

Department of Women's and
Children's Health

ANNUAL REPORT

2007

Introduction

During 2007 the Department of Women's and Children's Health expanded its field of action through the introduction of a new education programme for midwives and the incorporation of the unit for pediatric surgery. The national centre for men's violence against women, which was a unit within our department, became a department of their own during 2007. A fruitful cooperation has, however, continued especially within the research area.

The department recruited two associate professors, Agneta Skoog Svanberg and Margareta Larsson, with the main responsibility within the midwife programme. Their positions are combined, meaning that they work with clinical tasks for 30% and 70% is devoted to education and research. The department strongly advocates such positions, since presence in the clinical environment is a prerequisite to formulate relevant clinical research questions and to be updated as a clinical teacher. Cooperation with research groups from preclinical and biomedical departments will widen our research areas and make it possible to implement new methodologies in clinical research. The department has also, during 2007, had the pleasure to welcome two other well qualified associate professors, Lena Hellström Westas in perinatal medicine and Birgitta Essén in international maternal health.

To succeed as a clinical research department requires a well functioning cooperation with the hospital, Akademiska sjukhuset. The university as well as the hospital organisation has changed radically in the last years. The units are now, on either side, larger than before and it is considered impossible to have a common leadership, which previously was routine in Uppsala. Hopefully, this new organisation will turn out to be successful but today the ways of cooperation need improvement. The university departments are depending on the hospital leadership concerning key issues such as premises, bed-side teaching, recruitment of research students, tutors etc. A challenge for 2008 is to find new and better ways to cooperate with our clinical counterpart from the hospital.

Research within the department is highly diversified with focus on pediatrics, pediatric surgery, obstetrics and gynecology and international maternal and child health. The final version of the Kof-evaluation was presented during the autumn 2007. The department received high ranks for its research within international maternal and child health, pediatric inflammation and pediatric endocrinology. We are proud over these positive comments and believe that these areas have the potential to become even stronger in the years to come. It must, however, also be said that the Kof-report concerning our department contains misunderstandings and mix-ups of projects from different research groups, which does not add to its credibility.

The department of Women's and Children's Health has extensive assignments within education programmes for medical and nurse students in obstetrics and gynecology, pediatrics and global health, for nurses specialising in obstetrics and gynecology (midwifery) and pediatrics. Moreover, a great number of courses are organised on graduate and post-graduate levels to people working within the healthcare system. These courses are given to improve clinical skills for persons working in the Nordic countries as well as those engaged in international healthcare.

Finally, to be the head of the department of Women's and Children's Health is a privilege and a most inspiring task. Clinical research focusing on patients is a necessity to develop new diagnostic procedures and new treatment modalities. The department focuses on this kind of research and will continue to do so in the forthcoming years. A research staff with insight in the clinical world and active in teaching activities is the best guarantee to reach our goals.

Uppsala in February 2008

Ove Axelsson

Head of the department of women's and children's health

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

Yearly report 2007

During the year 2007 more than 600 students have participated in the broad range of programs available at the department of Women's and Children's Health, Uppsala University. The level of education ranges from undergraduate courses for nurses and medical students to Master Programs in International Health.

The undergraduate/graduate courses given by the department include:

Obstetrics and Gynecology within the Registered Nurse Programme

Pediatrics within the Registered Nurse Programme

The Registered Midwife Programme

Obstetrics and Gynecology within the Medicine Programme

Pediatrics within the Medicine Programme

Global medicine, which is an elective course for medical and nurse students and include a 2-week study visits to hospitals and health centres in a low-income country.

Postgraduate courses for nurses include:

Nursing care of children and adolescents with general pediatric conditions,

Child and adolescent health care, child and adolescent psychiatric care

Single courses include:

Fetal monitoring

Obstetric ultrasound

Breastfeeding

Neonatal intensive care

Children and pain

In January 2007 the Registered Midwife program was introduced. The Registered Midwife program is a 90 ECTS degree program including practical training and a 30 ECTS examination. The cornerstones of the education include formal training in reproductive health and obstetrics. Because of the available resources at the department particular emphasis on global reproductive health is provided.

The Master's program in International Health is a 2-year program that attract physicians, nurses, midwives, nutritionists as well as students with a social sciences background but interested in global health issues. Yearly 25-30 participants from all over the world are selected from several hundred applications. Core courses in international health and research methodology are followed by elective courses and completed by project planning, field work and compilation and defence of a master's thesis.

The department is also involved in an European joint masters programme in Humanitarian Assistance, the NOHA programme, contributing with, among other components, courses on public health in humanitarian assistance.

On behalf of Sida and jointly with Göteborg University and Karolinska Institute the department is running an International Training Programme focusing on global Child Survival issues. Senior colleagues with responsibilities for child health programs from ministries to non-governmental programs attend a monthly course and subsequent research/development work and follow-up workshop in their region. In 2007 the focus was on Asia.

Inger Sundström Poromaa
Director of undergraduate studies

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Richard Sindelar teacher representative

Matts Olovsson teacher representative, deputy

Inger Sundström Poromaa teacher representative, deputy

Karin Wennqvist representative for technical/administrative personnel

Barbro Westerberg representative for technical/administrative personnel, deputy

(from July 2007)

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2- Obstetrical Research

Ove Axelsson, MD, PhD, Professor

3- Gynaecological Endocrinology

Tord Naessén, MD, PhD, Associate professor

4. National Center for Knowledge on Men's Violence Against Women

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5- International Maternal and Reproductive Health

Elisabeth Darj, MD, PhD, Associate professor

6- International Child Health and Nutrition

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7- Paediatric Endocrinology

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8- Paediatric Oncology

Gudmar Lönnholm, MD, PhD, Professor

9- Paediatric Neurology

Gunnar Ahlsten, MD, PhD, Associate professor

10- Perinatal and Neonatal Medicine and Pediatric Cardiology

Anders Jonzon, MD, PhD, Associate professor

11- General Pediatric

Lennart Nordvall, MD, PhD, Associate professor

12- Pediatric Surgery and Pediatric Urology

Rolf Christofferson, MD, PhD, Associate professor

Scientific Reports

CLINICAL AND EXPERIMENTAL REPRODUCTIVE BIOLOGY

Matts Olovsson

PREECLAMPSIA

M Olovsson, O Axelsson, A-K Wikström, H Åkerud, P Nash, K Bjersand, C Eriksson, M Palm, G Wikstrand etc.

Studies of differences between early and late onset disease have been performed. Clinically there are clear differences between early and late onset preeclampsia and maybe they are two at least partly different diseases that should be diagnosed and treated differently. Our studies have so far been focussed on markers for inflammation, angiogenesis and oxidative stress in both serum/plasma and placental biopsies. Two thesis with data from these studies were presented during 2007, Peppi Nash and Anna-Karin Wikström. These theses also included data from an animal model for studies of preeclampsia and also an epidemiological study of the relationship between preeclampsia and cardiovascular disease later in life. Currently we are also studying potential markers to predict preeclampsia. We have also initiated a study where placental metabolism is studied in situ using MRS. Further, we have planned an initiated a study of the relationship between preeclampsia and different types of cardiovascular changes later in life. Understanding preeclampsia will make it possible to predict, diagnose and better manage a common disease that is a potential threat against both mother and foetus.

ENDOCRINE DISRUPTING CHEMICALS AND FEMALE REPRODUCTIVE HEALTH

M Olovsson, A Stavreus-Evers, C Bredhult, M Lundmark

It has been shown that several environmental contaminants such as PCB and DDT have endocrine disrupting capacity, thus meaning that they may have effects on female reproductive functions. Thousands of chemicals are thought to have this capacity but it is not known. A lot of information can be achieved from animal experiments. We are working with cell culture systems to screen for potential effects on female reproductive functions from chemicals. We use endometrial cells such as human endometrial endothelial cells in our test systems. This as a part of an EU project, ReProTect, within ECVAM. One thesis within this project was presented during 2007, Carolina Bredhult. Three manuscripts within this project were published during 2007. A new PhD-student will continue the work within this project. The work is done in cooperation with several other European groups. The aim with our part of the project is to develop a method that can be used to estimate the probability that a chemical might hamper normal female reproductive functions.

ENDOMETRIAL ANGIOGENESIS AND ENDOMETRIOSIS

M Olovsson, V Bourlev, C Moberg, N Iliasova

During the last years we have worked with the regulation of normal endometrial angiogenesis by performing micro array experiments and the first manuscript is on its way. This work is done in cooperation with a group in Cambridge. We have also continued our work with endometriosis and studied how the concentrations of several markers for angiogenic activity were reflected by surgical removal of the endometriotic lesions. There were two manuscripts prepared during autumn 2007 and they will soon be submitted. The work with endometriosis is done in cooperation with a group in Moscow.

