Fall 2017
Volume 7 Issue 2

UOJM JMUO

UNIVERSITY OF OTTAWA JOURNAL OF MEDICINE
JOURNAL MÉDICAL DE L'UNIVERSITÉ D'OTTAWA

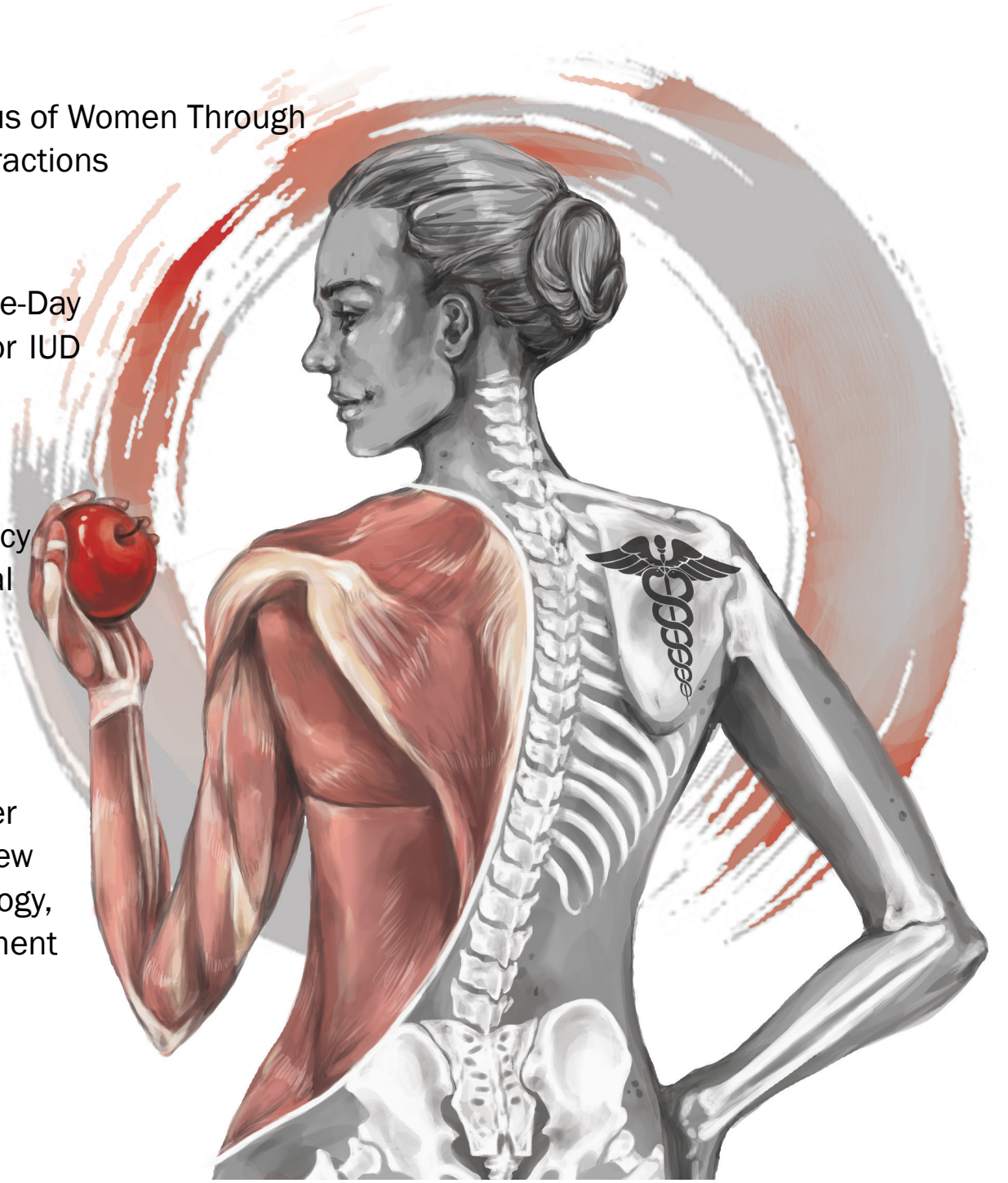
WOMEN'S HEALTH

ELECTIVE
Observing the Status of Women Through Health System Interactions

RESEARCH
Introducing A Same-Day Referral Program for IUD Insertion in Ontario

COMMENTARY
Optimizing Pregnancy for Intergenerational Health Benefits

REVIEW
Genito-Pelvic Pain/ Penetration Disorder (GPPPD): An Overview of Current Terminology, Etiology, and Treatment



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ISSN: 2292-650X

UOJM
UNIVERSITY OF OTTAWA JOURNAL OF MEDICINE

JMUO
JOURNAL MÉDICAL DE L'UNIVERSITÉ D'OTTAWA

VOLUME 7 ISSUE 2 NOVEMBER 2017

The student-run medical journal of the University of Ottawa

ABOUT US

UOJM is an international, peer-reviewed journal led and published by the students of the Faculty of Medicine. We welcome submissions in a variety of areas in biomedical research and feature original research, reviews, news and commentaries, case reports and opinion pieces. Our articles are written in both English and French, and represent the only student-run bilingual medical journal in Canada.

Le JMUO est un journal revu, édité et publié par les étudiants de la Faculté de médecine. Nous encourageons les soumissions d'une variété de différents domaines en recherche biomédicale et publions des articles de recherche originale, des articles de revue, des nouvelles et commentaires, des rapports de cas et des pièces d'opinion. Nos articles sont écrits en français et en anglais et représentent le seul journal médical bilingue géré par les étudiants au Canada

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Website: uojm.ca
ISSN: 2292-650X (print), 2292-6518 (online)

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UOJM: Preface

Now at the end of its 7th cycle, the University of Ottawa Journal of Medicine (UOJM) is coming to the end of another successful year. Dedicated efforts to engage medical and graduate students across Canada have resulted in a significant expansion of both readership and authorship, as well as an increase in the quality and number of submitted articles. We have also continued our presence at the Ontario Medical Students' Weekend (OMSW) in Sudbury, promoting UOJM and the broader discussion of basic and clinical research.

UOJM 7.2: Women's Health focuses on the ever-changing landscape of women's healthcare, as well as the significant medical advancements made over the years. Despite tremendous progress, there is still much to be done to address the specific healthcare needs of women at important moments in their lives. UOJM is proud to promote research that contributes to this through the development of better clinical medicine, medical education, public policy, and healthcare practices. This issue addresses the challenges of providing optimal care for women throughout their life, exploring improvements in diagnostic procedures, therapeutic protocols for the management of diseases, and innovative research in gender-based biology that impacts care and treatment. Specifically, health challenges and risks during pregnancy, female leadership in medicine, post-coital IUD insertion in Ontario, and more are discussed.

Looking towards next year, we are proud to announce our **Spring 2018** issue on **Surgery and Transplantation.** In the 21st century alone, we have seen incredible evolution in the field of surgery and transplantation. Innovative surgical and medical imaging, implementation of robotics and artificial intelligence, and better understanding of the immunological aspects of transplant recognition and rejection, have played important roles in enhancing patient outcomes and access to treatment. However, scientific and clinical challenges remain and warrant discussion by scientists, medical professionals, stakeholders, and policy makers. Issue 8.1 is therefore intended to explore the advances and challenges in the field of surgery and transplantation, the development of relevant techniques and technology, and the translational impact on patient care, Canadian healthcare policy, and clinical collaboration.

The submission deadline of our Spring 2018 issue is **March 1st, 2018**. High quality writing will be recognized with an honorarium award. Submissions can be made via our online submission system via this link: https://uottawa.scholarsportal.info/ojs/index.php/uojm-jmuo/about/submissions

We hope you enjoy UOJM's Women's Health issue!

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JMUO: Préface

À présent à la fin de son 7e cycle, le Journal de Médecine de l'Université d'Ottawa (JMUO) arrive à la fin d'une autre année couronnée de succès. Les efforts consacrés à la participation des étudiants en médecine et des cycles supérieurs partout au Canada ont entraîné une augmentation considérable du lectorat et de la paternité, ainsi qu'une amélioration de la qualité et du nombre d'articles soumis. Nous avons également continué notre présence à la fin de semaine des étudiants en médecine de l'Ontario (OMSW) à Sudbury, en promouvant le JMUO et la discussion plus large de la recherche fondamentale et clinique.

UOJM 7.2: La santé des femmes se concentre sur le cadre de l'évolution constante des soins de santé pour les femmes, ainsi que sur les progrès médicaux importants réalisés au fil des ans. Malgré d'énormes progrès, le chemin est encore long avant que nous parvenions à répondre aux besoins spécifiques des femmes en matière de soins de santé à des moments importants de leur vie. Le JMUO est fier de promouvoir la recherche qui contribue au développement de meilleures pratiques en médecine clinique, en éducation médicale, en politiques publiques et en soins de santé. Ce numéro aborde les défis d'offrir des soins optimaux aux femmes tout au long de leur vie, en explorant les améliorations des procédures diagnostiques, les protocoles thérapeutiques pour la gestion des maladies et la recherche innovatrice en biologie basée sur le sexe ayant un impact sur les soins et les traitements. Plus précisément, les défis et les risques pour la santé pendant la grossesse, le leadership féminin en médecine, l'insertion post-coïtale en Ontario, et plus encore sont discutés.

En ce qui concerne l'année prochaine, nous sommes fiers d'annoncer notre numéro du **printemps 2018** sur **la chirurgie et la transplantation**. Au 21ème siècle seulement, nous avons vu une évolution incroyable dans le domaine de la chirurgie et de la transplantation. L'imagerie chirurgicale et médicale innovante, la mise en œuvre de la robotique et de l'intelligence artificielle, ainsi qu'une meilleure compréhension des aspects immunologiques de la reconnaissance et du rejet des greffes, ont joué un rôle important dans l'amélioration des résultats et l'accès au traitement. Cependant, des défis scientifiques et cliniques demeurent et méritent d'être débattus par les scientifiques, les professionnels de la santé, les intervenants et les décideurs. Le numéro 8.1 vise donc à explorer les progrès et les défis dans le domaine de la chirurgie et de la transplantation, le développement de techniques et de technologies pertinentes et l'impact de la traduction sur les soins aux patients, la politique canadienne de soins de santé et la collaboration clinique.

