

# Department of Women's and Children's Health

Annual report 2014

Introduction Uppsala april 2015

During 2014 there was a change of the chairman position at the department of Women and Children Health (WCH) as I suceeded Jan Gustafsson on July 1. It is both a challenge and a privilege to be the Head of such an active and diversified department.

The year 2014 was successful as regards to both science and education. The WCH focuses on areas within Obstetrics/Gynecology, Pediatrics and International Maternal and Child Health. New challenges will always appear but they can be met by our committed researchers and teachers who are supported by our dedicated administrators.

The number of PhD students continues to increase and this means that there will be more publications and dissertations coming out in the following years. As far as research is concerned, it is particularly satisfying to note the continued progress within caring sciences. 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. It is important that more scholarships become available for this group of students in the future.

WCH has a wide range of teaching programs. The students generally give good evaluations of our educational programs. This would not have been possible without the extensive work of our teachers. We also have underlined the important requirement that our teachers are involved in scientific work.

The WCH is a clinical research and educational institution and it is important that there is a good relation and mutual understanding with the OB GYN Department and the Children Hospital of Uppsala. The majority of our lecturers, professors and researchers are working clinically at different levels.

During the year 2014 Lars-Åke Persson retired from his position as professor. He continues to work at the department with research and education matters as a senior professor. The administrator Christina Niska also retired last year and Ove Axelsson continues being a senior professor for another year.

A number of recruitment efforts are under way which will further strengthen research and education at the department. The department has had the pleasure to welcome Kjell Alving, who was appointed professor in airway pharmacology, Helena Åkerud was appointed adjunct professor in obstetrics/gynecology and Gustav Ljungman was appointed adjunct senior lecturer in pediatric oncology. Moreover, Maria Meden was recruited as a new administrator and the recruitment of a new professor in international child health has started.

Finally, I want to thank all teachers, researchers, administrators and laboratory technicians for their outstanding work during the past year.

Agneta Skoog Svanberg Chairman of the the department of Women's and Children's Health

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### Address List

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Eva Bergman Olle Eriksson
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Tina Hansson
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Dan Hellberg
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Paraidhi Jha Kine Johansen

Berit Höglund

Emily White Johansson Jennifer Johnsson

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Malin Jordal Katja Junus Ashish, K.C.

Wanjiku Kaime-Atterhög Helena Kaihola Pia Kalm-Stephens

Tove Kamsvåg-Magnusson

Victoria Karlsson Ylva Fredriksson Kaul Kristiina Kask Ashraful Islam Khan Hans Kollberg Christina Krantz Ingela Kristiansen

Theodora Kallak Kunovac Kristina Bolme Kuhn Merit Kullinger Karin Kårehed Carina Källestål Lillemor Källström Dagmar Lagerberg Birgitta Larsson Margareta Larsson Johannes Leidinger

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Lena Liljeström

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Åsa Lindholm
Gunilla Lindmark
Emma Lindström
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Gustaf Ljungman
Steven Lucas
Staffan Lundberg
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Maria Medeen Christian Moberg Lena Moby

Soheila Mohammadi Kajsa Åsling Monemi Cecilia Montgomery Projestine Muganyizi

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Christina Pedersen Wilton Perez Kristina Persson Lars Åke Persson

Stefan Swartling Peterson

Susan Pfeifer Jenny Pitkänen

Inger Sundström Poromaa

Lemm Proos

Soorej Jose Puthoopparambil

Jessica Påfs

Maria Ekstrand Ragnar

Anisur Rahman

Charlotte Heijkenskjöld Rentzhog

Ingrid Jönson Ring Christine Rubertsson

Mattias Rööst Raziye Salari Raghad Samir Filipa Sampaio Karin Sanner Anna Sarkadi Erica Schytt

Gunnar Sedin, deceased May 2014

Martin Selinus

Katarina Ekholm Selling

Fredrik Serenius

Rubina Shaheen Richard Sindelar Josefin Sjömark Gunnar Sjörs Alkistis Skalkidou Ingiridur Skirnisdottir Sara Sohlberg

Anneli Stavreus-Evers

Arne Stenberg Bo Strömberg Maria Stålhammar Kerstin Ståhlberg Agneta Skoog Svanberg

**Ingemar Swenne** Sara Sylvén Marie Säve

Elisabeth Söderberg Amare Worku Tadesse

Ellen Ternby Elin Ternström

Ylva Thernström-Blomqvist

Jenny Thor

Jenny Thorsell Cederberg

Ylva Tindberg Jill Trenholm Nikolaos Tsolakis Torsten Tuvemo Antónia Tökés Karin Törnblom William Ugarte Helena Volgsten Michelle Voon Anna Wahlberg Åsa Wahlberg Linda Wallström Lisa Wellander

Michael Wells Jan Wesström Maria Wickström Anna-Karin Wikström Ingrid Wikström Johan Wrammert Kjell Wånggren Shirin Ziaei Johan Ågren Annika Åhman Helena Åkerud Anders Öberg Mariella Öberg

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Lars Holmberg Eva-Britta Råssjö

Claes Sundelin

### Organization

### Chairman

Agneta Skoog Svanberg

### **Deputy Chairman**

Matts Olovsson

### **Department board**

(from July 2014)

Agneta Skoog Svanberg chairman

Birgitta Essén teacher representative
Lena Hellström-Westas teacher representative
Carina Källestål teacher representative
Stefan Swartling Peterson teacher representative

Gunn Engvall teacher representative, deputy Matts Olovsson teacher representative, deputy

Martin Selinus representative for technical/adm. personnel

Karin Törnblom representative for technical/adm. personnel, deputy

Anna Wahlblerg graduate student representative

Maria Stålhammar graduate student representative, deputy

Sara Bergman student representative Ulrika Hämberg student representative

Vacant student representative, deputy

### **Professors** emeriti

Mehari Gebre-Medhin Yngve Hofvander Elof Johansson Gunilla Lindmark Gudmar Lönnerholm Gunnar Sedin Torsten Tuvemo

### Director of graduate studies

Lena Hellström Westas

### **Director of undergraduate studies**

Tryggve Nevéus

### Administration

Hanna Andersson Cristina Niska Bachelet Malin Ghanem Gunilla Hedén Susanne Thorell Löberg Maria Medeen Martin Selinus Marie Säve Kerstin Ståhlberg Jenny Thor Karin Törnblom

### Computers/IT

Kristine Eklund Hans Lindgren

### **Technicians**

Eva Davey Lillemor Källström 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

Gustaf Ljungman, MD, PhD, Associate Professor

Pediatric Surgery and Pediatric Urology

Rolf Christofferson, MD, PhD, Associate Professor

Paediatric Inflammation

Kjell Alving, PhD, Professor

Child Health and Parenting Research Group

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

### Scientific Reports

### **Gynecological Endocrinology**

### Tord Naessén

With extensive inter-disciplinary collaborations our research group address: Effects of endogenous and exogenous steroid hormones with regard to the aging process in elderly, e.g. arterial aging, cardiovascular disease (CVD), cognition / brain volumes and survival. Environmental pollutants in elderly and possible associations to age-related diseases and whether these effects might be partly mediated via endogenous sex hormone levels. We also study premenstrual syndrome (PMS/PMDD), vascular effects of pre-eclampsia and the ovarian follicular fluid content of steroid hormones and proteins with regard outcome of in-vitro fertilization. We suggest and evaluate a new principle for non-invasive assessment of arterial aging/atherosclerosis, based on separate assessment of the artery wall layers by using non-invasive high-frequency ultrasound (20-50 MHz) and which we apply in many of the conditions mentioned above.

### 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: <a href="https://www.nck.uu.se">www.nck.uu.se</a>

### Members of the group during 2014

Tord Naessen Professor

Gun Heimer Professor (NCK)

Hannes Bohman Post doc.
Olle Eriksson M.D, Ph.D
Gunilla Hallberg M.D, Ph.D.
Tansim Akhter M.D, PhD

Mariella Öberg M.D, Doctoral student (NCK)

Jona Kristiansdottir M.Sc, Psychologist, Research student

Marita Larsson Research nurse

### Publications 2012-2014 (last 3 years)

- 1. Akhter T, Wikström A, Larsson A, Naessen T. Changes in the Artery Wall Layer Dimensions in Women with Preeclampsia: An investigation using non-invasive high frequency ultrasound. Acta Obstetricia et Gynecologica Scandinavica. 2012;91:28-28.
- 2. Comasco E, Hallberg G, Helander A, Oreland L, Sundelin Wahlsten V. Alcohol Consumption Among Pregnant Women in a Swedish Sample and Its Effects on the Newborn Outcomes. Alcoholism. 2012;36(10):1779-1786.
- 3. Kushnir M M, Naessén T, Wånggren K, Rockwood A L, Crockett D K, Bergquist J. Protein and Steroid Profiles in Follicular Fluid after Ovarian Hyperstimulation as Potential Biomarkers of IVF Outcome. Journal of Proteome Research. 2012;11(10):5090-5100.
- 4. Frisk P, Arvidson J, Larsson M, Naessén T. Risk factors for cardiovascular disease are increased in young adults treated with stem cell transplantation during childhood. Pediatric Transplantation. 2012;16(4):385-391.
- 5. Eriksson O, Landén M, Sundblad C, Holte J, Eriksson E, Naessén T. Ovarian morphology in premenstrual dysphoria. Psychoneuroendocrinology. 2012;37(6):742-751.
- 6. Comasco E, Hallberg G, Helander A, Oreland L, Sundelin-Wahlsten V. Alcohol consumption among pregnant women in a Swedish sample and its effects on the newborn outcomes. Alcohol Clin Exp Res. 2012 Oct;36(10):1779-86.

- 7. Naessén T, Bergquist J, Lind L, Kushnir M M. Higher endogenous estrogen levels in 70-year-old women and men: an endogenous response to counteract developing atherosclerosis? Menopause. 2012;19(12):1322-1328.
- 8. Kristjansdottir J, Olsson GI, Sundelin C, Naessen T. Self-reported health in adolescent girls varies according to the season and its relation to medication and hormonal contraception--a descriptive study. Eur J Contracept Reprod Health Care. 2013 Oct;18(5):343-54.
- 9. Akhter T, Larsson A, Larsson M, Wikstrom AK, Naessen T. Artery wall layer dimensions during normal pregnancy: a longitudinal study using noninvasive high-frequency ultrasound. Am J Physiol Heart Circ Physiol. 2013 Jan 15;304(2):H229-34.
- 10. Akhter T, Wikstrom AK, Larsson M, Naessen T. Individual common carotid artery wall layer dimensions, but not carotid intima-media thickness, indicate increased cardiovascular risk in women with preeclampsia: an investigation using noninvasive high-frequency ultrasound. Circ Cardiovasc Imaging. 2013 Sep;6(5):762-8.
- 11. Bergman L, Akhter T, Wikstrom AK, Wikstrom J, Naessen T, Akerud H. Plasma levels of S100B in preeclampsia and association with possible central nervous system effects. Am J Hypertens. 2014 Aug;27(8):1105-11.
- 12. Akhter T, Larsson M, Wikstrom AK, Naessen T. Thicknesses of individual layers of artery wall indicate increased cardiovascular risk in severe pre-eclampsia. Ultrasound Obstet Gynecol. 2014 Jun;43(6):675-80.

### **NCK** publications

- 13. Oberg M, Stenson K, Skalkidou A, Heimer G 2014 Prevalence of intimate partner violence among women seeking termination of pregnancy compared to women seeking contraceptive counseling. Acta Obstet Gynecol Scand 93:45-51.
- 14. Heimer G, Andersson T, Lukas S. Våld och hälsa en befolkningsundersökning om kvinnors och mäns våldsutsatthet. Uppsala universitet, NCK-rapport 2014:1.
- 15. Heimer G, Björck A, Kunosson C. Våldsutsatta kvinnor samhällets ansvar. Tredje upplagan av NCK:s lärobok, Studentlitteratur.

### Agencies that support the work/Funding

ALF, 800,000 SEK

Selanders foundation, 160,000 SEK

# 1. Endogenous sex steroid concentrations in elderly in relations to; prevalent age-related conditions (e.g. arterial aging, cardiovascular disease (CVD), brain volumes and cognition) as well as prediction of CVD events/death and as potential mediators of 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 as well as to arterial aging, assessed by high-frequency ultrasound (20 - 50MHz). Both findings most likely represent an endogenous attempt of 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 might elucidate effects of endogenous steroid hormones (esp. estrogens) on the aging process and thus guide the tailoring of hormone therapy regimens in elderly to hopefully reduce/modify some agerelated changes/diseases.

## 2. Suggestion and evaluation of 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 Thickness (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 preferable, compared to assessment of the total CCA-IMT, in imaging arterial effects of aging and menopausal hormone replacement (15), and cardiovascular risk factors and the prevalent CVD. Further, the suggested principle was preferable to CCA-IMT in imaging vascular effects of systemic lupus erythematosos, recurrent depressions in adolescents and effects of both normal pregnancy and pre-eclampsia

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). We also study possible vascular effects of 'ultra-low' local vaginal estrogens, pulmonary hypertension as well as obstructive sleep apnea

The suggested principle might become an alternative to the present 'gold-standard, 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.

### 3. Pregnancy complications: signs of artery wall aging during and after preeclampsia and whether some pregnancy complication might in part be caused by preexisting maternal vascular effects.

Our recent data indicated that normal pregnancy is a 'stress' on the artery system, especially n 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. preelampsia, intrauterine growth retardation etc.

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

### 4. 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 (PMDD). 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

### 5. Recurrent depressions in the adolescence and metabolic consequences later in life.

Prevalence of self-rated health in school children with regard to sex and seasonality are studied. A large prospective population-based cohort of adolescents, with and without a history of recurrent depressive periods during adolescence, has been followed up for 20 years. Associations to metabolic consequences, including arterial aging and inflammation markers are analyzed. Pilot results indicate negative effects with regard to arterial aging in early adult life in subjects with a history of recurrent depression in adolescence.

## 6. 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 aromatize enzyme function, which might be the background for the arrest in follicular development/anovulation in women with PCOS. Currently we study steroid hormones and proteins in stimulated ovarian follicular fluid with regard to 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. If proven useful, these methods might be applied more broadly when mass-spectrometry methods become easily available at university hospitals.