STUDIES ON EMBRYO, FALLOPIAN TUBE, ENDOMETRIUM AND THE IMPLANTATION PROCESS

The communication between the embryo and maternal tract seem to be important for transport through the fallopian tube and subsequent implantation. We have studied gene expression in human embryos, which has resulted in one manuscript ready for submission and one manuscript in preparation. Our study shows amazingly regulated development of the embryo which has very little communication with the maternal side. Better methodology in cryopreservation is important to increase successrate at IVF treatment. Our data on vitrification of embryos has resulted in one submitted manuscript, one manuscript in preparation and one additional ongoing study. One PhD student, F hambiligki is working on the project. **(A Stavreus-Evers, F Hambiliki, J Kere, O Hovatta, P Svalander, AJ Kartberg, PO Karlström etc.)**

The transport of the embryo through the fallopian tube is crucial for the reproduction. Our data show that prostaglandins are involved in the fallopian tube contractility, and that this event is hormone dependent. We have also found evidence of communication from the embruo to the meternal tract during the transport through the fallopian tube. These data was presented in K Wånggrens thesis. Cecilia Olsson's 10p project for BMA exam resulted in a new tissue culture method for studies on hormone regulation of fallopian tube in vitro and a manuscript will be finalized for submission. A new PhD student has been enrolled into the project. **(A Stavreus-Evers, K Wånggren, A Rumman, L Aghajanova).**

The development of the endometrium is crucial for embryo implantation. The development is regulated by steroid hormones. Our data show that not only the classical hormones, estrogen and progesterone is important, also thyroid hormone play a role in endometrial receptivity. All data showing the distribution and function of thyroid hormone in the human ovary is submitted. All samples for Frida Husseini's first study on the role of thyroid hormone in the human endometrium are collected. **(A Stavreus-Evers, L Skjöldebrand-Sparre, BM Landgren, F Hosseini).**

Paracrine, juxtacrine, and autocrine interactions through growth factors and cytokines are important for all phases of the human implantation process. Our group have studied severa factiors such as LIF, HB-EGF, Ghrelin and IGF1. The studies on endometrium have resulted in one 10p project, T Allhammar, BMA and one master thesis, A Rumman, BMA. These studies show the presence, regulation and function of ghrelin and its receptor in the receptive endometrium. One study Muc16 in the endometrium is accepted for publication in Biology of reproduction, January 2008. The first study on IGF1 receptor shows the importance for IGF1 receptor for embryo development is summarized for the first manuscript. The second study on the role of IGF1 for ovulation has resulted in a 10p project for Lisa Rådström BMA. The uterine tissue is not yet analyzed. Using cell culture models we show that down regulation of Muc16 for implantation and that mifepristone inhibits embryo attachment. **(A Stavreus-Evers, K Gemzell Danielsson, C Ha, J Inzunza etc.)**

The transport of water is important for endometrial function. We have shown that AQP1 in endometrium from women with menorrhagia compared to control women, which shows different expression of AQP1 in blood vessels between these two groups, is published. Anna Hildenbrand's second publication on AQP1 in the endometrium is submitted. Further studies using cell culture models are ongoing. Anna Hildenbrand held her half time seminar in November 2007. **(A Stavreus-Evers, H Åkerud, K Gemzell Danielsson, A Hildenbrand, PGL Lalitkumar)**

UNEXPLAINED INFERTILITY

These studies are performed in collaboration with colleagues in Hungary, Italy Estonia, UK and USA. **A Stavreus-Evers, T Syvänen, M Rees, C Vanhainen, L Aghajanova, A Yngve, A Skoog Svanberg, A Salumets, T Nilsson, K Wänggren, Z Kormyanos, C Lombardo etc.**

For women with unexplained infertility, there are reasons to believe that endometrial factors can be involved. Today, we lack good diagnostic tools for these women, and the treatment could be more efficient. Our studies show that LIF and its receptors (LIFR and gp130) and inhibitor (SOCS1) in endometrium from fertile and infertile women is submitted. This study shows that it is more common with low LIFR expression concomitantly with high SOC1 expression in endometrium from women with unexplained infertility compared to fertile controls. A similar study on HB-EGF and its receptors showing lower HB-EGF expression in endometrium from infertile women is accepted for publication in Reproductive Sciences.

Genetic variations might influence endometrial receptivity and infertility treatment. Signe Altmäe has published her first paper in her Tartu-project and statistical evaluation is ongoing for her second study. Almost all data is analyzed in the Tissue Factor study, the manuscript is planned for submission 2008. One additional study on sex steroid hormones is ongoing and has resulted in an abstract accepted for the congress in Gynecologic Endocrinology in Florence 2008.

Low folat levels have been related to fertility problems. Data from Tiina Syvänen's and Cecilia Vanhainen's master thesis's show that it is more common with the polymorphism in the MTHFR 677 TT in women with unexplained infertility compared to the general population. Statistical analysis of 10 different genes involved in the folate metabolism in relation to infertility is ongoing.

POSTPARTUM DEPRESSION

A Skalkidou, F Skalkidou, I Sundström Poromaa, M Olovsson etc.

Postpartum depression (PPD) affects approximately 10% of all mothers within one year of delivery. It seems as though some women are more prone to be affected, whether this is due to biological, psychological or social factors. There is growing evidence for a role of estrogen, progesterone, leptin and adiponectine, as well as of several gene polymorphisms in the pathogenesis of PPD. Seasonal variation for this condition has only been reported in one small study so far. A questionnaire containing the Edinburgh Postnatal Depression Scale (EPDS) as well as several other variables was given to all the women who gave birth in Uppsala's university hospital during the period May 2006 - May 2007, in order to complete (a) 5 days, (b) 6 weeks and (c) 6 months after delivery. Blood samples were collected from 533 women. The fact that 2.332 women (65% of all eligible women, 92% of those that consented to the study) responded to a least one of the three questionnaires, gives the unique opportunity to unveil and confirm several epidemiological associations. Biochemical and genetic analyses could give further insight in the pathogenesis of PPD, as well as the identification of markers that could help health professionals to promptly identify women at risk. This of paramount importance not only for the mental health of the new mother, but also for the normal psychosocial development of her infant, and well being of her whole family.

OVARIAN CANCER

I. Skírnisdóttir, B. Sorbe T. Seidal, E. Wilander, H. Garmo, L. Holmberg och K. Lindborg.

Prognostic factors for epithelial ovarian cancer in FIGO-stages I-II. We have studied the relevance of p53, bax, p21, p27, PUMA och c-MYC, EGFR, VEGF-R, VEGF and PTEN as prognostic factors. A future project within genomics has been planned. We have also published a paper about borderline ovarian tumours and ovarian cancer in Sweden in 1960-2005

RELATIONSHIP BETWEEN THE USE OF IUD AND PID

Case-control study of serious infections in the Fallopian tube in women >35 during 2001-2004 and the relationship to the use of intrauterine device (IUD). **Dr Ingrid Wikström** coordinates the study where users of IUD are compared with non-users among women with serious pelvic inflammatory disease. Data from patient files have been collected, statistics done and preparation of manuscripts initiated.

IMPROVEMENT OF ORGANISED CYTOLOGICAL SCREENING BY SELF-SAMPLING

I. Skírnisdóttir, B. Sorbe T. Seidal, E. Wilander, H. Garmo, L. Holmberg och K. Lindborg.

Women not attending organised cytological screening program are offered testing of vaginal smear obtained using a novel self-sampling device. We have shown that there is a high prevalence of oncogenic HPV in women not attending organised cytological screening and that about half of the women not attending the organised cytological screening program actually performs the self-sampling. The results have been presented in several publications, abstracts and presentations.

Members of the group during 2007

| | |
|-------------------------|--------------------------------|
| Olovsson, Matts* | Teacher representative, deputy |
| Alkistis, Skalkidou* | Ph.D |
| Arnadóttir, Ragnheidur* | Research student |
| Bourlev, Alexei | Research student |
| Bourlev, Vladimir | Professor |
| Bredhult, Carolina | Postgraduate student |
| Brodin, Thomas | Research student |
| Bäcklin, Britt Marie | Doctor of philosophy (Ph.D) |
| Dabo, Fatima* | Research student |
| Eriksson, Christoffer | Research student |
| Fu, Xin | Associate Professor |
| Gudmundsson, Johannes* | Medical doctor |
| Hambiliki, Fredwell | Ph.D |
| Holmgren, Corinne | Postgraduate student |
| Holte, Jan | Ph.D |
| Hudecova, Miriam* | Postgraduate student |
| Iliasova, Natalia | Research student |
| Karlström, Per-Olof* | Ph.D |
| Kask, Kristina* | Postgraduate student |
| Lindahl, Magnus* | Postgraduate student |

| | |
|---------------------------|----------------------|
| Lindborg, Katarina* | Research student |
| Lindholm, Åsa | Postgraduate student |
| Ljunger, Elisabeth* | Postgraduate student |
| Lundkvist, Örjan* | Associate Professor |
| Lundmark, Malin | Postgraduate student |
| Moberg, Christian* | Research student |
| Nash, Peppi* | Ph.D |
| Persson, Pär* | Research student |
| Rezapour, Masoumeh* | Associate Professor |
| Segebladh, Birgitta | Research student |
| Skirnisdottir, Ingridur* | Ph.D |
| Skoog Svanberg, Agneta | Senior Univ Lecturer |
| Stavréus-Evers, Anneli | Research assistant |
| Sundström Poromaa, Inger* | Professor |
| Syvänen, Tiina | Research student |
| Wesström, Jan | Postgraduate student |
| Wikstrand, Gölin | Research student |
| Wikström, Anna-Karin* | Ph.D |
| Wikström, Ingrid | Ph.D |
| Volgsten, Helena | Postgraduate student |
| Wångren, Kjell* | Ph.D |
| Åkerud, Helena | Ph.D |
| Geifalk, Ulla | Laboratory assistant |
| Nordling, Margareta | Laboratory assistant |
| Moby, Lena | Research nurse |