La date limite de soumission de notre numéro du printemps 2018 est le **1er mars 2017**. L'écriture de haute qualité sera récompensée par un prix d'honneur. Les soumissions peuvent être faites via notre système de soumission en ligne via ce lien: https://uottawa.scholarsportal.info/ojs/index.php/uojm-jmuo/about/submissions

Nous espérons que vous apprécierez le numéro de la santé des femmes du JMUO!

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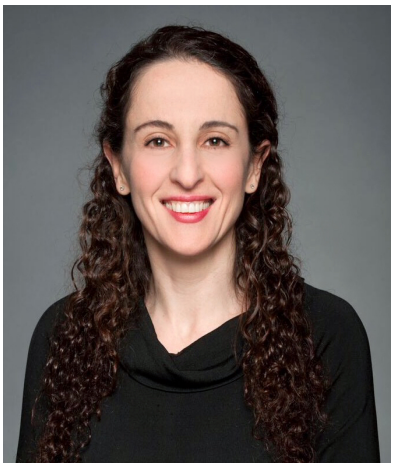
Promoting Female Leadership in Healthcare: An Interview with Dr. Lara Khoury, Co-Chair of the Female Physician Leadership Committee



Anna Liu[1], Gaeun Rhee[1]

[1] University of Ottawa

ABSTRACT

Dr. Lara Khoury, MD, FRCPC, is an assistant professor and geriatrician at The Ottawa Hospital (TOH). She holds numerous leadership positions, including the post-graduate Program Director of the Geriatrics Program of the University of Ottawa and the Medical Director of TOH Inpatient Geriatric Service. Currently, she is also a Co-Chair of the Female Physician Leadership Committee at TOH. In order to remove barriers faced by female physicians wishing to take on leadership roles at TOH, a number of aspiring and passionate female doctors, including Dr. Khoury, came together to form the Female Physician Leadership Committee. With the full support of TOH's senior management team, the committee has implemented several initiatives to encourage more female physicians to take on leadership roles. The committee's role is imperative as there has been an increasing awareness of the gender imbalance at TOH over the past years. According to a survey conducted by TOH in 2011, only 30 percent of the hospital's physicians are female, while less than 20% of them are division heads, and less than 8% of them are department heads [1]. Today, the numbers do not look very different. To gain further insight into the importance of female leadership in medicine and her extensive leadership involvement, we would like to share our interview with Dr. Khoury.

RÉSUMÉ

Dre Lara Khoury, MD, FRCPC, est professeure adjointe et gériatre à L'Hôpital d'Ottawa (L'HO). Elle occupe de nombreux postes de direction, y compris le poste de directrice des programmes poste-diplômés du programme de gériatrie de l'Université d'Ottawa et le poste de directrice médicale du Service de gériatrie de l'Hôpital d'Ottawa. Elle est actuellement co-présidente du Comité de leadership des femmes médecins de L'HO. Afin d'éliminer les obstacles auxquels sont confrontées les femmes médecins souhaitant assumer des rôles de leadership à L'HO, un certain nombre de femmes médecins aspirantes et passionnées, incluant Dre Khoury, se sont réunies pour former le Comité de direction des femmes médecins. Avec le plein appui de l'équipe de la haute direction de L'HO, le comité a mis en œuvre plusieurs initiatives pour encourager plus de femmes médecins à assumer des rôles de leadership. Le rôle du comité est impératif, suite à la sensibilisation accrue au déséquilibre entre les sexes à L'HO au cours des dernières années. Selon une enquête menée par l'Hôpital en 2011, seulement 30% des médecins de l'hôpital sont des femmes, alors que moins de 20% d'entre eux sont chefs de division et moins de 8% sont des chefs de service [1]. Aujourd'hui, les chiffres ne sont pas très différents. Pour mieux comprendre l'importance du leadership féminin en médecine et son implication considérable dans le leadership, nous aimerions partager notre interview avec la Dre Khoury.

Please tell us a bit about yourself and your career path.

I have been a geriatrician at TOH for the past 11 years and hold several leadership roles within my division. I am the Medical Director for the Geriatric Inpatient Medicine Unit and the Geriatric Consult Service, the Deputy Chief for the Division of Geriatric Medicine, as well as the post-graduate Program Director for my division. Corporately, I am a member of TOH's Credentials Committee and Co-Chair of TOH's Female Physician Leadership Committee.

How did you become involved with TOH's Female Physician Leadership Committee?

Keywords: Female Leadership; Leadership in Healthcare; Mentorship; Policy-Making

When I became a geriatrician, I only wanted to see patients and did not think I would ever become involved in administrative work at TOH. However, as I began to take on formal leadership roles, I found that I was good at it. Others saw potential in me as well, and recommended that I take formal leadership courses. During one such course, the Leadership Academy, I had the opportunity to speak with Dr. Jack Kitts, CEO of TOH, and he recommended me for the Female Physician Leadership Committee. After a couple of years on the committee, I was approached by Dr. Virginia Roth, the Co-Chair of the committee at that time and currently the Senior Medical Officer at TOH, who asked me to be her successor! I was both honoured and terrified at the same time, because I felt that I would not be able to do as well as she had in the role. However, Dr. Roth was a great mentor and helped guide me through my first few months in the role until I felt comfortable.

Could you give us an outline of how female leadership in the policy-making process and healthcare delivery system has evolved over time in Canada?

We all owe a great deal to Dr. Emily Stowe, the first female physician in Canada. She was denied admission to medical education at the Toronto School of Medicine in 1865 because of her gender, so she went on to earn her degree in New York City [2]. Her daughter, Augusta Stowe-Gullen, followed in her footsteps and actually became the first woman to graduate from a Canadian medical school [2]. They worked together to spearhead the creation of the Ontario Medical College for Women, a Toronto-based medical school for women that opened in 1883 [2,3]. The aim was not only to give women the right to study and practice medicine in Canada, but also to improve the delivery of women's healthcare in the country. I have a great deal of respect for women who refused to accept the status quo and knew that they were just as capable as their male counterparts. From Dr. Jennie Smillie Robertson, the first female surgeon in Canada and the founder of the Federation of Medical Women of Canada, to Dr. Noni MacDonald, the first woman to be named a Dean of Medicine in Canada, there is no shortage of female physicians to look up to.

To build upon the previous question, can you highlight some pivotal milestones of female leadership in The Ottawa Hospital?

Today, women comprise more than 50% of medical school graduates, but they remain under-represented in medical leadership roles. At TOH specifically, 38% of all the physicians with active or associate appointments are women, but only 21% are division heads (9 of 42), and 8% are department heads (1 of 12). This led to the creation of the Female Physician Leadership Committee, whose goal is to "encourage and support the engagement of female physicians in administrative leadership roles and positions and ensure equal access to leadership development and roles at The Ottawa Hospital. The committee will develop, provide, and support recommendations for TOH leadership development initiatives specific to female physicians at TOH."

I am so proud of the accomplishments of the Female Physician Leadership Committee since its inception. We have affected change in a number of areas at TOH:

1. In 2013, leadership activities and goals became part of a re-credentialing process. This has the goal of ensuring that female physicians have the opportunity to hear about leadership opportunities and discuss their potential interest in leadership positions with their supervisor.
2. Leadership selection committees have improved gender balance; each committee is now required to have a minimum of two female members. If a selection committee cannot find female members, the Female Physician Leadership Committee will provide two of its members to sit on that committee.
3. Many committee members have gone on to assume leadership roles at TOH.
4. The committee was instrumental in implementing the TOH Leaves Policy (September 2014).
5. The committee is embarking on an exciting new initiative. The "GoSponsorHer" social media campaign will ask the 12 Department Heads at TOH to identify a female physician working in their department that they have, or will, sponsor for leadership development. This will help showcase the wonderful female physician leaders at TOH.

What is your proudest achievement throughout your career thus far that has furthered female involvement and leadership in healthcare?

I am most proud when I see younger female physicians that the Female Physician Leadership Committee has mentored go for what they want, and have the full confidence in their ability to be leaders in any area they choose. A few examples include Dr. Barbara Power, who is the Vice-President of Education for the Department of Medicine; Dr. Kathy Gillis, the Chief of Department of Psychiatry; Dr. Caroline Gérin-Lajoie, the Medical Director and Physician Health and Wellness Director at TOH;

Dr. Kathleen Gartke, the Medical Lead of Patient Experience at TOH; and lastly, Dr. Lisa Calder, the Director of Medical Care Analytics and the Canadian Medical Protective Association. I am also proud of the fact that our committee has worked hard to identify future female physician leaders and provide them with opportunities to gain the skills needed to increase their level of confidence and become great leaders.

In your opinion, what are the major barriers currently facing women who want to be involved in the Canadian healthcare delivery system and policy-making process?

Personally, I believe the biggest barrier women face when contemplating leadership positions is the fact that women do not perceive themselves as leaders, but rather see themselves as collaborators and consensus-builders; in other words, "not wanting to tell people what to do." As a result, they are more likely to need to be tapped on the shoulder by others who see leadership potential in them. Another major barrier women face is the fact that they are more likely to perceive leadership as costly. The most important costs perceived are time taken away from their personal and family lives, as well as from their clinical practice. Therefore, when they measure what they feel they need to sacrifice against the gains of assuming leadership roles, they perceive that the cost most often outweighs the benefits. Many female physicians feel that it would be very challenging to find time and support to pursue leadership opportunities. Support would need to consist of providing access to day care, more administrative support, and on-site office space. In addition, departmental support would be crucial to providing the clinical coverage that would allow them to attend leadership training and become more involved in leadership activities. It would be beneficial to have discussions with female physicians during their yearly performance evaluation by their leaders about available leadership opportunities and the types of supports available. Lastly, more female leaders are needed to act as mentors and role models at various levels of the organization to show that it is possible to be excellent leaders and to inspire other females.

