 biobank has started 2012. Yearly 60 brain tumor biopsies and 15 neuroblastoma biopsies are expected to be biobanked The aim is to include all biopsied pediatric solid tumors (about 120/year). The purpose of the biobank is to facilitate research leading to improved diagnostics. estimation of prognosis, 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

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Publications

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Pediatric Surgery and Pediatric Urology

Rolf Christofferson

Metabolic balance in children with short bowel syndrome and home parenteral nutrition

Heléne Engstrand Lilja, Stefan Branth, Roger Olsson, Gertrud Angsten

A metabolic balance study in eight children with intestinal failure of different causes was performed. The children stayed 3 days in the hospital, and blood samples for analyses of liver function, acid-base-balance, thyroid function, hormones, glucose, lipids and amino acids were drawn. Loss of nitrogen, fatty acids and different ions were determined in urine and faecal samples. Measurements of bone mineral density was performed with Dual-energy X-ray absorptiometry (DEXA) and basal metabolic rate with indirect calorimetry. The study will give new data on the metabolic balance in children with home parental nutrition due to intestinal failure. The manuscript is in preparation for publication.

Basal metabolic rates in prematurely born babies during postnatal growth

Gertrud Angsten, Roger Olsson, Stefan Branth

The basal metabolic rates in six prematurely born babies have been determined with indirect calorimetry and are correlated to their development in weight and height during their first 6 years of life. The project will give new information on whether the basal metabolic rate can predict the energy demands in prematurely born babies or not.

Gastrostomy tube feeding – a successful therapy

Gertrud Angsten, Johan Danielson, Heléne Engstrand Lilja

In our hospital records, there are over 300 children that have received a surgical gastrostomy for enteral nutrition. We will collect data on their development in weight and height, and send them a questionnaire which questions about complications following surgery and their perceived quality of life. This will hopefully give us information how the procedure can be developed in terms of patient safety, quality of life and cosmesis. The study will be presented as a poster and a scientific paper.

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 comprizes 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.

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 months 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 number of 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 Högborg, 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 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.

A national, prospective study 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 not typically masculine or feminine. This disorder of sexual development (DSD) 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, Uppsala. The lead investigators are Agneta Nordenskjöld and Anna Nordenstam at the Astrid Lindgren Barnsjukhus. This work has led to collaborative work between the centres. One of these is an application to the Ethical Committee has been submitted to carry out a randomized controlled trial of a free foreskin graft in hypospadias repair, which will also be run in 3 centres (Uppsala, Stockholm and Göteborg).

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 (1993-8 and 1998-2003). In the first study, the hospital records (in Uppsala and the local hospital) of patients 1993-2003 (n=214) are reviewed, and parameters such as documented UTI, cystometry findings, micturition cystograms, renal scintigraphies, as well as morbidity and intercurrent diseases, are extracted. In the second study, a questionnaire is filled in by, and 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 52 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 214, 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. The project will reveal the long-term effects of Deflux in VUR, and 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.

Members of the group

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Pediatric inflammation

The Pediatric inflammation research group (PIRG), which was formerly called the research group for general paediatrics, covers a wide field, roughly divided into 6 interrelated subgroups focusing on allergology, pulmonology, rheumatology, gastroenterology, infectious diseases and nephrology.

Current research projects

The allergological research has been focused on asthma. A large cross-sectional survey of patients with asthma and healthy controls (n=532) aged 10-34 years was concluded during the year and data analysis started (MIDAS asthma cohort). Several PhD students both within and outside the department are now working on different parts of the material from this study. We have been involved in a study on adolescents reporting exercise-induced respiratory symptoms (n=150), a collaboration with Ass Prof Margareta Emtner, Dept of Medical Sciences (ANDAS). We are involved in several other larger national and international surveys, where we for example perform blood analyses in our lab (ECRHS, GA²LEN, NOAK, NHANES and more). The group collaborates with Aerocrine AB in the development of a new device for the measurement of exhaled and nasal nitric oxide in preschool children. We have also started studies on food allergy, among which a retrospective survey on acute food hypersensitivity reactions recorded at the Paediatric emergency department can be mentioned.

