Life Cycles: Human Reproduction, Growth, and Development

Thursday May 9th to Friday May 10th 2019

At "Jubileumsaulan" Lecture Hall, Jan Waldenströms gata 2-5,
Skåne University Hospital (SUS), Malmö, Sweden

Organised by:

The Strategic Research Area (SRA) Epidemiology for Health (EpiHealth) at Lund and Uppsala Universities in collaboration with ReproUnion 2.0, the Centre for Excellence in Reproduction and Perinatal Sciences (CERPS), Lund University, and "Svensk Andrologisk Förening", SAF (Swedish Society of Andrology).

Welcome to the Life Cycles Symposium in Malmo 9-10 May 2019!

We cordially welcome you all to attend this symposium dedicated to research and clinical experiences in the field of reproduction, infertility/fertility and early life programming of adult health and disease. The programme is focused on early life factors on May 9th and more on reproduction and fertility problems on May 10th. Finally there will be a debate on perspectives on reproduction and fertility support in the Öresund region with regional politicians, clinicians and researchers present in the panel. In the afternoon of May 10th there will also be organised two satellite meetings, one by the Swedish Association of Andrology, and the other one by a team of midwives from Uppsala and Lund universities interested in the concept of reproductive life plan (RLP) for young people. This links to the new and important focus on pre- and periconception health, as many new research findings indicate that this is a period in reproductive life of great importance for the health of the embryo and later the fetus. Many ethical, clinical and legal issues are linked with human reproduction, assisted reproduction and the prognosis of children born after pregnancy complications such as pre-eclampsia or gestational diabetes, some of the exposed to intrauterine growth retardation.

We hope for an interesting symposium and fruitful discussion!

Welcome!

Peter M Nilsson, MD, PhD, Professor, Malmö (CERPS, SRA EpiHealth)

Aleksander Giwercman, MD, PhD, Professor, Malmö (CERPS, ReproUnion 2.0)

Mats Holmberg, MD, PhD, Stockholm (SAF)

Symposium secretariat: Camilla Key (Camilla.key@med.lu.se)

Programme

May 9th		Lecturer	Title
09:00-10:00	**Registration, coffee**		
10:00-10:15	Welcome	Peter M Nilsson, Aleksander Giwercman, Katarina Link	*Welcome address from SRA EpiHealth, ReproUnion 2.0, CERPS, and SAF*
10:15-11:15	**Session 1 Periconceptional Health**		
	Chair: Peter M Nilsson		
		Shantanu Sharma	Peri-conception health from the Indian perspective
		Anders Nyboe Andersen	*Fertility drugs - time to prevent infertility*
		Tina Kold Jensen	*How to improve reproductive health in young adults?*
11:15-11:30	**COFFEE, posters**		
11:30-12:45	**Session 2 Early Life Programming**		
	Chair: Anna Rignell-Hybom		
		Peter M Nilsson	*The Helsingborg Birth Cohort*
		Zakir Hossin	Socioeconomic inequalities in health among Swedish men and women born 1915-20 across the course and intergenerational effects across the twentieth century.
		Karin Källén	*The Medical Birth Register - recent developments*
		Trine Flensborg-Madsen	*The Copenhagen Perinatal Cohort*
12:45-13:30	**LUNCH, posters**		
13:30-14:00	State-of-the-Art 1	Jessica Abbott	*Evolutionary perspectives on human reproduction*
	Chair: Peter M Nilsson		
14:00-15:00	**Session 3 Family planning and abortions - hot issues**		
	Chair: Aleksander Giwercman		
		Maria Ekstrand Ragnar	*Sexual risk taking and contraception use – trends and attitudes*
		Göran Samsioe	*Medical aspects of legal abortions/Selective abortions*
		Lars Nilsson	*Uterus transplantation, current status and future directions*
15:00-15:30	**COFFEE, posters**		
15.30-17:00	**Session 4 Female reproductive history and cardiometabolic risk**		
	Chair: Margrét Leosdottir		
		Isabel Drake	*Parity, breastfeeding and cardiometabolic consequences*
		Stefan Hansson	*Female reproductive health and cardiovascular risk – pre-eclampsia*
		Kerstin Berntorp	*Gestational diabetes and its consequences*
		Simon Timpka	*Prevention of cardiovascular disease in women after pregnancy complications*
17:00-17:30	Poster session		*Selected poster abstracts*
	Chair: Peter M Nilsson		
19.00-	Symposium reception	Malmö Rådhus	Reception, food and drinks. Host: Malmö City
		Kompanigatan 5, Stortorget	

May 10th		Lecturer	Title
09:00-10:15	**Session 5 Male infertility and comorbidities**		
	Chair: Mats Holmberg		
		Michael Eisenberg	*Male infertility and comorbidities*
		Yvonne Lundberg Giwercman	*Risk of prostate cancer in men undergoing assisted reproduction*
		Angel Elenkov	*Prescription of anti-metabolic syndrome medications and testosterone replacement therapy in men undergoing assisted reproduction*
10:15-10:45	**COFFEE**		
10:45-11:45	**Session 6 Parental cancer and health risk in the offspring**		
	Chair: Anders Bjartell		
		Jacquetta Trasler	*Impact of High Dose Folic Acid Supplements on DNA Methylation in Sperm and Embryos: Potential for Adverse Effects across Generations*
		Aleksander Giwercman	*Congenital malformation risk in children fathered by men diagnosed with cancer - why are we worried and clinical recommendations.*
		Yahia Al-Jebari	*Cancer, cancer therapy and the risk of birth defects in the offspring to men with cancer - what do the human studies show?*
11:45-12:15	State-of-the-Art 2 Chair: Aleksander Giwercman	Anja Pinborg	*Evolutionary benefits and risks of use of assisted reproduction*
12:15-13:00	Panel debate Chair: Aleksander Giwercman	Politicians, patients, professionals	How to promote healthy reproduction in the Öresund area Anna Mannfalk, Gilbert Tribo, Anja Pinborg, Margareta Kitlinski, Kirk Scott, Petter Hartman Magnusson, Eva Elmerstig
13:00-13:10	Price ceremony and farewell	A Giwercman, PM Nilsson	
13:10	**Lunch – grab and go**		
			Afternoon parallel sessions May 10th
14:10-16:00	Lecture Hall: “Professorn”, MFC	Mats Holmberg, Aleksander Giwercman	Swedish Society for Andrology Lectures and internal session, annual meeting
13:30-15:00	Lecture Hall: “Tidskriften”, MFC	Maria Ekstrand Ragnar, Tanja Tydén	Midwives and health care providers. The Reproductive Life Plan (RLP); why, for whom, how and when?

Barnmorskor och övriga intresserade. ”Reproduktiv livsplan” - vad, när, hur, varför?
Om preventivmedelsrådgivning som plattform för att öka ungas medvetenhet om ålderns och levnadsvanors betydelse för fruktsamhet samt om barnmorskan som nyckelperson inom pre-konceptionell hälsa och rådgivning.
Moderatorer: Maria Ekstrand Ragnar, R.N.M, PhD, Lund University; Tanja Tydén, R.N.M, senior professor, Uppsala University

13:30-14:15 (c:a) Föreläsning
Reproduktiv Livsplan vad, när, hur, varför

14:15-15:00 (c:a) Workshop
Reproduktiv Livsplan – hur fungerar det i praktiken? Gruppdiskussioner baserade på patientfall
Tid för kortare bensträckare mellan föreläsning och workshop. Föreläsningen hålls på svenska.

Evolutionary perspectives on human reproduction

Jessica K. Abbott[1], PhD.

[1]*Evolutionary Ecology, Biology department, Lund University, Lund, Sweden*

Reproduction is an important source of selection in many organisms, and reproductive strategies vary widely in the natural world. Research in animals has given us insight into the many factors that shape the evolution of sexual dimorphism, including sexual system (e.g. monogamy versus promiscuity), degree of intra-sexual competition and variance in reproductive success, conflicts over mating rate and investment, the role of the sex chromosomes, and genetic constraints arising from a shared genome.

I will give a short introduction to all of these factors and discuss their potential relevance in humans. I will also highlight some recent studies of contemporary sexually dimorphic selection in humans. I will conclude by synthesizing these various perspectives to show how factors related to reproduction can serve to increase or decrease the magnitude of sex differences in different traits.

Cancer, cancer therapy and the risk of birth defects in the offspring to men with cancer –what do the human studies show?