Moving forward, what are your personal goals for improving female physicians' involvement and influence on the Canadian healthcare delivery system?

Women bring many attributes and strengths to leadership roles. They have been identified as offering a higher level of emotional intelligence and openness to collaborative interaction [4,5]. Research on women in leadership positions reveals that there is advantage in gender diversity in leadership. Organizations with a higher proportion of women in leadership have been shown to outperform their peers in areas of innovation, accountability, and financial outcomes [6,7]. My goal is to ensure that increasing the number of female physicians in leadership roles remains a top priority at TOH, as harnessing the potential of all medical leaders will help to ensure successful healthcare transformation and optimal patient care.

Do you have any advice and resources for medical students who are interested in closing the gap between gender roles in our healthcare?

If I were to look back to my medical school days, and advise the younger me on what to do, I would give myself three pieces of advice:

1. Be the best you can be. Aim high. Know there is a place for you to lead in healthcare; I want you to commit to working hard to find it!
2. Get a mentor! Good leaders like to create the next generation of leaders!
3. Have fun along the way. If it's not fun, it may not be for you! I made sure I spent time with friends and family. Make sure you recharge and do things that rejuvenate you. It can't all be work after all!

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Optimizing Pregnancy for Intergenerational Health Benefits

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ABSTRACT

Pregnancy is a critical period of body weight regulation for both mother and baby. Vital energy-sensing processes are established in utero that aid in nutrient storage and metabolic control later in life. Excessive weight gain during pregnancy and a surplus of maternal resources leads to preferential shuttling of nutrients and growth-promoting peptides across the placenta, resulting in fetal overgrowth — a well-established predictor of childhood obesity. Physical activity during pregnancy offers a safe and accessible way in which one can modify these intricate cellular networks across the maternal-placental-fetal interface to prevent dysregulation and optimize fetal birth weight. This commentary highlights the clinical utility of physical activity during pregnancy and provides practical recommendations as a way to ensure the best health and safety of mother, baby, and future generations.

RÉSUMÉ

La grossesse est une période critique de la régulation du poids corporel pour la mère et le bébé. Des processus vitaux de détection d'énergie sont établis in utero qui contribuent au stockage des nutriments et au contrôle métabolique plus tard dans la vie. Une prise de poids excessive pendant la grossesse et un surplus de ressources maternelles conduit à un transfert préférentiel des nutriments et des peptides favorisant la croissance à travers le placenta, entraînant une prolifération fœtale - un prédicteur bien établi de l'obésité infantile. L'activité physique pendant la grossesse offre un moyen sûr et accessible pour modifier ces réseaux cellulaires complexes à travers l'interface materno-placentaire-fœtal afin de prévenir le dérèglement et optimiser le poids de naissance fœtal. Ce commentaire met en évidence l'utilité clinique de l'activité physique pendant la grossesse et fournit des recommandations pratiques pour assurer la meilleure santé et sécurité de la mère, du bébé et des générations futures.

Among the many factors that contribute to childhood obesity (i.e. maternal smoking, nutrition/sugar intake, air pollution, endocrine disruptors, sleep disturbance, lack of breastfeeding), there are two powerful maternal determinants: high maternal body mass index (BMI) and exceeding the Institute of Medicine (IOM) gestational weight gain (GWG) guidelines [1]. Furthermore, pregnancy weight-related issues increase the likelihood of adverse cardiovascular risk factors in offspring [2,3]. Excessive GWG is directly linked to giving birth to a large-for-gestational-age (LGA) neonate [4], which is predictive of downstream obesity and chronic conditions, including Type 2 diabetes and cardiovascular disease [reviewed in 5,6]. Recently, high birth weight and parental overweight/obesity were associated with lower levels of both physical activity (PA) and cardiorespiratory fitness in adolescence [7], further supporting the need for prenatal strategies that optimize fetal growth for long-term health. To the surprise of many, excessive GWG in normal-weight women is associated with higher neonatal fat mass and less favorable body composition (i.e. greater percentage of body fat, less muscle mass) [8]. This dysregulation in body composition suggests that an energy surplus in utero acts independent of parental genetics with respect to predisposition for excess weight. In fact, according to recent systematic reviews and meta-analyses, excessive GWG increases the risk of childhood overweight/obesity by 30-40% [9,10], thereby propagating the intergenerational cycle of obesity and the proliferation of chronic disease [5]. This may be due to a host of sociopolitical and physiological factors that promote maternal resource storage, decrements in PA, a loss of metabolic control, and a partitioning of excess energy reserves to the fetus [5,11].

Physical activity remains one of nature's best medicines for prevention and management of chronic disease [12]. However, it is seldom recommended in pregnancy [13]. Furthermore, population PA levels are at an all-time low [14] and reach a nadir during the prenatal period. The reasons for these observations are not well-established, but likely involve a patient-provider knowledge translation discrepancy [15]. Despite the historical dogma and the ensuing clinical recommendations, a pregnant

Keywords: Pregnancy; Physical activity; Pediatrics; Obstetrics; Exercise

Table 1. Sample exercise presciption for pregnant women without contraindications (adapted from [13,19]).

	Previously Sedentary	Active
Program Frequency	3 d/wk	4 d/wk
Program Intensity[†]	Low-moderate	Moderate-vigerous
Program Duration	15min, gradually increase to 30min sessions	30min per session
Program Type[‡]	Low impact aerobics (swim, walk, cycle Resistance/strength training	Low impact aerobics (swim, walk, cycle Resistance/strength training

* Brief warm-up and cool-down should be incorporated with each bout of activity
[†]The "talk test" may also confirm that women are not over-exerting
[‡]Avoid exercise in the supine position after approximately 16 weeks' gestation

women's response to PA is virtually identical to their non-pregnant counterparts and is safe during pregnancy [13]. It is well-established that PA has many beneficial physiological effects that lead to health improvements in both mother and baby [16].

In addition to healthy eating, regular PA is a critical mediator of weight gain and a vital component of weight maintenance strategies at all ages. Activity levels during pregnancy are also a predictor of maternal obesity and excessive GWG [17]. Given the importance of PA, the American College of Obstetrics and Gynecology, the Society of Obstetrics and Gynecology Canada/ Canadian Society for Exercise Physiology, and the International Olympic Committee have issued specific guidelines that encourage all pregnant women to engage in routine PA in the absence of contraindications [18-20]. Regular moderate intensity PA during pregnancy has consistently been shown to reduce the incidence of GDM [21-24] and pre-eclampsia [23, 25-29], two pregnancy-related complications implicated in poor neonatal outcomes and downstream child health. Systematic reviews and meta-analyses looking exclusively at PA interventions during pregnancy have shown success in restricting GWG (-0.36 kg, 95% CI: -0.64 to -0.09 kg [30]; -0.61 kg, 95% CI: -1.17, -0.06 [31]; -0.91kg , 95% CI: -1.76, -0.06 [32]) but few studies have been designed to examine the effects on longer-term child growth or body composition [33-35]. Data that are available from population-level surveillance, randomized controlled trials, and prospective birth cohorts suggest that regular, moderate amounts of PA can protect against birth weight extremes (i.e. small- and large-for-gestational age), and increase the likelihood of delivering an infant whose birth weight is appropriate for their gestational age [28-36]. Research demonstrating a reduction in fetal growth without an increased incidence of small-for-gestational-age infants suggests that sensible prenatal exercise may help normalize nutrient supply to the fetus, thus helping regulate fetal growth [37]. For instance, first and second trimester GWG are directly associated with cord blood hormone levels (e.g., insulin, c-peptide, insulin-like growth factor-I (IGF-I) and IGF-II) at delivery. These growth-promoting hormones are vital for glycemic control and somatic growth and, when in excess, have been implicated in obesity predisposition and metabolic dysregulation [38]. On the other hand, a reduction in growth-promoting peptides has been noted in offspring cord blood of maternal exercisers [39]. This suggests that an active pregnancy may alter nutrient partitioning to the fetus without any demonstrated effect on maternal insulin sensitivity or changes in GWG. Studies by Clapp et al. report that the reduction in birth weight of exercising mothers was entirely accounted for by a reduction of neonatal fat mass with no changes in lean mass compared to the offspring of matched controls [40]. Most striking is the finding that 5 years later the offspring of exercising mothers remained lighter and leaner than their comparators with no difference in other anthropometrics or health outcomes [41]. More recent work has shown that women with a higher total energy expenditure during pregnancy delivered babies with less fat mass, similar lean mass, and thus an improved body composition [42]. A recently published randomized controlled trial concluded that exercise may attenuate adverse pregnancy outcomes including infant size at birth (e.g., macrosomia) when complicated by overweight or obesity [43]. Taken together, PA during pregnancy helps optimize development by preventing overgrowth and inhibiting fetal growth restriction.

The optimization of infant birth weight in women who engage in regular PA is thought to result from an increased functional capacity of the placenta to appropriately shuttle nutrients across the maternal-placental-fetal interface. This involves mechanisms that increase placental surface area, improve blood flow, and enhance perfusion [44,45]. Evidence from animal and human studies suggests that fetal growth rate is matched with maternal nutrient availability via altered expression of placental transporters, receptors, and signaling pathways involved in nutrient sensing and delivery. This acts to restrict growth when maternal nutrition is limited and accelerates growth in nutrient excess conditions [46-49]. Even though the placenta is a pivotal regulatory organ [50], few groups have explored placental function and cellular mechanisms in pregnancies exposed to maternal exercise [51]. New data suggest that meeting PA guidelines (30 minutes of aerobic activity, 3-4 days/week) during the second trimester is associated with altered expression of genes involved in fatty acid and amino acid transport across the placenta [49,52], which may contribute to altered nutrient delivery to the fetus and subsequent changes in fetal body composition.