The group's pulmonological research is focused on cystic fibrosis (CF) and the related disorder primary ciliary dysfunction (PCD). The group participates in an EU-sponsored double-blind study investigating egg yolk-derived immunoglobulin (IgY) as a promising prophylactic treatment of pseudomonas infections. Since pseudomonas infections constitutes one of the most serious complications of CF, and is notoriously difficult to get rid of once established, this non-antibiotic treatment has the potential to greatly reduce morbidity, costs and antibiotic resistance. Different methods to evaluate lung function in CF are developed and nasal nitrous oxide (NO) measurements are evaluated as alternatives to electron microscopy in the diagnosis of PCD.

The main focus of the group's rheumatological research is patients with juvenile idiopathic arthritis (JIA). Potential risk markers are mapped in a large national cohort, European treatment regimens are compared and instruments for the measurement of physical and mental well-being are validated. The faecal micro-flora of JIA patients is evaluated in a population-based sample and compared with healthy children. Furthermore, orofacial signs and symptoms in JIA patients are evaluated in collaboration with a dentist.

Much of the group's gastroenterological research is focused on Crohn's disease. The presence of RNA viruses as a pathogenetic factor is examined retrospectively and prospectively, and the effect of exclusive enteral nutrition is evaluated as a treatment. In two pilot projects, the same therapy is tested against JIA and obesitas. In collaboration with the paediatric surgeons the treatment of enteral dysbiosis is evaluated in children with short bowel syndrome.

Neonatological research within the group is managed by Dr Erik Normann. Psychosocial and medical consequences of separation between newborns and their parents, in collaboration with centers in several other countries. Furthermore, the newborns' gut flora is followed over time and compared to that of their mothers'.

Uppsala University Children's Hospital is, through Dr Tryggve Nevéus, a recognized international centre of expertise in research into nocturnal enuresis. In international guidelines three therapies are recommended as first-line treatment of enuresis: the antidiuretic drug desmopressin, the enuresis alarm and day-time bladder training – i.e. urotherapy. The first two of these methods are evidence-based, whereas urotherapy is not. In a prospective, randomised study we aim to answer the question whether urotherapy is useful or not in this patient group. More than 25% of enuretic children do not respond to any of the standard therapies. In a double-blind, randomised, placebo-controlled, cross-over study we are evaluating whether noradrenergic medication, influencing arousal mechanisms, is useful in therapy-resistant enuretic children.

Active researchers within the group

Tryggve Nevéus, associate professor, senior lecturer

Kjell Alving, professor

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Magnus Borres, professor

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Social Paediatrics

Anna Sarkadi

Child Health Centres service development

Sweden is in the international forefront both in terms of children's rights and the equity of welfare services. For almost three decades there was no apparent need to change service delivery within the child health services. However, society structures as well as macroeconomic and political circumstances imply a need to develop more effective and equitable services. **Thomas Wallby** is the most recent PhD at the department: his work concerns the equity and accessibility of the CHC preventive health services. The contents of the CHC services also need to become increasingly evidence-based. PhD students **Laleh Nayeb** and **Kine Johansen** work directly on improving the evidence-base of child health services through developing better methods for screening of children with language and motor developmental problems, respectively. PhD student **Maria Cederblad** deals with a common issue at the top end of the CHC age-group: nocturnal enuresis where care at the CHC needs to improve to alleviate the social stigma of the condition.

An important question when reforming services is which interventions have effect on the long run. The BiF intervention was conducted in 2000-2004 by the research group and was initiated by **Claes Sundelin**. It consisted of screening for postpartum depression, a sensitivity enhancing curriculum for everyday parent-child interaction (ICDP), language stimulation including three book gifts and materials promoting reading to the child, a booklet about motor development, support of social networks, and client-centred counselling. **Dagmar Lagerberg** and **Margareta Magnusson** are still busy publishing results from the trial – results that affect service provision. In addition, a long-term follow up is now planned of the study, coordinated by research assistant **Lisa Wellander**: we will examine the school results and current health of the now teenage participants.

The senior members of the group, **Monica Östberg**, **Monica Westerlund**, and **Elisabeth Hagelin** are valuable resources and regularly visit the research seminars and participate in discussions on study design and PhD projects.