Yahia Al-Jebari[1], M.Eng., Ingrid Glimelius[2,3], MD., Carina Berglund Nord[4] MD., Gabriella Cohn-Cedermark[4] MD., Olof Ståhl[5] MD., Torgrim Tandstad[6], MD., Allan Jensen[7], PhD., Hege Sagstuen Haugnes[8] MD, PhD., Gedske Daugaard[9], MD., Lars Rylander[10], PhD., Aleksander Giwercman[1] MD.

[1] *Molecular Reproductive Medicine, Department of Translational Medicine, Lund University, Malmö, Sweden*

[2] *Department of Medicine, Division of Clinical Epidemiology, Karolinska Institute*

[3] *Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala, Sweden*

[4] *Department of Oncology-Pathology, Karolinska Institutet and Karolinska University Hospital, Stockholm, Sweden*

[5] *Department of Oncology, Skåne University Hospital, Lund, Sweden*

[6] *Department of Clinical and Molecular Medicine, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology, Trondheim, Norway and The Cancer Clinic, St. Olavs University hospital, Trondheim, Norway*

[7] *Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark*

[8] *Department of Oncology, University Hospital of North Norway, Tromsø, Norway; Institute of Clinical Medicine, UiT The Arctic University of Norway, Tromsø, Norway*

[9] *Department of Oncology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark*

[10] *Division of Occupational and Environmental Medicine, Lund University, Lund, Sweden*

Background

Based on animal studies, there are well-founded concerns that chemo- and radiotherapy, due to their gonadotoxicity and mutagenicity, might have detrimental health effects on children of men treated for cancer. Fears of genetic disease, especially congenital anomalies, have been seemingly confirmed in a register study finding a slight increased risk in children conceived after paternal cancer. Perplexingly, this increased risk was also present for children of men with skin cancer - a malignancy generally treated with surgery only. This talk will cover our epidemiological studies and aims to disentangle the risks of adverse health effects attributable to the fathers' cancer treatments, from the risks associated with the cancer per se.

Methods

The studies were based on data from Swedish national registries, including records on all children born in Sweden 1994 - 2014 (~1.8M) and their parents. We identified men with cancer (n=23 932), and identified their children (26 601 conceived before and 9926 conceived after cancer diagnosis). Using the SWENOTECA registry, we also identified a subgroup of men with testicular germ cell cancer, and stratified their children on paternal cancer treatment (+/- radiotherapy; +/- chemotherapy).

Results

Children conceived before their fathers cancer diagnosis, and therefore unexposed to cancer therapies, had a modest but statistically significantly increased risk of all and major malformations (odds ratio [OR] 1.08, 95% confidence interval [CI]: 1.02 - 1.15, and OR 1.09, 95% CI: 1.01 - 1.1, respectively). Eye, central nervous system, and testicular cancers were associated with the highest risk of malformations (~30% relative increase). Investigations in the subgroup of children with fathers having testicular cancer (for which treatment data was available), showed that no additional risk of birth defects is associated with paternal chemotherapy nor with paternal radiotherapy (OR 0.82, 95% CI: 0.54 - 1.25, and OR 1.01, 95% CI: 0.25 - 4.12).

Conclusions

The overall implications of these results are that there is a small risk of birth defects, and this risk is associated with the cancer itself, rather that its treatment. Radio- or chemotherapy do not entail additional risk of congenital malformations. The detected risk is so small, however, that patients do not need to worry about their children's health. From a clinical point of view, our data might indicate that use of spermatozoa cryopreserved before cancer treatment may not be safer than utilizing fresh post-treatment gametes. Scientifically, the mechanism linking paternal cancer to birth defects is puzzling and might indicate higher genomic instability among men with malignant disease.

Gestational diabetes and its consequences

Kerstin Berntorp[1, 2] MD, PhD.

[1]*Department of Endocrinology, Skåne University Hospital, Malmö, Sweden*
[2]*Department of Clinical Sciences Malmö, Lund University*

Background

Gestational diabetes mellitus (GDM) is generally defined as any degree of hyperglycemia first detected in pregnancy. Although glucose tolerance usually reverts to normal after delivery, affected women remain at high risk of developing type 2 diabetes during their lifetime, with an estimated lifetime risk of about 50–70%. In addition to hypertensive pregnancy disorders, GDM is associated with dyslipidemia and other components of the metabolic syndrome, and if present, an increased risk of cardiovascular disease.

Diagnostic criteria

Criteria for the diagnosis of GDM were initially designed to identify women at high risk for the development of diabetes after pregnancy rather than to identify women at high risk for adverse perinatal outcomes. The diagnosis is based on an oral glucose tolerance test. However, there has been no uniform international standards for the screening and the diagnostic thresholds. The "Hyperglycemia and Adverse Pregnancy Outcomes" (HAPO) study was conducted to address these questions and to clarify the risks of adverse neonatal outcomes associated with various degrees of maternal hyperglycemia less severe than that in overt diabetes. A strong continuous association of maternal glucose levels with increased birth weight and percent body fat was demonstrated. Based on these results new diagnostic thresholds for the diagnosis of GDM was suggested which are lower than those previously used in most parts of the world. In 2013, the WHO aligned to the recommendation and in 2015 the Swedish National Board of Health and Welfare as well. In an ongoing nationwide population based study in Sweden, the effects of these new criteria on the pregnancy outcome and health economy are under evaluation.

The trans-generational cycle of obesity and diabetes

GDM and maternal obesity are independently associated with adverse pregnancy outcomes, and children born to mothers with GDM and overweight/obesity are more likely to be macrosomic and large for their gestational age. In addition to short-term complications, they also have an increased risk of long-term complications similar to those in their mothers. Studies indicate that offspring exposed to maternal diabetes or GDM in utero are at a higher risk of developing childhood obesity and impaired glucose tolerance in early adulthood than offspring not exposed to maternal diabetes. Moreover, if the offspring is female, she is more likely to develop GDM herself and

thereby create a vicious circle. Genetics, lifestyle and epigenetics may be the mediators of these effects. Prevention of GDM and fetal over-nutrition in pregnancy could be important strategies to interrupt this trans-generational cycle of obesity and diabetes.

Parity, breastfeeding and cardiometabolic consequences

Isabel Drake[1], PhD.

[1] *Diabetes and cardiovascular disease – genetic epidemiology, Department of Clinical Sciences in Malmö, Lund University, Malmö, Sweden*

Background

Established risk factors for cardiometabolic diseases (CMDs) are shared between men and women but differences in prevalence and effect has been noted. In addition, female-specific reproductive factors have been shown to associate with risk of CMD.

Methods

The presented work is ongoing and relies on data from the Malmö Diet and Cancer Study (MDCS), in particular the cardiovascular arm (MDC-CC). We examined gender differences in established CMD risk factors as well as in novel genome-wide polygenic risk scores (PRS) for coronary artery disease (CAD) and type 2 diabetes (T2D). Using two targeted proteomics panels (Olink Biosciences, Uppsala) we explored potential gender differences in 138 circulating biomarkers for cardiovascular mortality. The interplay between parity and breastfeeding in relation to CAD and T2D as well as potential mediating factors will be presented.

Results

Established CMD risk factors are similarly associated with increased risk of CAD and T2D in men and women of the MDC-CC. However, for both CAD and T2D, HbA1c is a stronger risk factor in women compared to men. Novel genome-wide PRSs predict CAD and T2D similarly in men and women, with the T2D PRS performing slightly better among women. Gender-specific biomarker models improve prediction of cardiovascular mortality in addition to established risk factors. High parity is associated with an increased risk of T2D and CAD and the effect is to a large extent mediated by adiposity and weight gain as well as HbA1c. A longer duration of breastfeeding may potentially offset the increased risk observed with high parity.

Conclusions

Prediction models for CMD may potentially improve in the future with the inclusion of more gender-specific risk factors. The causal nature between reproductive factors in relation to CMD in women remains to be ascertained.

Male infertility and comorbidities

Michael L. Eisenberg, MD, PhD, Associate Professor

Stanford University | SU · Department of Urology, Palo Alto, CA, United States

Infertility impacts approximately 1 in 7 couples in the U.S. Nearly 50% of infertile couples will have a male factor to explain reproductive difficulties. Importantly, male fertility may provide a window into future health with data suggesting that men with infertility have higher rates of cancer, metabolic disease, and mortality [1]. Select comorbid conditions (e.g. obesity, smoking) are known to impact male fertility and health; however, the etiology of the association remains unknown.