Although considerable animal research has illustrated that maternal diet alters developmental pathways and offspring body composition through epigenetic changes in metabolic control genes [52], there is a burgeoning body of literature investigating the effect of maternal PA on these processes. Controlled experiments of maternal PA in animal models has shown beneficial impact on many offspring variables; hippocampal neurons and angiogenesis [53], insulin sensitivity [54,55] and metabolism [56], expression of molecules known to attenuate placental dysfunction [57], high fat diet induced changes in metabolic regulator genes [58], as well as hippocampal neurogenesis, learning, and memory [59]. Thus, it is not unrealistic to presume that PA behaviors, affecting maternal metabolism and the metabolic milieu, could affect fetal body composition and downstream health. As such, PA should be considered alongside dietary factors as keystones to childhood obesity prevention [60].

In summary, it is advisable that trainees and physicians be aware of the tremendous physiological benefits of active living during pregnancy. Every little bit counts and the physiological benefits precede phenotypical change. This is an important talking point to address with patients. With respect to physically active pregnancy, some is better than none, and more is better than some in the absence of contraindications. Patients should listen to their bodies and be open with their physicians about the activities they are involved in and the symptoms that present. For the latter to occur, doctors must engage patients in non-judgmental dialogue and provide encouragement to support patients to live the healthiest life that they can enjoy, while maintaining balance and well-being. After all, small changes during pregnancy have the potential to improve public health on a population level and minimize intergenerational disease risk.

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Freezing Eggs to Get Ahead: A Look at Oocyte Cryopreservation for Non-Medical Reasons

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ABSTRACT

The age of first pregnancies for women has been on the rise, partly due to prioritization of career development. Maternal aging is a significant factor affecting fertility, and is correlated with infertility and several adverse pregnancy outcomes. Oocyte cryopreservation (OC), currently recommended to cancer patients pending treatments affecting fertility, is now being explored as an option for extending female fertility due to its efficacy in in vitro fertilization (IVF). However, there is a paucity of data confirming the superiority of the procedure over natural pregnancy in healthy women, given the potential complications. Caution in recommending the procedure should therefore be taken.

RÉSUMÉ

L'âge des premières grossesses chez les femmes a augmenté, en partie à cause de la hiérarchisation du développement de carrière. Le vieillissement maternel est un facteur important affectant la fertilité, et est corrélé avec l'infertilité et plusieurs résultats défavorables de la grossesse. La cryoconservation des ovocytes (CO), recommandée aux patients cancéreux en attendant les traitements affectant la fertilité, est actuellement explorée comme une option pour augmenter la fertilité féminine en raison de son efficacité dans la fécondation in vitro (FIV). Cependant, il y a un manque de données confirmant la supériorité de la procédure sur la grossesse naturelle chez les femmes en bonne santé, étant donné les complications potentielles. La prudence dans la recommandation de la procédure devrait donc être prise.

First comes love, then comes marriage, then comes baby in the baby carriage. For a long time, this has been upheld as the dream that little girls are supposed to have. With the feminist movement slowly gaining rights for women in recent decades, gender equality is starting to take hold in many aspects of society. One such aspect is the workforce, where women now stand proudly as CEOs, scientists, teachers, doctors; in fact, they play a vital role in all fields of work in Canada. The age at which women have their first pregnancies has also been on the rise, with 42.8% of first-time mothers being over 30 years of age in 2013, up from 26.6% in 1993 [1]. The peak of female fertility is during a woman's early to mid-twenties, but that is also a critical period for career establishment [2,3]. Pregnancy becomes gradually more difficult as maternal age increases, and several risk factors for both the mother-to-be and the baby begin to arise [3]. Many careers can force a choice to be made between work and family, yet for many, the traditional dream of the baby carriage and the newer dream of career success are not mutually exclusive ideals. Despite these challenges, women have the right to both a fulfilling career and a family.

"Taking control of fertility" is a phrase often heard in reference to the accessibility of effective contraception. Given our resources in Canada, women can more easily avoid pregnancy. Unfortunately, the converse is not true. Technology to extend female fertility such as oocyte cryopreservation (OC), or the preservation of eggs through freezing, sounds like something out of a sci-fi novel, and yet it is a procedure that is rising in popularity. In the science community, it is being debated whether or not to use OC for non-medical purposes. Meanwhile, society has taken interest in the possibilities with optimistic excitement.

AGE AS A RISK FACTOR IN FEMALE FERTILITY

Women are still having children in their 30s and even 40s. Thus, on the surface, the age effect on fertility does not seem like a significant issue. However, this glosses over the experiences and challenges that stand in the way of having children at a later age. Not only does the average length of time it takes for a woman to conceive increase with age, but even upon conception miscarriage is a concern. The likelihood of fetal loss is strongly correlated with maternal age, increasing from less than 10% in women in their early 20s to nearly 75% in mothers age 45 and over, and this is observed with natural pregnancy

Keywords: Reproduction; Women's Health; Fertility; Oocyte Cryopreservation; Oocyte Vitrification; Infertility; IVF

or through IVF using the patient's own oocytes [4,5]. This may partly be due to the increased incidence of trisomic conception such as Down syndrome, a result of improperly executed meiosis during oocyte development [6]. For women in their 20s, the occurrence of trisomic conception is only around 2%, a shocking contrast to the 35% prevalence for women in their 40s [7].

Pregnancy is possible later in life, but it becomes more difficult with age. Furthermore, adverse pregnancy outcomes that become increasingly prevalent with maternal aging, such as gestational diabetes and preterm delivery, can add excessive emotional and financial burden to what should be a joyous period of one's life [5].

COUNTERING THE MATERNAL AGE PROBLEM

In Vitro Fertilization (IVF)

Infertility is not an insignificant problem for men or women. As such, in vitro fertilization (IVF) is gaining popularity. The procedure is even partially covered by the Ontario and Quebec provincial governments, and the federal government also supports its use with a 15% tax break for associated costs [8,9]. However, at the moment it does not guarantee success; only around half of the couples that begin treatment succeed in giving birth to a child [10]. The factors affecting fertility are still largely a mystery, and there are ongoing studies to refine the procedure, or attempt to predict the IVF outcome based on factors such as cause and duration of infertility, ethnicity, and so on [10]. One clear conclusion from these studies is that maternal age and therefore oocyte age is a major factor affecting the success of IVF treatment.

One solution to counter this problem is the use of donor eggs from young, healthy women in their 20s. While this increases the success rates, some women are understandably hesitant about choosing this option, as they will not be able to contribute genetically to their children. To address this, the technique for oocyte vitrification, a form of oocyte cryopreservation, has been refined in recent years and in 2013 was officially declared as no longer experimental by both the Society for Assisted Reproductive Technology (SART) and the American Society for Reproductive Medicine (ASRM) [11].

For those who prioritize having a genetic link with their offspring, oocyte cryopreservation has the potential to become a useful tool in fertility treatment as it demonstrates similar results to IVF involving fresh oocytes [12]. This sounds very optimistic for expanding reproductive freedom for women, but reality may paint a slightly different picture.

Preservation of Fertility

Oocyte cryopreservation (OC) can be defined as the preservation of oocytes through freezing. Vitrification is a type of cryopreservation, using ultra-fast freezing rather than the traditional slow freezing process that results in the formation of ice crystals, yielding deleterious results [13]. Research to refine techniques for both oocyte cryopreservation, as well as IVF, is ongoing in order to improve live-birth occurrences.

Presently, it is recommended that cancer patients of childbearing age whom are due to undergo treatments that may result in gonadotoxicity be engaged in a discussion regarding a potential loss of fertility. Counselling for these life changing events are accepted as the standard of care, and oocyte vitrification is sometimes offered as an option to preserve fertility for the future [14,15]. For women who face an immediate loss of fertility, the choice to undertake this procedure is understandable. However, there is now rising interest in using OC as a way to delay childbirth in healthy women [16].

Elective Oocyte Cryopreservation

Full control over fertility is a tempting idea, and the benefits of having that choice are abundantly clear. Being able to push back the pressures of childbirth and parenthood without worrying that by delaying, you are increasing the chances of congenital disorders would certainly be beneficial to many women. However, our knowledge and standard procedures cannot support such confidence at present, as there are several risk factors to consider, as well as a body of literature that is far from robust to support the benefits of OC for non-medical reasons.

The first step of OC is oocyte retrieval, a process that may largely be a mystery to the general population, and involves certain health risks. Firstly, obtaining the oocytes for freezing requires the patient to undergo hormonal treatment for ovarian stimulation. This treatment can be lengthy, and can cause side effects such as hot flashes, nausea, and dizziness depending on the type of medicine being used [17]. One potential adverse outcome, ovarian hyperstimulation syndrome (OHSS), can result from the use of human chorionic gonadotrophin (hCG), the hormone used to promote ovulation. This hormone is administered 36 hours prior to the procedure and in rare cases, OHSS can result in patients who are overly responsive to hormonal

stimulation. OHSS manifests as cystic enlargement of ovaries, and the symptoms can include severe abdominal pain, nausea, and hypercoagulation. Severe cases can even result in fatality. For women suffering from polycystic ovary syndrome, this is particularly dangerous [18]. Medical professionals, however, have strategies put in place regarding hCG dosage and hormone regime for patients in order to prevent this from happening [19].

Other risks involve the surgery portion of the retrieval process. Oocyte retrieval requires sedation, and as with all surgical procedures, there are risks involved in both the surgery and the use of anaesthesia. However, it is a short and relatively safe procedure lasting only a half hour, and the patient is able to leave shortly after. Currently the process used is transvaginal oocyte retrieval (TVOR), during which a catheter tipped with a needle is guided via ultrasound through the vaginal wall to enter follicles. To obtain the oocytes, mild suction pressure is used [20]. Complications of TVOR include haemorrhage and pelvic abscesses, although they only occur in around 0.08% and 0.6% of cases, respectively [21].