### 7. Violence against women (NCK project).

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

### **Obstetrical Research**

### **Ulf Högberg**

### Members of the group during 2014

Ove Axelsson Professor
Ulf Högberg Professor
Helena Åkerud Professor

Ulf Hanson Associate professor Solveig Lindeberg Associate Professor Anna-Karin Wikström Associate Professor

Hashem Amini M.D, PhD Eva Bergman M.D, PhD Annika Esscher M.D, PhD Karin Eurenius M.D. PhD Maria Jonsson M.D, PhD Peter Lindgren M.D, PhD Ajlana Mulic-Lutvica M.D, PhD Marie Bolin M.D, PhD Maria Palm M.D, PhD

Karin Kårehed MD, PhD, postdoc Marija Simic MD, PhD, postdoc

Sarah Nordquist MD. PhD Johanna Belachew Research fellow Lina Bergman Research fellow Evangelia Elenis Research fellow Michaela Granfors Research fellow Johanna Gunnarsdottir Research fellow Susanne Hesselman Research follow Helena Kaihola Research fellow Lena Liljeström Research fellow Karin Lindgren Research fellow Maria Nelander Research fellow Anna Palm Research fellow Ellen Ternby Research Fellow

Linda Lindström Research fellow (in preparation)
Christopher Eriksson Research fellow (in preparation)

Research fellow

Research fellow

#### PhD students:

Sara Sohlberg

Åsa Wahlberg

- 1. Johanna Belachew: Retained placenta and postpartum haemorrhage. Planned thesis defence in 2015.
- 2. Michaela Granfors: Hypothyreosis and pregnancy. Planned thesis defence in 2015.
- 3. Karin Lindgren: Infertility, biological mechanisms, diagnosis and treatment. Planned thesis defence in 2015.
- 4. Sara Sohlberg: Placental function an epidemiological and magnetic resonance study. Planned thesis defence in 2015.
- 5. Evangelia Elenis: Portraying pregnancy through oocyte donator from a genetic, molecular and clinical perspective. Planned half-time examination in 2014.
- 6. Lina Bergman: Cerebral biomarkers in preeclampsia. Planned half-time examination in 2015.
- 7. Lena Liljeström: New perspectives on fetal scalp blood sampling

- 8. Johanna Gunnarsdottir: Epidemiological studies of placental dysfunction disorders.
- 9. Susanne Hesselman: Maternal complications of abdominal delivery Planned half-time examination in 2015
- 10. Anna Palm: Adolescent's somatic and mental health in association to violence exposure and risk-consumption of alcohol, a randomized intervention at Youth Clinics. Planned half-time examination in 2015
- 11. Åsa Wahlberg: Severe obstetric events and posttraumatic stress-reactions among obstetricians and midwives. Planned half-time examination in 2016
- 12. Maria Nelander: Preeclampsia and the brain Planned half-time examination in 2015

### **Publikations (2012-2014)**

### 2014:

- 1) Ahman A, **Axelsson O**, Maras G, Rubertsson C, Sarkadi A, **Lindgren P**. Ultrasonographic fetal soft markers in a low-risk population: prevalence, association with trisomies and invasive tests. Acta Obstet Gynecol Scand. 2014 Apr;93(4):367-73.
- 2) Akther T, **Wikström A-K**, Larsson M, Naessen T. Thicknesses of individual layers of artery wall indicate increased cardiovascular risk in severe pre-eclampsia. Ultrasound in Obstetrics and Gynecology. 2014 Jun;43(6):675-80.
- 3) Baba S, **Wikström A-K**, Stephansson O, Cnattingius S. Changes in snuff and smoking habits in early pregnancy and risks of stillbirth and early neonatal mortality. Tobacco research. 2014. Jan 16 (1):78-83
- 4) **Belachew J**, Cnattingius S, Eurenius K, **Lutvica A**, **Axelsson O**, **Wikström A-K**. Risk of retained placenta in women previously delivered by caesarean section: a population-based cohort study. BJOG. 2014. Jan 121(2):224-9.
- 5) **Bergman L**, Naessen T, **Wikström A-K**, Wikström J, Akther T, Å**kerud H**. Plasma Levels of S100B in Preeclampsia and Association with CNS affection. American Journal of Hypertension. 2014 Aug;27(8):1105-11
- 6) Blom H, **Högberg U**, Olofsson N, Danielsson I. Strong association between earlier abuse and revictimization in youth. BMC Public Health. **2014** Jul 14;14:715. doi: 10.1186/1471-2458-14-715.
- 7) Ekéus C, **Högberg** U, Norman M. Vacuum assisted birth and risk for cerebral complications in term newborn infants: a population-based cohort study. BMC Pregnancy and Childbirth 2014, **14**:36 doi:10.1186/1471-2393-14-36
- 8) **Elenis E**, Lindgren KE, Karypidis H, Skalkidou A, Hosseini F, Bremme K, Landgren BM, Skjöldebrand-Sparre L, Stavreus-Evers A, Sundström-Poromaa I, Åkerud H. The histidine-rich glycoprotein A1042G polymorphism and recurrent miscarriage: a pilot study. Reprod Biol Endocrinol. 2014 Jul 27;12:70.
- 9) Endler M, Saltved S, Cnattingius S, Stephansson O, **Wikström A-K**. Retained placenta is associated with pre-eclampsia, stillbirth, giving birth to a small-for-gestational-age infant, and spontaneous preterm birth: a national register-based study. BJOG. 2014 Nov;121(12):1462–1470
- 10) **Esscher A,** Binder-Finnema P, Bødker B, **Högberg U**, **Mulic-Lutvica A**, Essén B. Suboptimal care and maternal mortality among foreign-born women in Sweden: maternal death audit with application of the 'migration three delays' model. BMC Pregnancy Childbirth. 2014 Apr 12;14:141. doi: 10.1186/1471-2393-14-141.
- 11) Fadl H, Magnuson A, Östlund I, Montgomery S, **Hanson U**, Schwarcz E. Gestational diabetes mellitus and later cardiovascular disease: a Swedish population based case-control study. BJOG. 2014 Nov;121(12):1530-6. doi: 10.1111/1471-0528.12754. Epub 2014 Apr 25.
- 12) Fottrell E, **Högberg** U, Ronsmans C, Osrin D, Azad K, Nair N, Meda N, Ganaba R, Goufodji S, Byass P, Filippi V. A probabilistic method to estimate the burden of maternal morbidity in resource-poor settings: preliminary development and evaluation. Emerg Themes Epidemiol. 2014 Mar 13;11(1):3. doi: 10.1186/1742-7622-11-3.
- 13) Granfors M, Åkerud H, Skogö J, Stridsberg M, Wikström A-K, Sundström-Poromaa I. Detection

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### Awards 2014

Susanne Hesselman, Best oral presentation NFOG Congress 2014. Johanna Gunnarsdottir, Best Obstetric presentation & Annika Esscher, Best Poster, Swedish Society of Gynecology and Obstetrics Annual meeting.

#### PhD D Thesis 2014

Sarah Nordqvist: Biological Markers of Fertility

Half-time examinations 2014

Johanna Belachew, Michaela Granfors, Karin Lindgren, Sara Sohlberg,

Half-time examinations 2014

Lena Liljeström

### Agencies that support the work (2014)

SLS	163 000
Familjeplaneringsfonden	100 000
Spädbarnsfonden	20 000
Gillberska stiftelsen	40 000
Jerringfonden	30 000
Födelsfonden	300 000
Fou Uppsala/Örebro	615 000
Brottsofferfonden	480 000
AFA	2 000 000
VR	3 500 000

The overall research theme is human reproduction from conception to birth adding knowledge about adverse outcomes why, how and then. The research group is developing an integrative approach in a life course perspective from the womb to child and young adult's health with the ultimate aim to improve reproductive health. The research methods are translational, experimental clinical and reproductive epidemiology.

Senior professor Ove Axelsson has research profile in perinatal, obstetrical and clinical research and head supervisor for Johanna Belachew. Professor Ulf Högberg, head of the research group, has a research profile is clinical and reproductive epidemiology integrating Swedish and low-income country research settings. Professor Helena Åkerud has a broad translational research profile in infertility, gynecology and obstetrics. Associate professor Anna-Karin Wikström has a research profile in clinical and reproductive epidemiology and experimental design. PhD Maria Jonsson's research profile clinical obstetric epidemiology addressing fetal and maternal and complications as asphyxia, metabolic acidosis and complications of abdominal delivery. In 2015 she will qualify as an associate professor. Associate professor Ulf Hanson has a research profile in clinical and epidemiologic research.

The Obstetric research group has extensive collaboration with other research groups in the department: Reproductive Biology, Gynecological Endocrinology, Reproductive Health, International Child Health and Nutrition, International Maternal and Reproductive Health and Migration, Perinatal Neonatal and Pediatric Cardiology, Social Pediatrics.

One core theme in the research group is short- and long term follow-up of the child after fetal and birth exposure. Together with two research groups Reproductive Biology and Reproductive Health we are responsible for an ongoing collection of plasma and leucocyte samples from women pregnant at about I8 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. Helena Åkerud and Ulf Högberg are in the steering group of the BASIC- Biobank (Research Group Reproductive Health) collecting prospectively maternal blood samples, salivary cortisol and samples from placenta in association to maternal and child mental health. In 2014 a research database Uppsala Mother-Child Cohort has been created, with Ulf Högberg as principal investigator. It is comprising 35,000 mother-child pairs, with clinical information from birth, neonatal and child health care linked to the national Swedish Health Registries. Analysis of fetal exposure as preeclampsia, diabetes, maternal mental disease and psychotropic, to child growth deviations, visits to children's psychologists are in process. In 2013, Ulf Högberg principal

investigator and in collaboration Neuroscience/Children psychiatry, pregnancy cohorts in Nicaragua (in collaboration with UNAN-Léon University) and Ethiopia (in collaboration with Addis Ababa University) have been revisited 9-10 years after birth addressing mental health among the mothers and their off-springs. In 2014 a new project has been planned with the aim to follow up mothers and their offspring who were part of the NICHD Scandinavian Successive Small-for-Gestational Age Births Study during the years 1986-88 (all together 5,722 pregnancies, where of 2,623 from Uppsala). The project is in collaboration with Professor Geir Jacobsen and co-workers at NTNU, Trondheim. Responsible researchers at Uppsala University are Ulf Högberg, Anna-Karin Wikström and Mia Ramklint, associate professor, children and adult psychiatrist. The objective of the study is to analyse the physical and mental health in the mothers and the offspring after being exposed to birth of a SGA infant, preterm birth and/or preeclampsia. Especially the relation between the pregnancy complications and the development of Attention Deficit Hyperactivity Disorder (ADHD) and autism spectrum disorder (ASD) will be examined. The project includes follow up in the national registers and with questionnaires and clinical examinations.

Ove Axelsson is head supervisor for Johanna Belachew.

In 2014 Helena Åkerud was appointed as professor. 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. Helena Åkerud was head supervisor of Sarah Nordqvist defending her thesis in 2014. She is head supervisor of Lina Bergman, Helena Kaihola, Lena Liljeström, Karin Lindgren, Evangelia Elenis, and deputy supervisor of Michaela Granfors, Johanna Gunnarsdottir, Maria Nelander and Margit Endler. Postdoc in her team is Karin Kårehed.

Anna-Karin Wikström focuses on placental dysfunctional disorders, with preeclampsia as the main focus. She has since her postdoc period at Clinical Epidemiological Unit at Karolinska Institutet has developed a close collaboration with the unit, particularly with professor Sven Cnattingius and MD, PhD Olof Stephansson. She is now extending her research lines within one of the core themes of the research group, long-term follow-up of the mother-child dyad. Wikström is tutoring a post doc at the unit, MD Marija Simic, who is working with a database including longitudinal collected blood pressure measurements from almost 200,000 pregnancies. In 2014 she became an invited member in the international Eurotox, a recently founded expert group in preeclampsia with regular meetings. Wikström has an extensive Nordic collaboration: 1) Addressing maternal long-term follow-up cross generations from joint Swedish and Norwegian Birth and Patient Registries (Professor Rolv Skjaerven, Global Public Health and Primary Care, Bergen University); 2) Polycystic ovarian disease and pregnancy outcome (professor Eszter Vanky, NTNU); 3) PI for Swedish part of the IPPH Nordic study: Immigrant Perinatal and Placental Health - A joint Nordic population-based register study from Denmark, Finland, Norway and Sweden (professor Annetine Staff, Oslo University). In 2014 the network on clinical studies in obstetrics and gynecology (SNAKS) was started and Anna-Karin is in the steering committee of the network. The first study planned within the network is a nation-wide study of management of post-term pregnancy. Anna-Karin is also in the steering committee of that study. Anna-Karin Wikström is principal supervisor of the PhD students: Sara Sohlberg, Johanna Gunnarsdottir, Michaela Granfors and Maria Nelander. One new PhD project has started during 2014 focusing on intrauterine growth restriction. The project is in collaboration with Eva Bergman (MD, PhD) and Linda Lindström is in registration as the PhD student (Anna-Karin as head supervisor). Within the project a new national reference curve for fetal growth and birth weight based on ultrasound measurements will be created, with Eva Bergman as the responsible investigator. Anna-Karin Wikström is also deputy supervisor of Lena Liljeström, Katja Junus (Pro-BNP in preeclampsia, Research Group Reproductive epidemiology) and Patricia Eckerdahl (Pregnancy complications and postpartum depression, Research Group Reproductive Health) at Uppsala University and Margit Endler (Placental retention) and Siavash Maghsoudlou (Pregnancy complications in Golestan) at Karolinska Institutet. Anna-Karin Wikström has further collaborators also with other departments, particularly in the magnetic resonance

studies of the placenta and the brain during preeclampsia (MD, PhD Johan Wikström and PhD Jan Weis). In 2014 the Obstetrical research group (Anna-Karin Wikström, Ajlana Lutvica, Karin Eurenius) has in collaboration with professor Inger Sundström-Poromaa (Reproductive Health) started a new project on obesity and pregnancy complications. The main aim is improved risk assessments of obese women in obstetric care by development of risk scores for any obesity-related adverse outcome that may have repercussions for the short- and long-term morbidity of the mother and her infant. Secondary aims are to study the endocrine consequences of obesity during pregnancy and the gene-environmental interaction in the interplay between obesity and pregnancy complications.