Data suggests genetic, in utero, and hormonal factors may contribute. The findings suggest an opportunity to positively affect men's health. If infertility is confirmed as an early marker of chronic disease, screening practices could be adjusted, as they are for patients with a family history of malignancy.

1. Choy JT, Eisenberg ML. Male infertility as a window to health. *Fertil Steril.* 2018; 110(5):810-814.

Sexual Risk Taking and contraception use – Trends and attitudes

Maria Ekstrand Ragnar[1, 2], R.N.M., PhD.

[1]*Department of Womens and Childrens Health, Uppsala University, Uppsala, Sweden*
[2]*Region Skåne, Primary health care clinic Najaden, Helsingborg, Sweden*

Background

In many aspects the Swedish health care organization provides good conditions for sexual and reproductive health; contraceptive counselling and testing of sexually transmitted infections (STI) are free of charge, contraceptives are subsidized, and Sweden has one of the world's most liberal abortion laws. Despite this, there are worrying trends of increased sexual risk taking, high numbers of sexually transmitted infections and an unchangingly high number of induced abortions. Attitudes studied among young women and men in Sweden revealed an underestimation of risk towards unintended pregnancy in combination with inconsistent contraceptive use. The responsibility regarding pregnancy prevention and contraceptive use was viewed as a 'girls' issue' and knowledge about abortion and contraception was often scarce.

In 2014, the Swedish Medical Products Agency published new national guidelines for contraceptive use which emphasised the recommendation of long acting reversible contraceptives (LARC), especially for young women and highlighted that the aim of contraceptive counselling is to avoid unwanted pregnancies and to preserve a woman's fertility until she wants to conceive.

In a study comparing contraceptive use in the Nordic countries, Sweden was next after Denmark, reported to have the highest contraception use (41%). Another nationwide study on contraceptive trends between 2013 and 2017 reported that use of short acting reversible contraception (SARC) had decreased significantly whereas use of LARC had increased. Still, a large proportion of women have unmet needs for effective contraception methods; one in five women have experienced unintended pregnancy and women do not always use contraceptive methods suitable for their reproductive intentions.

References

Stenhammar C, Tiblom Ehrsson Y, Åkerud H, Larsson M, Tydén T. Sexual and contraceptive behavior among female university students in Sweden – repeated surveys over a 25-year period. *Acta Obstet Gynecol Scand.* 2015; 94(3):253-9.

Ekstrand M. *Sexual Risk Taking – perceptions of contraceptive use, abortion, and sexually transmitted infections among adolescents in Sweden*. Acta Universitatis Upsaliensis Uppsala 2008.

Lindh I, Skjeldestad FE, Gemzell-Danielsson K, Heikinheimo O, Hognert H, Milsom I, Lidegaard. Contraceptive use in the Nordic countries. *Acta Obstet Gynecol Scand*. 2017; 96(1):19-28.

Hellström A, Gemzell Danielsson K, Kopp-Kallner H. Trends in use and attitudes towards contraception in Sweden: results of a nationwide survey. *Eur J Contracept Reprod Health Care* 2019 Mar 28:1-7.

Prescription of anti-metabolic syndrome medications and testosterone replacement therapy in men undergoing assisted reproduction

Angel Elenkov MD, PhD[1,2], Yahia Al-Jebari [1], Aleksander Giwercman, Professor [1,2]

[1] *Molecular Reproductive Medicine, Department of Translational Medicine, Lund University, Malmoe, Sweden*
[2] *Reproductive medicine center, Skåne University Hospital, Malmoe, Sweden*

Background

Register-based studies have indicated that men with impaired fertility are at higher risk for developing hypogonadism and various adult-onset diseases than fertile men. The majority of men undergoing ICSI treatment are sub-fertile and since they are in contact with the health care system.

Methods

Our study included all men (N = 459 766) who had fathered children in Sweden between 2006 and 2016. Swedish registry data was used for obtaining information regarding conception method and defining three groups of fathers - ICSI -treated, IVF - treated and non-IVF/ICSI. By sourcing data from the Swedish Prescribed Drug Register, we specifically searched for information regarding prescription and usage of at least one prescription for testosterone diabetes mellitus, hypertension (HT) or dyslipidemia to serve as a proxy for metabolic disease among the study groups. Since long-term treatment for opioid addiction is known to negatively affect the hypothalamo-gonadal axis, reducing the serum testosterone levels, also this group of men was excluded from the analysis (1,594 men), leaving in total 418 847 men in the study.

Results

Our results indicate male partners in couples who became parents using ICSI to be at higher risk for being treated for hypertension (HR 1.15, 95% CI: 1.06-1.24, p= 0.001) and metabolic syndrome (HR 1.28 95% CI: 1.01-1.58, p = 0.042) when compared to non IVF/ICSI men. After mean follow-up of 6.7 years, age and educational level adjusted HRs of testosterone replacement therapy (TRT) prescription were statistically significantly increased in ICSI and IVF fathers as compared to controls (HR 3.81, 95% CI: 3.09-4.69, p<0.001 in the ICSI and HR 1.54, 95% CI: 1.15-2.05, p=0.003 in the IVF group, respectively).

Conclusions

Our analysis revealed statistically significant increase in the risk of developing hypertension and various metabolic disorders requiring prescribed medicines when using ICSI as proxy for male infertility. ICSI-treated men presented with four times higher risk for TRT compared to general population Whereas our study identifies ICSI-treated men as being at risk for hypogonadism, metabolic and cardiovascular disease it cannot answer the question regarding the causal factors driving this association.

The Copenhagen Perinatal Cohort

Trine Flensborg-Madsen, MD, PhD [1] and Erik Lykke Mortensen, PhD[1]

[1]*Unit of Medical Psychology, Department of Public Health, University of Copenhagen, Denmark*

Background

The Copenhagen Perinatal Cohort (CPC) was initially established with data on 8949 mothers and their 9125 consecutive deliveries at the Copenhagen University Hospital between 1959 and 1961. When the cohort was established, demographic, socioeconomic, prenatal, and postnatal medical data were recorded prospectively and during pregnancy, at delivery, and at 1, 3 and 6-year follow-ups. Additionally, developmental milestones were obtained from the mothers who were instructed to use a standardized diary to record the ages at which the child reached a variety of developmental milestones.

Methods

Subsamples from the CPC participated in the Prenatal Development Project (PDP) and the Copenhagen Aging and Midlife Biobank (CAMB), both of which contains information on personality and intelligence in addition to a range of other factors related to lifestyle and health. Utilizing the CPC and the follow-up studies it has therefore been possible to conduct several studies investigating the importance of early predictors in the first years for outcomes in adulthood.

Results

Results will be presented from several studies focusing on the associations of perinatal factors and early developmental milestones with adult intelligence and personality.

Conclusion

CPC is a cohort with several opportunities to explore the importance of the first years of life for outcomes in adulthood.

Flensborg-Madsen T, Mortensen EL. Associations of Early Developmental Milestones with Adult Intelligence. *Child Dev*. 2018; 89(2):638-648.

Congenital malformation risk in children fathered by men diagnosed with cancer – why are we worried and clinical recommendations

Aleksander Giwercman, MD, PhD, Professor

Reproductive Medicine Centre and Dept. of Translational Medicine. Skane University Hospital and Lund University. Malmö, Sweden.

During the past few decades the survival rates for young cancer patients have significantly increased, which means that the issue of their future life quality, including reproductive function, is of significant importance. One of the aspects of reproductive function is the question of the health of the children of young cancer survivors.

For some years ago we performed a survey among male survivors of testicular and childhood cancer showing that approximately 40% of those men are worried about heredity and genetic sequelae of cancer. This is an important message which needs to be addressed by the health care system.

Whereas we have some knowledge about the heredity of cancer, our knowledge regarding the impact of cancer and anti-neoplastic treatment on the genome of spermatozoa is still rather limited. In the clinical practice we recommend all adolescent and young adult men, prior to chemo- or radiotherapy, to cryopreserve spermatozoa. Furthermore, we strongly recommend them to use contraception in order to avoid pregnancy during and at least 6 months after ongoing cancer therapy. This recommendation is based on animal studies indicating that such treatment implies increased risk of genetic alteration in sperm DNA. However, the human data are still very scarce, why we have problems with giving evidence based recommendations to young male cancer patients asking whether a pregnancy accomplished during or shortly after cancer therapy should be terminated or not and if they, following cancer treatment, should use fresh or cryopreserved spermatozoa.

In this presentation, I will present some existing molecular data regarding this topic whereas the following talk, given by Yahia Al-Jebari, will focus on epidemiological human data.