Given the risks, assurance that the procedure will successfully result in live birth down the road would be ideal. However, there is a paucity of data available that addresses fertility preservation in healthy women. While it is promising that cryopreserved oocytes have IVF success rates on par with fresh oocytes, most studies focus on women with low fertility. Elective OC, on the other hand, would typically be considered by young women with no fertility concerns. Unfortunately, there are no current studies comparing OC to naturally occurring pregnancy later in life for this demographic. Despite this, many recently surveyed women are in support of using oocyte cryopreservation as a means for extending fertility, but this openness towards the procedure has yet to translate into data [19]. A recent survey of 96 healthy Australian women who had opted for OC indicated that only 6 returned for the oocytes; of those, only half succeeded in giving birth [16]. The mean age for this cohort, however, was 37 years for oocyte freezing, which is past the point of peak fertility, and the small sample size makes this study only minimally effective at demonstrating the potential of OC for young, healthy women hoping to extend their fertility. Despite this, the study is one of the few that assess the efficacy of non-medical OC [16].

Here we have a conundrum. Without data that explicitly proves the procedure's efficacy at preserving fertility, how can we recommend the procedure? And if we do not recommend this procedure, how can data be obtained? Surveys of a cohort of European women between the ages of 30-39 shows that many are optimistic towards elective OC, and while there is controversy surrounding the topic, fertility clinics worldwide are offering fertility preservation services [11]. However, current information surrounding the procedure are not made widely known. A 2017 study evaluating 376 SART fertility clinics found that of the 90% offering elective OC, less than a fifth disclose the cost [22]. More concerning is the lack of a disclaimer that this procedure cannot guarantee future fertility in 90% of these clinics [22]. Information is vital in making a decision regarding any surgical procedures, and yet it seems that the facilities providing the services are not fully transparent with the potential outcomes of OC. The lack of information may potentially mislead women into considering the option of elective OC and overestimating the security that this procedure could provide.

CONCLUSION

Both the science community and society at large are becoming more interested in the idea of elective oocyte cryopreservation, which has the potential to extend the fertile years of women who may feel conflicted between pursuing a career and having a child. However, while many fertility clinics are pushing for the procedure in young healthy women in prime reproductive years, there is little data to support any advantages of OC over natural conception slightly later in life. Furthermore, several health risks involved in oocyte retrieval can cause complications that would not otherwise arise.

More data is needed before oocyte cryopreservation can be recommended with any kind of certainty, and this can only be obtained through more reproductively healthy women opting for OC. As to whether the procedure should be recommended, there is no clear answer. However, it is vital to provide all the necessary information to women considering this option so that they can make a well-informed decision with tempered expectations. The future is exciting as techniques in preserving fertility continue to improve, and the reproductive science community is constantly gaining a deeper understanding into the mechanisms surrounding fertility and gamete health. Certainly, it is within the realm of possibility that women can someday truly take full control of their fertility.

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Is There Evidence for the Use of Acupuncture in Post-partum Depression?

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ABSTRACT

Postpartum depression is a significantly debilitating condition that affects up to 12% of women, resulting in immense distress to the mother, child, and family. Conventional therapy involves the use of psychotherapy and antidepressant medications. Nevertheless, more women are turning towards alternative medicine such as acupuncture due to recent research citing its effectiveness and reduced potential for adverse effects. This paper reflects on the current evidence for the use of acupuncture as monotherapy, the challenges encountered in acupuncture research and its effectiveness as adjunctive therapy in postpartum depression.

RÉSUMÉ

La dépression post-partum est une condition débilitante importante qui affecte jusqu'à 12% des femmes, entraînant une détresse immense pour la mère, l'enfant et la famille. La thérapie conventionnelle implique l'utilisation de psychothérapie et d'antidépresseurs. Néanmoins, plus de femmes se tournent vers la médecine alternative comme l'acupuncture en raison de la recherche récente citant son efficacité et sa réduction du potentiel d'effets indésirables. Cet article se penche sur les preuves actuelles de l'utilisation de l'acupuncture en monothérapie, les défis rencontrés dans la recherche en acupuncture et son efficacité en tant que thérapie d'appoint dans la dépression post-partum.

A 27-year-old new mother of a 4-month-old son reports severe fatigue, loss of interest, poor concentration, insomnia, low energy, and tearfulness that has lasted for 3 months. She had similar symptoms for several weeks when she was 18 and was diagnosed with depression and treated on citalopram. She is concerned with the effects of antidepressant medications on breast-feeding and has read online about the benefit of acupuncture in relieving depression as a safer alternative. What would you advise?

INTRODUCTION

For many women, the idea of becoming a new mother is a time of celebration but for some it can also be a time of stress, fear and despair. Postpartum depression (PPD) is a common and debilitating condition with a prevalence of approximately 12%, with the highest rate of occurrence in the last two trimesters [1]. PPD is a diagnosis classified within the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as a major depressive episode with "peripartum onset if onset of mood symptoms occurs during pregnancy or within 4 weeks following delivery" [2]. Clinically, this period is more variably defined and can include depressive episodes that last up to one year after childbirth [3]. Symptoms of postpartum depression often include decreased mood and mood swings, excessive crying, withdrawal from family and friends, appetite problems, insomnia, worthlessness, fatigue, and irritability [2]. Rapid decline in levels of reproductive hormones and changes in neurotransmitters, including serotonin (5-HT), norepinephrine (NE), dopamine (DA), and endorphins is thought to contribute to development of symptoms [3]. Pregnancy and postpartum are associated with marked alterations to the mother's hypothalamic pituitary adrenal and hypothalamic pituitary gonadal axes, which subsequently alter levels of corticosterone, estrogen, and progesterone [3].

Postpartum depression is a significant mental illness that impacts not only the affected mother but also the fetus and child. PPD can directly interfere with a child's attachment with the caregiver and their physical and psychosocial maturation. Moreover, women with PPD are at increased risk for smoking, alcohol and illicit substance abuse [4,5]. The aim of this paper is to explore the current evidence for the use of acupuncture as monotherapy in PPD, the challenges encountered in acupuncture research and its effectiveness as adjunctive therapy in women with PPD.

MAINSTAY THERAPY

Given the high prevalence and severe consequences of PPD, prompt recognition and management is paramount. To date,

Keywords: Acupuncture; Post-partum depression

there have been four randomized control studies that have evaluated the use of antidepressant medications on PPD [5]. In one landmark trial, 87 women were randomized into four groups: those receiving fluoxetine or placebo, plus one or six sessions of cognitive behavioural therapy (CBT) [6]. Greater reduction in depressive symptoms was observed in the fluoxetine group compared to placebo medication, with greater improvement in the 6-session CBT group [6].

Despite the efficacy in selective serotonin reuptake inhibitor (SSRI) use for PPD, many mothers are reluctant due to the potential effects of antidepressant medications on breastfeeding. Young infants are particularly vulnerable to drug effects as a result of their newly developing hepatic, renal, and nervous systems [5]. There is a relative paucity in research regarding the effects of antidepressant medications in breast milk and it is recommended that non-pharmacological modalities be employed when possible. Of the existing SSRIs, several reviews indicate that sertraline and paroxetine are least detectable in infant plasma following breast-feeding [5]. Contrastingly, fluoxetine and citalopram have higher penetration in the infant's plasma following breast-feeding and are more likely to be associated with adverse effects including gastrointestinal problems, respiratory issues, sleep disturbances, and seizures [7-9].

EVIDENCE FOR ACUPUNCTURE

A growing percentage of the population is seeking alternative therapies to antidepressant medications and recent research has suggested some preliminary evidence regarding the use of acupuncture. Acupuncture, a Traditional Chinese Medicine technique, involves inserting needles into the skin with the aim of restoring physiological imbalances within the body via stimulation, either manual or electrical, at various acupoints [10]. Psychiatric symptoms of depression are thought to be associated with neurotransmitters 5-HT, NE, DA, and endorphins and also dysregulation of the hypothalamic-pituitary-adrenal axis [5]. Though the mechanism is not fully elucidated, acupuncture has been shown to influence the neuroendocrine and immune system and regulate levels of 5-HT, NE, DA, endorphins, and glucocorticoids thereby modifying existing neural functioning [5]. A review by Wu et al. in 2012 identified 114 reports of acupuncture use in depression, including 53 randomized control trials (RTCs), 17 simple RCTs, 12 animal studies, 6 theoretical articles, and 30 review articles [11]. In an article in the Journal of Obstetrics and Gynecology, the utility of acupuncture specific to postpartum depression was evaluated [12]. 150 pregnant women who met DSM criteria for major depressive disorder were randomly allocated to one of 3 groups: acupuncture treatment specific for depression, control acupuncture group, or massage. The authors concluded that women who received acupuncture specific for depression at 8 weeks experienced greater reductions in symptom severity as evaluated by the Hamilton Rating Scale [12].

Despite these promising results, there are several noteworthy limitations that apply not only to this study, but trials evaluating the efficacy of acupuncture in the clinical setting at large. First, it is often difficult to institute a proper sham control that is entirely inert. Most acupuncture sham designs assume that variations in needling parameters such as depth, placement, and stimulation influence the clinical response [10]. As such, more superficial needling or placements at non-acupoints would theoretically result in no clinical benefit and constitute a reasonable control. However, no study thus far has examined whether these parameters may indeed play a therapeutic role, and thus researchers are handicapped by a lack of a standardized sham group. Implementing the above sham control group would further supplement the validity of future acupuncture trials. Moreover, it is difficult to institute a double blind study since patients who do not believe in the efficacy of acupuncture are unlikely to partake in a study involving the technique. Likewise, since acupuncturists are the investigators providing the therapy, they will be aware if they are performing a sham or real procedure. Lastly, most studies to date are limited by a relatively small sample size and plagued with low statistical power, thus further large-scale, multi-center studies are required [11].

ACUPUNCTURE AS ADJUNCTIVE THERAPY

Given the efficacy and wealth of research devoted to antidepressant medications, it is difficult to dispute their role in treating postpartum depression. Nevertheless, higher doses of medication often increase side-effect profile including weight gain, nausea, drowsiness, insomnia, and sexual dysfunction, which subsequently reduces patient adherence [5]. Acupuncture has been employed with reasonable efficacy in managing physical symptoms including nausea, vomiting, and weight gain [13,14]. A Cochrane review on the effect of acupuncture in controlling nausea and vomiting following chemotherapy and pregnancy showed that P6 stimulation was superior to antiemetic medication for nausea and equivalent for vomiting [15].