Ulf Högberg is principal investigator of a study initiated in 2014 about second victim addressing posttraumatic symptoms among obstetricians and midwives after severe events in maternity care in collaboration with department of Neuroscience /Psychiatry, Uppsala University, LIME/Medical Management Centre, Karolinska Institutet, Social medicine and global health, Lund University. A new projected started by Högberg in 2014 addressing perinatal differential diagnostics to shaken baby syndrome (SBS)/abusive head trauma (AHT). Högberg is head supervisor of Susanne Hesselman, Anna Palm and Åsa Wahlberg, deputy supervisor at the departments of Clinical science/obstetrics & gynecology (planned thesis defence in 2015) and Public Health/Epidemiology & Global Health (planned thesis defence in 2015), Umeå University, and one PhD project exploring patient safety in perinatal care at Department of Clinical Science and Education, Unit of Obstetrics and Gynecology (Southern Hospital, KI (planned thesis defence in 2015). A new PhD candidate, Sibone Mocumbi, University Eduardo Mondlane (UEM), was initiated in 2014 addressing unmet and met needs of obstetric services in Mozambique and to deepen the understanding of how local health system contextual factors influence the provision of these services. PhD registration will follow in 2015 with Högberg as main supervisor, and as deputy supervisor Anna Bergström (Research Group International Child Health and Nutrition), in collaboration with UEM and KI.

Maria Jonsson is deputy supervisor for Lena Liljeström, Susanne Hesselman and Åsa Wahlberg. She is also principal investigator for two clinical multicenter RCT: s that are conducted at the delivery ward, Akademiska hospital, one national and one international trial.

PhD Peter Lindgren's research area is ultrasound and MR, starting a comparative study on MR, ultrasound and MR for fetal malformation diagnostics, and supervising the PhD candidate Christopher Falkeby. Lindgren was co-supervisor for Annika Åhman defending her thesis in 2014. PhD Ajlana Lutvica is deputy supervisor of Johanna Belachew and Sara Sohlberg.

Associate professor Ulf Hanson has been continuing his studies on diabetes during pregnancy in collaboration with KI and Örebro university: 1) the effect of overweight and obesitas in the outcome of GDM women; 2) national register studies of outcome of pregnancies complicated by type-1-diabetes, type-2-diabetes and Gestational Diabetes Mellitus; 3) addressing the issue of, different screening criteria for OGTT in relation to different diagnostic levels for hyperglycemia during pregnancy by using 3500 consecutive OGTT during pregnancy. He and associate professor Solveig Norden Lindeberg has ongoing register studies regarding preeclampsia and malformations.

### Reproductive Biology

### **Matts Olovsson**

### Members of the group during 2014

Olovsson, Matts Professor Bourley, Vladimir Professor

Stavréus-Evers, Anneli Associate professor Edelstam, Greta Associate professor Rezapour, Masoumeh Associate professor Skirnisdottir, Ingridur Associate professor Wånggren, Kjell Associate professor

MD, PhD Holte, Jan Wikström, Ingrid MD, PhD Lindström, Annika MD, PhD Brodin, Thomas MD, PhD Karypidis, Helena MD, PhD Helmestam, Malin PhD Sanner, Karin MD, PhD Altmäe, Signe PhD

Hambiliki, Fredwell PhD-student Jansson, Caroline PhD-student Junus, Katia PhD-student Kunovac Kallak, Theodora PhD-student Moberg, Christian PhD-student Murto, Tiina PhD-student Haroun, Sally PhD-student Arnio, Riina Research student Iliasova, Natalia Research student Norenhag, Johanna Research student Research student Rauden, Anna Malin Karlberg Research student

Davey, Eva Biomedical laboratory scientist

Båth, Ann-SofieStudy nurseVictoria EngströmStudy nurse

### Publications 2012-2014

- 1. **Rhenman A**, Berglund L, **Brodin T**, **Olovsson M**, Milton K, Hadziosmanovic N, **Holte J**. Which set of embryo variables is most predictive for live birth? A prospective study in 6252 single embryo transfers to construct an embryo score for the ranking and selection of embryos. Hum Reprod. 2015 Jan;30(1):28-36.
- 2. **Moberg C, Bourlev V, Ilyasova N, Olovsson M**. Endometrial expression of LIF and its receptor and peritoneal fluid levels of IL-1α and IL-6 in women with endometriosis are associated with the probability of pregnancy. Arch Gynecol Obstet. 2015 Jan 29. [Epub ahead of print]
- 3. Sohlberg S, Mulic-Lutvica A, **Olovsson M**, Weis J, Axelsson O, Wikström J, Wikström AK. MRI estimated placental perfusion in fetal growth assessment. Ultrasound Obstet Gynecol. 2015 Jan 14. doi: 10.1002/uog.14786. [Epub ahead of print]

- 4. Aghajanova L, Mahadevan S, **Altmäe S, Stavreus-Evers A**, Regan L, Sebire N, Dixon P, Fisher RA, Van den Veyver IB. No evidence for mutations in NLRP7, NLRP2 or KHDC3L in women with unexplained recurrent pregnancy loss or infertility. Hum Reprod. 2015 Jan;30(1):232-8.
- 5. **Murto T, Kallak TK**, Hoas A, **Altmäe S**, Salumets A, Nilsson TK, Skoog Svanberg A, **Wånggren K**, Yngve A, **Stavreus-Evers A**. Folic acid supplementation and methylenetetrahydrofolate reductase (MTHFR) gene variations in relation to in vitro fertilization pregnancy outcome. Acta Obstet Gynecol Scand. 2015 Jan;94(1):65-71.
- 6. **Helmestam M**, Lindgren KE, **Stavreus-Evers A**, **Olovsson M**. Mifepristone-exposured human endometrial endothelial cells in vitro. Reprod Sci. 2014 Mar;21(3):408-14.
- 7. **Junus K**, Wikström AK, Larsson A, **Olovsson M**. Placental Expression of proBNP/NT-proBNP and Plasma Levels of NT-proBNP in Early- and Late-Onset Preeclampsia. Am J Hypertens. 2014 Sep;27(9):1225-30.
- 8. Sohlberg S, Wikström AK, **Olovsson M**, Lindgren P, Axelsson O, Mulic-Lutvica A, Weis J, Wikström J. In vivo(31)P-MR spectroscopy in normal pregnancy, early and late preeclampsia: A study of placental metabolism. Placenta. 2014 May;35(5):318-23.
- 9. **Helmestam M, Davey E, Stavreus-Evers A, Olovsson M**. Bisphenol A affects human endometrial endothelial cell angiogenic activity in vitro. Reprod Toxicol. 2014 Jul;46:69-76.
- 10. **Moberg C, Bourlev V, Iljasova N and Olovsson M**. AlphaB-crystallin expression in the eutopic endometrium in women with minimal to moderate pelvic endometriosis. Hum Fertil (Camb). 2014 Jun 19:1-8.
- 11. Yung HW, Atkinson D, Campion-Smith T, **Olovsson M**, Charnock-Jones DS, Burton GJ. Differential activation of placental unfolded protein response pathways implies heterogeneity in causation of early- and late-onset pre-eclampsia. J Pathol. 2014 Oct;234(2):262-76.
- 12. Haroun S, **Altmäe S**, Karypidis H, Kuningas M, Landgren BM, Akerud H, Skjöldebrand-Sparre L, Hosseini F, Bremme K, Sundström-Poromaa I, **Stavreus-Evers A**. Association between trefoil factor 3 gene variants and idiopathic recurrent spontaneous abortion. Reprod Biomed Online. 2014 Dec;29(6):737-44
- 13. Elenis E, Lindgren KE, Karypidis H, Skalkidou A, Hosseini F, Bremme K, Landgren BM, Skjöldebrand-Sparre L, **Stavreus-Evers A**, Sundström-Poromaa I, Åkerud H. The histidine-rich glycoprotein A1042G polymorphism and recurrent miscarriage: a pilot study. Reprod Biol Endocrinol. 2014 Jul 27;12:70
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- 15. **Wånggren K**, Baban M, Svanberg AS. Attitudes toward embryo donation among staff at in vitro fertilization clinics. Acta Obstet Gynecol Scand. 2014 Aug;93(8):765-70.
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- 18. **Brodin T**, Hadziosmanovic N, Berglund L, **Olovsson M**, **Holte J**. Antimullerian hormone levels are strongly associated with live-birth rates after assisted reproduction. J Clin Endocrinol Metab. 2013 Mar;98(3):1107-14.
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- 21. **Murto T**, Bjuresten K, Landgren BM, **Stavreus-Evers A**. Predictive value of hormonal parameters for live birth in women with unexplained infertility and male infertility. Reprod Biol Endocrinol. 2013 Jul 11;11:61.

- 22. Ronquist KG, Ek B, Morrell J, **Stavreus-Evers A**, Ström Holst B, Humblot P, Ronquist G, Larsson A. Prostasomes from four different species are able to produce extracellular adenosine triphosphate (ATP). Biochim Biophys Acta. 2013 Oct;1830(10):4604-10.
- 23. Lindgren KE, Kårehed K, Karypidis H, Hosseini F, Bremme K, Landgren BM, Skjöldebrand-Sparre L, **Stavreus-Evers A**, Sundström-Poromaa I, Akerud H. Histidine-rich glycoprotein gene polymorphism in patients with recurrent miscarriage. Acta Obstet Gynecol Scand. 2013 Aug;92(8):974-7.
- 24. Baumgart J, Nilsson K, **Evers AS, Kallak TK**, Poromaa IS. Sexual dysfunction in women on adjuvant endocrine therapy after breast cancer. Menopause. 2013 Feb;20(2):162-8.
- 25. **Hambiliki F**, Hanrieder J, Bergquist J, **Hreinsson J, Stavreus-Evers A, Wånggren K**. Glycoprotein 130 promotes human blastocyst development in vitro. Fertil Steril. 2013 May;99(6):1592-9.
- 26. Ronquist KG, Ek B, **Stavreus-Evers A**, Larsson A, Ronquist G. Human prostasomes express glycolytic enzymes with capacity for ATP production. Am J Physiol Endocrinol Metab. 2013 Mar 15;304(6):E576-82.
- 27. **Altmäe S**, Martinez-Conejero JA, Esteban FJ, Ruiz-Alonso M, **Stavreus-Evers A**, Horcajadas JA, Salumets A. MicroRNAs miR-30b, miR-30d, and miR-494 regulate human endometrial receptivity. Reprod Sci. 2013 Mar;20(3):308-17.
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- 34. Bergh C, Lindenberg S; Nordic Crinone Study Group. A prospective randomized multicentre study comparing vaginal progesterone gel and vaginal micronized progesterone tablets for luteal support after in vitro fertilization/intracytoplasmic sperm injection. Hum Reprod. 2012 Dec;27(12):3467-73.
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- 40. Hambiliki F, Ström S, Zhang P, **Stavreus-Evers A**. Co-localization of NANOG and OCT4 in human pre-implantation embryos and in human embryonic stem cells. J Assist Reprod Genet. 2012 Oct;29(10):1021-8.
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- 42. **Kunovac Kallak T**, Baumgart J, **Stavreus Evers A**, Sundström Poromaa I, Moby L, Kask K, Norjavaara E, Kushnir MM, Bergquist J, Nilsson K. Higher than expected estradiol levels in aromatase inhibitor-treated, postmenopausal breast cancer patients. Climacteric. 2012 Oct;15(5):473-80.
- 43. **Skirnisdottir** I, Mayrhofer M, Rydåker M, Akerud H, Isaksson A. Loss-of-heterozygosity on chromosome 19q in early-stage serous ovarian cancer is associated with recurrent disease. BMC Cancer. 2012 Sep 12;12:407.
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- 45. Eriksson O, Landén M, Sundblad C, **Holte J**, Eriksson E, Naessén T. Ovarian morphology in premenstrual dysphoria. Psychoneuroendocrinology. 2012 Jun;37(6):742-51.

### Reviews (last 3 years)

- 1. Stavreus Evers A. Paracrine interactions of thyroid hormones and thyroid stimulation hormone in the female reproductive tract have an impact on female fertility. Front Endocrinol (Lausanne). 2012 Mar 30;3:50.
- 2. Altmäe S, Esteban FJ, Stavreus-Evers A, Simón C, Giudice L, Lessey BA, Horcajadas JA, Macklon NS, D'Hooghe T, Campoy C, Fauser BC, Salamonsen LA, Salumets A. Guidelines for the design, analysis and interpretation of 'omics' data: focus on human endometrium. Hum Reprod Update. 2014 Jan-Feb;20(1):12-28.

### **Dissertations 2014**

Tiina Murto Folate, Hormones and Fertility, 2014-05-22 Frewell Hambiliki *Culture and Vitrification of Human pre-embryos*, 2014-06-04

### Agencies that support the work/Funding

ALF, 1 224 000 SEK Vinnova/Eurostar 350 000 SEK Lions cancerforskningsfond, 300 000 SEK The Swedish Research Council, 700 000 SEK

For a successful implantation and pregnancy it is important that both the embryo and the endometrial development is normal. Failure of embryo development will result in miscarriage while failure of endometrial development could be an explanation of unexplained infertility.

The embryo development is studied using a broad range of methods from basic protein chemistry to new proteomic methods. These studies were included in Fredwell Hambiliki's thesis work. The maternal side of endometrial receptivity has been studies from different aspects. Markers of receptivity is studied in a project involving, University of Tarry and IVI Valencia, the project is financed by grants from

Eurostar/Vinnova. The endometrial receptivity is also studied using cell culture models, where the effect of prostasomes, exosomes from the prostate gland, is studied.

We can show stat genetic variations besides endometrial receptivity offer an explanation for unexplained infertility and also for recurrent miscarriage. Experience of miscarriage is measured using a new instrument, these studies will be included in Caroline Janssons thesis work.

Hormonal regulation of vaginal atrophy show the importance of estrogen but also new data showing that the atrophy in this case is related to lack of growth and differentiation rather than an degeneration of the vaginal mucosa. Anneli Stavreus-Evers is coordinating these studies.

**Preeclampsia**, a project aiming at a better understanding of the pathogenesis of PE and how to diagnose, predict and treat the disease. Within the PE-projects we have cooperation with Professor Graham Burton in Cambridge (UK) on placental/trophoblast metabolism. We are currently studying the possible involvement of NT-proBNP in the pathogenesis of PE. Matts Olovsson is coordinating these studies.

**Endometriosis**, we have done a large questionnaire study on cost of illness and quality of life. We can also show that women with symptomatic endometriosis cost about 90 000 SEK/year compared with about 20 000 SEK/year in a age and gender matched background population.