Potential mechanisms causing increased cardiovascular risk after preeclampsia

Auth Tina Cronqvist MD, PhDc[1], Mimmi Rhenström MD, PhDc[1], Lena Erlandsson PhD[1], **Stefan R. Hansson** MD, PhD[1]

[1]*Affilation Obstetrics and Gynecology, Department of Clinical Sciences Lund, Lund University, Sweden*

Background

Preeclampsia (PE) is a pregnancy-specific vascular disease characterized by *de novo* maternal hypertension and proteinuria, and resolves after the delivery of the placenta. PE annually affects at least 8.5 million women worldwide and is a leading cause of maternal and perinatal morbidity and mortality. PE is associated with 10-fold increased risk for future chronic hypertension, cardiovascular disease (CVD), cerebrovascular disease, and death. The risk of dying from ischemic heart disease following PE has been estimated to 2.5-fold higher than that of women without PE. A growing body of evidence supports the view that PE begins in the utero-placental unit, and is amplified by oxidative stress and inflammation that lead to general maternal endothelial damage responsible for the clinical manifestations.

The oxidative stress in combination with utero-placental ischemia cause tissue damage and increased shedding of placenta derived extracellular vesicles (STBEV) into the maternal circulation, which, in turn, causes inflammation and vascular damage. The STBEVs contain microRNAs (miRNAs) that may play a role in the vascular endothelial disease. The specific mechanisms by which STBEVs cause permanent endothelial dysfunction in PE was studied *in-vitro*.

Methods

We isolated placenta-derived STBEVs from normal and PE placentas perfused with buffer.

a) Specific uptake pathway inhibition assays were used to study the mechanisms by which STBEVs were internalised by endothelial cells. The STBEVs were fluorescently labelled and their uptake analysed using flow cytometry, as well as fluorescence and confocal microscopy. The specific intracellular pathways and compartments were identified by immunohistochemistry and visualised by transmission electron microscopy (TEM). The effect of placenta specific miRNA transfer on gene expression was analysed using qRT-PCR.
b) Arterial contractility was evaluated before and after STBEV exposure using wire myography.

Results

We have shown that STBEVs are internalised by primary human coronary artery endothelial cells (HCAECs) *in vitro* and transfer their miRNA content to the rough endoplasmic reticulum (ER) and mitochondria of the cells. This in turn causes down-regulation of specific target genes, including genes related to angiogenesis. Furthermore, we have shown that PE-derived STBEVs cause extensive cell membrane ruffling on HCAECs and recent preliminary data show altered contractility after PE STBEV exposure.

Conclusions

The findings suggest that STBEVs may contribute to the endothelial dysfunction and arterial stiffness described in PE. The reprogramming of the endothelial cells may permanently alter the vascular function and thereby contribute to the increased risk for CVD.

Socioeconomic inequalities in health among Swedish men and women born 1915-2010: life course and intergenerational effects across the twentieth century

M. Zakir Hossin[1], Ilona Koupil [1,2] (on behalf of the UBCoS Multigen study team)

[1] *Department of Public Health Sciences, Karolinska Institute, Stockholm, Sweden*
[2] *Department of Public Health Sciences, Stockholm University, Stockholm, Sweden*

Background

Socioeconomic inequalities in health have been observed worldwide, including in welfare states like Sweden. Our research goal is to explore how the socioeconomic environment interacts with health, growth and development in order to predict health and social outcomes across the life course and across generations.

Methods

The Uppsala Birth Cohort Multigenerational Study (UBCoS Multigen: www.chess.su.se/ubcosmg) started with a representative cohort of 14,192 males and females born in Uppsala University Hospital from 1915-1929. This cohort has been combined with social and health data on all their descendants obtained from routine registers and additional data collected from church parish records, school archives, obstetric records and Census 1930. The resulting multigenerational study comprises over 150,000 individuals followed till end 2009/2010.

Results

Multiple UBCoS studies demonstrated associations between social and health characteristics across more than two generations. These studies have also highlighted that early-life predictors of social outcomes show both important similarities and important differences between men and women and between generations. Based on data from the UBCoS Multigen, we have recently demonstrated that early-life biological and social disadvantage in our original cohort members predicts lower school achievement, educational continuation and income in later life, and that this in turn predicts lower socioeconomic position (SEP) in their children and lower school achievement and SEP in their grandchildren. These studies indicate the presence of multigenerational effects on social outcomes and suggest that these may operate via the social mobility of intervening generations. Current research focuses on social mobility, ageing and women's health.

Conclusions

The uniqueness of UBCoS Multigen stems from combination of routine registry data (available in Sweden since 1960) with manually collected social and health data stretching back to early 1900. We believe understanding of intergenerational determinants of health and health inequality will not only clarify disease etiologies at

individual level, but also generate evidence for effective policy interventions. Further results are coming out soon.

How to improve reproductive health in young adults?

Tina Kold Jensen[1-3], MD, PhD

[1] *University of Southern Denmark, Department of Environmental Medicine, Denmark*
[2] *University Department of Growth and Reproduction, Rigshospitalet, Copenhagen, Denmark*
[3] *The International Research Centre in Endocrine Disruption of Male Reproduction and Child Health (EDMaRC), Rigshospitalet, University of Copenhagen, Denmark.*

Background

Semen quality among men in the industrialized world has decreased substantially in the last few decades according to a recent meta-analysis that included over 185 studies; total sperm counts have declined by 50–60% from 1973–2011 in Western countries. A growing concern and evidence that environmental exposures such as endocrine disrupting chemicals, lifestyle or behavioral factors could explain this decline.

Effects of lifestyle (BMI, smoking, exposure to smoking in utero, alcohol and caffeine intake, diet, supplement intake and use of recreational drugs) and behavior (cell phones, exercise and psychological stress) as well as current exposure to endocrine disrupting chemicals on semen quality will be reviewed in this lecture. Generally, the evidence of an adverse association between semen quality and high or low BMI, exposure to smoking in utero or current smoking is strong. Likewise, the evidence for association of adherence to a healthy diet and exercise pattern and semen quality is convincing. The evidence is less convincing for the rest of the exposures and needs to be elaborated further.

Widely used chemicals with endocrine disrupting properties are phthalates, bisphenol A and perfluorinated alkylated substances used in consumer products such as cosmetics, plastic types, and protective coatings of clothes, furniture and food packaging. Studies have suggested an adverse association between current exposure to these chemicals and semen quality, however, exposure during vulnerably time periods during development, e.g. in utero, is more hazardous and it has been hypothesised that semen quality, testicular cancer and malformation in the male reproductive tract are manifestations of the same eternity founded in utero.

Most of the studies included heterogeneous groups of infertile men and were observational with no interventions. Therefore, it is impossible to make any firm conclusions about causation and reverse causation cannot be excluded. In addition, it may be difficult to disentangle the separate adverse effect of a single lifestyle factor.

Conclusion

Men in fertile age can be recommended to stop smoking, have a normal weight and follow national guidelines for exercise and healthy diet habits.

Risk of prostate cancer in men undergoing assisted reproduction

Yahia Al-Jebari [1], Angel Elenkov [1,2,3], Elin Wirestrand, medical student researcher [1], Indra Schütz[1], Aleksander Giwercman[1,3], **Yvonne Lundberg Giwercman** [1]

1. *Lund University, Dept. of Translational Medicine, Malmö, Sweden;*
2. *Medical University Sofia, Department of Urology, Sofia, Bulgaria;*
3. *Skåne University Hospital Malmö, Reproductive medicine Center, Malmö, Sweden.*

Background

The association between infertility and prostate cancer has been studied previously, with contradicting results.

Methods

Register excerpts on all children born alive in Sweden during 1994-2014 (n=2 108 569) as well as their fathers were retrieved.

Results

Infertile fathers had statistically significantly increased risk of prostate cancer compared to men conceiving naturally.

Conclusions

Men with fertility issues are at risk for prostate cancer and thus constitute a risk group in which careful hormonal evaluation and long-term follow-up is warranted.