Likewise, in another study on postpartum depression, the ther-

apeutic effect of acupuncture was assessed in conjunction with standard psychological intervention [16]. 43 patients were randomly allocated to the treatment group who received acupuncture in addition to psychological therapy, whereas the control group received oral fluoxetine hydrochloride. At six weeks the patients were scored using the Hamilton depression scale, which demonstrated effective outcomes in both groups, but no significant difference between the two. Adverse effects were observed in the control group, however, with five reporting nausea, dizziness and poor appetite. The reported side effects were not evident in the treatment group [16]. Hence for PPD, there is relative evidence that acupuncture is a useful adjunct to conventional care. It is worthwhile exploring the combination of acupuncture with medication therapy to see if there is evidence for augmented effects and if the technique is able to mitigate adverse effects of conventional antidepressants.

CONCLUSIONS

Revisiting our case example, given the concern for the use of antidepressants and their side effects on breastfeeding, evidence based medicine suggests the use of sertraline and paroxetine. Nevertheless, when it comes to the use of acupuncture, much of the existing evidence from studies using randomized control trials for acupuncture in PPD have a relatively limited sample size and homogeneity. Given the lack of rigorous sham control and repeatability, it is too early to recommend the use of acupuncture as a single treatment modality in patients with postpartum depression. However, it is undeniable that observable benefits can be cited based on small-scale studies warranting further research.

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Celiac Disease and Maternal Infertility and Pregnancy Outcomes: Is Screening Necessary?

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ABSTRACT

Celiac disease is a common autoimmune condition that is often underappreciated in pregnant women. Due to the difficulty in conducting high-quality studies involving pregnant patients, the evidence supporting the association between celiac disease and maternal fertility and pregnancy outcome, and the benefits of screening for celiac disease in this population are unclear. Therefore, we sought to review the relevant literature to gain a better understanding of the impact of celiac disease on maternal fertility and fetal outcome. Our findings suggest a role for celiac screening in women with unexplained infertility.

RÉSUMÉ

La maladie cœliaque est une maladie auto-immune commune qui est souvent sous-estimée chez les femmes enceintes. En raison de la difficulté à mener des études de haute qualité impliquant des patientes enceintes, les preuves soutenant l'association entre la maladie cœliaque et la fertilité maternelle et l'issue de la grossesse, et les avantages du dépistage de la maladie cœliaque dans cette population ne sont pas claires. Par conséquent, nous avons cherché à examiner la littérature pertinente pour mieux comprendre l'impact de la maladie cœliaque sur la fertilité maternelle et l'issue fœtale. Nos résultats suggèrent un rôle pour le dépistage de la maladie cœliaque chez les femmes présentant une infertilité inexpliquée.

Pregnancy provides unique challenges to healthcare providers. A plethora of questions remain regarding the effects of investigations, management options, and conditions on pregnancy. Incomplete knowledge of these aspects stems from the difficulty in conducting high-quality studies involving pregnancy because of the many patient, ethical, and legal factors involved in researching this vulnerable group consisting of the mother and the fetus [1].

Celiac disease is more common in females and its effect on pregnancy and fetal outcome is controversial [2]. In celiac disease, the immune system inappropriately reacts to gluten in the small intestine, which results in varying degrees of small bowel damage. It can be diagnosed using a combination of serological testing for autoantibodies and small bowel biopsy, depending on the clinical index of suspicion for the disease. By going on a gluten free diet, patients can prevent the inflammation and subsequent damage that occurs in the small intestine. Previous studies have hinted at a possible increased prevalence of celiac disease in pregnant women. For example, a study by Martinelli et al. found that 1.4% of a study population of 845 pregnant women had previously undiagnosed celiac disease [3], which was comparable to the prevalence of other routinely screened conditions [4]. They found that there was in turn a statistically significant increase in adverse pregnancy outcomes in this population. Based on the study results, the authors recommended routine testing of celiac disease during pregnancy. Despite these studies, there is insufficient evidence supporting the association between celiac disease and maternal fertility and pregnancy outcome. The benefits of screening for celiac disease in this population remain unclear. Therefore, we sought to review the relevant literature to gain a better understanding of the impact of celiac disease on maternal fertility and fetal outcome, and based on this evaluate the utility of routine screening of celiac disease in pregnancy.

PROPOSED IMPACTS OF CELIAC DISEASE ON PREGNANCY

Celiac disease has been postulated to affect maternal fertility and pregnancy outcomes through two mechanisms: nutritional deficiency and autoimmune dysregulation [4]. Celiac disease can result in the malabsorption of zinc, selenium, and folic acid, which are essential compounds for pregnancy [4,5]. The autoimmune hypothesis postulates that either anti-transglutaminase (tTG) antibodies bind to the trophoblast layer of the embryo, causing damage to the future placenta, or that anti-tTG antibodies can harm the maternal endometrial endothelial cells

Keywords: Celiac Disease; Infertility; Fetal Outcome; Screening

[4,5]. Studies have shown that women who suffer from infertility associated with villous atrophy caused by celiac disease do not have signs of absorption deficiency [6,7]. This suggests that celiac disease affects pregnancy through an autoimmune process that affects the placenta before and during the pregnancy, rather than through inducing nutritional deficiency. Celiac disease is frequently asymptomatic for long periods while still having histological effects, so it is possible undiagnosed celiac disease may impact pregnancy while being clinically undetected.

INFERTILITY

Infertility, defined as the inability to conceive for 1 year, can have devastating impacts on mental health [8]. In 15-30% of infertility cases, no cause can be found [9]. An often undiagnosed disease, celiac disease has been postulated to influence fertility and could explain a portion of infertility cases.

A study by Collin et al. from 1996 compared 150 controls with 98 women with infertility of unknown origin [10]. Of the 98, four had previously undiagnosed celiac disease that was diagnosed by serological testing for autoantibodies, compared to none from the control group, a statistically significant difference. Another study conducted by Meloni et al. from 1999 demonstrated similar results showing 4 out of 99 women with unexplained infertility having positive serological markers for celiac disease, and 3 of those 4 having histological evidence, a statistically significant difference compared to the prevalence of celiac disease in the general population (0.5-1%) [7].

There were two recent studies by Shamaly et al. and Tiboni et al. on 192 women and 200 women, respectively. Although they both found an association between previously undiagnosed celiac disease and infertility, neither study reached statistical significance with their outcome [6,11]. Shamaly et al.'s study had 4 patients with celiac disease in their infertility group with celiac compared to one in the control group, and Tiboni et al. found 5 and 2, respectively [6,11]. The authors of both papers attributed the lack of statistical significance due to the studies being underpowered. On the surface, it may seem that both had a large sample size, but given the very low prevalence of celiac disease (0.5%), even reasonably large sample sizes will not yield many celiac cases, making comparisons difficult. It is therefore not possible to make strong conclusions based on the data currently available.

There is very limited data present that suggests the possibility that a gluten free diet may improve fertility outcomes in women with celiac disease. A study performed by Sher & Mayberry utilized questionnaires to survey 80 patients with undiagnosed celiac disease and 70 age and sex-matched controls, and found that women with celiac disease had statistically significant less children overall (120) compared to the control group (161). Using the questionnaires they found women with celiac disease had fewer children overall (120) compared to controls - a finding that was statistically significant.Furthermore, a case report by Rajput and Shatterjee outline the case of an infertile woman found to have infertility which was successfully treated using a gluten free diet [12,13].

Clearly, the data regarding celiac disease and infertility, as well as the possible effect of a gluten free diet, is highly limited. However, given the presence of an association in all of the studies, when faced with infertility unexplained by other factors, we feel it is reasonable to consider a workup for celiac disease in this population as a possible contributing factor to infertility. A screening test simply requires looking for serological presence of autoantibodies and so is straightforward, and yet could potentially help explain some infertility cases. This may be especially important as there are very small amounts of data suggesting the possibility that treatment of celiac disease may lead to subsequent fertility improvement.

FETAL OUTCOME

Several retrospective studies have examined the potential impact of undiagnosed celiac disease on fetal outcome [3,14–16]. All of them examined parents of children with poor birth outcomes. Among these, a noteworthy retrospective study by Salvatore et al. investigated 1,714 parents (868 women, 846 men) of preterm and/or small for gestational age (SGA) infants for celiac disease [14]. The study found previously undiagnosed celiac disease to be a risk factor for these adverse outcomes. However, despite the very large sample size, the absolute number of subjects with celiac disease in this study was still low, and thereby precluded further subgroup analysis. Despite the limitations of sample size, the trend among all of these retrospective studies suggests that celiac disease is associated with adverse fetal outcomes such as SGA, preterm, low birth weight (LBW), miscarriage, and intrauterine growth restriction (IUGR). When simply basing off of the collection of evidence in these relatively small studies, it would appear that there is some evidence to suggest celiac disease may have a link with adverse birth outcomes.

However, more recent population-based studies with very large sample sizes cloud the picture. Two large retrospective cohort, population-based, studies using the United Kingdom (UK) population, one involving over 2.5 million women, did not demonstrate an association between undiagnosed and diagnosed celiac disease and adverse pregnancy and birth outcomes [17,18]. Conversely, a population study of the Danish population with a sample size over 1.5 million demonstrated that untreated celiac disease could lead to poor fetal outcomes, but presumed treatment (as defined by those with celiac diagnosis prior to 90 days before the start of pregnancy) led to no discernible difference [19].