Publications 2005-2007

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Dissertations 2007

Peppi Nash,

Kjell Wånggren,

Anna-Karin Wikström,

Carolina Bredhult,

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The Swedish Research Council 1.095.000 SEK

Åke Wibergs foundation 150.000 SEK

FORMAS 600.000 SEK

EU 300.000 SEK

OBSTETRICAL RESEARCH

Ove Axelsson

During 2007 two dissertations were presented. Karin Zetterström's thesis, entitled "Chronic Hypertension and Pregnancy", showed that chronic hypertension in pregnant women increases the risk for stillbirth and neonatal death in male, but not in female, offspring. The mortality risk was mediated by severe preeclampsia, placental abruption and disturbed fetal growth. Moreover, the thesis could show that women born small for gestational age (SGA) had a significant increased risk for severe, but not mild, preeclampsia. Another thesis, also presented in 2007 from another research group at our department, presented a hypothesis that early – and late-onset preeclampsia might be different disorders. Preeclampsia is an enigmatic syndrome associated with an increased maternal morbidity and an increased perinatal mortality and morbidity. In developing countries it is also a substantial cause of maternal mortality. Our research group focuses on several projects with the aim to elucidate the etiology of preeclampsia and to improve the clinical management of severe cases. We cooperate with the research group in clinical and experimental reproductive biology at our own department as well as professor Anders Larsson from the department of medical sciences and associate professor Samar Basu from the department of public health and caring sciences. Our concentration on this subject has led to that the Swedish society of medicine has localized a Berzelius symposium on preeclampsia to Uppsala with Ove Axelsson as the chairman of the organising committee.

The other thesis presented in 2007, "Postpartum Ultrasound", was written by Ajlana Mulic-Lutvica and gave us new knowledge on how to diagnose placental remnants in the uterus postpartum. Placental remnants might cause severe postpartum bleedings and the recommended treatment is surgical curettage, which is a procedure with evident side effects. The findings presented in Ajlana Mulic-Lutvica's thesis is of clinical importance since unnecessary invasive procedures can be omitted if ultrasound rule out placental remnants in the uterine cavity.

Three half-time seminars were held in 2007. Karin Stålberg is engaged in an epidemiological project aimed to clarify if prenatal risk factors, such as x-ray and ultrasound are associated with infant morbidity e.g. brain tumours and schizophrenia. She will defend her thesis in 2008. Maria Jonssons' research project is on oxytocine and its potential risk to cause fetal asphyxia during delivery and also its effect on maternal cardiac function. Asphyxia during delivery is associated with an increased risk of intrauterine fetal death and infant morbidity such as cerebral palsy. Overstimulation with oxytocine is most probably one of the reasons leading to asphyxia. Thus, increased knowledge of the use and misuse of oxytocin creates a basis for improving recommendations on how to use it properly and thereby saving lives and decrease severe morbidity. Eva Bergmans' project deals with prenatal diagnosis of SGA-fetuses. We know that prenatally undiagnosed cases of SGA-fetuses have a higher perinatal mortality compared with diagnosed cases. The reason for this is that we have access to effective methods, especially Doppler ultrasound, to monitor SGA-fetuses. The dominating problem today is that we identify less than 50% of these pregnancies prenatally. Together with researchers in statistics from the University in Gothenburg we are exploring if self-administered symfysis-fundus measurements and the conception of relative growth can be of help to improve prenatal detection rate of SGA-fetuses.

Gestational diabetes and diabetes in pregnancy are the main research subjects for associate professor Ulf Hanson. During 2007 he has commenced the planning of a comprehensive multi-centre randomized study concerning treatment of gestational diabetes.

Members of the group during 2007

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

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Dissertations 2007

Karin Zetterström

Ajlana Mulic-Lutvica

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The Swedish Council for Working Life and Social Research (FAS) 400.000 SEK,

The Regional Research Foundation Uppsala-Örebro 1.250.000 SEK

The Uppsala County Research Foundation 150.000 SEK

GYNECOLOGICAL ENDOCRINOLOGY

Tord Naessén

I: HRT and effects on postural balance function: 'Non-vertebral 'Osteoporotic' fractures - a Brain disease or a Bone disease?' was the title of a leader accompanying our article in 'Menopause' 2007.

We study effects of endogenous and exogenous sex hormones on bone mass and fracture risk. For the fracture protective effect on peripheral fractures (hip and forearm fractures) our results indicate that menopausal hormone replacement therapy (HRT) positively affect the brain and improve postural balance function.

Significance: Over 50% of all fractures have normal DEXA. We have shown that HRT improves postural balance function. If HRT can affect the brain and improve postural balance this might explain the rapid dynamic between HRT exposure and reduced fracture risk, the paradoxically stronger reduction in hip fracture risk when HRT is initiated soon, compared with late, after menopause and might also explain that it seems hard to show substantial effects on hip fracture risk after treatment with bisphosphonates.

II. Effects of endogenous and exogenous sex steroids (Hormone Replacement Therapy) on the vascular system and cardiovascular disease (CVD)/ death in women and men.

Evaluate the significance of subtle differences in sex hormone levels (within the 'normal ranges) with regard to the risk of CVD and death in elderly women and men. Endogenous hormone levels are analyzed in 1016 samples from a population-based study, the PIVUS study.

Effects of ultra-low estrogen doses in elderly

To our knowledge we were the first group to report systemic effects of real 'ultra-low' doses of estrogens with systemic effects on bone markers, bone mass and serum lipid levels.

In early 2008, we will start a RPC-study on low-dose hormone replacement therapy initiated soon after menopause with regard to effects on the artery wall composition (arterial ageing).

Significance: many of these projects started before the report from the Women's Health Initiative (WHI) and they are therefore 'well-timed'. There is a need to better understand effects of HRT with regard to age at start of therapy and potential benefits of HRT when started soon after menopause.

III: We suggest a new principle for non-invasive ultrasound assessment of the artery wall with regard to arterial aging and screening for cardiovascular disease (CVD).

With increasing age and development of atherosclerosis the artery wall intima alyer increases whereas the media layer decreases. The differential directions of changes in these two artery wall layers will reduce the usefulness of the present 'Gold-standard' for non-invasive assessment of the artery wall the Carotid IMT assessing the intima+media complex. We have therefore used another approach for assessment of the artery wall, separate assessment of the artery intima and media layers and the use of the Intima/Media thickness ratio.

We currently evaluate the strength of the method to predict incidence of CVD events and death, within the PIVUS-75 study. Up to date we have investigated over 440 subjects of estimated 750.

The method/principle is also used in evaluations of effects on the artery system in women with SLE, young subjects with previous major depression and in studies on preeclampsia in pregnancy.

Significance: I consider the principle superior to present 'gold-standard', (Carotid-IMT) in discriminating groups of subjects with and w/o a diagnosis of CVD and also for assessment of individual subjects.

IV: Long term estrogen therapy and preservation of brain tissue and function.

We study effects of long-term estrogen therapy on mental function, total and relative brain volumes (esp. hippocampal region) with MRI. By using Positron Emission Tomography (PET), we study the function of the aromatase system (local estrogen synthesis in the brain) and effects of age-related amyloid deposits (PIB).

Significance: to assess if HRT can preserve cognitive function, brain substance and aromatase activity (local estrogen production) (11C-Vorozole) and reduce the normal age-related increase in amyloid deposits (PIB).

V: Premenstrual syndrome (PMS or PMDD).

The normal variations sex steroids during the menstrual cycle give in some women a negative effect on mood and temper, especially in the form of increased irritability and depressed mood (PMS). We study differences in the brain sensitivity to changes in sex hormone levels in women with and without a diagnosis of PMDD (PMS). The methods include studies with Positron Emission Tomography (PET).

Significance: to understand the susceptibility to changes in hormone levels in relation to degree of symptoms and explore the influence of the serotonin system in women with PMS.

VI: Basic regulation of the menstrual cycle and the dysregulation in PCOS

We investigate follicular fluid (FF) from women with and w/o a diagnosis of PCOS. The effects of pooled FF on the aromatase enzyme in granulosa cells are studied. In addition, we compare the concentrations of FF hormones in the two groups and also compare the product/precursor ratios (illustrating specific enzyme activities) in the two groups.