The Swedish Medical Birth Register

Karin Källén, PhD, Professor

Clinical Sciences, Lund, Dep of Obstetrics and Gynecology, Lund University, Sweden

Background

The Swedish Medical Birth Register (MBR) is, especially in combination with the other health registers kept at the National Board of Health and Welfare (Sw. "Socialstyrelsen"; SoS), a goldmine for epidemiologic research in Sweden. The MBR was revised in 1998, and a new revision is heavily due. However, despite the fact that a revision is needed, the register is frequently used by researchers all over Sweden, and is also used to produce numerous reports from SoS - reports that are often commissioned by the Swedish government. The current speech will give a short overview of the planned revision of the MBR, and will also present highlights from four recent reports published by SoS (Socio-economic factors and maternal and child health during pregnancy and delivery, Congenital malformations and chromosomal abnormalities, 2018, Maternal complications after child birth, and Stillbirth in Sweden-an inventory and suggested interventions).

Methods

The highlights of four reports published between December 2016 and December 2018 will be presented. In all four publications, the MBR was linked with the patient register (PAR) and the cause of death register (DOR). For one report, data from Statistics Sweden were also used, and for another, data from the certain data collection on congenital malformations was used.

Results

1. Socio-economic factors have a substantial impact on maternal- and child perinatal health. Women born in Africa south of Sahara, and their children, have substantial increased risks for poor perinatal outcome when giving birth in Sweden. Women born in Middle East (and their children) were also at higher risk than Swedish women and their offspring, but far less pronounced than African women and their children. Maternal and paternal educational level also influenced the maternal- and child health, but the income level did not have any major impact on the selected outcomes.
2. Because of the expanding prenatal screening for chromosomal abnormalities, the rate of children born with Down syndrome has not increased in spite of the increased maternal age at child birth. In 2018, (data from 2016), the rate of children born with Down syndrome rapidly decreased.

3. Vaginal birth is associated with perinatal ruptures immediately at birth, and risk of anal- and urine incontinence, and prolapse, respectively, in the long run. Cesarean section, on the other hand, is associated with bleedings and infections immediately after birth, life-threatening conditions like placenta percreta or uterine rupture in subsequent deliveries, and abdominal hernias and adhesions in the long run. The complications after caesarean section are more, and are more severe than the complications after vaginal births. Thus, if no certain risk situation is present, jeopardizing maternal or fetal health, vaginal birth is to prefer.
4. Until some years ago, Sweden was one of the countries with the lowest stillbirth rate. Since then, the other Nordic countries have managed to lower their stillbirth rate, while the Swedish stillbirth rate has been stable. Now, Sweden has the highest stillbirth rate among the Nordic countries. Large regional differences indicate that more could be done to lower the stillbirth rate in Sweden.

Conclusions

The health registers kept by SoS are important tools for reproduction epidemiology in Sweden. The SoS publish numerous reports of public interest in the field of reproduction epidemiology.

Uterus transplantation, current status and future directions

Lars Nilsson MD, PhD and Mats Brännström, MD, PhD, Professor

Department of Obstetrics and Gynaecology, Sahlgrenska University Hospital, University of Goteborg, Sweden

Background

Uterus transplantation is more and more becoming an alternative to treat severe subfertility and absolute infertility on the basis of uterine factors, where the only treatment option, hitherto, has been surrogacy.

Methods

Case material from one complete and one ongoing study in Sweden. Women with absolute uterine infertility, most of them with a Rokitansky (MRKH) diagnosis, have been treated by IVF to accumulate a sufficient number of frozen embryos before receiving a donor uterus. Thereafter, immunosuppressive treatment was instigated, and the recipients treated with single or repeated transfer of their own frozen and thawed embryos, one at a time. In a few cases, a new hormonal treatment with harvest of oocytes for IVF was performed, when the first embryos had been used without success. In the ongoing study robotic assisted surgery is being used.

Results

Of the first 6 women who in the completed study all became pregnant and 5 out of 6 gave birth at least once, resulting in 7 healthy babies, whereas one patient had repeated miscarriages without a birth. A seventh patient, who dropped out of the study, later became pregnant and gave birth after new IVF treatments with donor sperm. In the ongoing Swedish study, so far 1 out of 3 women has given birth. After the first 8 babies, all of them in Sweden, other centres in the world have produced additionally 6 healthy children.

Conclusions

The results from our ongoing studies, as measured as the birth of healthy babies per couple seem excellent indeed, as compared with normal IVF results. In addition to the now 9 Swedish babies there are a number of other children worldwide. This proves the efficacy of uterus transplantation. The cost of treatment is still high for the method but can be expected to decrease in the future. Robotic assisted surgery reduces the trauma for the donor, but still the time for surgery must be shorter. The use of deceased donors will spare living donors and takes less time, which both will further lower the cost.

Using bio-engineered uterine material from the recipients' own stem cells for transplantation will most probably be a realistic method in the future and make treatment to prevent rejection unnecessary. The indications for the treatment will probably widen and include other patient groups - maybe even chromosomally male individuals with gender dysphoria.

The Helsingborg Birth Cohort

Claes Ignell [1,2], MD, PhD, **Peter M Nilsson** [1], MD, PhD

[1] *Department of Clinical Sciences, Malmö, Lund University, Sweden*
[2] *Department of Obstetrics and Gynecology, Helsingborg Hospital, Helsingborg, Sweden*

Introduction

Specific components of the intrauterine environment, such as the influence of maternal smoking during pregnancy, have been shown to affect risk factors of adult health and disease. To establish effects long-term studies are needed, and fifty years ago a prospective cohort study including pregnancy- and neonatal data was started. In 2006 a national record linkage was performed including 4,060 pregnancies[1]. The material was upgraded with data from medical records based on a new national record linkage performed in 2017 with the aim of investigating long-term health of mothers (cardiovascular disease) and off-spring (i.e. respiratory disease).

Material and methods

Information was collected on all pregnancies diagnosed in the Helsingborg area between February 1, 1964 and January 31, 1967, and ending in a delivery (after gestational week 27) at the Department of Obstetrics and Gynecology at Helsingborg Hospital, a port town with a mixed urban-rural population (78,000 in 1965) in southern Sweden.

At the initial early pregnancy visit, the women were asked to complete a questionnaire, and throughout pregnancy use another one. This, alongside perinatal information on mother and child, was assessed after the delivery before discharge. Examples of data collected with the standards of the time: smoking, medication, preeclampsia, placental weight and appearance, children's asphyxia, pulmonary complications, dysmaturity index and debilitas congenita. Deliveries of 4060 women remained after exclusions of twin deliveries (n=53) and repeated deliveries during the study period (n=218). In 2016 maternal medical records were accessible for 3890 deliveries adding data on date of last menstrual period and maternal weights (but not length), blood pressures, and albuminuria. In a national record linkage 2017 data was included from 4,006 women and children.

Results

Half of the women reported smoking at some time during pregnancy, 5% ceased smoking during pregnancy, and 9% smoked more than 10 cigarettes daily during the whole pregnancy. By standards during pregnancy 115 (4.7 %) of the women were diagnosed with preeclampsia. Preliminary results indicate that preeclampsia and blood pressure > 95th percentile at first maternal healthcare visit compromise similar hazards

for cardiovascular disease of the mother. Maternal sedative use and smoking during pregnancy were independently associated with subsequent respiratory disease in offspring, while small-for-gestational-age (< 10^{th} percentile, adjusted for gestational length by modern weight curves) was not.

Conclusions

The preliminary results are being scrutinized to be published. Despite the relatively limited size of the cohort, the wide range of original data might prove its value the research area. Further, being based on a limited geographical area, the cohort could be used to target study groups for future examinations regarding metabolic and vascular status, for example small-for gestational-age.

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Fertility counselling – Time to prevent infertility

Anders Nyboe Andersen, MD, PhD, Professor

The Fertility Clinic 4071, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Blegdamsvej 9, 2100 Copenhagen, Denmark

Background

For many years "family planning" exclusively focused on contraception which was promoted through 1) public campaigns 2) education and 3) individual counselling and assistance to women and men. With today's delayed childbearing and low fertility rates, efforts to improve Reproductive Health should include similar initiatives, but with a pro-fertility perspective. As Seifer *et al.* 2015[1] phrased it: Putting "family" back in family planning.

Methods and Results

In 2011 we established The Fertility Assessment and Counselling Clinic in Copenhagen (Hvidman et al, 2015[2]) providing individual assessment and guidance on how to protect fertility and to guide women and men to fulfil their reproductive life-plans.

The concept is to offer women, men and couples a structured review of their risk factors for subfertility. Such risk factors are based on reproductive history with focus on threats to their fertility including lifestyle factors. Additionally, women have ovarian reserve testing with transvaginal sonography with Antral Follicle Counts (AFC) and measurement of anti-Mullerian Hormone (AMH). Men have a similar review of known risk factors for male subfertility, and additionally a sperm analysis "on-line", with visualisation on the screen. All data are presented to the clients in a colour sheet with green, yellow/orange and red colours – indicating specific threats for their fertility.