Costs, reach, and effects of parenting support interventions

Research has shown that there is a strong association between parental behaviour and developmental outcomes in children. Previous studies have shown that when parents are taught strategies that are more consistent, warm, authoritative, moderate and firm in the context of parenting programs, children's rates of problematic behaviours decrease. Several research project in our group therefore concern parenting programs. **Raziye Salari** is looking at factors that influence parents' motives to participate in parenting programs and how that might be influenced. We received major funding for a project on long-term effects of parenting programs as preventive interventions, where **Helena Fabian** is project leader. The study is planned as a quasi-experimental design with three arms: two intervention arms and a comparison condition. The aim of the project is to determine what mix of parenting support interventions will lead to best outcomes on children's mental health on the population level. The intervention is Triple P (Positive Parenting Program) and the two intervention types are universal and universal plus selected intervention, where the latter is more intense and involves identification of vulnerable groups/individuals. **Anna Backman** is project coordinator in both the above projects and **Antónia Tökés** does research administration.

From the parenting literature we also know that harsh and over-reactive discipline correlates with difficulties in marital adjustment. PhD student **Natalie Engsheden** therefore focuses on evaluating preventive couple relationship education aiming to improve couple communication and conflict solving strategies.

In parenting program research the extent of health economic evaluations is limited, nationally as well as internationally. An important focus of our group is therefore to conduct such analyses. **Inna Feldman** leads this research and PhD students **Filipa Sampaio** and **Michael Wells** are involved in this quite ground-braking effort to model long-term effects of early interventions and thus provide decision-makers tools to base investment decisions on.

Another aspect of decision-making is that done before fetal diagnostics by expectant parents. PhD student **Annika Åhman** has adapted and is now testing a web-based decisional aid to improve the chances of fetal diagnostics actually being based on an informed decision.

Child maltreatment and its consequences

The law forbidding corporal punishment passed 1979 reflects the Swedish values and ideologies that recognize children's rights and the importance of meeting their needs. However, the rates of severe forms of physical abuse have been stable since the early 1990s, and there has been an increase in mild forms of physical punishment, such as grabbing or shaking the child, especially in stressful situations, by "average" Swedish parents. **Steven Lucas**, chief medical officer of Child Health Services and **Gabriel Otterman** from the Child Protection Team both do important research on the correlates and consequences of violence exposure in the home, with special focus on bullying and abusive head trauma, respectively. Preschool children are in an especially vulnerable situation when it comes to child maltreatment investigations, as their capacity to communicate their experiences in unaided face-to-face interviews is limited. Two PhD students in the group, **Karin Fångström** and **Pär Bokström** are therefore working on validating a computer-assisted interview called In My Shoes, for use with preschool children.

Research group members 2012

Anna Backman	Project coordinator
Pär Bokström	PhD student
Maria Cederblad	RN, PhD student
Natalie Engsheden	RN, PhD student
Helena Fabian	Postdoc
Inna Feldman	Research fellow
Karin Fångström	Clinical Psychologist, PhD student
Elisabeth Hagelin	PhD
Kine Johansen	Licensed Physiotherapist, PhD student
Dagmar Lagerberg	Docent emeriti
Steven Lucas	M.D., PhD
Margaretha Magnusson	RN, PhD
Laleh Nayeb	Licensed Speach Therapist, PhD student
Gabriel Otterman	M.D., MPH
Raziye Salari	Research fellow
Filipa Sampaio	PhD student
Anna Sarkadi	M.D., PhD, Associate Professor
Claes Sundelin	Professor emeritus
Antónia Tökés	Project Assistant
Thomas Wallby	RN, PhD
Lisa Wellander	Research Assistant
Michael Wells	PhD student
Monica Westerlund	PhD
Annika Åhman	RM, PhD student
Monica Östberg	PhD

Former PhD students (2010-2012)