Significance: the results are expected to have implications for a better understanding of anovulation in e.g. PCOS and for infertility.

Members of the group during 2007

| | |
|----------------------|-------------------------|
| Tord Naessén | Associate professor |
| Tansim Akther | Research student |
| Gunilla Hallberg | Postgraduate student |
| Olle Eriksson | Ph.D |
| Kenny Rodriguez | Ph.D |
| Dmitrijus Kirilovas | Ph.D |
| Jona Kristjansdottir | Research student |
| Bengt Långström | Professor , PET centrum |
| Alexander Medvedev | Professor |
| Ingemar Persson | Professor |
| Jonas Bergquist | Professor |
| Kjell Carlström | Professor |
| Vladimir Chaika | Professor |

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Agencies that support the work

| | |
|---|-------------|
| The Medical Faculty, Uppsala University, the Amersham Foundation: | 280.000 SEK |
| Hjärt- och Lungsjukas Förening: | 100.000 SEK |
| Selanders Foundation: | 100.000 SEK |

NATIONAL CENTER FOR KNOWLEDGE ON MEN'S VIOLENCE AGAINST WOMEN

Web site

www.nck.uu.se

Gun Heimer

National Centre for Knowledge on Men's Violence Against Women (NCK) works by order of the Swedish Government with education, research, development, information and the compilation of research findings in the area. Women subjected to violence are treated at the centre's outpatient clinic at Uppsala University Hospital. The centre also supports women subjected to violence via a national hotline.

VIOLENCE AGAINST WOMEN IN A MEDICAL PERSPECTIVE

The research at the National Centre for Knowledge on Men's Violence Against Women is mainly concerned with violence against women in a medical perspective, with violence during pregnancy and rape as the principal areas of interest. The studies are concerned with physical, sexual and psychological violence alike. Violence against women is a serious problem in all parts of the world representing a grave threat against women's health and therefore also, regrettably, a growing future field of research.

Members of the group during 2007

| | |
|---------------------|----------------------|
| Gun Heimer | Professor, MD, PhD |
| Kristina Stenson | Midwife, MD, PhD |
| Mariella Öberg | Postgraduate student |
| Elisabeth Tønnessen | General practitioner |

Publications 2005--2007

1. Stenson, Kristina; Sidenvall, Birgitta; Heimer, Gun, Midwives' experiences of routine antenatal questioning relating to men's violence against women.. // *Midwifery*. - 2005 (21) : 4, s. 311-21
2. Stensson, Kristina; Claesson, Ingrid; Heimer, Gun, Våldsutsatta kvinnors hälsa och livssituation : -en longitudinell deskriptiv studie. - Akademiska sjukhuset, Uppsala Universitet, 2006. - 1-56 s. - (Rikskvinnocentrum rapportserie 2006-1, ISSN 1652-3482)
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INTERNATIONAL MATERNAL AND REPRODUCTIVE HEALTH

Elisabeth Darj

More than a third of the ill-health in women is related to their reproductive functions and maternal mortality remains the health indicator with the largest difference between countries in relation to their economic and social development. Research must address the individual and structural factors that contribute to these health problems, as well as the health interventions and health programs that can be effective to alleviate the suffering.

Maternal health care is a core component of the basic health care in all countries. IMCH has conducted systematic studies of maternal health care programs and interventions for many years in countries in Asia, Africa, Eastern Europe, as well as in Sweden. Ongoing studies address effectiveness and quality of high-risk referrals in rural Tanzania and delivery care in Sri Lanka. Experiences of mothers and fathers during the postpartum period are analysed in Tanzania to give basis for improved support to families.

Maternal nutrition is essential for reproductive outcome. Ongoing studies in Bangladesh, Indonesia and South Africa focus on the effects of supplementation in pregnancy to increase birth-weight and protect against toxic effects of arsenic in drinking water. Ongoing studies in South Africa with focus on exclusive breast feeding to improve child HIV-free survival.

Gender-based violence is recognised as a major health problem for women all over the world. IMCH is collaborating with universities in Sri Lanka and Bangladesh in studies of program for support to women victims for gender-related violence. Studies in Nicaragua and Bangladesh focus on consequences for the newborn of violence during pregnancy, and in Tanzania on attitudes to violence in all sectors of the community and the legal system. A specific form of violence is seen in the culture related female genital cutting and the consequent health hazards.

STD and HIV/AIDS are potential threats to all young people who begin their sexual life. IMCH has studies of behaviours, perceptions and attitudes among adolescents in Uganda, South Africa and Sweden. Projects on appropriate health care programs are conducted in Uganda and the impact of information from the churches in South Africa.

Adolescent reproductive health is given more attention but well designed health care programs are few in low-income countries. IMCH research projects evaluate youth programs in Uganda, South Africa and Sweden.

Contraception and abortion are key components of efforts to improve reproductive health but also controversial in many countries. Ongoing studies are related to effects of increasing access of the emergency contraception.

Public Health in Humanitarian Assistance is given special attention at IMCH with research directed at experiences, motivation and training needs of health care workers, as well as reproductive health aspects in refugee situations.

Information seeking training for researchers is provided in all areas through INFORM, a specialised program offered to all collaborating partners and all research students.

Members of the group during 2007

| | |
|------------------------|----------------------------------|
| Elisabeth Darj, | M.D., Associate Professor |
| Beth Maina Ahlberg, | Adjunct Professor |
| Gunilla Aneblom, | RNM, Ph.D. |
| Anna Berglund, | M.D., Ph.D. |
| Eva-Charlotte Ekström, | Epidemiologist, Ph.D. |
| Birgitta Essén, | M.D., Ph.D., Associate Professor |
| Gunilla Lindmark, | M.D., Guest Professor |
| Viveca Odling, | M.D., Adjunct Professor |
| Pia Olsson , | RNM, Ph.D. |
| Tanja Tydén, | RNM, Professor |

Publications 2005-2007

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Agencies that support the work

| | |
|----------------------------|---------------|
| SIDA | 4.920.600 SEK |
| EU | 339.000 SEK |
| ÖEK (Östereuropakommittén) | 344.000 SEK |
| Spider | 1.411.345 SEK |
| SASNET | 150.000 SEK |
| ISP | 150.000 SEK |

INTERNATIONAL CHILD HEALTH AND NUTRITION

Lars Åke Persson

Every year almost 10 million children die before the age of 5 years. Most of these deaths occur in low- and middle-income countries. It is estimated that two thirds of these deaths could be preventive by evidence-based and cost-effective methods and half of these deaths are associated with child undernutrition. The research programme International Child Health and Nutrition focuses on strategies for improved child survival, on interventions against child malnutrition and undernutrition, and on equity in child health and survival.

Global child survival chances have been considerably improved since the 1960s. However, during the last decade the improvement has slowed down. A persistent problem in many countries is a high neonatal mortality. This is addressed in a collaborative project in Quang Ninh province in Vietnam, where a community-based approach towards improved neonatal survival is tested.

It is estimated that almost 15% of global under-five deaths could be prevented by exclusive breast feeding during the first six months of life. In studies in Tanzania care providers' perceptions of infant feeding are focused. In a collaborative project in South Africa infant feeding is studied in the perspective of prevention of mother-to-child transmission of HIV (MTCT).

In an extensive prenatal intervention trial in Matlab, Bangladesh, effects of food and micronutrient supplements are investigated in a short- and long-term perspective. In this project, that has got the acronym MINIMat, effects are studied on infant mortality, foetal and child growth, micronutrient status, immune function, morbidity and psycho-motor development. The mothers are followed into the next pregnancy. We collaborate with, among others, the research institution ICDDR, Bangladesh, and research groups at London School of Hygiene and Tropical Medicine, Institute of Child Health, London, University of California at Davis and Cornell University in Ithaca, US.

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

We have contributed with epidemiological expertise in population-based studies on arsenic in tube wells in Bangladesh. Due to the newly discovered arsenic catastrophe in that country we took the initiative to epidemiological studies on health consequences of arsenic contamination of drinking water. The research activities are closely linked to mitigation activities for safe drinking water. Among other research questions we study the effects of arsenic in drinking water for the pregnant woman on the health of the foetus and the offspring. We collaborate with ICDDR and BRAC, Bangladesh and with the department of Metals and Health, Karolinska Institutet.

Below a few of the projects are presented with a few more details.

MINIMat – MATERNAL AND INFANT NUTRITION INTERVENTIONS IN MATLAB, BANGLADESH

Lars Åke Persson, Shams Arifeen, Eva-Charlotte Ekström, Hanna Eneroth, Emma Lindström, Ashraf Khan and several collaborating partners (see below)

Malnutrition accounts for a major part of the global burden of diseases, especially among women and children. MINIMat - Maternal and Infant Nutrition Interventions in Matlab - is a large food and multiple micronutrient supplementation trial in pregnant women, including long-term follow-up of their children, and of the mothers into the next pregnancy. 4436 women living in Matlab, Bangladesh were invited and randomised to the different interventions. Several outcomes are monitored, including size at birth and mortality of the child. Growth, morbidity, immune function and cognitive development are assessed. The cohort is very well characterised during pregnancy and onwards enabling studies of foetal and early infant development and risk indicators of adult chronic diseases, including the possible influence of improved nutrition during pregnancy.