Attendants (n; >3.000) are mostly nulliparous women who are concerned about their future fertility. Female mean age is around 35 years, and 35% were single. Follow-up studies providing cumulative birth rates indicate that we may to some extend predict future fertility. Qualitative and quantitative studies show that most of the clients find the advices useful for their decisions on how and when to try to conceive.

Conclusions

Individual fertility assessment and counselling has been very "popular" in terms of attendances, and clients assess the activity to be valuable. Our ability to predict long-term failure or success in completing their desired goal in terms of family size remains to be shown.

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Evolutionary benefits and risks of use of assisted reproduction

Pinborg A[1] MD, PhD, Professor

[1] *Fertility Clinic, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark*

Background

Worldwide more than 7 million children have been born after assisted reproductive technologies (ART). Meanwhile the European populations are shrinking due to delayed childbearing and less children born per woman. Hence ART contributes substantially to the birth cohorts in the developed countries, but is there a risk?

Methods

This presentation summarizes the advantages and benefits of ART and scrutinize the short- term risks and possible long-term effects.

Results

It is common knowledge that twin pregnancies should be prevented in ART as these pregnancies carry considerable risks for mothers and progeny. However also singletons born after ART have slightly higher perinatal risks than children born after natural conception and freezing/thawing of embryos are associated with a higher risk of preeclampsia and being large-for-gestational age. These increased risk factors may be related to a higher risk of metabolic and cardiovascular disease in adulthood as studies have indicated a higher blood pressure in ART children and cardiovascular changes. These changes may be related to epigenetic modification during the early embryonic development, implantation and placentation.

Conclusions

It is a human right to have biological children but the long-term risks related to different ART procedures still need to be scrutinized to tailor ART treatment to create the highest success rates with the lowest risks.

Medical aspects of legal abortions/Selective abortions

Göran Samsioe MD, PhD Emeritus Professor

Dept. of Obstetrics and Gynecology, Lund University Lund Sweden

Albeit still vastly restricted world-wide, induced abortion saw its legalization in several countries during the 1970s and prevailing legislation introduced an array of techniques to ensure a safe procedure. Historically, surgical procedures using vacuum aspiration were used for early abortions while a forced induction of labour followed by curettage of the placenta was the preferred method for abortions later than weeks 14-16.The forced induction principle was emotionally exceedingly unpleasant and irksome as the fetus was not compulsory stillborn and hence legally a baby which had to be registered and buried The introduction of prostaglandins and anti-progesterones replaced or vastly modified existing techniques some of which decayed or even were abandoned.

The abundant usage of primarily non-surgical methods resulted in altered recommendations regarding preferred performance of abortion procedures and currently most countries enhance medical procedures .Regarding early abortions guidelines include Mifepristone 200 mg orally followed by vaginal misoprostol 0.8 some 30 hours later. If no bleeding occurs an additional 0.4 mg of misoprostol could be administered to ensure the maximal amount of complete abortions.

Following this procedure complications are extremely rare prior to week 9.Thereafter infections, commonly caused by retained fetal material may occasionally occur.

Should a woman be uncomfortable with the above recommendation she can select a surgical method if not directly infelicitous. When doing so a plastic catheter or a metal tube is inserted into the uterine cavity and by suction its content is emptied. Complications, mainly infections are more common than by medical abortion. A simple vacuum aspiration could be performed till week 12. At later stages until week 15, cervical dilatation followed by uterine cavity emptying is possible. However uterine perforation is a feared complication particularly with greatly flexed wombs. Other surgical procedures are inappropriate.

Contraception should be discussed beforehand and is preferably to be commenced in absolute adjacency to the abortive procedure. Despite information and advice by multiple sources one of four pregnancies are artificially terminated; a number that has remained fairly constant over decades.

Terminology regarding selective abortion is amalgamated .To disambiguate the term selective abortion it should be restricted to the removal of one or several fetuses in multifetal pregnancies. This procedure could be carried out when a fetus carries a chromosomic aberration rendering it susceptible to a serious disease but also when quadruples or triplets pose a threat to pregnancy or maternal well-being. An injection of potassium chloride directly into the fetal heart is the method commonly preferred. If not directly illegal the use of gender selection is disgustingly unethical.

Peri-conception health from the Indian perspective

Shantanu Sharma[1] MD, Peter M Nilsson[1], MD, PhD

[1]*Department of Clinical Sciences, Lund University, Skåne University Hospital, Malmö, Sweden*

Background

The peri-conception period is crucial for health across generations. This period presents a window of opportunity to improve health before and after conception and reduce the determinants of peri-conception risks. This holds importance for Low Middle-Income countries like India undergoing demographic and obstetric transition. The presentation aims to present the needs of the young population, evidence of interventions and gaps in policy implementation of peri-conception care (PCC) actions in Indian settings.

Methods

We studied data from national family health surveys, policy reports, white papers, peer-reviewed articles and websites of institutions (for example, http://mamta-himc.org/) working on PCC. A total of 30 such documents were referred, which were available in the public domain (accessed until 15 April 2019).

Results

53% of women in India are anemic, 23% are underweight, and another 21% are overweight or obese. More than 50% of women had dietary diversity score less than 4. Around 13% of women had unmet needs for family planning in India.[1] A group of experts including consultants from World Health Organization proposed a basic package of six intensive interventions and an expanded package of eight additional interventions on PCC in the Indian context. The basic package will cover issues of family planning, protection from vaccine-preventable diseases, nutrition intake, tobacco cessation, reduction in exposure to harmful environment and improved sexual health and behavior.[2] When considering the need for preconception care interventions, the government of India launched reproductive, maternal, newborn, child and adolescent health program in 2014 with the objective of working on life-course epidemiology. The programs aimed at engaging adolescents, young couples, pregnant and lactating women for improved maternal and child health.[3]

Conclusion

A consistent need is emerging of the importance of PCC among women of reproductive age. Besides the adequate evidence on high impact PCC interventions, the policy makers are also in favour of mainstreaming PCC in the routine maternal health care program. However, there is a dire need to push the active implementation of PCC

interventions effectively at the ground level in conjunction with community-based organizations and development partners.

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Prevention of cardiovascular disease in women after pregnancy complications

Simon Timpka MD, PhD[1, 2]

[1]*Genetic and Molecular Epidemiology Unit, Lund University Diabetes Centre, Lund University, Malmö, Sweden,*
[2]*Department of Obstetrics and Gynecology, Skåne University Hospital, Malmö, Sweden*

Summary

A history of certain prevalent pregnancy complications (including preterm birth and preeclampsia) is associated with at least twice the risk of cardiovascular disease (CVD) in women. The predominating framework suggests that pregnancy is a "stress-test" for CVD later in life, with the development of pregnancy complications being an indicator of higher susceptibility also to age-related cardiovascular changes. Current CVD prevention guidelines recommend that reproductive history should be part of a woman's CVD risk assessment but are vague on specific recommendations. Only recently have studies - published by our group and others - which investigate the extent to which pregnancy complications improve 10-year CVD risk prediction emerged.

This presentation will summarize findings from a recent review, in which we focus on the potential of pregnancy complication history to improve 10-year CVD risk prediction models. We found that several pregnancy complications are still associated with incident CVD in middle-aged women even when conventional predictors are concomitantly considered. However, comprehensive evaluation suggests that these associations are translated only into minor, if any, clinically relevant improvement of CVD prediction.

Thus, current evidence suggests that 10-year CVD risk prediction in women is not substantially improved by pregnancy complications history. Future studies should identify subgroups to target with prevention efforts post-pregnancy. In the meantime, conventional models are also appropriate for estimating 10-year CVD risk in women with history of pregnancy complications.

Impact of High Dose Folic Acid Supplements on DNA Methylation in Sperm and Embryos: Potential for Adverse Effects across Generations

Jacquetta Trasler, PhD

James McGill Professor, Departments of Pediatrics, Human Genetics and Pharmacology & Therapeutics, McGill University; Senior Scientist, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

Background

DNA methylation patterns are remodelled in developing germ cells and early embryos and play key roles in the regulation of gene expression. Abnormalities in DNA methylation are associated with growth, genomic imprinting and neurodevelopmental disorders as well as cancer. Folate in the diet is an important source of methyl groups for DNA methylation. Folate deficiency, either due to diet or folate pathway enzyme defects, and folate supplementation are important clinical situations in which methyl donors required for DNA methylation are either lower or higher than normal. While moderate and high dose folic acid supplements (1.0-5.0 mg/day) are prescribed in the treatment of pregnant women and men with infertility, the potential adverse effects of such treatments on the epigenome have received little attention.