We have evaluated the Swedish version of the questionnaire Endometriosis Health Profile -30. We are currently performing several studies on new medications for the treatment of endometriosis associated pain as well as new markers to diagnose endometriosis. We are performing studies on endometriosis associated pain. There are also studies of endometrial factors associated with endometriosis related infertility. Our endometriosis research is done at our National Endometriosis Centre. Matts Olovsson is coordinating these studies.

Cervical cancer is the second most frequent cancer among women worldwide and caused by persistent infection by oncogenic types of human papillomavirus (HR-HPV). We are studying self-sampling for the analysis of HR-HPV. We have a large study where screening based on cytology is with HPV-testing. We will start a new study where we compare self-sampling wits sampling by a midwife, for the analysis of HR-HPV. We are studying the prevalence of HR-HPV in women aged 60-75 years. We are currently performing a questionnaire study to find out why women do not take part in the screening program and what would make do.

The studies are coordinated by a steering group consisting of Matts Olovsson, Ulf Gyllensten, Erik Wilander, Annika Lindström, Ingrid Wikström, Karin Sanner and Riina Aarnio.

We have studied **prognostic factors in assisted reproduction techniques**. Currently we are studying which of several embryo scoring variables that have independent predictive power for pregnancy and live birth following embryo transfer. These studies are coordinated by Jan Holte, Thomas Brodin and Matts Olovsson.

**Ovarian cancer**, prognostic factors for epithelial ovarian cancer are studied. These studies are coordinated by Ingridur Skirnisdottir.

### **Reproductive Health**

### Inger Sundström Poromaa

The Reproductive Health research group focuses on all aspects of reproductive health, with an aim of improving mental and sexual well-being of women at all ages. The studies range from investigator-initiated clinical trials, to neuroimaging, and laboratory analyses of human tissue. Women throughout the entire reproductive span are included in these studies, from young women requesting contraception, to pregnant and newly delivered women, and finally also postmenopausal women.

### Members of the group during 2014 (last year)

Inger Sundström Poromaa, professor

Dan Hellberg, adjunct professor

Agneta Skoog Svanberg, associate professor

Alkistis Skalkidou, associate professor

Jocelien Olivier, post doc

Charlotte Hellgren, post doc

Juliane Baumgart (fd Schlenstedt), PhD

Elin Bannbers, PhD

Catrin Borneskog, PhD

Fatimah Dabo, PhD

Malin Gingnell, PhD

Miriam Hudecova, PhD

Kristiina Kask, PhD

Åsa Lindholm, PhD

Annika Lindström, PhD

Helena Lundgren, PhD

Karin Stålberg, PhD

Birgitta Segebladh, PhD

Sara Sylven, PhD

Jan Wesström, PhD

Inger Wallin Lundell, PhD

Helena Volgsten, PhD

Emma Billström, PhD student

Kathrine Bjersand, PhD student

Patricia Eckerdal, PhD student

Åsa Edvinsson, PhD student

Anna-Karin Hannerfors, PhD student

Sussy Hofmayer, PhD student

Stavros Iliadis, PhD student

Paridhi Jha, PhD student

Theodora Kunovac Kallak, PhD student

Merit Kullinger, PhD student

Gyula Pekar, PhD student

Raghad Samir, PhD student

Lena Moby, research nurse

Emma Bränn, research assistant

#### Publications 2012-2014

- 1. Aldrimer M, Ridefelt P, Rodoo P, Niklasson F, Gustafsson J, Hellberg D. Reference intervals on the Abbot Architect for serum thyroid hormones, lipids and prolactin in healthy children in a population-based study. Scand J Clin Lab Invest. 2012; 72:326-32.
- 2. Bannbers E, Gingnell M, Engman J, Morell A, Comasco E, Kask K, Garavan H, Wikstrom J, Sundstrom Poromaa I. The effect of premenstrual dysphoric disorder and menstrual cycle phase on brain activity during response inhibition. J Affect Disord. 2012; 142:347-50.
- 3. Bolin M, Wikstrom AK, Wiberg-Itzel E, Olsson AK, Ringvall M, Sundstrom-Poromaa I, Axelsson O, Thilaganathan B, Akerud H. Prediction of preeclampsia by combining serum histidine-rich glycoprotein and uterine artery Doppler. Am J Hypertens. 2012; 25:1305-10.
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- 6. Gingnell M, Morell A, Bannbers E, Wikstrom J, Sundstrom Poromaa I. Menstrual cycle effects on amygdala reactivity to emotional stimulation in premenstrual dysphoric disorder. Horm Behav. 2012; 62:400-6.
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- 14. Kunovac Kallak T, Baumgart J, Stavreus Evers A, Sundstrom Poromaa I, Moby L, Kask K, Norjavaara E, Kushnir MM, Bergquist J, Nilsson K. Higher than expected estradiol levels in aromatase inhibitor-treated, postmenopausal breast cancer patients. Climacteric. 2012; 15:473-80.
- 15. Mavromatis ID, Antonopoulos CN, Matsoukis IL, Frangos CC, Skalkidou A, Creatsas G, Petridou ET. Validity of intraoperative gross examination of myometrial invasion in patients with endometrial cancer: a meta-analysis. Acta Obstet Gynecol Scand. 2012.
- 16. Petridou ET, Sergentanis TN, Panagopoulou P, Moschovi M, Polychronopoulou S, Baka M, Pourtsidis A, Athanassiadou F, Kalmanti M, Sidi V, Dessypris N, Frangakis C, Matsoukis IL, Stefanadis C, Skalkidou A, Stephansson O, Adami HO, Kieler H. In vitro fertilization and risk of childhood leukemia in Greece and Sweden. Pediatr Blood Cancer. 2012; 58:930-6.
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#### **Reviews 2012-2014**

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## **Dissertations 2014**

Inger Wallin Lundell, Induced abortions and posttraumatic stress – is there any relation?

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## The PADIA study

# Agneta Skoog Svanberg, Inger Sundström Poromaa, Ulf Högberg, Gunilla Sydsjö, Örjan Frans, Susanne Georgesson Öhmnan, Inger Wallin Lundell

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 the two additional manuscripts from this study have been published, and Inger Wallin Lundell defended her thesis in September 2014.

## The Swedish multicenter study on gamete donation.

## Agneta Skoog Svanberg, Gunilla Sydsjö, Claudia Lampic, Catrin Borneskog, Stina Isaksson, Evangelia Elenis, Sara Nordqvist

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. Fourteen papers from the study have thus far been published and the long-term follow-up of couples started during 2013

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

# Agneta Skoog Svanberg, Maria Jonsson, Alkistis Skalkidou, Inger Sundström Poromaa, Margareta Larsson, Thomas Parling, Josefine Sjömark

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. Following a pilot study, the project started including patients in 2014.

#### Obstetric care in India

## Agneta Skoog Svanberg, Margareta Larsson, Kyllike Christensson, Mallavarapu Prakasamma, Paridhi Jha

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

Alkistis Skalkidou, Inger Sundström Poromaa, Sara Sylven, Stavros Iliadis, Patricia Eckerdal, Charlotte Hellgren, Malin Gingnell, Erika Comasco, Mia Ramklint, Carin Marziscko, Gustaf Gredebeck

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 have been 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 4100 women and tissue sampling at delivery is obtained in more than 80% of cases. During the past year, 6 papers using information or tissue from the BASIC study have been published and at 5-6 manuscripts are currently underway. Extensive genotyping of the population has been performed in 2014, which is expected to yield further publications.

A follow-up study on the offspring of the cohorts UPPSAT (2006-7) and BASIC (2009-ongoing), trying to elucidate complex genetic and environmental interactions in shaping child psychopathology has been initiated (U-BIRTH study). The children at followed at 18 months, 6 years and 11 years with questionnaires and saliva sampling. Umbilical cord blood is also available for a large proportion of the BASIC paticipants. In addition, a study in collaboration with Uppsala Barn and Baby Labbet, Dept of Psychology, Uppsala University, in which children to healthy (n=100) and depressed mothers (n=20) from the BASIC cohort are subjected to a battery of elaborate psychological tests.

## Adverse mood effects on combined oral contraceptives.

### Inger Sundström Poromaa, Cecilia Lundin, Lena Moby

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. During fall 2013, a multi-center, placebo-controlled oral contraceptive trial was started. Participating sites include Uppsala, Stockholm, Linköping, Örebro, Göteborg and Umeå. By the end of the inclusion period (June 2015) it is expected that more than 250 have been included. Preliminary data thus far not available.

## Urogenital symptoms in breast cancer patients on adjuvant endocrine therapy.

## Inger Sundström Poromaa, Annelie Stavreus Evers, Theodora Kunovac Kallak, Juliane Baumgart

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. The use of both tamoxifen and aromatase inhibitors (AI) is however associated with severe urogenital atrophy and impaired sexual function. Additional profiling of the vaginal mucosa in AI users is underway, and the ultimate goal of the project is to develop a possible intervention for these women. Seven papers have thus far been published from this project, and Theodora Kunovac Kallak is expected to defend her thesis in 2015.

### New biomarkers for cervical cancer

## Dan Hellberg, Inger Sundström Poromaa, Emma Billström, Anna Asplund

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.

## Karin Stålberg, Inger Sundström Poromaa, Kathrine Bjersand

The U-CAN project in Uppsala has continued to include gynecologic cancers, i.e. cervical, endometrial and ovarian cancer, with excellent coverage. Samples include tumor tissues at surgery and blood samples. Tissue samples are biobanked at the pathology unit according to U-CAN routines. Clinical data and patient information is stored as quality registry forms (both gynecologic and pathologic), together with information on family history, general and reproductive health. Karin Stålberg is chairman of the U-CAN gynecology research team.

## Ultrasound dating and perinatal morbidity and mortality

## Alkistis Skalkidou, Merit Kullinger, Helle Kieler

A study based on Swedish register data, testing the hypothesis that missclassification of estimated date of delivery by second trimester ultrasound dating has negative outcome in perinatal morbidity and mortality. One article is published in EPIDEMIOLOGY and the second is under submission.

## EMBLA project- En internet based informationsplatfrom for vulvodyni patienter

## Alkistis Skalkidou, Ulf Högberg, Agneta Skoog Svanberg, Monica Burhman

Vulvodynia is a very prevalent disorder among young women, affecting their relationships and quality of life. This is a randomized study testing the efficacy and cost-effectiveness parameters of an internet-based randomized intervention based on a CBT-ACT treatment approach. The study will pilot in August 2015.

### **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.

### **Group members**

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## **Dissertation 2014**

Petrida Ijumba. *Interventions for improved newborn feeding and survival where HIV is common:* perceptions and effects of a community-based package for maternal and newborn care in a South African township. Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 1027. Uppsala: Acta Universitatis Upsaliensis 2014. ISBN 978-91-554-9035-5

## Agencies that support the work/Funding

Currently the research program is supported by grants from Swedish Research Council (Vetenskapsrådet 9 650 000 SEK in 2014), 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.

ALF	2 316 000
Ograderade medel	84 139
Sida	32 218
Landstinget Dalarna	413 585
Karolinska institutet	666 419
EU	72 793
Stiftelser & fonder	400 000

## Reducing neonatal mortality.

A persistent problem in many countries is a high neonatal mortality, and inequity in neonatal survival chances. 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, 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. This project and linked initiatives have generated several papers on neonatal health, including three completed PhD theses (Mats Målqvist 2010, Leif Eriksson 2012 and Nguyen T Nga 2013). One more PhD student has on-going studies related to the trial. Sida is the main funder of this project and Swedish Research Council has provided additional funds. In 2014 we conducted a follow-up of the NeoKIP trial, three years after its completion, to assess the sustainability of the approach. The evaluation included data on neonatal mortality rate, the local health system context, experiences concerning processes during the post-intervention period and factors that influence the sustainability of (communitybased) knowledge translation interventions. Further, we have also received initial funding to conduct the NeoKIP+ project, which will test the scalability of the NeoKIP intervention at commune level in combination with a facilitated approach at district hospitals. The project will include 280 poor Vietnamese communes in 6 provinces with high burden of neonatal mortality.

Most health departments in low- and middle-income countries, Vietnam included, do not assess the prevalence of stillbirths. As a result, knowledge around stillbirth has long been a neglected field of research although, if correctly assessed, intrapartum-related stillbirths could serve as a sensitive marker of the quality of care during delivery. The NeoKIP follow-up survey offered an excellent opportunity to also study the prevalence of stillbirths, to distinguish between antepartum vs. intrapartum stillbirths and to identify risk factors through the application of a verbal and social autopsy instrument developed by the group. The instrument also included questions on the coverage and utilization of health services. Stillbirth data collected as part of the follow-up is currently being analysed.

The Uganda Newborn Study (UNEST) funded by Gates via Saving Newborn Lives demonstrated that community health worker (CHW) home visits in pregnancy and newborn period improves delivery and newborn practices. Christine Nalwadda further demonstrated in her articles and thesis that CHWs can identify sick newborns in need of referral from the home to health centres, and that referral compliance was high. However, the first level health facilities are largely unable to cater for the sick newborns for policy gaps, and lack of skills, drugs and equipment. Uganda Ministry of Health has adopted the UNEST home visiting counselling materials for national use. Dialogue around policy changes to empower first level health units to cater for sick newborns is ongoing. A journal supplement on UNEST will be published in March 2015.

An EU-funded project EQUIP – essential quality improvement using information power – was completed in Uganda and Tanzania. It demonstrated the capacity of quality improvement to improve facility level care, but also that community level dialogue with expecting parents can increase care seeking for delivery care beyond what the health facilities can meet. In a pilot study funded by the Einhorn Family Foundation we are now pursuing quality improvement at hospital level, and IDRC has funded an EQUIP scale-up in Tanzania with 1 million dollars.

Evidence based district planning is the focus for the UNICEF-Gates funded study CODES – Community and District Empowerment for Scale up. Focusing on child health and child health care this study set in Uganda is a randomized controlled trial of a governance intervention on coverage of essential child health services. A series of manuscripts were submitted during the year.

Private sector implementation of Integrated Community Case Management of Malaria and Pneumonia and Diarrhea (ICCM) was evaluated in Uganda. A publication by Phyllis Awor et al. attracted a lot of international interest and is now followed up by a WHO/Alliance and Swedish Science Council funded study in Uganda.

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. Studies have been completed on perinatal audit and risk factors for early neonatal death.