The MINIMat trial is a collaborative effort by ICDDR,B, Uppsala University, Cornell University, BRAC, London School of Hygiene & Tropical Medicine, Institute of Child Health, University of California Davis, Karolinska Institutet and University of Tsukuba. The MINIMat research study is funded by United Nations Children's Fund (UNICEF), Swedish International Development Cooperation Agency (Sida), UK Medical Research Council, Swedish Research Council, Department for International Development (DfID), International Centre for Diarrhoeal Disease Research, Bangladesh, Global Health Research Fund-Japan, Child Health and Nutrition Research Initiative (CHNRI), Uppsala University and United States Agency for International Development (USAID).

KNOWLEDGE INTO PRACTICE FOR NEONATAL SURVIVAL; NEOKIP PROJECT IN VIETNAM

Uwe Ewald, Nguyen T Nga, Tran Quang Huy, Lars Wallin, Lars Åke Persson, Leif Eriksson, Mats Målqvist, Dinh Phuong Hoa and collaborating partners.

Yearly 4 million neonatal deaths happen because effective yet simple interventions do not reach those in need. Research on implementation of such knowledge is a priority. Vietnam has achieved major improvements in infant and child but not in neonatal survival. In a baseline study we have shown that neonatal mortality is much higher than the officially reported figures and with great differentials between different districts. This project is a cluster randomised intervention on key issues for neonatal health and survival targeting health care staff, decision makers and a local Women's Union in the Quang Ninh province. The hypothesis is that an enabling and supportive approach for knowledge utilization on the community level with local women working as facilitators would result in a successful change of practice. Primary outcomes are neonatal mortality and the use of evidence-based care procedures in the neonatal period, e.g. clean delivery, establishment of exclusive breast-feeding and home visits during the first week after delivery.

The project is collaborated between Uppsala University, the regional hospital in Uong Bi, Quang Ninh province and the Ministry of Health, Vietnam, and is funded by Sida/SAREC.

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Dissertations 2007

Tanya Doherty

Agencies that support the work/Funding

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PAEDIATRIC ENDOCRINOLOGY RESEARCH GROUP

Jan Gustafsson

GROWTH AND METABOLISM DURING FETAL LIFE AND INFANCY

Glucose is the most important fetal nutrient and the production of this substrate increases in the pregnant woman. After birth the newborn must produce its own glucose, primarily to prevent the effect of hypoglycemia on the brain. Our research is directed on mechanisms behind glucose production and lipolysis in the pregnant woman and in the newborn infant during normal and pathological conditions. Much interest is presently focused on developmental origin of adult disease, especially on the metabolic syndrome in subjects born small for gestational age infants. Large for gestational age infants have also an increased risk to develop metabolic disease later in life, but there is only limited data concerning energy metabolism in pregnant females giving birth to large infants. Measurements of glucose production and lipolysis are performed by use of stable isotope labelled compounds and gas chromatography-mass spectrometry. Methods have also been developed to study glucose metabolism in adipose fat tissue in vivo by a combination of microdialysis and stable isotope technique. This methodology is presently used in studies of glucose metabolism in the brain.

NEONATAL AND CHILDHOOD NUTRITION

In the studies of nutrition of infants effects on growth by active early nutrition has been investigated in infants belonging to risk groups, i.e. immature infants or those born small for gestational age. In addition factors influencing breastfeeding of extremely immature infants have been studied. In a longitudinal project the development of the visual system in extremely immature infants is investigated.

The prevalence of overweight and obesity among children in Sweden increases. Studies of relations between eating habits, physical activity and energy metabolism in children and adolescents are ongoing. The studies are performed in collaboration with the unit for overweight and obesity at the University Children's Hospital.

Eating disorders influence growth and somatic development. In collaboration with the department of Child Psychiatry a project on endocrine, metabolic and somatic consequences of anorexia nervosa is ongoing since several years. Among the studies performed so far are investigations of anthropometrical predictors of anorexia nervosa, studies of energy substrate production and of the risk for cardiac disease.

VIRUS INFECTIONS AND TYPE 1 DIABETES

In the research on the relationship between virus infections and type 1 diabetes the focus is on in vitro studies of isolated human pancreatic islet cells following infection with different strains of enteroviruses. Infections with these viruses activate genes which may start an autoimmune process. Results from the group have also shown that an antiviral compound is not toxic to human β -cells and that it is effective on most strains of enteroviruses. When viruses, isolated from patients newly diagnosed with type 1 diabetes, are used to infect β -cells chemokines are secreted and the secretion of insulin is impaired. A recent finding is related to the identification of enterovirus protein in the β -cells of a newly diagnosed patient with type 1 diabetes. The β -cells of this patient had similar characteristic findings as those seen in human pancreatic islets

infected in vitro. Presently much interest is focused on the connection between coeliac disease and type 1 diabetes since a significant proportion of patients, newly diagnosed with type 1 diabetes, have antibodies associated with coeliaci.

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Dissertations 2007

Anna Elmund

Renée Flacking

Agencies that support the work

Sarec-Sida, Swedish Diabetes Association, Novo Nordisk Foundation, Novo Nordisk, Pfizer, Gillbergska foundation, Sävstaholmsföreningen, ALF.

PEDIATRIC ONCOLOGY

Gudmar Lönerholm

LEUKEMIA – FACTORS DETERMINING DRUG RESPONSE

G. Lönerholm, B-M. Frost, J. Palle

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

LATE EFFECTS AFTER BONE MARROW TRANSPLANTATION

P. Frisk, J.Arvidson

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

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

PROCEDURAL PAIN IN CHILDREN WITH CANCER

G. Ljungman

The effects of midazolam, morphine, paracetamol and ibuprofen are examined in four separate double blind RCTs in parallel groups with intervention vs placebo. 50 children are included in each of the 4 different studies. Children, parents, and nurses will report children's anxiety, distress, and pain on VAS

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

Funding: The project started in 2005 and is since then funded by the Swedish Children's Cancer Foundation and the Swedish Cancer foundation. Total funding MSEK 2.0, 0,7 MSEK for 2007.

In addition to being a part of the Pediatric Oncology research group at the Department of Women's and Children's Health, Uppsala University, Gustaf Ljungman takes part in, and shares leadership of, the research group Psychosocial Oncology headed by Professor Louise von

Essen. The title of the main projects are: 1 Cancer during adolescence. Psychosocial and health economic consequences and 2 Occurrence, development, and treatment of posttraumatic stress disorder among parents of children with cancer

GENETIC AND FUNCTIONAL ASPECTS OF NEUROBLASTOMA

F. Hedborg

1. The most labour-intensive project during 2007 concerns aspects of hypoxia-induced effects in neuroblastoma cells. An expression array analysis on cultured tumor cells has been completed and data have been verified by quantitative RT-PCR and further studies of the expression of the most pertinent genes during human development and in clinical tumor tissues are ongoing.
2. Animal experiments have been performed to test the hypoxia-dependence of targeting neuroblastoma with meta-Iodo-benzoguanidin (mIBG) in tumors xenografted to mice.
3. In collaboration with prof. Jonas Blomberg, clinical virology, a study on hypoxia-induced expression of endogenous retroviral genes has been completed.
4. A genetic study on neuroblastoma has been initiated based on a high-resolution whole-genome tiling arrayCGH platform.

MOLECULAR GENETIC DIAGNOSTICS OF PEDIATRIC BRAIN TUMORS

S.Pfeifer

With the aim of increasing our understanding of the molecular biology of pediatric CNS tumors, we have started a broad collaborative research project between the Departments of Genetics and Pathology Rudbeck laboratories, Neurosurgery, Pediatric Neurology, and Pediatric Oncology at the University Hospital, Uppsala University, and the Department of Tumor Biology, Karolinska Hospital. The project has the following main goals. 1. Global analysis of tumor specific genetic changes in pediatric CNS tumors. Analyses of tumor DNA are performed in collaboration with prof Jan Dumanskys group, USA, which has developed a whole genomic 32 BAC (bacterial artificial) high resolution (45kb, a gene is in average 100kb) array, which covers 99% of the whole human genome. A unique biobank of about 200 pediatric CNS tumor biopsies, at the Uppsala University Hospital, enables the analysis of a large number of different pediatric brain tumor types. 2. Identification of specific genetic changes for diagnostic and prognostic purposes. Genes of importance identified by the global array analyses are further studied in brain tumors by FISH and pcr techniques. Our aim is to set up a molecular genetic diagnostic unit at the Uppsala University Hospital. The projects above are in progress.

STEM CELL TRANSPLANTATION (SCT). LATE EFFECTS AFTER CANCER TREATMENT IN CHILDHOOD.