Methods

We are using array and next generation sequencing based assays to identify DNA methylation alterations associated with high dose folic acid supplements and altered ability to use dietary folate.

Results

In men with no history of infertility, low doses of folic acid (0.4 mg/day) given for 3 months did not result in alterations in sperm DNA methylation. In contrast, in men with idiopathic infertility receiving supplements of 5.0 mg/day of folic acid for 6 months, DNA methylation at imprinted loci remained unchanged; however, there was unexpected loss of methylation across the sperm epigenome, effects that were exacerbated in men homozygous for a common polymorphism in the folate pathway enzyme methylenetetrahydrofolate reductase (MTHFR). Lifelong perturbations in folate metabolism have more severe effects on the sperm epigenome than do short term exposures to high doses of folic acid supplements. Model system studies indicate that high dose folic acid supplements can impact the offspring of exposed males.

Conclusions

Ongoing studies are examining the impact of gestational exposures to high dose folic acid supplements and whether induced DNA methylation defects are heritable and have adverse effects on future generations. (Supported by the Canadian Institutes of Health Research).

POSTER Section

Compensatory role of FSH in the PSA production of healthy men with low testosterone?

Magdalena Bentmar Holgersson [1], Yvonne Lundberg Giwercman[1], and The European Male Ageing Study (EMAS)

1) Lund University, Dept. of Translational Medicine, Malmö, Sweden

Introduction

The prostate is testosterone (T) dependent, with T not only controlling the production of prostate specific antigen (PSA) but also the progression of prostate cancer (PCa). A common treatment for PCa is therefore chemical castration targeting gonadotropin release by both agonists and antagonists. Both agonists and antagonists will downregulate luteinizing hormone (LH) effectively, but follicle stimulating hormone (FSH) has been found to escape complete downregulation by agonist treatment. As FSH can compensate for lack of T in spermatogenesis, the question is if FSH also can compensate for low T and increase PSA production in men without PCa?

Methods

In the European Male Ageing Study (n=3369), men without PCa n=2200 were selected. Age normalized z-scores were calculated for each hormone, with subsequent stratification into three groups for each hormone: highest 10%, lowest 10% and middle 80%. By combining the three T groups with the three FSH groups, nine groups were created. Linear regression was used to compare ln-transformed PSA concentrations in group 1 (lowT/lowFSH, n=33), group 2 (lowT/middleFSH, n=158) and group 3 (lowT/HighFSH, n=29) to the reference group (middleT+middleFSH, n=1417).

Results

The median PSA in the reference group was 1.0 (range: 0.0-35.4) ng/mL. The groups with low testosterone all had lower PSA (group 1: 0.8 ng/mL, *p=0.025**; group 2: 0.9 ng/mL, *p=0.007**; group 3: 0.7 ng/mL, p=0.015*) than the reference group.

Conclusion

All three groups with low T had lower PSA regardless of FSH. The group with low T combined with high FSH had lower median PSA than the low T/low FSH group. Thus, in men with low T but no PCa, a compensatory effect of FSH could not be found.

Higher Risk of Major Adverse Cardiovascular Event and All-cause Mortality among Childless Men – Population Cohort Based Study with 30 years follow-up

Angel Elenkov[1,2], Ane Berger Bungum[3], Katia Keglberg Haervig[3], Sandra Sogaard Tottenborg[3], Clara Helene Glazer[3], Jens Peter Ellekilde Bonde[3,4], Aleksander Giwercman[1,2], Peter M Nilsson[5]

[1]*Molecular Reproductive Medicine, Department of Translational Medicine, Lund University, Malmoe, Sweden*
[2]*Reproductive medicine center, Skåne University Hospital, Malmoe, Sweden*
[3]*Department of Occupational and Environmental Medicine, Bispebjerg Hospital, Denmark;*
[4]*Department of Public Health, Faculty of Health Sciences, University of Copenhagen, Denmark;*
[5]*Internal Medicine Research Group, Director SRA EpiHealth, Jan Waldenströms street 15, 5th floor, Skåne University Hospital,*

Background

In recent years, studies from both the United States and Europe have shown association between impairment of male reproductive health and risk of various non-communicable adult-onset diseases. In a recent study an indication of higher risk of MetS and type 2 diabetes in childless men was found as compared to those who have fathered one or more children. Therefore, by using a larger cohort from the same background population we expand our observations in order to evaluate the metabolic profile of childless men and estimate the risks for cardiovascular disease, mortality and diabetes accounting for various lifestyle and biochemical factors.

Methods

In order to study the association between male childlessness and disease risks we used data from Malmo Preventive Project in Sweden. Men were stratified according to fatherhood status based on data from baseline questionnaires and Swedish Tax Agency.

Composite cardiovascular end point was defined as major adverse cardiovascular event (MACE). It included fatal or non-fatal myocardial infarction, fatal or non-fatal stroke, death due to ischemic heart disease, coronary artery bypass graft surgery (CABG) or Percutaneous coronary intervention (PCI).

The risk for developing all-cause mortality, MACEs was evaluated using multivariate Cox regression and presented with hazard ratios (HR) and corresponding 95% confidence intervals (95%CI) with accompanying Kaplan-Meier curves. Age was used as underlying time scale following the men until first episode of MACE or diabetes, death, emigration, or end of follow-up.

Non-stroke MACEs were defined as separate end point in order to determine whether childlessness modifies the risk of other types of MACE except stroke

Results

Childless men presented with higher risk for developing both MACEs (HR 1.11; 95%CI: 1.02 – 1.20), and non-stroke MACEs (HR 1.20; 95%CI: 1.12 – 1.29), but also for all-cause mortality (HR 1.50; 95%CI: 1.43 – 1.57) in the adjusted model. The majority of risk estimates remained unchanged in the sub-analysis including only married childless men Risk estimates for MACEs lost statistical significance after adjustment for metabolic co-variates.

Conclusions

Since men´s fertility status and therefore their reproductive potential is often known relatively early in life, our study provides interesting insights into potential mechanisms driving CVD risk. Furthermore, a possibility exists for identifying risk groups at a relatively young age that could benefit from early intervention and closer follow-up with preventive intent. The latter has to be tested in randomized controlled studies.

Prenatal exposure to paternal smoking and semen quality in the adult offspring

Hærvig, KK.[1, 2]; Høyer, BB.[1,6]; Giwercman, A.[3]; Hougaard, KS.[2,4]; Ramlau-Hansen, CH.[5]; Specht, IO.[6]; Toft, G.[7]; and Bonde, JP[1, 2]; and Tøttenborg, SS.[1]

[1]Department of Occupational and Environmental Medicine, Bispebjerg-Frederiksberg Hospital, Denmark; [2] Department of Public Health, The Faculty of Health Sciences, University of Copenhagen, Denmark; [3]Molecular Reproductive Medicine, Department of Translational Medicine, Lund University, Sweden; [4]National Research Centre for the Working Environment, Denmark; [5]Department of Public Health, Section for Epidemiology, Aarhus University, Denmark; [6]The Parker Institute, Research Unit for Dietary Studies, Bispebjerg-Frederiksberg Hospital, Denmark; [7]Department of Clinical Medicine, Department of Clinical Epidemiology, Aarhus University, Denmark.

Study question: Is prenatal exposure to paternal smoking related to adult offspring semen parameters independently of prenatal maternal smoking?

Summary answer: Paternal smoking is associated with lower sperm concentration and total sperm count and more non-progressive sperm independent of maternal smoking and other relevant risk factors.

What is known: The negative impact of maternal smoking during pregnancy on offspring semen quality is well established. Evidence is emerging that also pre-conception paternal smoking can induce epigenetic alterations in the sperm genome which can be transmitted to the cells of the offspring. Two recent studies found that paternal smoking was associated with lower sperm counts independently of maternal smoking. However, these studies lacked information on key confounders, relied on retrospectively collected smoking information, and had small populations. Larger follow-up studies with extensive confounder information are needed to corroborate findings.

Study population: Population-based follow-up study of 536 young men aged 19 years from the Fetal Programming of Semen Quality (FEPOS) cohort, a sub-cohort of sons to mothers enrolled in the Danish National Birth Cohort (DNBC) during 1996-2002. Semen parameters were assessed at the Department of Occupational and Environmental Medicine at Bispebjerg Hospital in Copenhagen and the Department of Occupational Medicine at Aarhus University Hospital in Aarhus from March 2017 through February 2019.

