Evaluation of Complement Cascade Factors in Serum and Follicular Fluid of Patients with Lean Polycystic Ovarian Syndrome (PCOS)

Shlomit Kenigsberg¹, Esther Lau¹,², Bahar Behrouzi-Homa¹, Andrée Gauthier-Fisher¹, Clifford L. Librach¹,²,³,⁴

¹CReATe Fertility Centre. ²Faculty of Medicine, University of Toronto. ³Department of Obstetrics and Gynecology, University of Toronto. ⁴Division of Reproductive Endocrinology and Infertility Departments of Obstetrics and Gynecology, Women’s College Hospital; Ontario, Canada

Introduction: The etiology of polycystic ovary syndrome (PCOS) is poorly understood. One of the key clinical features of PCOS is anovulation. Ovulation is a process involving tissue inflammation followed by oocyte expulsion, and tissue repair – events that are tightly controlled by innate immunity⁵. The complement component cascade, part of the innate immune system is thought to play a crucial regulatory role in the ovulation process ²,³. We have previously reported higher expression levels of component C3 transcripts in cumulus cells from lean PCOS patients compared to lean controls ⁴. We hypothesize that, due to the involvement of complement cascade in the process of ovulation, the ovarian dysfunction in PCOS may in part caused by perturbations in FF complement components. Here, we aimed to investigate the levels of complement components in FF and serum between lean PCOS patients and non-PCOS controls and examined the potential role of granulosa cells (GLC) in regulating the levels of complement components.

Methods: After obtaining informed consent, ovarian follicle contents including cumulus cells, GLCs and FF were obtained from patients undergoing controlled ovarian hyperstimulation for IVF at our clinic. Samples were gathered from women ≤35 years of age, have a normal BMI (18.5-24.9), and diagnosed with PCOS (lean variety) (n=9). Samples were also gathered from normally ovulating women (control group) matched for age and BMI (n=8). FF and serum were analyzed for total complement activity (CH50) and levels of major complement factors (C3, C4) using ELISA kit. GLCs were isolated and immediately lysed for RNA isolation or cultured for 2 days and fixed for immunofluorescence.

Results: C3 levels were lower in the FF of lean PCOS patients when compared to age- and BMI-matched controls. GLCs of PCOS patients had a higher C3 mRNA expression compared to controls. Intracellular localization of activated C3 and C4 was detected in GLCs using indirect immunofluorescence.

Conclusions: Our data demonstrate lower levels of C3 in FF of lean PCOS patients when compared to age- and BMI-matched controls. This suggest that the complement factors may play a role in the pathogenesis of this variant of PCOS. Future studies will evaluate the levels of C3 protein secreted by GLCs and investigate the potential role of complement regulatory proteins in the modulation of C3 in ovarian follicles.

A Motherless Scar: The Lived Experience of Permanent, Unintentional Childlessness after Delayed Childbearing

Emily Koert

University of British Columbia, British Columbia, Canada

Introduction: Recent census data reports that an increasing number of women are delaying childbearing. The latest research suggests that many women do not know that their eggs are as old as they are, and assume that should they have difficulty becoming pregnant in the future, they can resort to medical technologies such as IVF to have a child. Unfortunately, for many women, medical intervention cannot overcome the realities of age-related fertility decline. There is a growing concern in the field that more women will end up “permanently, unintentionally childless” as they delay childbearing into their 40s and 50s. However, we know little about the lived experience of this phenomenon. An exploration and understanding of the experience of permanent unintentional childlessness for women who have delayed childbearing is the focus of this study.

Materials and Methods: A qualitative, phenomenological approach was undertaken in order to gain an in-depth understanding of the meanings that women give to their experience of permanent, unintentional childlessness after delayed childbearing. In-depth, tape recorded interviews were conducted with 15 women who identified themselves as being permanently and unintentionally childless after postponed childbearing. The interviews were transcribed, coded, and analyzed using an interpretive phenomenological method. Thematic representations and rich descriptions of the experience of this phenomenon were developed.

Results: Common themes identified in the experiences of these 15 women were: Sense of Grief and Loss about their permanent childlessness after expecting to become mothers; Sense of Powerlessness to their circumstances, relationships, aging bodies, and passing time; Sense of Being an Outsider and Feeling Judged in a world that privileges and normalizes motherhood; Making Sense of Childlessness by revisiting decisions and delays in the past; Revisioning the Future to include alternative roles that would be meaningful and fulfilling; and Sense of Reconciliation and Acceptance as they came to terms with their permanent childlessness.