Johan Arvidson

In the above mentioned study on survivors for more than 10 years after autologous SCT we are also measuring psychosocial and sexual functioning. We use instruments that has been used and developed by L Wettergren from Dep of Neurobiology, Care Sciences and Society, Karolinska Institutet, Stockholm. Our collaboration will result in a paper submitted next week, titled "Positive and negative consequences of childhood cancer influencing life of young adult survivors". These and earlier results will serve also as comparison to the SCT study results.

SCT patients are all the time included in studies, for example a comparison between two different strategies to prevent CNS relapse of leukaemia after SCT, a collaborative study between Centre for allogeneic transplantation (CAST), Huddinge hospital and ourselves (B-M Frost). Manuscript submitted. Viral infection after SCT. One article published, study ongoing. In collaboration with A Kinch and others (Infectious disease department, Akademiska, Uppsala). We are all the time including SCT patients in collaborative studies, and also publish case reports, see recent publications.

Meningioma as a late late effect after treatment with cranial irradiation. Starting up a project with neurosurgeons in Uppsala, O Gudjonsson and G Hesselager and others.

Johan Arvidson is also working on organising a program for the transition from pediatric to adult health care, including collecting results from locally performed health supervision according to the Swedish recommendations for follow-up after treatment for childhood malignancies. This would be a base for future research on long-time complications to disease and treatment.

Johan Arvidson is the chairman of the Swedish working party for paediatric SCT and a member of the Swedish working party for late complications after treatment for paediatric malignancies (SALUB).

Members of the group during 2007

| | |
|----------------------|----------------------|
| Gunnar Lönnerholm | Professor |
| Johan Arvidson | Ph.D |
| Per Frisk | Ph.D |
| Britt-Marie Frost | Ph.D |
| Kleopatra Georgantzi | Postgraduate student |
| Fredrik Hedborg | Associate professor |
| Lena Högberg | Postgraduate student |
| Åke Jakobsson | Associate professor |
| Anders Kreuger | Associate professor |
| Gunnar Liminga | Ph.D |
| Gustaf Ljungman | Associate professor |
| Josefine Palle | Postgraduate student |
| Susan Pfeifer | Associate professor |

Publications 2005-2007

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Agencies that support the work

Funding: Lions 100.000 SEK, Barncancerfonden 200.000 SEK

Funding: Lions 100.000 SEK

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

Funding 2007: Barncancerfonden 150.000 SEK Barncancerfonden 800.000 SEK for Dumanskys group (Susan Pfeifer collaborator)

PAEDIATRIC NEUROLOGY RESEARCH GROUP

Gunnar Ahlsten

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

EPILEPSY.

There are several ongoing studies. One study deals with a specific form of childhood epilepsy “Rolandic epilepsy” where especially the metabolism of the hippocampus of the brain is studied with Magnetic resonance. The hippocampus and anatomical variations in its anatomy and how this has any importance for the development of epilepsy is the subject of another study.

Other studies (in collaboration with international centers) deals with the genetic background of Rolandic epilepsy and childhood absence epilepsy, There are also an ongoing follow-up study of children previously treated for epilepsy.

SPINA BIFIDA.

Research on this group of children has been carried out for at least 15 years. Different medical factors especially the Chiari II-malformation 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.

FOLLOW-UP STUDIES OF PREMATURELY BORN INFANTS.

Together with the Departments of Psychology, Ophtalmology, Neuroscience and Neonatology a longitudinal study of the development of visual perception in infants born before 32 weeks of gestation and its relation to periventricular leucomalacia or other perinatal brain damage has been going on for 3 years. 100 children is included so far. The study will provide much new information in this field.

Another study is a national prospective study on neurological, ophtalmological and psychological development of infants born after less than 27 weeks of gestation. The children will be examined at the age of 2 ½ years. The results of the study may have great importance for future perinatal care.

EVALUATION OF MOTOR FUNCTION

Different studies with different techniques are used to study children with cerebral palsy and spina bifida regarding balance, posture and muscle tone. The development of the motion analysis laboratory of the University Hospital is an important part of some of these studies

ARTHROGRYPHOSIS MULTIPLEX CONGENITA

An ongoing doctoral thesis project deals with this diagnose. In this condition the newborn child have multiple congenital joint contractures. After a national collection of cases the aim is to study underlying causative factors, describe the development of the children and evaluate the treatment that has been used.

Members of the group during 2007

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

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Agencies that support the work

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

PERINATAL, NEONATAL AND PEDIATRIC CARDIOLOGY RESEARCH

Anders Jonzon

The neonatal research group has been reorganized during 2007 and a new director has been appointed. Unfortunately a lot of energy has been spent on issues concerning space and office. The group is now established and we are focusing on ongoing and new research areas.

Projects

Maria Stålhammar & Richard Sindelar

Studies concerning inflammatory substances and their migration in neonatal lung tissue.

Annika Öhman & Anders Jonzon

Studies concerning heart rate in newborn and small children.

-Tachycardia – effects of different treatment modalities on heart rate.

-Bradykardi – The role of autoimmune and genetical factors in the development of congenital heart block.

Linda Simonsson & Richard Sindelar

Studies of ventilatory support in small children.

-Ventilation mode and stress in extremely premature children

-Evaluation of stress – how to measure, when to measure, what to measure

Gunnar Sedin

Studies concerning followup of extremely premature children on national and international level

Members of the group during 2007

| | |
|------------------|----------------------|
| Anders Jonzon | Associate professor |
| Richard Sindelar | Ph.D |
| Johan Ågren | Ph.D |
| Maria Stålhammar | Postgraduate student |
| Annika Öhman | Postgraduate student |
| Linda Simonsson | Postgraduate student |
| Josanne Münsters | Med stud (Holland) |
| Gunnar Sedin | Professor emeritus |

Publications 2005-2007

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Agencies that support the work

| | | |
|------------------|-----------------------|-------------|
| Gunnar Sedin | Kronprinsessan Lovisa | 101.200 SEK |
| Johan Ågren | Kronprinsessan Lovisa | 138.000 SEK |
| Richard Sindelar | Kronprinsessan Lovisa | 138.000 SEK |

GENERAL PEDIATRIC RESEARCH GROUP

Lennart Nordvall

The "General Paediatric Research Group" is a heterogeneous group made up of one entity with focus on Paediatric inflammatory diseases and in addition to that other general paediatric research areas i.e Paediatric pulmonary diseases with focus on cystic fibrosis and other pulmonary diseases, Paediatric nephrology and Neonatal infectious diseases. Another entity focuses on Child Health Care and Social Paediatrics.

CENTRE FOR PAEDIATRIC INFLAMMATION RESEARCH

A "Centre for Paediatric Inflammation Research" has been established within the research group. Research focus is put on improved clinical phenotyping of childhood inflammatory diseases and improved characterization of inflammatory characteristics of diseases in collaboration between clinical and preclinical scientists. The purpose of these efforts is to be able to improve diagnosis and to tailor and optimize anti-inflammatory treatment in patients. Minimally-invasive sampling methods suitable for use in paediatric patients are being developed. A large Vinnova grant has been received for the purpose.

AIRWAY INFLAMMATION

In asthma focus is put on airway inflammation by measuring exhaled nitric oxide, a surrogate marker of allergic inflammation. A research prototype NIOX Flex is being evaluated and enables monitoring of nitric oxide (NO) in various compartments of the airways (bronchi, alveoli) of which the therapeutic implication is to be able to tailor treatment. In patients with very low levels of NO emphasis is put on differential diagnosis in childhood asthma. Further, studies of the importance of food allergy in asthma are under way.

GASTROINTESTINAL INFLAMMATION

Patients with gastrointestinal inflammatory disease are characterized using sets of disease specific antibodies and panels of inflammatory molecules. We currently investigate possible associations between celiac and other inflammatory diseases, and if undiagnosed inflammatory states that may disturb the intestinal barrier and lead to the development of type 1 diabetes. We analyse faeces and biopsy samples for the presence of cytokines, inflammation molecules, enteroviral RNA and the microflora to elucidate if celiac disease or other intestinal inflammatory states precede type 1 diabetes or vice versa. Focus is also put on IgE-mediated and non-IgE allergies to foods, milk in particular.

RHEUMATIC INFLAMMATION

The paediatric rheumatology project consists of

The Nordic study in paediatric rheumatology. A prospective, incidence based cohort of patients from Scandinavia and Finland has been analysed with respect to clinical features in HLA-B27 positive as compared to negative patients (paper submitted in 2007). Analyses of variables important for disease activity have been done. One result of the study is that the size of the

joints that are active are of importance in assessment of disease activity (paper accepted during 2007). Further analyses are in process.

The regional study of JIA and its relation to celiac disease, and/or gut inflammation. The study is running according to the protocol. Data analyses will not be possible until another few years.

The national registry in paediatric rheumatology. The project is running and a computerized programme is tested by a group of paediatric rheumatologists.

A study of the role of autoantibodies in juvenile idiopathic arthritis, in collaboration with assoc. prof. Sandra Kleinau BMC. Sera from paediatric patients are collected and data will be available during 2008.