Statistics: Smoking information came from the mother around gestational week 16. Semen and testicle size were analyzed according to WHO recommendations. Ratios of semen volume, sperm concentration, count, and motility were calculated using negative binomial regression, difference in morphology with linear regression, and risk of testicle size< 12 ml with logistic regression, adjusting for maternal smoking and age, pre-

pregnancy BMI, alcohol and caffeine consumption, paternal age, household occupational status, and son's abstinence time.

Results: In adjusted analyses, sons of fathers who smoked daily had 15% lower sperm concentration (RR 0.85, 95%CI: 0.69; 1.04), and 21% lower total sperm count (RR 0.79, 95%CI: 0.62; 1.02), but same semen volume compared to sons of fathers who never smoked. A 21% increase in non-progressively motile sperm was observed for sons of father's who smoked compared to those who never smoked (RR 1.21, 95%CI: 1.01; 1.46). Results also suggested that paternal smoking was associated with a 16% higher risk of small testicle size as compared to paternal never smoking.

Limitations: Information was self-reported and not cotinine verified. Paternal smoking was assessed around gestational week 16 and may be less frequent than pre-conceptional smoking, though studies have shown a high correlation between pre-and postconceptional smoking.

Wider implications of the findings: Paternal smoking affected offspring sperm concentration and total sperm count independently of maternal smoking and other relevant factors. Men looking to become fathers should avoid tobacco use if they wish to protect their sons' reproductive health.

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Risk factors and prognosis associated with low Apgar scores of newborns in a population-based cohort.

Ankita Sharma, MPH, Peter M Nilsson, MD, PhD

Department of Clinical Sciences, Lund University, Skane University Hospital, Malmo, Sweden

Background

Early life factors may influence adult health and disease risk. One marker of this is birth weight and another is the viability of the newborn as measured by Apgar scores (AS). In 1952, the paediatrician Virginia Apgar proposed a score system (AS) as means of evaluating the clinical status (alertness) of the new-born child and the need for medical intervention [1]. A total score of >7 is considered as normal and a lower Apgar score (<7), especially if prolonged over time, indicates increased risk of neonatal hypoxia with consequences such as encephalopathy, subsequent cerebral palsy (CP) and learning difficulties [2]. The aim was to investigate associations of risk factors with low AS, and prediction of adverse health outcomes as well as burden of hospitalization for somatic disorders in adult life.

Methods

This was a retrospective cohort study including 1387 participants from the Malmö Offspring Study (MOS) with birth data, including birth weight, gestational age, and AS (0-10 scores) at 1, 5 and 10 minutes post-partum, as well as health data in adult life. Pearson's correlation and multiple regression analysis was used to assess possible associations between risk factors/markers like maternal age, BMI, parity, and smoking status with low AS. In addition, low AS was analysed for associations with adult life morbidity and mortality.

Results

Low AS (<7 scores) was associated with lower birth weight ($r=0.11$, $p<0.05$), but inversely associated with birth length ($r= -0.10$, $p= 0.01$). There was also a significant inverse association between increasing maternal BMI ($r= -0.05$, $p=0.04$) and low AS. The prevalence rate of maternal smoking at late pregnancy (week 30-32) was found to be 2.6%, which was inversely associated with AS ($r= -0.14$, $p=0.01$). In addition, there was an association between prematurity (<37 weeks) and low AS ($r=0.06$, $p=0.02$). Very few individuals with low AS developed self-reported chronic disease in adult mid-life. In addition, low birthweight of the new born, but not AS, was significantly associated with increased number of hospitalization days for somatic disease in later life ($p <0.001$).

Conclusion

Low Apgar score less than 7 is significantly associated with maternal smoking during late pregnancy. In addition, high maternal BMI, lower birth weight, and higher birth length were also significantly associated with low Apgar scores.

1. Apgar V. Proposal for new method of evaluation of new born infant. *Curr Res Anesth Analg* 1953; 32:260-267.
2. Moster D, Lie RT, Irgens LM, *et al.* The association of Apgar score with subsequent death and cerebral palsy: A population-based study in term infants. *J Pediatr* 2001; 138:798–803.

Birth weight and cancer prognosis: A meta-analysis of current evidence

Shantanu Sharma, MD, Peter M Nilsson[1], MD, PhD

[1]*Department of Clinical Sciences, Lund University, Skåne University Hospital, Malmö, Sweden*

Background

Substantial evidence implicates the crucial role of birth weight (BW) in the occurrence of adult-onset cancers. However, less attention has been given to explore the effects of BW in predicting prognosis (survival or mortality) among adult cancer patients. Moreover, there is conflicting evidence on BW associations with cancer prognosis from the existing literature. Hence, we conducted a meta-analysis to determine whether BW is associated with prognosis in established cancer patients.

Methods

We systematically searched MEDLINE (PubMed), EMBASE, and Web of Science to identify recent studies that have reported on associations between BW adjusted for gestational age and *prognosis* of adult-onset cancers. All cohort and case–control studies were included. For studies reporting results with categorical BW, we used the fully adjusted risk estimates and 95% confidence intervals (CI) for the highest versus reference category. For studies reporting results with continuous BW, we used the reported fully adjusted risk estimates and their CI. We calculated the log odds ratios (OR) per kilogram (kg) increase in BW and their standard errors for all the studies. All the estimates were pooled in generic inverse variance meta-analyses. Revman software version 5.3 was used to generate forest plots and summary effect estimates for BW.

Results

We identified 11 studies published until the end of April 2019. Out of 11 studies, four were nested case-control and seven were cohort studies. Fixed effects models found that per kg increase in BW, this was associated with increased mortality due to cancers (OR 1.04, 95% CI: 1.02, 1.06; I^2=48%). Heterogeneity among studies was significant (p=0.02). However, sensitivity analysis restricted to studies specifying BW relations with prostate cancer demonstrated stronger association (OR 1.13, 95% CI: 1.01, 1.27; I^2=0%). Most of the studies were from the Nordic countries.

Conclusions

This meta-analysis provides evidence that higher BW may be associated with increased risk of mortality from cancer, especially prostatic cancer. It can also be hypothesized that the association is not uniform across all cancer types.

Birth weight and central hemodynamics in Malmö Birth Data Cohort and Malmö Offspring Study

Johannes Sperling, Research student, Peter M Nilsson MD, PhD

Internal Medicine Research Group, Dept. Clinical Sciences, Lund University, Malmö, Sweden.

Background

Our aim was to investigate possible associations between birth weight (BW) and markers of central hemodynamics in adult life such as carotid-femoral Pulse Wave Velocity (cfPWV) and augmentation pressure index (AIx).

Methods

This study including 1598 participants, 340 elderly subjects from the Malmö Birth Data Cohort (MBDC) and 1258 young-middle aged subjects from the Malmö Offspring Study (MOS). Participants underwent cfPWV and AIx measurements with Sphygmocor® (AtCor, Australia). Multiple linear regression was used to asses associations between BW and cfPWV, as well as AIx, with adjustments for age, sex, gestational age, hemodynamic parameters and fasting glucose. Further analysis was made in three age-groups (18-28, 28-44, and 65-84 years). In addition, comparisons between participants born small-for-gestational-age (SGA) or appropriate-for-gestational-age (AGA) was performed with Mann-Witney U-test and t-test.

Results

BW was positively associated with cfPWV (β=0.057; P<0.001), a finding that remained significant in the younger age group 18-28 year (β=0.138, P=0.008). Fasting glucose was significantly and positively associated with cfPWV (β=0.0384, P=0.009). Furthermore, BW was inversely associated with AIx (β= -0.058, P=0.001). Subjects born SGA had significantly higher AIx, systolic blood pressure (SBP), Mean Arterial Pressure, LDL cholesterol, and total cholesterol, but lower height (p<0.05) compared to AGA born subjects. Preterm born subjects showed significantly higher SBP compared to term born (P=0.034).

Conclusions

Birth weight is positively associated with cfPWV, shown strongest in the youngest age group. This could possibly be explained by maternal factors, such as obesity because there is a secular trend for increasing BMI in young women. Birth weight was inversely associated with Aix, a more complex measure, reflecting not only central arterial stiffness, but also total peripheral resistance and arterial vessel impedance. SGA associates with increased risk markers of cardiovascular diseases, more so than preterm birth.