In Nepal there is an on-going trial on the evaluation of delayed versus early cord clamping and its effects on the prevalence of anaemia when the newborn has reached the age of four months. A total of 540 live births have as been included in this randomized controlled trial. The study is conducted at the Paropakar Maternity and Women's Hospital, Nepal. Pregnant woman of gestational age 34-41 weeks, who deliver vaginally, have been included in the study. The interventions consist of delayed clamping of the umbilical cord ( $\leq$ 180 seconds after delivery) or early clamping of the umbilical cord ( $\leq$ 60 s). At 8 and 12 months of age, infant's iron status and developmental milestones will be measured.

Recognition of danger signs and deteriorated state of admitted patients is vital to prevent adverse event and improve survival chances. At the University Pediatric Hospital in Uppsala, Sweden an evaluation of a Pediatric Early Warning System (PEWS) is currently under way. This simple tool has shown promising results in reducing admittance to intensive care unit and reducing time to initiation of adequate treatment.

## 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. We have also evaluated research questions related to the DOHaD hypotheses (Developmental Origin of Health and Disease) studying the impact by the interventions on child growth, body composition, metabolic markers at 4.5 and 10 years and oxidative stress in pregnancy and birth weight. Ongoing is an add-on to the MINIMat trial that is evaluating trans-generational effects of poor nutrition in fetal life. The publications from MINIMat also include micronutrient status in pregnancy and infancy, risk factors for infant anaemia, breastfeeding and micronutrient status, maternal-infant interaction, household food security and child growth and development, morbidity and psychomotor development, and violence against women and child growth and morbidity. A follow-up at age 10 years has recently been completed. We collaborate with, among others, the research institution icddr,b in Bangladesh, and research groups at London School of Hygiene & Tropical Medicine, University of California at Davis and Cornell University in Ithaca, US. The Swedish Research Council and Sida have, among others, provided funding and the research partners have received funding from several agencies.

A study of health system aspects of the rapidly increasing diabetes prevalence in low and middle-income countries was funded by EU Horizon 2020. Entitled SMART2D – self management and reciprocal learning for type 2 diabetes management – the study will run over the next four years with partners in South Africa, Uganda, Belgium, Finland and Sweden.

## **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. Swedish Research Council has financed the ongoing collaboration between our groups and Save the Children (US) has provided support to our collaborating partners.

#### Children with fever.

In different studies in Uganda the diagnosis and management of children with fever are addressed. 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. We have shown that iCCM may also work in private sector drug shops in Uganda, 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.

In 2010, the World Health Organization revised malaria treatment guidelines to recommend diagnostic testing of all suspected malaria cases prior to treatment. Recent studies, however, suggest that the full potential of malaria rapid diagnostic tests (mRDT) are not being achieved given poor adherence to test results by health workers in areas of intense malaria transmission. Emily White Johansson (PhD student) uses new data recently collected from standardized national cross-sectional household and health facility surveys conducted in multiple sub-Saharan African countries to improve understanding of extent and determinants of diagnostic test use and adherence across different contexts, including in different malaria risk settings in sub-Saharan Africa.

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.

Since 2010, 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. The development of the Context Assessment for Community Health (COACH) tool has been undertaken in, and with partners from, Bangladesh, Vietnam, South Africa, Uganda and Nicaragua. Development of the tool including undertaking and statistical analysis was completed in November 2013. During 2014 we have been piloting collecting COACH data using mobile phones in Kenya. The COACH tool is also undergoing further psychometric

testing and was integrated into the NeoKIP follow up project in 2014 whereby all health workers involved in maternal and neonatal health services and about half of the village health workers in the NeoKIP project study areas were invited to undertake the survey. Data on test-retest reliability has also been collected from Vietnam and response process with a smaller selection of health workers undertaken to understand the cognitive validity of the Vietnamese COACH tool.

The main article from the project was submitted in October 2014. The COACH project has been presented at three international conferences in 2014; Oral presentation at the *Third Global Symposium on Health System Research* in Cape Town, South Africa, October 2014, followed by panel discussion; Poster presentation at the *BMC Health Service Research conference* in London, July 2014; Poster presentation at the *Knowledge Utilization Colloquia*, Tällberg, June 2014.

## 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 in 2012 analysing the effect of stimulation (play therapy) in addition to food supplementation in the rehabilitation of severely malnourished children. PhD students from Ethiopia have 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.

### 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 earlier shown an association between VAW and child mortality, size at birth, child growth and morbidity. More recently a paper on the association with child malnutrition was also published.

## The Millennium Development Goals 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 forth 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. A new update of the *Los Cuatro Santos* Health and Demographic Surveillance System, which was the basis for these studies, has been made during 2014 providing more information on the community development work and the ability to achieve the development and health goals in a local setting.

Since spring 2012, Katarina Selling, PhD and senior biostatistician, is part of the research group. Having a skilled statistician in the group has increased the methodological quality and skills in analysis of data and in reporting results. This has included analyses of complex data from cluster-randomized trials or cluster-based Demographic Health Surveys, DHS, which require multi-level modelling, and also meta-analysis in systematic reviews.

## 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. One new doctoral student has been registered during the year.

#### Members of the group during 2014

Birgitta Essén MD, Associate Professor, Senior Lecturer

Research group leader

Jonna Arousell Doctoral student Anna Arvidsson Doctoral student

Pauline Binder PhD

Magdalena Bjerneld PhD, and 2013 appointed Excellent teacher

Ulrika Byrskog Doctoral student Annika Esscher MD, PhD

Bengt Haglund Associate Professor

Hussein Kidanto MD, PhD Marie Klingberg-Allvin Senior lecturer Johannes Leidinger Senior lecturer Helena Litorp Doctoral student Andrew Mgaya Doctoral student Soheila Mohammadi Doctoral student Cristina Niska Bachelet Administrator Barni Nor RN, PhD

Viveca Odlind MD, Associate Professor

Mandira Paul Doctoral student
Christina Pedersen Research assistant
Soorel Jose Puthoopparambil Doctoral student
Jessica Påfs Doctoral student

Mattias Rööst MD, PhD

Karin Törnblom Financial administrator

William Ugarte PhD

Anna Wahlberg Doctoral student

#### Publications 2012-2014

#### 2014

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#### **Dissertations 2014**

Annika Esscher

Maternal deaths in Sweden. Classification, quality of care, and country of birth.

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Vetenskapsrådet	2 269 000
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Swedish International Development Cooperation Agency (Sida)	849 203
MSF	426 240
Ograduerade	62 209

Collaborating centres

Karolinska institutet

Malmö Högskola

Uppsala universitet, Department of Public Health and Caring Sciences

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 Autótoma de Nicaragua UNAN - Leon, Nicaragua

Shahid Beheshti University of Medical Sciences/ Infertility Reproductive Health Research Center

## 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 analyzing the political positions that have given rise to decisions to advocate, accept or criminalize certain surgical genital modifications. The phenomena analyzed 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 politicized 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. In the end of November/beginning of December 2013 a concluding meeting took place in Delhi with representatives from the Swedish Embassy and Sida.

# 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 form countries outside EU. Most of the European countries use detention centers 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 centers. 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 analyzed 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 Puthoopparambil.

## 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 fist 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 analyze 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**

- SFOG
- NFOG
- One research group seminar has taken place during 2014, Falsterbo, February 10-11 "Interdisciplinary research seminar regarding women and maternal health care and migration".

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

## **International Sexual and Reproductive Health**

### **Margareta Larsson**

This research group studies women's health and rights, youth health and nutrition as well as care and support related to pregnancy, birth, breast-feeding and parenthood. The group works in international collaboration with scientists from several disciplines such as medicine, public health, social science, gender studies, nursing and midwifery. Two PhD students defended their thesis during 2014 and several new doctoral students have been registered. Our projects span over the following main areas:

## Reproductive Health and Healthcare

This area focuses on quality of care throughout the continuum of care from home, through the community and on to health services and referral hospitals. The different projects are described in more detail below. **Sexual Health and Rights** includes projects among young people in different contexts, in Sweden as well as in other countries. Several projects are related to gender-based violence and interventions for prevention of violence. The projects are described in more detail below.

**Nutrition and Women's Health** is another focus of the group. Studies are on-going in several countries and described in more detail below.

## Members of the group during 2014

Abeid Muzdalifat Muganyizi Doctoral student

Ahlberg Beth Maina PhD, Adjunct Professor

Furaha August Doctoral student

Axemo Pia PhD, Associate Professor

Berglund Anna PhD

Bodin Maja Doctoral student

Cato Karin Doctoral student

Contreras Mariela Doctoral student

Darj Elisabeth PhD, Guest Professor,

Ekström Eva-Charlotte PhD, Professor

Haines Helen PhD

Hildingsson Ingegerd PhD, Professor

Hoque Waheedul Doctoral student

Högberg Hjördis Doctoral student

Höglund Berit PhD

Jordal Malin PhD

Kaime-Atterhög Wanjiku PhD

Kidanto Hussein PhD

Larsson Birgitta Doctoral student

Larsson Margareta PhD, Associate Professor, Senior Lecturer

Lindmark Gunilla PhD, Professor emerita

Makenzius Marlene PhD

Malm Mari-Cristin Doctoral student

Mattebo Magdalena Doctoral student

Mbekenga Kokusiima Colomba PhD

Muganyizi Projestine PhD

Olsson Pia RNM, PhD, Associate Professor, Senior Lecturer

Omer-Salim Amal Doctoral student

Pallangyo Eunice Doctoral student

Pembe Andrea PhD

Rubertsson Christine PhD, Associate Professor, Senior Lecturer

Råssjö Eva-Britt PhD Tydén Tanja Professor Ternström Elin Doctoral student Trenholm Jill PhD Törnblom Karin Administrator Wickström Maria Doctoral student

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#### **Dissertations 2014**

- 1. Magdalena Mattebo
- 2. Malin Jordal

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Aga Khan University	270 000
The Public Health Agency of Sweden	125 000

## Reproductive Health and Healthcare

## **Project 1: Child Birth related fear**

#### PI: Ingegerd Hildingsson and Christine Rubertsson

Fear of birth scale (FOBS) is an instrument to identify women with CBRF. More knowledge is needed to find out if FOBS also can be used in clinical practice. A randomized controlled trial compares two different treatments of CBRF; standard care and internet-based cognitive behavioral treatment. We study background factors and outcomes in women undergoing counseling with specially trained midwives and also the organization of such counseling in Sweden.

## Project 2: Dysfunctional labour in a National Hospital in Dar es Salaam

## PI: Elisabeth Darj

In this project at Muhimbili National Hospital in Tanzania we will analyse lactate in amniotic fluid in 1000 women. The aim is to test the hypothesis, that if lactate levels are low, it is possible to attain a normal vaginal delivery by augmentation of labour with oxytocin. It will also be investigated whether high levels of lactate indicate an increased risk of caesarean section.

# Project 3: Home based lifesaving skill education within maternal and newborn care in Tanzania

### PI: Elisabeth Darj and Pia Axemo

The study is a cluster randomised structured education intervention to investigate if home based education has any impact on knowledge and behaviour in seeking professional care for mother and child during pregnancy and birth. Furthermore, we will study the involvement of men during pregnancy and birth and the views of health care workers.

## Project 4: Introducing and evaluating a Reproductive Life Plan

## PI: Margareta Larsson and Tanja Tydén

Randomized controlled trials among women and men using the RLP are ongoing and a study about the implementation of the RLP in midwifery clinics has been completed. A longitudinal questionnaire study on health, life style and pregnancy planning is on-going in collaboration with several partners in Sweden and Europe.

# Project 5: Postpartum experiences of women and men in a suburb of Dar es Salaam

#### PI: Pia Olsson

The study aims to gain a deeper understanding of family health and support after childbirth from the perspective of first-time parents and informal support persons in low-income, multi-ethnic, suburban areas in Ilala, Dar es Salaam, Tanzania. Interviews and focus group discussions with first time parents and informal support persons.

# Project 6: Sexual/reproductive health among young people with intellectual disability – the health of their children

PI: Margareta Larsson and Berit Höglund

Women with intellectual disability (ID) and their children are risk groups. This project investigates health risks among children born to mothers with ID. Interview studies regarding sexual health and reproduction among young adults with ID are also planned. Parents, professionals and young people will be interviewed.

## Project 7: Reproductive health, gender and migration in Sri Lanka

#### PI: Pia Olsson

This program investigated strategies in handling changing gender relations and SRHR risks of young, unmarried women migrating from rural to urban factory areas. Interviews and group discussions among working women and with men residing in or near free trade zones. The knowledge will guide SRHR programs, education curricula and for theory development.

# Project 8: The quality of referrals of pregnant women in rural Tanzania PI: Elisabeth Dari

In-depth-interviews of referred women or relatives to deceased women, who did not follow advice to go to the hospital for care.

## Project 9: The midwife's dialogue about alcohol with parents-to-be

#### PI: Margareta Larsson

The aim of the project is to develop and to evaluate a method and a theory about social and psychosocial support for an alcohol-free pregnancy and for responsible alcohol consumption during parenthood, involving both parents-to-be. It will also evaluate the feasibility of the implementation of such a method.

## Project 10: Unintended pregnancy, abortion and prevention

#### PI: Margareta Larsson

The project investigated women and men's experiences and needs in relation to an induced abortion. The project had a public health perspective and care before and during an abortion as well as prevention of unintended pregnancies were investigated.

## Sexual Health and Rights

# Project 1: Health seeking behavior and care of survivors of child sexual abuse and rape

## PI: Pia Axemo, Elisabeth Darj and Pia Olsson

An intervention to improve health care seeking behaviour and care among survivors of rape and child sexual abuse in Morogoro, Tanzania by education of health care workers, police and the population by radio and other channels. A standardised rape-kit is used. The effects are evaluated by comparing the situation before and after the intervention and also with a control area.

## Project 2: Pornography, youth and health

## PI: Margareta Larsson

A prospective longitudinal questionnaire study among 800 high school students showed that pornography has become a part of everyday life for many adolescents and the use is associated with some risky health behaviours. In the longitudinal analyses frequent use of pornography was more associated to psychosomatic symptoms compared with depressive symptoms.

## **Project 3: Sri Lankan Males perspectives of Gender**

### PI: Pia Axemo, Elisabeth Darj and Gunilla Lindmark

The aim of study is to investigate male university student's perception on GBV, male dominance and female subordination and the willingness to actively engage in prevention of GBV in future occupations. It is a pilot study, and will serve as the base for a later intervention study.