Clearly, the assumption regarding the definition of the treated group is a large one, but nonetheless the difference in the results for the two study groups in the Danish study may help to explain the discrepancy between the results of the UK population-based studies and the smaller retrospective studies mentioned earlier. It is possible that the difference in results between the studies may be due to differences in study designs. The non-population-based studies performed retrospective analyses to correlate the presence of parental celiac disease and poor offspring outcome. Simply put, they examined the parents of children who have already had an adverse birth outcome (i.e. SGA), and then worked back in order to see if celiac disease was more common in these parents (i.e. look at effect, and work back to find the cause). This form of study design meant the researchers were only capturing previously undiagnosed celiac disease. On the other hand, the population studies track a large number of individuals with celiac disease, and then look at what happened to all of their children (i.e. look at a potential cause, and go forward to see the outcome). This form of study design would capture outcomes of patients with known celiac disease, which the other studies did not. We theorize, therefore, that the retrospective studies are only capturing a subset of celiac patients that may have a specific feature that put them at higher risk (i.e. they were all undiagnosed celiac disease), but this risk does not translate across celiac patients in general who may be receiving treatment.

Furthermore, this theory also follows the autoimmune mechanism mentioned earlier—anti-tTG antibodies are typically found in patients with active celiac disease which would explain why a gluten free diet eliminates most of the pregnancy complications found by the researchers. Taken in combination with our postulated theory, it would certainly appear that a factor such as disease severity may play a role in the relationship between celiac and pregnancy, and could very well explain the inconsistency between the population-based studies and the retrospective ones.

CELIAC DISEASE SCREENING

Given that, on the population level, celiac disease has not been shown to be associated with adverse birth outcomes, we do not recommend the universal screening of pregnant women for celiac disease. Even though some retrospective studies showed a link between poor birth outcome and celiac disease, this finding may only be associated with a subset of previously undiagnosed celiac disease patients, which is a very small group. This recommendation is supported by a study by Greco et al. from 2004 which demonstrated that screening of 5,055 pregnant women near delivery for celiac did not result in prevention of adverse fetal outcome [20]. However, they only screened with antibodies, and never confirmed the diagnosis with a tissue biopsy. On the basis of the aforementioned evidence, the benefits of screening for celiac disease in pregnant women does not appear to be clinically significant.

CONCLUSION

Celiac disease is a common autoimmune condition that is an often underappreciated disease in pregnant women. Increased awareness and adherence to an appropriate gluten free diet should be promoted among this population to mitigate infertility rates and improve reproductive health. Healthcare providers may consider investigating women with unexplained infertility. However, more studies are needed to evaluate the utility of universal screening for celiac disease in pregnant women.

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Introducing a "same day referral" program for post-coital IUD insertion in Ontario: A mixed-methods study with pharmacists

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ABSTRACT

Objectives: Post-coital insertion of the Copper-T intrauterine device (IUD) is the most effective method of emergency contraception (EC). However, few women use this method of pregnancy prevention in Canada. Our study aimed to explore Ontario pharmacists' knowledge of the IUD as EC and interest in a hypothetical "same day referral" program that would provide women seeking progestin-only EC with information about and a timely referral for post-coital IUD insertion.

Methods: We received 198 mailed surveys from representatives of Ontario pharmacies and conducted 17 in-depth interviews with a subset of respondents in 2015. We analyzed the survey data using descriptive statistics and interviews for content and themes using both deductive and inductive techniques.

Results: Our results suggest that Ontario pharmacists underestimate the efficacy of the IUD as EC and lack awareness of the protocols for use. Survey respondents and interviewees expressed support for a "same day referral" program in Ontario and believe more effective methods of EC should be easily accessible. Interviewees discussed current barriers to the use of IUDs as EC, including the up-front costs associated with insertion and a general lack of awareness about EC among health professionals and communities.

Discussion: There is a significant need for continuing education on the full range of EC methods among pharmacists. Considerable enthusiasm exists for undertaking efforts to expand access to more effective EC methods. Developing a pilot project to facilitate timely referrals for post-coital IUD insertion appears warranted.

RÉSUMÉ

Objectifs: L'insertion postcoïtale d'un dispositif intra-utérin (DIU) au cuivre est la méthode la plus efficace de contraception d'urgence (CU). Toutefois, peu de femmes au Canada utilisent cette méthode de prévention de la grossesse. Notre étude visait à explorer les connaissances des pharmacien(ne)s ontarien(ne)s sur le DIU utilisé comme CU, ainsi que leur intérêt pour un programme hypothéque d'orientation du même jour, qui fournirait en temps opportun de l'information et une insertion postcoïtale d'un DUI aux femmes désirant une CU à progestatif seul.

Méthodes: Nous avons reçu 198 sondages par la poste de la part de représentants de pharmacies ontariennes, et avons mené 17 entrevues détaillées avec un sous-ensemble des répondants en 2015. Nous avons analysé les données de l'enquête à l'aide de statisques descriptives, ainsi que le contenu et les thèmes des entrevues au moyen de méthodes déductives et inductives.

Résultats: Nos résultats indiquent que les pharmacien(ne)s de l'Ontario sous-estiment la capacité du DIU utilisé comme CU et ne con- naissent pas les protocoles nécessaires. Les répondants à l'enquête et les sujets interrogés ont exprimé leur soutien au programme d'orientation du jour même en Ontario et croient que des méthodes plus efficaces de CU devraient être facilement accessibles. Les personnes interrogées ont discuté des obstacles actuels à l'utilisation du DIU utilisé comme CU, incluant les coûts initiaux associés à l'insertion, et le manque général de connaissances sur la CU parmi les professionnels de la santé et les communautés.

Discussion: Il existe un besoin important de formations professionnelles continues pour les pharmacien(ne)s sur la gamme complète de CU. Plusieurs démontrent un enthousiasme considérable quant au déploiement d'efforts pour améliorer l'accès à des méthodes plus efficaces de CU. Il semble justifié d'instaurer un projet pilote qui faciliterait l'orientation pour la pose postcoïtale d'un DIU, et ce, en temps opportun.

Keywords: Emergency Contraceptions; IUDs; Canada

Unintended pregnancies continue to be a major public health issue in Canada; nearly one in three Canadian women experience an unintended pregnancy over the course of their reproductive lives [1]. Methods of long-acting reversible contraception (LARC), including the hormonal intrauterine device (IUD), the Copper-T IUD, and implants, are safe and extremely effective at preventing pregnancies for 3-10 years [2]. In addition, the post-coital insertion of the Copper-T IUD is the most effective method of emergency contraception (EC) [3-5]. Insertion of the IUD within 7 days of unprotected or under-protected sexual intercourse represents an important option for women who not only want to prevent pregnancy after a specific event but also desire highly effective, ongoing contraception [5,6].

In Canada, the IUD remains underused for both contraceptive and EC purposes [7,8]. A number of factors likely influence this dynamic, including lack of awareness and misinformation about the device, the up-front costs associated with insertion, and the limited availability of heath care professionals trained in insertion and removal. Indeed, a study conducted in Ontario found that a limited number of family medicine residents felt adequately prepared to perform an IUD insertion [9]. Although overarching trends suggest that the use of the IUD, in general, is increasing, use of the IUD as EC is minimal [4].

Progestin-only emergency contraceptive pills (ECPs) have long been available in Canada and are the most widely used method of post-coital pregnancy prevention [10]. In Ontario, progestin-only ECPs (commonly referred to by the brand name Plan B®) have been available directly from pharmacies for more than a decade [11]. However, a number of studies suggest that there are barriers to "real world" access [12-14]. Further, some evidence suggests that progestin-only ECPs may be less effective when used by women weighing 165 pounds or more [15].

Consequently, health professionals have repeatedly identified developing mechanisms to increase access to the IUD as EC as a priority. Currently, there are four brands of IUDs that can be used for EC, Flexi-T®, Liberté UT®, Mona Lisa®, and Nova-T® [16]. In recent years, a team in British Columbia developed a pilot project to explore the possibility of implementing a timely referral program [17]. This program trained pharmacists to offer women seeking progestin-only ECPs the option of being referred for an IUD and created a network of area providers that would then be able to schedule an insertion within seven days [18]. Participating pharmacists and clinicians found the initiative acceptable and the program successfully improved the accessibility of IUDs for post-coital contraception [17].

To date no similar projects have been undertaken in Ontario. However, pharmacists play a critical role in EC service delivery in the province and as the most available, accessible, and approachable health care professionals they could play a central role in increasing timely access to the IUD as EC. Using a mixed-methods approach, we explored Ontario pharmacists' EC knowledge, attitudes, and provision practices; in a previous publication we presented the results related to progestin-only ECPs [19]. In this paper, we specifically focus on the findings related to the IUD as EC and explore pharmacists' opinions regarding a hypothetical "same day referral" program similar to that which was implemented in British Columbia.

METHODS

As we have detailed previously [19], our study comprised two components—a mailed survey to a representative sample of retail pharmacists in Ontario and in-depth interviews with a sub-set of survey respondents. We received ethics approval from the Research Ethics Boards at the University of Ottawa to conduct this study (File#H03-14-20 and File#02-15-12).

Component I: Mailed survey

Based on a questionnaire developed by Dunn and colleagues [10], we developed a 56-item survey to explore Ontario pharmacists' EC knowledge, attitudes, and provision practices. Our survey included five primary sections: 1) demographic questions about the respondent and the pharmacy; 2) knowledge of different modalities of EC; 3) EC provision practices; 4) attitudes toward EC and patients seeking EC; and 5) a free space for additional comments. Six questions specifically focused on the IUD as EC. We piloted the survey instrument, in both English and French, with 13 pharmacists in the greater Ottawa region and integrated feedback into the final instrument.

We used the Ontario College of Pharmacists (OCP) database to identify our sample of retail pharmacies. Using a stratified random selection process, we selected 1,428 pharmacies—or roughly one third of retail pharmacies in the province for inclusion; we intentionally oversampled independent pharmacies and pharmacies located in rural and Franco-Ontarian communities in order to capture a range of perspectives and experiences. We invited the head pharmacist—or the best-po-

sitioned person at the pharmacy—to complete the survey. We fielded our four-contact survey over a four-month period (June 2015-September 2015). We initiated the study by mailing a full bilingual survey package including the instruction letter, survey instrument, stamped return envelope, and lottery and key informant interview response card to pharmacies in our sample. We used unique identifiers to track respondents and sent a reminder postcard, a second survey package, and a final postcard reminder to non-respondents at 2-4 week intervals. After accounting for incorrect addresses and returns, we ultimately contacted 1,396 pharmacies. We included all surveys received before the end of the 2015 calendar year in our analysis.