Christina Stenhammar
Kirsten Holmberg

Publications 2010-2012

2012

1. Abbasian, S. Sarkadi, A. Co-producing parenting support in sparsely populated areas: a successful Swedish example. *Barn* 2012; 30(4):129-148
2. Åhman, A. Lindgren, P, Sarkadi, A. Facts first, then reaction – Expectant fathers' experiences of an ultrasound screening identifying soft markers. *Midwifery* 2012 Oct;28(5):e667-75.
3. Bröms K, Norbäck D, Sundelin C, Eriksson M, Svärdsudd K. A nationwide study of asthma incidence rate and its determinants in Swedish pre-school children. *Eur J Epidemiol.* 2012 Sep;27(9):695-703.
4. Engsheden, N., Sarkadi, A., Fabian, H. Offering Preventive Marital Educational Program (PREP) for Couples During Pregnancy: Self-Selection and Program Effects. *In press Family Relations*
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6. Lagerberg D, Magnusson M. Infant gender and postpartum sadness in the light of region of birth and some other factors: a contribution to the knowledge of postpartum depression. *Arch Womens Ment Health.* 2012 Apr;15(2):121-30
7. Magnusson, Margaretha, Lagerberg, Dagmar, Sundelin, Claes. Organizational differences in early child health care: mothers' and nurses' experiences of the services. *Scandinavian Journal of Caring Sciences*(ISSN 0283-9318) 2012;26:1(161-168)
8. Ostberg M, Rydell AM. An efficacy study of a combined parent and teacher management training programme for children with ADHD. *Nord J Psychiatry.* 2012 Apr;66(2):123-30.
9. Salari, R. & Sarkadi, A. Parenting Scale – which version should we use? *Journal of Psychopathology and Behavioral Assessment.* 2012;34(2):268-281
10. Sampaio, Filipa, Feldman, Inna, Sarkadi, Anna. A Cost-Effectiveness Analysis of the Triple P Program in Uppsala Municipality, Sweden. 5th European Public Health Conference. *European Journal of Public Health* 2012;22:S2:101-101
11. Stenhammar, C. Wells, M. Åhman, A. Edlund, B. & Sarkadi, A. “Children are exposed to temptation all the time” - parents' lifestyle-related discussions in focus groups. *Acta Paediatrica Scandinavica* 2012;101(2):208-15.
12. Wallby T, Modin B, Hjern A. Child health care utilisation in families with young or single mothers in a Swedish county. *J Child Health Care.* 2012 Nov 28. [Epub ahead of print]
13. Wells, M & Sarkadi, A. Do father-friendly parental leave policies promote early father involvement? A review of Swedish fathers' participation in parental leave and child health services. *Journal of Child and Family Studies* 2012;21(1):25-31
14. Widarsson, M. Kerstis, B. Sundquist, K. Engström, G. Sarkadi, A. Support needs of expectant mothers and fathers: a qualitative study. *Journal of Perinatal Education,* 2012;21(1):36–44.

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15. Gottvall M, Tydén T, Larsson M, Stenhammar C, Höglund AT. Challenges and opportunities of a new HPV immunization program perceptions among Swedish school nurses. *Vaccine*. 2011 Jun 20;29(28):4576-83
16. Kristjánsdóttir J, Olsson GI, Sundelin C, Naessen T. Could SF-36 be used as a screening instrument for depression in a Swedish youth population? *Scand J Caring Sci*. 2011 Jun;25(2):262-8.
17. Lagerberg D, Magnusson M, Sundelin C. Child health and maternal stress: does neighbourhood status matter? *Int J Adolesc Med Health*. 2011;23(1):19-25.
18. Lagerberg D, Magnusson M, Sundelin C. Drawing the line in the Edinburgh Postnatal Depression Scale (EPDS): a vital decision. *Int J Adolesc Med Health*. 2011;23(1):27-32.
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21. Stenhammar, C, Bokström, P, Edlund, B, Sarkadi, A. Using different approaches to conducting postal questionnaires affected response rate and cost-efficiency. *Journal of Clinical Epidemiology* 2011; 64 (10):1137-43
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Major research grants

2011-13	<i>National Institute of Public Health</i> . The impact of different marketing strategies on parents' participation in parenting programs. A joint project with Östersund municipality	3 510 000 SEK
2011-13	<i>National Institute of Public Health</i> . Health economic evaluation of parenting programs in the community. A joint project with Västervik municipality	2 795 000 SEK
2012-2018	<i>FORMAS, FAS, VINNOVA, VR common grant for child and youth mental health research</i> . Long-term effects of population-based parenting interventions. Outcomes, costs and benefits	29 400 000 SEK
2012	<i>ALF</i> .	779 000 SEK

2012	<i>Örebro University</i> . Health economic calculations on the national comparison study of parenting programs.	651 800 SEK
2012	<i>Uppsala Municipality</i> . Follow-up of Triple P as parenting support at preschools in Uppsala	225 000 SEK

Dissertations 2012

Thomas Wallby: Lika för alla? Social position och etnicitet som determinanter för amning, föräldrars rökvanor och kontakter med BVC