## Project 4: Use of skin-lightening cosmetics among immigrant women

#### PI: Elisabeth Dari

The aim of this project is to increase knowledge around the potentially dangerous bleaching products used in Sweden by immigrant women. We investigate the market, patterns of use and views on skin bleaching among immigrant women from Africa, Asia and Caribbean. Furthermore we have analysed the content of the products bought in East-Africa and Sweden.

## Nutrition and Women's Health

## **Project 1: Nutrition and women's health in Bangladesh**

#### PI: Eva Charlotte Ekström

Randomized trials in Bangladesh are evaluating the effects of nutrition interventions in early life on maternal and child health over time, currently the effects on pre-puberty are in focus.

## Project 2: Community-based promotion of exclusive breastfeeding

#### PI: Eva Charlotte Ekström

Promotion of exclusive breastfeeding in South Africa. The importance of women's empowerment in infant and young child health and nutrition in Nicaragua and Ethiopia are also studied.

### **Project 3: Combining breastfeeding with employment in India**

### PI: Pia Olsson

This is a project about strategies for enabling women to combine breastfeeding, domestic work and employment. A qualitative study among public education and health sector workers in New Delhi, India.

## **Project 4: Initiation of breastfeeding**

### PI: Christine Rubertsson

A successful breastfeeding initiation is crucial for continued breastfeeding, hence the importance of studying the first breastfeeding session, breastfeeding support during the first breastfeeding session and its consequences. Therefore the aim of this project is to investigate care giving routines during the first breastfeeding session, possible effects and breastfeeding duration.

## **Project 5: A world on the move**

### PI: Beth-Maina Ahlberg

This project studies challenges and opportunities for HIV/AIDS/Tuberculosis care and prevention among immigrants from countries in Sub-Saharan Africa and another ethnographic study of war rape in Eastern Democratic Republic of Congo has been performed..

## **Project 6: Jigger infestation**

## PI: Beth-Maina Ahlberg

This is a project with a transdisciplinary approach for understanding a visibly deforming but simultaneously invisible and neglected public health problem in the East African Region.

## **Pediatric Endocrinology**

#### Jan Gustafsson

Research within pediatric endocrinology contributes to the understanding of hormonal influences on growth and metabolism during infancy, childhood and puberty.

We study conditions behind intrauterine growth retardation and increased fetal growth as well as energy substrate metabolism in newborn infants. Since fetal conditions are important for adult life we use Swedish registers to study relationships between conditions at birth and growth, intellectual performance and development of adult disease.

Since eating disorders influence somatic development studies of endocrine and metabolic consequences of anorexia nervosa are also ongoing.

Overweight and obesity during childhood represents an increasing problem globally. Within the research group a large cohort of obese children is followed within the two projects ULSCO and Beta JUDO. Several aspects of type 1 diabetes during childhood are also studied by the research group. In particular research on the relation between neurodevelopmental problems and disease control as well as metabolic control, weight gain during treatment and remaining endogenous insulin production is performed.

#### Members of the group during 2014

Gustafsson, Jan, Professor Ahlsson, Fredrik, MD, PhD Berglund, Marie, Research nurse Ciba, Iris MD, Doctoral student Diderholm, Barbro MD, PhD Forslund, Anders MD, PhD Gebre-Medhin, Mehari Professor em. Grönberg, Annika MD, Doctoral student Halldin-Stenlid, Maria MD, PhD Hedberg Nykvist, Kerstin Associate professor Jonsson, Björn PhD Koltowska, Maria MD, PhD Lundgren, Maria MD, PhD Myrelid, Åsa MD, PhD Nylander, Charlotte MD, Doctoral student Proos, Lemm MD, PhD Staaf, Johan Doctoral student Strand-Brodd, Katarina MD, PhD Swenne, Ingemar Associate professor Söderberg, Elisabet laboratory technician Tindberg, Ylva MD, PhD Tuvemo, Torsten Professor em.

Wahlström Jonsson, Inger MD, Doctoral student Wester Oxelgren, Ulrika MD, Doctoral student

#### **Publications 2012 - 2014**

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## Energy substrate metabolism during infancy and childhood

### Jan Gustafsson, Barbro Diderholm, Fredrik Ahlsson, Inger Wahlström Johnsson

After birth the newborn infant has to produce its own glucose to supply the brain with energy. Infants, born small as well as large for gestational age, are at risk for neonatal hypoglycemia and also metabolic disease later in life. The research is directed on metabolism both in newborn infants, children and adults. Studies on effects of hypothermia after perinatal asphyxia on glucose homeostasis and cerebral glucose consumption is ongoing as well as studies on metabolic effects in adult life of being born large for gestational age with regard to weight. A project related to metabolism and hormonal balance in infants and children, who develop obesity later in life has also recently been started. In collaboration with child psychiatry a study on blood glucose regulation in children with ADHD has recently been performed.

## Register based studies on fetal origin of adult disease

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

We use a number of Swedish registers in epidemiological studies. The registers are the Medical Birth Register, the Conscript register, the Inpatient Care Register, the Drug Register and the Causes of Death Register. Different circumstances during fetal life may influence morbidity during childhood and adult life. We have particularly studied effects of conditions during fetal life and childhood on growth, development

of obesity and cognitive function. The results show an association between overweight/obesity and impaired intellectual performance in young adults, particularly those with a low birth weight. Other data demonstrate that women, who have been treated with mood stabilisers due to bipolar disease risk an adverse pregnancy and birth outcome. Studies on the effect of being born large for gestational age have pointed out long term effects of a high birth weight, particularly a weight >3SD, on adult metabolic disease. An epidemiological project on development and health in children of mothers with intellectual disability has recently been started together with the research group of International Sexual and Reproductive Health at the department

## Mechanisms behind precocious puberty

### Lemm Proos, Maria Halldin, Jan Gustafsson

Precocious puberty has been a field of research within the group for several years. Precocious puberty occurs more frequently in girls than in boys. Particularly girls with hydrocephalus and myelomeningocele are prone to develop early or precocious puberty. This may lead to practical and psychological problems in addition to those caused by the myelomeningocele. In an ongoing project which is performed partly in collaboration with the pediatric neurology group predictors for development of precocious puberty in case of myelomeningocele as well as other conditions are being studied.

## **Down syndrome**

## Ulrika Wester Oxelgren, Åsa Myrelid and Jan Gustafsson

Our research group has studied endocrine disease in Down syndrome for many years in collaboration with professor Göran Annéren at Department of Immunology, Genetics and Pathology. Within this project data on secretion of growth hormone and effects of growth hormone treatment on growth and psychomotor performance have been published. By use of Swedish registers data on mortality and causes of death in Down syndrome have been collected. There are indications that there may be an association between Down syndrome and ADHD and autism. A thesis project related to these questions is ongoing in collaboration with professor Elisabeth Fernell at the university of Gothenburg.

### **Endocrine consequences of stem cell transplantation**

### Per Frisk, Anders Öberg and Jan Gustafsson

Children with hematologic malignancies, who have been treated with stem cell transplantation (SCT), may later develop metabolic disease. Together with associate professor Per Frisk and the doctoral student Anders Öberg in the pediatric oncology research group we study mechanisms behind that young adult subjects, treated with bone marrow transplantation during childhood, devlop decreased insulin sensitivity and decreased BMD. An extended study on insulin resistance is presently ongoing including young adults with stem cell transplantation during childhood both in Uppsala and Stockholm.

## **Growth and endocrine function in eating disorders**

### **Ingemar Swenne**

Adequate energy supply is necessary for growth and pubertal development. Eating disorders may have effects both on metabolism and hormone balance. Studies on girls with eating disorders have been ongoing for several years and models predicting growth and menarche during the treatment of eating disorders have been created. In a recent study clinical features of adolescent males with eating disorders have been presented. In a study together with professor Helgi Schiöth, Department of Neuroscience the arousal response to food stimuli in female adolescents with eating disorders have recently been published.

## **Childhood obesity**

### **Anders Forslund and Johan Staaf**

Overweight and obesity during childhood are major health problems both in Sweden and on a global level. A large cohort of obese children followed at the obesity clinic at Uppsala University Children's Hospital is presently being studied within the project ULSCO (Uppsala Longitudinal Study of Childhood Obesity). During the year the cohort within the EU project Beta JUDO has reached 400 obese children and 100 controls. Within the project studies of hypersecretion of insulin as a possible mechanism behind childhood overweight and obesity are ongoing together with professor Peter Bergsten at the Department of Medical Cell Biology. Knowledge on how secretion of insulin develops over time in subjects who later become obese, is fundamental since there may be a window during which it may be possible to change the pattern of insulin secretion.

## **Energy homeostasis in fatty acid oxidations defects**

### Maria Halldin and Jan Gustafsson

The project represents 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 severely decreases the energy production from oxidation of fatty acids. The patients risk 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 and VLCHAD. In a recent publication lipolysis and glucose production were measured in children with LCHAD in order to optimise nutrition of patients with this disorder.

#### **Diabetes**

## Charlotte Nylander, Ylva Tindberg, Jan Gustafsson, Ingemar Swenne and Annika Grönberg

In a doctoral project Charlotte Nylander in Eskilstuna studies factors which influence treatment adherence in the care of chronically ill adolescents, particularly those with type 1 diabetes. The association between risk factors and protective factors for development of risk behaviour has been shown to be particularly important. Revealing "invisible" disabilities, such as neurodevelopmental problems like ADHD is also essential, since such 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.

In another project metabolic control, weight gain during treatment and remaining endogenous insulin production is being studied in children and adolescents with type 1 diabetes. The problem of excessive weight gain during treatment is analysed using growth charts from the school health services and related to aspects of insulin therapy and metabolic control. Remaining endogenous insulin production, which may protect against long-term complications of diabetes, is analysed using an ultrasensitive C-peptide assay and related to insulin treatment, metabolic control and genetic predisposition.

## Perinatal, Neonatal and Paediatric Cardiology Research

### Lena Hellström-Westas

The perinatal, neonatal and paediatric cardiology research group spans over a broad research field but has a main focus on perinatal epidemiology, and physiology of term and preterm infants in the NICU which includes brain physiology (EEG, NIRS), cardiology and lung physiology, pain and stress responses, skinto-skin care and breast feeding.

### Members of the group

Lena Hellström-Westas Professor

Fredrik Serenius Visiting professor

Eva-Lotta Funkquist RN, PhD, Senior lecturer
Margareta Jennische Associate professor
Anders Jonzon Associate professor
Kristina Persson Associate professor

Ola Andersson MD, PhD Ann Edner MD, PhD Laszlo Markasz MD, PhD Elisabet Mattsson RN, PhD MD, PhD Erik Normann Richard Sindelar MD, PhD Gunnar Sjörs MD, PhD Ylva Thernström Blomqvist RN, PhD Sverre Wikström MD, PhD Johan Ågren MD, PhD

Josanne Munsters MD, Guest researcher Victoria Karlsson RN, Research fellow Ylva Fredriksson Kaul MSc, Research fellow Cecilia Montgomery MSc, Research fellow Karl Wilhelm Olsson MD, Research fellow Paola Oras RN, Research fellow Maria Stålhammar MSc, Research fellow Linda Wallström MD, Research fellow Annika Öhman MD, Research fellow Nima Naseh MD, Research fellow

### Collaboration

Professor Geraldine Boylan, Cork

Professor Raffaele Dellaca, Milano

Associate professor Lena Douhan Håkansson, Uppsala

Assoc. professor Renée Flacking, Falun/Uppsala

Professor Roland Flink, Uppsala

Professor Claes von Hofsten, Uppsala

Assoc. professor Karin Källén, Lund

Professor Anders Larsson, Uppsala

Professor Elna-Marie Larsson, Uppsala

Professor Liisa Lehtonen, Åbo

Professor David Ley, Lund Professor Mikael Norman, Stockholm Professor Ingmar Rosén, Lund Professor Karin Stjernqvist, Lund Assoc. professor Sampsa Vanhatalo, Helsinki Professor Linda de Vries, Utrecht

### **Dissertations 2014**

Ylva Thernström Blomqvist (Kangaroo Mother Care), Sverre Wikström (aEEG/EEG in preterm infants), and Ola Andersson (Umbilical cord clamping) had their dissertation in 2012 and 2013, respectively. There were no dissertations in the research group in 2014.

### **Publications**

- 1. Chetaille P, Preuss C, Burkhard S, **Jonzon A**, et al. Mutations in SGOL1 cause a novel cohesinopathy affecting heart and gut rhythm. *Nat Genet* 2014:46(11):1245-9.
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Heart and Lung Foundation

## 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 multicenter clinical study (Uppsala and Åbo) will investigate early effects 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. Oxygenation, heat exchange and fluid balance in extremely preterm infants in the NICU and during surgery

### Johan Ågren, Victoria Karlsson, Laszlo Markasz

These investigations measure oxygenation, 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.

## 5. Maternal, neonatal and long-term effects of delayed, as compared to early, cord clamping in healthy term 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. At 12 months, delayed cord clamping was associated with a modest, but statistically significant positive effect on neurodevelopment in boys. The four-year follow up is in press 2015. There were no effects on maternal haemorrhage from time to cord clamping.

## 6. Neonatal neurocritical care

## Lena Hellström-Westas, Johan Ågren

We have introduced neonatal neurocritical care in the NICU at Uppsala University Hospital, and will investigate mechanisms for perinatal brain injury in high-risk infants, including asphyxiated infants, infants with seizures and very preterm infants. These 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 and soon after birth. We have previously shown that subclinical seizures are prevalent also in extremely preterm infants, and effective treatment may limit brain injury in infants with seizures. Methods include monitoring of amplitude-integrated EEG (aEEG), EEG, NIRS, cerebral ultrasound, MRI, and measurement of various biomarkers. We are part of an EU FP7-funded project, NEMO (Treatment of neonatal seizures with medication off-patent: evaluation of efficacy and safety of bumetanide).

## 7. Early oculomotor function and long-term outcome in very preterm infants Lena Hellström-Westas, Katarina Strand-Brodd, Ylva Fredriksson Kaul, Cecilia Montgomery, Nima Naseh, Claes von Hofsten, Kerstin Rosander, Kristina Persson

This project follows a population-based cohort of very preterm infants, born in Uppsala in 2004-2007. The infants have been followed with repeated evaluation of motor function (the Structured Observation of Motor Performance, SOMP-I), neurological assessment and psychological assessment at  $2\frac{1}{2}$  and  $6\frac{1}{2}$  years. Visual eye tracking ability was tested at two and four months, and in half of the infants MRI was performed at  $2\frac{1}{2}$ -5 years. We are currently investigating if early eye tracking performance is a predictor of neurodevelopment in very preterm infants, and whether it is related to motor function and cerebral MRI findings.