Conclusions: As more women are delaying childbearing, the number of those who end up permanently, unintentionally childless is growing. This study’s findings can inform the development of clinical and mental health services and support for this growing group of women.
Brain-Derived Neurotrophic Factor as a Clinical Marker of Endometriosis

Jocelyn M. Wessels¹, Nicholas A. Leyland¹, Sanjay Agarwal², Ally Murji¹, and Warren G. Foster¹

¹Department of Obstetrics and Gynecology, McMaster University, Hamilton, Ontario, Canada
²Department of Reproductive Medicine, University of California, San Diego, La Jolla, California, USA

Introduction: Endometriosis is a chronic gynecological condition affecting up to 10% of women of reproductive age. Extra-uterine glands and stroma implant at inappropriate sites, causing significant pain during menstruation, intercourse, urination, and defecation. Diagnosis is delayed because there is no clinical marker for endometriosis, and this results in worsening of symptoms and a substantial financial burden on the healthcare system. Recently, circulating levels of brain-derived neurotrophic factor (BDNF) were found to be elevated in women with endometriosis, and fell after surgical removal of lesions. BDNF is a soluble protein known for its role in nerve differentiation, growth, and maintenance. However, BDNF also activates other processes including proliferation, adhesion, angiogenesis, and resistance to apoptosis. As such BDNF may provide a reliable clinical marker of disease. Here, we measure circulating BDNF in cases and controls, and examine the relation to disease severity, pain, and menstrual cycle stage.

Materials and Methods: Plasma was collected from cases (N=37), and controls (N=9) at McMaster University Medical Centre in a prospective study. Participants provided informed consent, and completed a questionnaire about demographics, menstrual cycle, and pain. Cases were categorized by ASRM stages by a gynaecological surgeon. BDNF was measured in duplicate using the Emax ELISA (Promega). Circulating BDNF was statistically compared between cases and controls, stages of disease, relation to pain, and menstrual cycle stage by t-test, one-way ANOVA, or linear regression.

Results: Circulating BDNF was significantly higher in women with endometriosis than controls (P=0.014), and was elevated in women with Stage 2 disease as compared to controls (P=0.006). Circulating BDNF did not positively correlate with self-reported pain scores, but had a tendency towards a correlation in patients with Stage 2 disease (P=0.101, R²=0.647). Overall pain scores were significantly higher in cases than controls (P<0.001). In cases, BDNF was unchanged over the menstrual cycle.

Conclusions: Preliminary results indicate that plasma BDNF may provide a reliable clinical marker for endometriosis. A tendency for circulating BDNF to decrease as disease progressed suggests a relation to the number of active lesions (red, black) in early disease. The amount of circulating BDNF did not correlate with pain in women with endometriosis, and did not fluctuate over the menstrual cycle in cases, contrary to what has been reported in women without endometriosis.
The Impact of Government-Funded IVF on Patient-Centered Care in Quebec: The Perspectives of Physicians, Nurses, and Support Staff

Phyllis Zelkowitz¹, Suzanne C. Read², Marie-Eve Carrier¹, Togas Tulandi³, Peter Chan³, Sophia Ouhilal⁴, Neal Mahutte⁵, Hananel Holzer³, Sharon Bond⁴, Carolyn Ells¹, Nancy Feeley¹, Ian Gold¹, Zeev Rosberger¹, Neal Mahutte⁵

¹ Lady Davis Institute, Jewish General Hospital, Montreal, Quebec. ² McGill University, Montreal, Quebec. ³ McGill University Health Centre. ⁴ Montreal Fertility Centre. ⁵ Douglas Mental Health University Institute

Introduction: Quebec is the first North American jurisdiction to fund 3 cycles of in-vitro fertilization (IVF). This policy, effective as of August 2010, has led to an upsurge in the number of infertility clinic patients and greater ethnocultural and socioeconomic diversity in the patient population [1, 2]. Little research to date has explored clinicians’ perspectives on barriers to providing patient-centered care in the field of infertility. Given the unique situation in Quebec, it is important to understand the impact of government funding on clinicians’ ability to respond to patients’ needs for emotional support and information. This study describes the professional challenges faced by fertility care professionals since the inception of government funding for IVF in Quebec.

Method: Seven focus groups were conducted with 28 staff at 2 Montreal fertility clinics. Participants included physicians, nurses, and administrative staff. Maximal variation sampling was used to ensure a range of fertility-related professions. Focus groups were audiotaped and transcribed, and analyzed using thematic analysis.

Results: Since government funding began, professionals described patients as being less informed about reproduction and infertility and overly optimistic in their expectations of treatment. Professionals also had less time to spend with each patient, resulting in an overwhelming workload. Nurses and administrative staff in particular reported spending more time with uninformed, confused, and disrespectful patients than prior to the implementation of government funding. Clinic staff emphasized that patient education materials (e.g. DVDs, comprehensible information booklets) and psychosocial support resources (e.g. support groups, psychology services) would enhance patients’ adjustment to treatment, and that these resources would help professionals as well by alleviating their teaching and counseling roles.

Conclusions: This in-depth exploration of fertility clinic staff’s professional experiences with a government-funded IVF program revealed its stressful impact on healthcare professionals and patients. Developing educational and emotional support resources for patients may help both patients and professionals: patients will be better informed about the process and likely outcomes of treatment, thereby allowing professionals to more efficiently manage large numbers of patients.