Agencies that support the work

The Vinnova Foundation, Aerocrine AB, Phadia AB, The Gillbergska Foundation

Members of the Center for Paediatric Inflammation Research,

Publications 2005-2007:

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12. Kull I., Böhme M., Wahlgren C.F., Nordvall L., Pershagen G, Wickman M. Breast-feeding reduces the risk for childhood eczema. *J Allergy Clin Immunol* 2005;116:657-661

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PAEDIATRIC NEONATAL INFECTIONS.

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

Normann E, Gnarpe J, Wettergren B, Janson C, Wickman M, Nordvall L.

The association between *Chlamydia pneumoniae* antibodies and wheezing in young children and the influence of sex. *Thorax* 2006;61:1054-8.

Normann E, Gnarpe J, Gnarpe H, Wettergren B.

Chlamydia pneumoniae infection predicts a reduced risk for subsequent atopic disease. Acta Paediatr 2005;94:705-10.

PEDIATRIC NEPHROLOGY.

Therapy-resistant enuresis. New and old second-line treatment alternatives for previously "incurable" cases have been evolved. A PhD student will be linked to the team

Urinary tract infections and vesicoureteral reflux. Uppsala is one of the coordinating centres for a nationwide study in this field

Global coordination of research and educational activities in the field of the pediatric lower urinary tract. Dr Nevéus is secretary general of the International Children's Continence Society (ICCS)

Publications 2005-2007

1. Nevéus T, Läckgren G, Stenberg A, Norgaard JP (2005) Anticholinergic treatment for nocturnal enuresis: Current understanding and future expectations.
2. Dialogues in Paediatric Urology 26(6):9-11
3. Nevéus T (2006) The evaluation and treatment of therapy-resistant enuresis: a review. Upsala J Med Sci 111(1):61-71
4. von Gontard A, Nevéus T (2006) Elimination Disorders in Children – Nocturnal Enuresis, Urinary Incontinence and Encopresis. (Handbook) Mac Keith Press, London
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7. Nevéus T (2006) Reboxetine in therapy-resistant enuresis: Results and pathogenetic implications. Scand J Urol Nephrol 40(1):31-4
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9. Nevéus T. The Dilemmas of Refractory Nocturnal Enuresis (Editorial). J Urol.2008 Jan 24

External funding:

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

Smaller funds and contributions.

STUDIES ONGOING AT THE UPPSALA CF CENTER

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

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

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

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

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

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

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

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

Published articles and book chapters from Uppsala CF center 2005 through 2007

1. Wexler ID, Johannesson M, Edenborough FP, Sufian BS, Kerem E Pregnancy and chronic progressive pulmonary disease *Am J Respir Crit Care Med.* 2007 Feb 15;175(4):300-5
2. Döring G, Elborn JS, Johannesson M, de Jonge H, Griese M, Smyth A, Heijerman H; Consensus Study Group Clinical trials in cystic fibrosis *J Cyst Fibros.* 2007 Apr;6(2):85-99. Review
3. Nilsson H, Dragomir A, Ahlander A, Johannesson M, Roomans GM Effects of hyperosmotic stress on cultured airway epithelial cells *Cell Tissue Res.* 2007 Nov;330(2):257-69
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5. Vanthanouvong V, Kozlova I, Johannesson M, Nääs E, Nordvall SL, Dragomir A, Roomans GM. Composition of nasal airway surface liquid in cystic fibrosis and other airway diseases determined by X-ray microanalysis *Microsc Res Tech.* 2006 Apr;69(4):271-6
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***RESEARCH ACTIVITIES AT THE CENTRAL UNIT OF CHILD HEALTH CARE,
UPPSALA UNIVERSITY CHILDREN'S HOSPITAL, DURING 2007.***

Ongoing and completed projects:

Child Health Care in transition. A prospective controlled intervention trial with new psychosocial methods in preventive health care of children.

Primrose. Primary prevention of obesity in childhood through parent dialogue concerning healthy nutrition and exercise habits at the child health centres. A prospective multi-centre randomized controlled study which is to be started during 2008.

Breast-feeding in relation to social background and parental ethnicity. A population-based register study.

Trials of tastes and flavours enhancing young children's pleasure in eating. A comparison between children with and without food problems.

A long-term (5-10 years) follow-up of infants with severe sleeping and/or feeding problems. A clinical population study.

Stability and prediction of parenting stress. A clinical and population-based approach.

Rational prescription of antibiotics in a population of Swedish children. An intervention trial using information to prescribers to reduce prescription without negative effects.

Language development, linguistic ability and neuropsychiatric disorders in toddlers and preschool children.

Parenting stress, feeding behaviour and childhood obesity. A population-based cross-sectional study.

Vaccination During Childhood. The project group aims to review the scientific literature to assess the effects and side effects of the vaccines used in the Swedish childhood vaccination program. (SBU)

Grants:

STRAMA (The Swedish strategic programme against antibiotic resistance)

The Uppsala-Örebro Region

Allmänna Barnhuset

Uppsala County Council

FAS (Swedish Council for Working Life and Social Research)

Publications 2005-2007

1. Berglund E, Eriksson M, Westerlund M. Communicative skills in relation to gender, birth order, childcare and socioeconomic status in 18-month-old children. *Scand J Psychol* 2005; 46: 485-491.
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4. Bröms K, Svärdsudd K, Sundelin C, Norbäck D. A nationwide study of indoor and outdoor environments in allergen avoidance and conventional daycare centers in Sweden. *Indoor Air* 2006; 16: 227-235.
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PEDIATRIC SURGERY AND PEDIATRIC UROLOGY

Rolf Christofferson

DOCOSAHEXAENOIC ACID OXIDATION IN PRETERM INFANTS

Angsten G

Abstract: Dietary supply of fatty acids in preterm infants has recently received considerable interest with focus on long chain polyunsaturated fatty acids (LCPUFA). Although LCPUFA can be endogenously synthesized from essential fatty acids, synthesis seems not to meet infantile requirements. Several studies have provided evidence that preterm infants without dietary supply of LCPUFA exhibit lower plasma concentrations of LCPUFA than infants receiving LCPUFA in amounts as contained in breast milk. Furthermore, improved visual and neurological development could be demonstrated in preterm infants receiving LCPUFA compared to infants not supplemented. To improve nutrition of preterm infants further it is important to obtain a more detailed – preferably quantitative – analysis of the LCPUFA metabolism. The project focuses on the n-3 LCPUFA docosahexaenoic acid (DHA), a metabolite of α -linolenic acid. Since DHA is an important component of the cell membrane, it is incorporated into the membranes of e.g. neural cells at high concentrations. Thus, the DHA requirement is assumed to be high during the period of rapid brain growth during the first months of life. In this project, breast fed preterm infants are given an oral dose of uniformly ^{13}C labelled DHA and the fractions of oxidized tracer are determined. The project will give new information on the LCPUFA metabolism and may contribute to development of formulas meeting preterm infantile requirements.

IN VITRO TESTING OF THE PEDIATRIC CODMAN HAKIM SHUNT

Arnell K

Abstract: Ventriculo-peritoneal shunting is the most commonly used method in treating hydrocephalus in children. The shunts have become more sophisticated, and the introduction of adjustable shunts has made it possible to non-invasibly adjust the shunt opening pressure. The adult Codman Hakim adjustable valve has been used also in children. A new shunt model, the Codman Hakim micro valve, is specifically designed for pediatric use. The micro valve has not yet been tested extensively in vitro and has not yet been proven more suitable for children than other shunts. The aim of this project is to investigate the hydrodynamic characteristics of the micro valve and to compare it with the adult model. Six new Codman Hakim micro valves will be tested in an automated, computerized test rig with the possibility to regulate pressure and collect data of opening pressure, resistance and sensitivity to different abdominal pressures. The testing will be performed in the shunt laboratory at the Neurocenter, Norrlands Universitetssjukhus, Umeå. The project will show if the micro valve works according to the manufacturer and if it is a more suitable valve for children.

AN ALTERNATIVE VENTRICULO-PERITONEAL SHUNTING IN EXTREMELY PREMATURELY BORN CHILDREN

Arnell K

Abstract: Extremely prematurely born children are at high risk of developing intracranial hemorrhage, which can induce secondary hydrocephalus that require intervention.

Unfortunately, it is hazardous to implant a proper ventriculo-peritoneal shunt with a valve in children with a body weight of less than 1,700 g due to the risk of erosion of the thin skin over the valve. Historical alternatives to shunting have been external ventricular drainage or repeated ventricular aspirations, with risks of over-drainage in the former, under-drainage and leukomalacia in the latter, and intraventricular infections in both. The aim of this project is to evaluate the efficacy and safety of ventriculo-peritoneal shunting by implantation of a simple ventricular catheter connected to an abdominal catheter with an intrinsic resistance, but without a shunt valve. A retrospective review of the medical records of all infants treated with a simple ventriculo-abdominal catheter at Akademiska Hospital will be performed regarding the age and weight at shunting, technical difficulties encountered at surgery, indication for shunting, and the age when switching to a proper ventriculoperitoneal shunt with a valve was made. The project will elucidate if ventriculo-peritoneal shunting by implantation of a simple ventriculo-peritoneal catheter is efficient for relief of hydrocephalus and safe in terms of avoiding complications such as intraventricular infections and skin erosion in extremely prematurely born children with hydrocephalus.