## 8. Breastfeeding in term and preterm infants

## Eva-Lotta Funkquist, Ylva Thernström Blomqvist, Paola Oras

Rates of breastfeeding are decreasing in Sweden, both among term and preterm infants, but the reasons for this are not known. The current projects aim at investigating factors that promote successful breast-feeding

and parental bonding, and includes evaluation of skin-to-skin care, observations of development of breast-feeding patterns in moderately preterm and term infants, and specific interventions for promoting breast-feeding in NICU graduates and healthy infants in the postnatal ward.

## 9. Epidemiological research

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

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. The project also includes register-based research on neonatal seizures and postnatal epilepsy.

## **Pediatric Neurology**

#### **Gunnar Ahlsten**

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

### Members of the group

Ahlsten, Gunnar Associate professor Borgestig, Maria Postgraduate student

Bratteby-Tollerz, Linda MSc

Dahl, MargaretaAssociate professorEeg-Olofsson, OrvarAssociate professorEhrstedt, ChristofferPostgraduate student

Höglund, AnetteMScJonsson, PysseMed LicKimber, EvaPh.DKratz, ÅsaMSc

Kristiansen, Ingela Postgraduate student

Lidström, HelenePh DLiminga, GunnarPh.DLundberg, StaffanPh.DStrinnholm, MargaretaMSc

Strömberg, Bo Associate professor

Söderström, Helena MSc

### Award

Associate professor Orvar Eeg-Olofsson received **Frank Ford Memorial Award** at the meeting of the **International Child Neurology Association (ICNA)** in Foz do Iguacu (Brazil), where he also gave an award lecture.

### **Dissertation 2014**

Pysse Jonsson: 10 year Outcome of Childhood Epilepsy in Well-functioning Children and Adolescents. April 25th 2014.

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Norrbacka-Eugenia foundation
Margaretahemmet foundation
Sunnerdahl foundation
Josef and Linnea Carlsson foundation

## **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 has now been investigated with respect to social and psychological factors and published as a thesis in 2014 with the title: 10-year Outcome of Childhood Epilepsy in Well-functioning Children an Adolescents.

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.

## 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 and att 6½ years chronological age. The results from the 2½ year examinations were published in JAMA May 2013. The results from the 6½ year study are analysed and the process of writing a manuscript for publication is proceeding. Furthermore the follow-up of the same cohort of children at the age of 11 will start in October 2015.

### **Evaluation of motor function**

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 project with the aim to co-ordinate the psychological, neurocognitive and pedagogical long-term follow-up with the medical follow-up of children diagnosed with brain tumours in the Stockholm and Uppsala-Örebro healthcare regions in Sweden is ongoing. Patients were included between October 1<sup>st</sup> 2010 and June 2012. Sixty-two patients met the inclusion criteria. The results are now analysed and the process of writing a manuscript for publication is almost finished.

During 2011 two different doctorial projects were started dealing with brain tumours in children and adolescents diagnosed and treated in the Uppsala-Örebro health care region in Sweden. One part of the projects is to give a broad description of the initial presentation, clinical course and late effects for all children treated for brain tumours in the region 1995-2006. This part is now finished and a manuscript for publication is ready for submission.

In the other parts two different kinds of tumours with low WHO grade of malignancy will be studied.

1/ neuroglial tumours (gangliogliomas and dysembro neuroepithelial tumours (DNET) grade I.

2/ astrocytomas grade I in the posterior fossa.

The objectives are focused on medical, motor and cognitive late effects as well as possible methods for intervention. This project will end up in two different thesis.

### 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.

## **Pediatric Oncology**

## **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.

### Research group

Ljungman, Gustaf Associate professor, adjunct lecturer, research group leader

Arvidson Johan Associate professor Englund, Annika MD, PhD student

Engvall, Gunn RN, PhD

Frisk, Per Associate professor

Frost, Britt-Marie MD, PhD

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Palle Josefine MD, PhD

Pfeifer Susan Adjunct professor in pediatric oncology

Stenmarker, MargaretaMD, PhDThorsell Cederberg JennyMS, PhD studentÖberg, AndersMD PhD student

#### **Publications**

- 1. Hedén L, von Essen L, Ljungman G. Effect of single-dose paracetamol for needle procedures in children with cancer a RCT. Acta Paediatr. 2014 Mar;103(3):314-9. doi: 10.1111/apa.12509. Epub 2013 Dec 19.
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## PhD dissertations

Hedén, Lena RN, PhD dissertation June 2, 2012

### **Funding**

ALF 0,89 milj to the research group 2013

BCF coapplicant 18,5 milj SEK Nistér M, Pfeifer et al. (National biobank for brain- and other solid tumors) 2013-2015

VR coapplicant 40 milj SEK (von Essen et al; Ljungman - U-CARE) 2010-2015

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

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

CF 500.000/year, 3 years (Ljungman et al- oral mucositis) 2014-2016

BCF 500.000/year, 3 years (Ljungman et al- oral mucositis) 2014-2016

BCF 750.000/year, 3 years (Ljungman et al- oral mucositis) 2011-2013

BCF 288 000/year, 2 years (Englund research time Hodgkin project) 2013-2014

BCF 345.000/year, 2 years (Englund research time Hodgkin project) 2015-2016

BCF 750.000/year, 6 years (Ljungman 50% senior research position) 2012-2017

BCF 620.491 kr /year, 2 years; Palle , PostDoc 2012-2013 BCF 300.000/year, 2 years; NovoNordisk 200.000 (Frisk et al- insulinresistance) BCF 400.000/year, 3 years (Frost et al- intersection of curative /palliative treatment) BCF 300.000/year, 2 years (Hedborg, Pfeifer - noncoding RNA in neural tumors) BCF 350.000/year, 3 year 2012-2014 (DiazdeSTåhl, Pfeifer et al)

### Awards and appointments

Gustaf Ljungman winner of the research prize of Uppsala County Council 2012

## Childhood leukemia: biology, treatment, and consequences Targets and function of DNA methylation in acute childhood leukemia

## Lönnerholm, 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.

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, Per Frisk.

A longstanding topic has been long term complications in a special cohort of survivors of autologous bone marrow transplantation for hematological malignancies. Studied complications have included both somatic function and quality of life. 1) Psychosocial functioning including sexual functioning 20 years after treatment with autologous bone 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) Together with Lund (Cecilia Follin) and endocrinologist in Uppsala Britt Edén, we have started a study on patients with ALL who received cranial radiation before 6 years of age. The main investigation consists of measuring growth hormone response after insulin infusion.

## Insulin resistance and bone health in young adults who underwent stem cell transplantation for childhood leukemia

### Per Frisk, Anders Öberg

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 – etiological 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) Compare disease presentation and late effects of treatment in adolescents and young adults based on the hypothesis that they share the same disease characteristics but despite that receive different treatment (collaboration with Denmark).

## Interventions for procedural pain in children and adoslescents 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 its 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 rigor 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 hematological 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) was introduced in the daily routine at the medical, surgery, and orthopaedic wards, excluding neonatology, at the University Hospital of Pediatrics in Uppsala 2013 (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.

# Neuroblastoma: somatostatin receptors as prognostic markers Georgantzy et al.

Neuroblastoma (NB) is the most frequent extracranial malignant tumor of childhood, originating from cells of the adrenal medulla or the sympathetic nervous system and exhibits a unique biological and clinical heterogeneity. Chromogranin A (CgA) is a protein that serves as circulating tumor marker in adult neuroendocrine tumors (NETs), where increasing concentrations indicate disease progression. Elevated CgA concentrations in blood have been reported in NB. Chromogranin B (CgB) is a peptide less studied in tumors derived from nervous system. Neuron-specific enolase (NSE) is a well-established tumor marker in NB, and its concentrations in blood is elevated in advanced staged disease, and is a prognostic marker of poor outcome. Neuroendocrine cells as in NB have certain biochemical similarities with normal nerve cells, and express both general and specific markers/proteins. NB cells have certain neuroendocrine properties like CgA and catecholamine secretion. The aims of this study are to investigate the expression of different neuroendocrine markers, CgA, CgB, NSE etc in in clinical NB, and to determine how these proteins are correlated to tumor stage, biological markers, prognosis and outcome.

## Functional and genetic studies of pediatric neural tumors

### Pfeifer with collaborators Diaz de Ståhl, 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 abberrations in many pediatric medulloblastomas, necessating 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 bio bank 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 o 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.

## **Pediatric Surgery and Pediatric Urology**

#### **Rolf Christofferson**

### Members of the group

Ammar Al-Mashhadi, MD, PhD-student
Gertrud Angsten, MD, PhD
Gillian Barker, MD, PhD
Rolf Christofferson, associate professor, MD, PhD
Johan Danielson, MD, PhD-student
Felipe Donoso, MD
Helene Engstrand Lilja, associate professor, MD, PhD
Peter Flacker, MD
Fanny Fredriksson, MD, PhD-student
Elisabet Gustafson, MD, PhD-student
Niclas Högberg, MD, PhD
Ann-Marie Kassa, RN, research nurse
Göran Läckgren, professor, MD, PhD
Erik Sköldenberg, MD, PhD
Anders Stenbäck, MD, PhD

### Publications 2012-2014

- 1. Dantonello T M, Lochbühler H, Schuck A, Kube S, Godzinski J, Sköldenberg E, et al. Challenges in the Local Treatment of Large Abdominal Embryonal Rhabdomyosarcoma. Annals of Surgical Oncology. 2014;21(11):3579-3586.
- 2. Engstrand Lilja H. Barnkirurgi, Terapikompendium Pediatrik. 2014.
- 3. Fredriksson F, Christofferson R H, Carlsson P, Lilja H E. Locally increased concentrations of inflammatory cytokines in an experimental intraabdominal adhesion model. Journal of Pediatric Surgery. 2014;49(10):1480-1484.
- 4. Reutter H, Draaken M, Pennimpede T, Wittler L, Brockschmidt F F, Ebert A, et al. Genomewide association study and mouse expression data identify a highly conserved 32 kb intergenic region between WNT3 and WNT9b as possible susceptibility locus for isolated classic exstrophy of the bladder. Human Molecular Genetics. 2014;23(20):5536-5544.
- 5. Wester T, Borg H, Naji H, Stenstrom P, Westbacke G, Lilja H E. Serial transverse enteroplasty to facilitate enteral autonomy in selected children with short bowel syndrome. British Journal of Surgery. 2014;101(10):1329-1333.
- 6. Danielson J, Karlbom U, Wester T, Graf W. Efficacy and quality of life 2 years after treatment for faecal incontinence with injectable bulking agents. Techniques in Coloproctology. 2013;17(4):389-395.
- 7. Fredriksson F, Nordborg C, Hallén T, Blomquist E. Haemangiopericytoma presenting with acute intracerebral haemorrhage: a case report and literature review. Acta Oncologica. 2013;52(4):753-758.
- 8. Georgantzi K, Sköldenberg E, Stridsberg M, Jakobson A, Christofferson R. Chromogranin A In Neuroblastoma: Correlation To Stage And Prognostic Factors. 45th Congress of the International Society of Paediatric Oncology (SIOP) 2013, 25th-28th, 2013, Hong Kong, China. Pediatric Blood & Cancer. 2013;60(S3):228-228.
- 9. Hermansson O, George M, Wester T, Christofferson R. Local delivery of bupivacaine in the wound reduces opioid requirements after intraabdominal surgery in children. Pediatric surgery international (Print). 2013;29(5):451-454.

- 10. Högberg N. Experimental and Clinical Necrotizing Enterocolitis. [Thesis]. Uppsala: Acta Universitatis Upsaliensis; 2013. Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine, 898.
- 11. Högberg N, Stenbäck A, Carlsson P, Wanders A, Engstrand Lilja H. Genes regulating tight junctions and cell adhesion are altered in early experimental necrotizing enterocolitis. Journal of Pediatric Surgery. 2013;48(11):2308-2312.
- 12. Normann E, Fahlen A, Engstrand L, Engstrand Lilja H. Intestinal microbial profiles in extremely preterm infants with and without necrotizing enterocolitis. Acta Paediatrica. 2013;102(2):129-136.
- 13. Angsten G, Finkel Y, Lucas S, Kassa A, Paulsson M, Engstrand Lilja H. Improved outcome in neonatal short bowel syndrome using parenteral fish oil in combination With ω-6/9 Lipid Emulsions. JPEN Journal of Parenteral and Enteral Nutrition. 2012;36(5):587-595.
- 14. Högberg N, Carlsson P, Hillered L, Meurling S, Stenbäck A. Intestinal ischemia measured by intraluminal microdialysis. Scandinavian Journal of Clinical and Laboratory Investigation. 2012;72(1):59-66.
- 15. Högberg N, Carlsson P, Hillered L, Stenbäck A, Engstrand Lilja H. Intraluminal intestinal microdialysis detects markers of hypoxia and cell damage in experimental necrotizing enterocolitis. Journal of Pediatric Surgery. 2012;47(9):1646-1651.

#### **Dissertations 2014**

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### Agencies that support the work/Funding

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# 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 percieved 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).

## 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 wirh home parental nutrion due to intestinal failure. The manuscript is in preparation for publication.

## 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 Lilia

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=1017) 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. Kineret (Anakinra) an IL-1 receptor antagonist, Rapamycin (Sirolimus), PVAC (Carbazate-modified

polyvinyl alcohol). 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 peritoneal tissue 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 inhibitors controlling different aspects of thromboinflammation. The aim of this project is to gain knowledge that may improve the short- and long term survival of transplanted hepatocytes

## Microdialysis studies in experimental and clinical necrotizing enterocolitis

### Niclas Högberg, Anders Stenbäck och Helene Engstrand Lilja

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

## Implementation of the national follow-up program for anorectal malformations in a tertiary university hospital

### Björn Sjöström, Rolf Christofferson

Anorectal malformation means absence of a normal anus, most oftenly with a fistula from rectum to the perineum, vestibulum or urethra. Approximately forty children are born with anorectal malformations annually in Sweden, and of these, 10-12 children are operated at Akademiska sjukhuset. Up to 78% of children with ARM have associated malformations, e.g. genitourinary, spinal, cardiac or skeletal. Adults and adolescents that have been operated for ARM report impaired anal continence and less quality of life than matched controls, which underlines the importance of a

structured follow-up with early and aggressive treatment of e.g. constipation and soiling. In order to harmonize the follow-up, the Swedish Pediatric Surgical Association launched a national follow-up program in 2010. The aims of this study are to (1) to validate the implementation of the program at Akademiska, (2) to classify ARM according to the Krickenbeck classification, and (3) to analyze the functional outcome at 5 and 14 years, during the interval of 1999 to 2014.