The Orphan Nuclear Receptor Liver Receptor Homolog-1 (Lrh-1, NR5A2) Regulates Transcriptional Reprogramming During Decidualization in a Human Endometrial Cell Line

Sandra Ruiz Orduna¹, Kalyne Bertolin¹, Stephanie Bianco², Nicolas Gévry², Bruce D. Murphy¹

¹Centre de recherche en reproduction animale, Université de Montreal, St-Hyacinthe, Québec,
²Département de biologie, Université de Sherbrooke.

During human menstrual cycle a dramatic transcriptional reprogramming of endometrial stromal cells occurs, leading to a receptive state of the endometrium in a process known as decidualization. This differentiation is dependent on progesterone and involves several signaling pathways and genes and multiple transcriptional regulators. Liver homolog receptor-1 (Lrh-1) is an orphan nuclear receptor and a transcriptional regulator known to be involved in many reproductive events, including ovulation and steroidogenesis. Our recent studies have shown that Lrh-1 is expressed in the mouse uterus and is essential for proper decidualization of the endometrial stroma in this species. We have further demonstrated its occurrence in human endometrium during both the secretory and proliferative phases of the menstrual cycle. Our goal is to define the Lrh-1 transcriptional network regulating reprogramming of stromal cells into decidual cells by characterizing the gene expression pattern during decidual fibroblast differentiation. To address this goal, we employed an in vitro model using a human endometrial stromal cell line (hESC). Our experiments demonstrated that the hESC cell line undergoes decidualization in vitro when treated with the progestin medroxyprogesterone acetate (MPA) and cAMP. The expression of Lrh-1 increases multiple fold during decidualization in vitro, parallel with increased expression of the markers for decidualization, prolactin (PRL) and insulin like growth factor binding protein-1 (IGFBP1) gene activation. To assess the effect of Lrh-1 overexpression, we created a model by transfecting the cells with a construct constitutively expressing Lrh-1, resulting in six fold increases in abundance of transcripts for the decidualization marker genes PRL and IGFBP1 and a precocious development of the decidual reaction. Western blot analysis showed that the expression of known Lrh-1 target genes, also essential to decidualization, including wingless type-4 (WNT4) increases during in vitro decidualization. Moreover, ChIP-seq analysis using a breast cancer human cell line (MCF7) demonstrated that the decidual marker gene PRL has a distal Lrh-1 binding site at -170kb from the PRL transcription start site. These results using a human cell line indicate that Lrh-1 regulates distinct sets of target genes during decidualization of the human stroma. In order to extrapolate this results to the in vivo condition, further studies will be perform using human endometrial biopsy samples taken in a different phases of the cycle from woman suffering from recurrent miscarriages.

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Qualitative Findings: The Impact of IM Progesterone Injections on Fertility Patients

Danielle Dubois, Valerie Wilkie
Ottawa Fertility Centre, Ottawa, Ontario, Canada

Introduction: While there are multiple routes available for progesterone administration, there is no conclusive standard of care in progesterone supplementation for the fertility patient. A literature search (n=382) identified an array of studies comparing efficacy of vaginal and IM progesterone; however, the patient experience and tolerability of IM progesterone injections is notably missing. Two systematic reviews identified both physical burden of treatment and physical comfort to be significant predictors of a patient’s satisfaction and continuation of fertility treatment\(^1\)\(^2\).

Methods: In 2012, our Centre performed 66 FET cycles in which IM progesterone was used. We used a qualitative unstructured phone interview with patients who completed treatment with IM progesterone within the past 6mos. Our sample of 20 patients was randomly selected. The sample was representative in patient demographics and pregnancy rates in comparison to our overall FET patient population.

Results: All interviewed participants identified some form of pre-treatment anxiety. Anxieties included: relinquishing control, concern regarding the risks of medications, potential treatment failure, needle phobia, and anticipated pain. Inductive content analysis of the documented phone conversations identified several categories, providing perspective on the IM injection fertility patient experience. Categories included: injection teaching, partner involvement, side effects, clinic support, and comfort measures. The patients with a positive pregnancy outcome had an overall increased positive description of the IM injection experience even though their injections continued 8 weeks longer than the negative outcome population. Almost all patients interviewed concluded that the IM injection experience was not as bad as they had initially predicted; however, they did still require comfort measures for some injection site discomfort.

Conclusion: If the fertility patients’ needs for coordination, information, comfort, support, partner involvement, and a good relationship with the fertility centre are met; the post treatment concerns regarding IM injections are far less than pre-treatment anxieties. Since this study’s categorized findings are similar to those found within a fertility patient’s general perspective on fertility care\(^2\), it is difficult to know if this study’s findings are specific to the IM injection patient population or due to the overall fact of being a fertility patient. Lastly, it was found that a patient’s desire for a positive outcome outweighed their anxieties, and this motivation compels patients to complete treatment regardless of their apprehensions.

References:  