LONG TERM OUTCOME OF RENAL AND BLADDER FUNCTION IN CHILDREN WITH MYELOMENINGOCELE

Barker G, Läckgren G, Stenberg A

Abstract: Children with neural tube defects such as myelomeningocele (MMC), but also milder forms of craniospinal dysraphism, are at risk for neurogenic bladder dysfunction. Most of these children are born with normal renal function, but progression of bladder dysfunction without intervention will lead to upper tract deterioration due to obstruction or vesico-ureteral reflux and subsequent infections. Clean intermittent catheterization (CIC) every 3-4 hours was introduced in 1970-80 to provide low-pressure emptying of the bladder, thereby protecting the upper tracts. Today, CIC is usually introduced in newborns with MMC. The aim of this study is to retrospectively compare three groups of patients with MMC treated at our Department in terms of renal function, bladder function, presence of urinary tract calculi, frequency of follow-up, incidence of urinary tract infections, and the need for major reconstructive surgery. Also, the impact of MMC complications such as tethered cord will be audited.

The first group is children born 1970-1986. These children have been followed-up carefully, but will not have started CIC as babies. Their upper urinary tracts will have been monitored closely, and many of them have undergone major reconstructive surgery due to high-pressure, unstable bladders.

The second group is children born 1987-2000. These children will have started CIC at a much younger age, but will not have been followed-up at as regular intervals as group one, since CIC usually reduces upper tract deterioration. The older patients in this cohort may also have undergone major reconstructive surgery. The children in both groups that have undergone major reconstructive surgery such as bladder augmentation, continent urinary diversion, and bladder neck plasty or artificial sphincters will be assessed for continence, condition of the upper urinary tracts and renal function.

The third group, children with MMC born since 2000, is looked at prospectively, since they have all undergone urodynamic assessment and started CIC as newborns. Many of these children will also have continuous night-time catheterization of the bladder, which might reduce bladder instability and reduce the need for major reconstructive surgery. With a longer follow-up, the outcome in terms of renal and bladder function, urinary tract calculi, upper tract condition and incidence of urinary tract infections can be compared to the other two cohorts.

SHORT BOWEL SYNDROME AND BACTERIAL TRANSLOCATION

Högberg N, Meurling S, Stenbäck A

Abstract: Short bowel syndrome (SBS) is a malignant condition with a high morbidity and mortality in infants and children. SBS is caused by congenital intestinal atresias or impaired intestinal circulation causing bowel gangrene such as necrotizing enterocolitis and volvulus, making extensive bowel resection necessary. In SBS, the absorption of fluid, salts, vitamins and minerals is impaired, the intestinal microbial flora is changed, and the intestinal immune system is compromised. The child is partly or totally dependent on parenteral nutrition, administered through an intravenous line. The composition of the parental nutrition in SBS is important to avoid malnutrition, impaired growth and development, secondary liver failure, and susceptibility to infections. Septicemia is a common, sometimes lethal, complication to SBS. Septicemia can be caused by bacterial translocation through the damaged bowel wall or through the intravenous line. In this project, we evaluate the outcome of children with SBS with regard to the length of remaining bowel, the fraction and composition of the parenteral nutrition, the incidence of septicemia and causative microbes, and its chemotherapeutic intervention. We are also investigating if microdialysis of ischemia markers in the premature intestine can indicate necrotizing enterocolitis before it is clinically evident and requires bowel resection. In order to dissect the processes of microbial overgrowth, subsequent translocation, and the host's response to it, we have developed an animal model for intestinal translocation. The project will give new information on the clinical management of SBS in infants and children.

ENDOSCOPIC TREATMENT OF VESICoureTRAL REFLUX IN CHILDREN

Läckgren G, Sköldenberg E, Stenberg A

Abstract: Patients with vesicoureteral reflux (VUR) can be treated with antibiotic prophylaxis, open surgery, or by endoscopic treatment. Antibiotic prophylaxis is intended to avoid infections while waiting for VUR to resolve spontaneously. It involves daily medication, and breakthrough infections can occur with a risk for extended antibiotic resistance. Open surgery – i.e. ureteral reimplantation - offers a high cure rate (80-99%), but it is an extensive surgical procedure with a risk for complications such as obstruction of the ureterovesical junction. Also it entails a hospital stay, increasing the impact on the patient and associated costs.

Endoscopic injection offers cure rates similar to those of open surgery, and has the advantage of being a minimally invasive procedure. If parents are given information on all three approaches, the majority chose endoscopic treatment for their children. The safety and efficacy of the procedure is dependent on the injectable material chosen. The ideal material would be biocompatible, easy to inject, non-migratory, durable, and provide high VUR response rates. Deflux® consists of dextranomer spheres (80–250 µm in diameter) in a gel of stabilized, non-animal hyaluronic acid. The properties of Deflux are well suited as an injectable material for VUR. It is biocompatible and has excellent tolerability and safety. The material does not migrate from the injection site. Also, both components are biodegradable over time, preventing long-term accumulation. Despite a certain degradation, a long-term durability of Deflux has been demonstrated. Deflux is the only substance approved by the FDA for treating children with VUR in the USA. The first large, long-term study of Deflux was performed by us and involved 221 children with VUR. 22% of patients required repeat endoscopic treatment. In total, 68% of

children demonstrated a positive response (VUR grade I or less) at their last voiding cystourethrogram. The initial positive response was sustained: 96% of ureters free from VUR at 3–12 months post-treatment remained free from VUR grade >II until 2–5 years after treatment. Endoscopic treatment with Deflux was well tolerated with adverse events occurring in only 2% of patients.

Among children predisposed to urinary tract infection (UTI), VUR increases the risk that the infection will reach the upper urinary tract and cause renal scarring and impaired kidney function. The ultimate aim of VUR treatment is to reduce the risk of renal scarring, so the post-treatment incidence of febrile UTIs is an important consideration when choosing VUR therapy. Studies indicate that antibiotic prophylaxis has a 5-year incidence of febrile UTIs of 21–22%, and open surgery a 5-year incidence of 8–10%. We performed a questionnaire-based study to investigate long-term outcomes and the experiences of patients and their parents associated with Deflux treatment. Endoscopic treatment showed a 10-year incidence of febrile UTIs of only 3.4%. However, there is no requirement to differentiate children with complications such as VUR associated with double ureters, small kidneys or bladder dysfunction as treatment with Deflux is similarly effective in these patients.

ANGIOGENESIS IN CHILDHOOD CANCERS

Azarbayjani F, Christofferson R, Fuchs D, Georgantzi K, Schiller P, Sköldenberg E

Abstract: The survival in childhood cancer has improved considerably the last 30 years, but still 25-50% of children with solid tumors die of their disease. The ultimate cause of death is usually metastatic disease. In order to grow and form metastases, a cancer must acquire the ability to induce new blood vessel formation, angiogenesis, and also new lymph vessels, lymphangiogenesis. The aims of this project are to explore the mechanisms of metastasis, to identify targets for restricting metastasis, and to challenge new therapies in relevant and reproducible animal models for metastatic childhood cancer. Cancer cells must enter, survive in, and then exit from the vascular or lymphatic system in order to establish metastases. Angiogenesis and lymphangiogenesis are cross-talking, complex processes involving endogenous stimulators, inhibitors, and their receptors. The signals are modulated by cancer cells, endothelial cells, macrophages, and the extracellular matrix. Vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) are two of several growth factors involved in angio- and lymphangiogenesis. Their importance in clinical cancer is without doubt, since administration of a VEGF-antibody (bevacizumab) in combination with chemotherapy prolongs survival in patients with metastatic colorectal cancer and non-small cell lung cancer, and so does a VEGF/PDGF-receptor inhibitor (SU11248) in metastatic renal cancer. We use cell cultures, in vitro-cytotoxicity assays, orthotopic and heterotopic xenotransplantation of human cancer cells, mainly neuroblastoma cells, to immunodeficient mice, ultrasound with contrast-tuned imaging to quantify tumor perfusion, small animal PET/CT, immunohistochemistry, FACS, stereological quantification of angiogenesis, and microarrays. Our project will dissect the biology and therapeutic intervention of metastasis in childhood cancers. New targets for restricting metastasis can be identified. New drugs, and new combinations of drugs and chemotherapy, will be evaluated with respect to their ability to inhibit angiogenesis, lymphangiogenesis, and metastatic spread and growth. The translational design of the project permits direct clinical applications. Angiogenesis inhibition has already become a valuable adjunct in adult cancer. Angiogenesis inhibition is likely to reduce late effects of chemotherapy and improve survival and quality of life in children with cancer.

Members of the group during 2007:

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