## 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 Nordensköld and Anna Nordenstam at the Astrid Lindgrens 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 alla 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 bladde 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.

### **Paediatric Inflammation**

### **Kjell Alving**

The group of Paediatric Inflammation Research covers a wide spectrum of paediatric specialties, roughly divided into five interrelated subgroups focusing on allergology, pulmonology, rheumatology, gastroenterology, and nephrology, respectively. During 2014, Kjell Alving was appointed Professor of Respiratory Pharmacology.

## Members of the group during 2014

Kjell Alving, professor Lillemor Berntsson, PhD Magnus Borres, adjunct professor Maria Cederblad, PhD student Gianni Celsi, associate professor Ingrid Dahlbom, PhD Sten Dreborg, associate professor Tony Hansson, associate professor Charlotte Heijkenskjöld Rentzhog, PhD student Annika Hollsing, PhD Lars Holmberg, PhD Jennifer Johnsson, PhD student Johan Kaarme, PhD student Pia Kalm Stephens, research nurse Birgitta Karanikas, research nurse Hans Kollberg, associate professor Stina Krantz, PhD student Elisabet Lundmark, PhD student Åsa Neuman, PhD student Tryggve Nevéus, senior lecturer Lennart Nordvall, associate professor Britt-Inger Nyberg, research assistant Niklas Nyström, PhD student Christophe Pedroletti, PhD Inger Jönson Ring, PhD student Jörgen Syk, PhD Nikos Tsolakis, PhD student Monica Westerlund, associate professor

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Anders Öman, paediatrician

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During the year Kjell Alving (co-applicant) received a 5-year grant of SEK 35 million from the Swedish Foundation for Strategic Research together with Karolinska Institutet and Gothenburg University.

## Current research projects within the group

## **Allergy**

The allergological research is focused on the characterization (phenotyping) of children and young adults with asthma with the help of biomarkers. Senior researchers in this subgroup are Kjell Alving, Magnus Borres, Lennart Nordvall, Christophe Pedroletti and Sten Dreborg, and PhD students are Charlotte Heijkenskjöld Rentzhog, Jennifer Johnson and Nikos Tsolakis. The research is mainly based on large patient cohorts where clinical data and biobank material are collected. For example, the MIDAS cohort (532 asthma patients and controls, age 10-35 years at baseline survey), the SPAIS cohort (959 children, age 13-14 years at baseline survey), and the NOAK cohort (187 adults with asthma participating in an interventional study over one year) are utilized in our research. A threeyear follow up of the MIDAS cohort and a 15-year follow up of the SPAIS cohort has been ongoing during 2014. Main research objectives are: 1. Development of feasible biomarkers in preschool children. 2. Development and clinical evaluation of local and systemic biomarkers of Th2-driven inflammation, alone and in combination. 3. Characterization of non-atopic asthma in young subjects. 4. The influence of IgE sensitisation pattern on inflammation and astma morbidity. The collaboration with Karolinska Institutet has been further developed during the year, resulting in a large grant from the Swedish Foundation for Strategic Research. Further, collaboration with diagnostic industry in the region (Aerocrine, Thermo Fisher Scientific and Olink) has been ongoing and further developed. The common theme for these collaborations is the development of clinical biomarkers in asthma.

## **Pulmonology**

The group's pulmonological research is focused on cystic fibrosis (CF) and the related disorder primary ciliary dysfunction (PCD) and involves Annika Hollsing, Stina Krantz and Hans Kollberg. The group participates in an EU-sponsored double-blind study investigating egg yolk-derived immunoglobulin (IgY) as a promising prophylactic treatment of pseudomonas infections in CF. 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. The group is also conducting a prospective 5-year study on the evaluation of novel lung function tests and non-invasive exhalation tests, to enable the early detection of decline in lung function, signs of upcoming exacerbations, and bacterial colonisation in CF. The group is specifically looking at the clinical utility of exhaled and nasal nitric oxide in CF and PCD. The group is also part of a Nordic research consortium that perform multicentre research on CF. During the year, the concortium has focused on Staphylococcus aureus and aspergillus infections in CF, and planning has been undertaken for a study investigating the influence of different fatty acids on pulmonary function as well as for two pharmaceutical studies on gene modification and potentiation in patients with CF.

#### Rheumatology

The main focus of rheumatological research is on patients with juvenile idiopathic arthritis (JIA). The Nordic multicenter study on JIA is ongoing, and preparations for a 15-year follow-up study were made during 2014. Lillemor Berntson will continue as the Swedish coordinator and supervisor, and Maria Ekelund (paediatrician, Jönköping) will start PhD studies within the project. Also within the project, a study on potential serological risk markers has been finalised and published in collaboration with Johan Rönnelid, Department of Medical Sciences. Yet another study within the project, on ankle arthritis as a risk marker for severe disease, has continued during the year. This is part of a PhD project by Anna-Clara Esbjörnsson (physiotherapist, Karolinska Institutet). In a regional project on medical treatment of children with JIA for the last 10 years, the medical burden

of current medical strategies and difficulties in clinical practice has been presented. In the frame of an odontological PhD project, a publication on risk factors for temporomandibular alterations in patients with JIA has been published. The project on microbiota and anti-inflammatory effect of exclusive enteral nutrition in JIA has continued. The project has expanded during 2014 to include patients from the Sach's Children and Youth Hospital, Stockholm. Results from the first patient in a pilot study was published in 2014.

## Gastroenterology

Much of the group's gastroenterological research is focused on paediatric Crohn's disease. A translational research group with preclinical and clinical researchers from Uppsala University and Karolinska Institutet work on a hypothesis based on the potential role of RNA viruses as a pathogenic factor in Crohn's disease. Two retrospective studies have been finished and a large prospective cohort of paediatric Crohn's disease patients is now ready for further examination. In a subcohort, the effect of exclusive enteral nutrition therapy (ENT) on intestinal virome and microbiome is studied. Together with colorectal surgeons, a prospective cohort of Crohn's disease patients who need surgical treatment with ileocecal resection is being developed. A collaboration with SciLifeLab is under development. In a pilot projects, ENT is tested against obesity. In collaboration with paediatric surgeons, the treatment of enteral dysbiosis is evaluated in children wtih short bowel syndrome.

## **Nephrology**

Uppsala University Children's Hospital is a recognized international centre of expertise in research on paediatric lower urinary tract function. Tryggve Nevéus, who leads these activities, has recently been elected President of the International Children's Continence Society (ICCS), which is the relevant global research organisation in this field. 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 - the latter called urotherapy. The first two of these methods are evidence-based, whereas urotherapy is not. In a prospective, randomised study the group has during 2014 been able to provide evidence that urotherapy is in fact ineffective for this indication. These results, which have been provided by Tryggve Nevéus and Maria Cederblad, will have global impact. 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, conducted by Tryggve Nevéus and Elisabet Lundmark, it has been evaluated whether noradrenergic medication, influencing arousal mechanisms, is useful in therapy-resistant enuretic children. This study has just been completed and it can be seen that active treatment is indeed better than placebo. The results will be published during 2015. A prospective study on the treatment of therapy-resistant enuresis with an orthodontic device that widens the nasal airways during sleep has been started, and approximately one third of the patients have been evaluated. This study is performed by Tryggve Nevéus and Ingrid Jönson Ring.

## Child health and parenting

The group is interdisciplinary and focuses on societal support to children and their families. Projects range from prevention through early intervention to specialised child protection. Our special area of interest is parenting support, including both universal services and parenting programmes. We specifically deal with effectiveness studies as well as implementation research and translating research results into practice. All trials we conduct include a health economic evaluation of the intervention as well as qualitative studies with different stakeholders, including users.

## **Child Health and Parenting Research Group**

### Anna Sarkadi, M.D., PhD, Associate professor, Adjunct senior lecturer

### Members of the group during 2014

PärBokströmPhD studentMariaCederbladRN, PhD student

Anton Dahlberg Psychologist, Research Assistant

Natalie Engsheden RN, PhD student

Helena Fabian Postdoc

Inna Feldman Research fellow

Karin Fängström Clinical Psychologist, PhD student Kine Johansen Licensed Physiotherapist, PhD student

DagmarLagerbergDocent emeritaStevenLucasM.D., PhDMargarethaMagnussonRN, PhD

Laleh Nayeb Licensed Speach Therapist, PhD student

GabrielOttermanM.D., MPHJennyPitkänenResearch AssistantRaziyeSalariResearch fellowFilipaSampaioPhD student

Anna Sarkadi M.D., PhD, Associate Professor

Claes Sundelin Professor emeritus Antónia Tökés Research Assistant Michelle Voon Research Assistant

Thomas Wallby RN, PhD Michael Wells PhD student

Monica Westerlund PhD, Docent emerita

Annika Åhman RM, PhD

Monica Östberg PhD, Docent emerita

#### Dissertations 2014

Annika Åhman

#### Publications 2011-2014

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#### Agencies that support the work/Funding

2012-2018	FORMAS, FAS, VINNOVA, VR common grant for child and youth mental health research.
	Long-term effects of population-based parenting interventions. Outcomes, costs and benefits
	29 400 000 SEK
2014	ALF 851 000 SEK
2014	Skandia Health economic evaluation of prevention of mental health problems in children
	1 600 000 SEK
2014	Allmänna Barnhuset. A validation study of the computer software In My Shoes
	350 000 SEK

## **Project 1: 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**'s 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 and to provide children with evidence-based advice.

Although child health services should address both mothers and fathers, the latter are often omitted in both research and child health care. **Michael Wells** is a PhD student with focus on father-inclusive policies and practices in Sweden. In his upcoming dissertation he makes the point that father-friendly policies do not necessarily need to father-friendly practices in the frontline services for children's healthcare.

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 Professor emeritus **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.

The senior members of the group, **Monica Östberg and Monica Westerlund** are valuable resources and regularly visit the research seminars and participate in discussions on study design and PhD projects. Monica Westerlund is also co-supervisor for Laleh Nayeb.

# Project 2: Effects, costs, and cost-effectiveness 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. **Antónia Tökés and Jenny Pitkänen** are research assistant in the project, responsible for the sorting and scanning of more than 6000 questionnaires yearly.

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 student **Filipa Sampaio** and research assistant **Michelle Voon** 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. Our most recent PhD **Annika** Åhman has adapted and is now concluding the RCT of a web-based decisional aid to improve the chances of fetal diagnostics actually being based on an informed decision.

## **Project 3: 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 the circumstances of child abuse in Swedish society, 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 Fängström** and **Pär Bokström** are therefore working on validating a computer-assisted interview called In My Shoes, for use with preschool children. Of today, 46 of the 50 planned interviews have been conducted and research assistant **Anton Dahlberg**, also a psychologist, assist the group with important work rating the interviews to ensure that there is an objective observer, not involved in the project that rates accuracy of children's accounts in relation to a video-recorded child health visit.

## Student projects at the research group

Rebecka Lindsten. Svenska förskolebarns beteenden skattade av föräldrar och förskolepedagoger genom Strenghts and Difficulties Questionnaire

**Supervisors:** Helena Fabian and Raziye Salari

Åsa Nordenhäll. FÖRÄLDER I FACEBOOKLAND – En kvalitativ intervjustudie med föräldrar

födda på 80-talet om information och stöd i föräldraskapet

Supervisor: Anna Sarkadi

## **Undergraduate Teaching**

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

#### **Tryggve Neveus**

During 2014, as in previous years, a large number of students have participated in the broad range of programmes available at the Department. 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. We have a crucial role in the education of biomedical laboratory scientists. The Department also gives the postgraduate Registered Midwife course, the postgraduate course in Specialist Paediatric Nursing as well as the International Health Masters program.

## The postgraduate Registered Midwife Programme

The registered Midwife Programme is a 90 ECTS degree program. The cornerstones of the education are reproductive health and midwifery, and the students are prepared for independent work within the fields of maternal health, youth health (contraceptive counselling), and infertility. The programme provides theoretical as well as clinical education and has a profile in global reproductive health and violence against women because of excellent resources at the department. 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 ECTS, is a part of the fourth semester of the three-year Nursing programme, which involves several departments at Uppsala University. Both theoretical and practical education, as well as web-based seminars and seminars using problem-based learning methods are included, and the course is given every semester. The nursing programme is presently undergoing extensive restructuring, which also affects the courses within the program given by our Department. One consequence will be that an elective course on paediatric and gynaecologic nursing in a global perspective will be started.

#### The Biomedical Laboratory Science Programme

Students attend their first course, Basic Biomedical Laboratory Science, during their first semester, and their project work during their last semester. The students from Mittuniversitetet are also examined at our department. Collaboration with Ghent and Dublin within the Erasmus programme include several students each year.

# 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 several hospitals outside Uppsala for parts of the students' clinical education. The students' rating of the courses have been steadily improving during recent years: the paediatric course is rated highest of all clinical courses within the medical study program. A restructuring of the medical study program is under way and will be implicated during 2015.

## The International Health Master Programme

The International Health Master Programme is a 120 ECTS degree program that yields a M.Sc. in International Health. The programme starts with a course on basic Global Health which is followed by courses in research methods, global nutrition, sexual and reproductive health and rights, public health in humanitarian action and child health. The studies end with a 30 ECTS thesis on a global health issue.

## Research Education

#### Lena Hellström Westas

The department has extensive PhD education within Paediatrics (including paediatric nursing), Paediatric Surgery, Obstetrics/Gynecology (including midwifery) and International Maternal and Child Health (IMCH). The number of doctoral students has increased during the last years and is now stable above 100. Fourteen new doctoral students were admitted in 2014 (Paediatrics 5; Obstetrics/Gynecology 4; IMCH 5). During the year, there were 8 dissertations (Paediatrics 1; Obstetrics/Gynecology 3; IMCH 4), 1 licentiate dissertation and 15 half-time seminars, as compared to 2014 when there was 14 dissertations, and 16 half-time seminars. At the end of 2014 there were 114 registered doctoral students at the Department of Women's and Children's Health (Paediatrics 45; Obstetrics/Gynecology 38; IMCH 31).

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 has increased during the last years. International doctoral students constitute a substantial proportion of the doctoral students. The projects are often 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.