Component II: In-depth interviews

We invited all survey respondents to participate in a follow-up in-depth interview (IDI). AC, who at the time was a master's student in the Interdisciplinary Health Sciences program at the University of Ottawa, conducted all telephone/Skype interviews in English or French after being trained by her thesis supervisor (AMF), a medical doctor and medical anthropologist. The semi-structured interview guide comprised a series of questions related to initiatives to improve and expand evidence-based EC service delivery practices. We presented participants with information about a hypothetical "same day referral" program, modelled after the BC initiative, and asked interviewees about their interest in the program and to comment on perceived facilitators and barriers to establishing a program in Ontario. The IDIs averaged 35 minutes and occurred between July and October 2015; with the permission of interviewees, we audio-recorded and later transcribed all interviews. In addition AC took intensive notes during the interview and formally memoed shortly after. As a small token of our appreciation, we gave all participants a CAD20 gift certificate to Amazon.ca.

DATA ANALYSIS

We entered survey data into FluidSurveys and later exported the information to IBM Statistics SPSS 23.0. We analyzed the demographic, knowledge, and attitudinal data using descriptive statistics and performed cross tabulations to explore differences in knowledge and attitudes by region and rural/urban location. We used ATLAS.ti to manage the IDI notes, memos, and transcripts. AC developed an initial codebook based on the interview guide and added and defined new codes that emerged from the data. AMF reviewed the codebook and a sample of coded transcripts, and discussed the findings regularly with AC. We analyzed the two project components separately and in the final phase reviewed both components for concordance and discordance. We have removed or masked all identifying information of both participants and their pharmacies.

RESULTS

Description of survey participants

Of 1,396 pharmacies in Ontario that we contacted, representative from 198 returned the questionnaire, for a response rate of 14.2%. Close to two thirds of respondent pharmacies (65%) were located in an urban area of Ontario. Respondents reported that all pharmacies were open weekdays, almost all (95%) on Saturdays, and the overwhelming majority (82%) on Sundays. One out of 10 pharmacies was located more than a 15 minute drive from another pharmacy. We present demographic information about the pharmacies of our survey respondents in Table 1.

Survey participants' knowledge of and attitudes toward the IUD as EC

Results from surveys indicate that pharmacists' knowledge of the IUD as EC is limited. Survey respondents incorrectly responded to the recommended timeframe for the post-coital insertion of the IUD, as well as the number of years for which the IUD could provide ongoing contraceptive benefit. Indeed, only 36% (n= 69) knew that the IUD could be used for up to 10 years. Our respondents correctly reported a Copper allergy as a contraindication to use (75%) but also incorrectly reported other contraindications, including history of ectopic pregnancy (45%). A significant minority (22%) incorrectly reported that use of the IUD increases the risk of ectopic pregnancy. Pharmacy representatives generally underestimated the efficacy of the IUD for both post-coital and ongoing pregnancy prevention; only 40% knew that the Copper IUD is the most effective EC modality. Finally, 14% of respondents (n=28) indicated that they lacked knowledge of the IUD as EC entirely. We detail these results in Table 2. Finally, survey participants expressed considerable interest in continuing education dedicated to EC (n=166, 86%) and nearly two thirds (n=122, 64%) reported that they would participate in a project dedicated to post-coital IUD referrals (data not shown).

Description of in-depth interview participants and their pharmacies

We conducted 17 IDIs with Ontario pharmacists, 15 in English and two in French. The majority of our participants were women, worked in urban areas, and had been practicing for

Table 1. Characteristics of the pharmacies reported on by survey respondents (N=198)*

Characteristic	n	%
Type of pharmacy (n=197**)†		
Independent	77	39
Chain	60	31
Banner	51	26
Region of the pharmacy (n=195)		
South	91	47
Central	41	21
East	34	17
North	29	15
Location of pharmacy (n=197)		
Urban	128	65
Rural	69	35
Other pharmacy located within a 15 minutes' drive (n=198)		
Yes	180	91
No	18	9
Store Hours (n=198)		
Weekdays	198	100
Saturdays	189	96
Sundays	163	82

*We have presented information contained in this table in a previous publication [19].
**The overall number of respondents was 198; however, the number provided denotes how many respondents answered that particular question.
†These questions included an "other" response that allowed participants to write-in information. We have not presented those results in **Table 1**.

Table 2. Survey respondents' knowledge of the IUD as EC (N=198)*

Knowledge statement	Number and percentage of correct answers	
	n	%
The IUD is the most effective modality of emergency contraception (n=188*) [Correct answer: Yes]	78	42
IUDs increase the risk of ectopic pregnancy (n=186) [Correct answer: No]	40	22
Both the Copper-T IUD and the levonorgestrel-releasing IUD (the Mirena®) can be used as EC (n=186) [Correct answer: No]	100	54
In Ontario, the Copper-T IUD must be inserted by a physician (n=189) [Correct answer: Yes]	149	79

*We provide the number of responses to each question in parentheses and the correct answer to each knowledge statement in brackets.

Table 3. Demographic information of IDI participants (N=17)

Characteristic	n (%)
Gender	
Female	12 (71)
Male	5 (39)
Number of years working in a pharmacy	
<2	2 (12)
2–5	8 (47)
6–10	6 (35)
>10	1 (6)
Location of current pharmacy	
Urban	11 (65)
Rural	6 (35)

2-10 years. We present basic demographic information in Table 3. Seven pharmacists in the interview component of the study reported that they currently had a Copper-T IUD in stock; seven additional pharmacists reported that they did not have any type of IUD in stock but would order one on request.

Interviewees evinced limited knowledge of the IUD as EC

Consistent with the findings from the survey, our interviewees were interested in the IUD as EC but generally lacked knowledge about this modality of post-coital contraception. Nine pharmacists were able to provide some information about the provision of an IUD as EC but had incomplete knowledge regarding the timeframe for use or the type of IUD that could be used. These pharmacists explained that they gained this knowledge on the job. As Pharmacist #8 commented, "I think that we did not cover this at all in school. As a recent grad, I remember exactly what happened. And we did not cover using IUDs as [emergency contraception]."

Participants were generally positive about the prospect of a "same day referral" program

Only one pharmacist in the interview component of the study had heard of efforts to provide "same day referrals." However, once we described a hypothetical initiative, participants responded positively. Pharmacists indicated the need for introducing and promoting more effective EC methods in the province, efforts that could be supported with the introduction of a referral system. As Pharmacist #11 asserted, "Yes, like it is definitely an option for people to consider…probably have a higher chance of preventing pregnancy…a prime over Plan B®." Several interviewees also noted the advantages of having an automatic bridge to an ongoing contraceptive that is more effective than daily oral contraceptive pills.

All of our interviewees expressed the view that community pharmacists are accessible health service professionals and excellent resources for patients seeking information and advice. Participants practicing in smaller communities and rural areas noted that sometimes pharmacists in these settings are the only accessible provider. As a consequence, interviewees felt that pharmacists, once trained and informed, were well positioned to participate in a referral program and facilitate increased access to timely IUD insertion by working with clinics and physicians.

Perceived facilitators and barriers to same day referrals

Interviewees believed that pharmacists have the appropriate skills, in general, to participate in a "same day referral" program. A number of participants specifically mentioned that pharmacists already serve as trained and autonomous health service professionals and are well-positioned to initiate discussions, counsel patients, and ultimately make referrals. As explained by Pharmacist #7, "That sort of thing, [that] is a huge role for pharmacists that we already do. We have the knowledge and we have the expertise to be able to educate people about [the IUD as EC]…and we are accessible and have the resources." Interviewees view pharmacists as having key responsibilities in educating, counseling, and screening potential patients; some interviewees also noted that pharmacists could play an important role in following-up with the patient once the IUD was inserted.

However, our interviewees also perceived that there would be a number of barriers to implementing an initiative in Ontario. Our interviewees noted that for a program to be effective, raising awareness of the initiative, among pharmacists and physicians, would be required and appropriate screening tools and continuing education resources would need to be developed. Pharmacists suggested that an educational letter in the monthly Canadian Pharmacist's Letter could be an important initial step. However, pharmacists also expressed concern that the lack of qualified personnel to perform the insertion—and to do so in a timely way—would be a barrier to implementation; this issue was especially salient for our rural participants. Interviewees also felt that the considerable lack of awareness about the IUD, in general, and the IUD as EC, in particular, among women in the general population, as well as the high up-front costs as-

sociated with IUD insertion, would constitute significant barriers.

DISCUSSION

Expanding access to emergency contraception in Canada has long been identified as a priority among reproductive health and rights stakeholders [8,11,20]. Further, in recent years there has been a plethora of efforts in North America to expand access to long-acting, reversible contraception [21-23]. Misinformation among providers, a dearth of trained providers, high up-front costs, and lack of awareness among women have limited the availability and accessibility of IUDs, both as ongoing methods of contraception and as EC [24-26]. Yet research also suggests that when women are informed about the IUD as EC, demand increases [27].

Our findings suggest that creation of a "same day referral" initiative in Ontario could be a viable first step in expanding access to more effective modalities of EC. Although pharmacists in both components of our study had relatively limited knowledge of the IUD as EC, a finding that is consistent with other studies of health professionals in North America [25], our participants expressed considerable interest in participating in such an initiative. Importantly, pharmacists saw themselves as being well-positioned to offer these types of referrals and identified that this type of program would meet a demonstrable need. Although content-specific information would need to be developed to ensure that pharmacists provided women with accurate information, pharmacists in our study feel confident in their ability to leverage their overarching skills in educating, counseling, and referring patients. Creating a pilot initiative modelled after the BC initiative as a proof of concept appears warranted.

However, even in the absence of a dedicated "same day referral" program, our findings suggest that developing continuing education resources and training modules for pharmacists would be well received. Our survey participants indicated considerable enthusiasm for participating in such efforts and our interviewees further elaborated on potential avenues for disseminating information. Our interviewees, even those who had recently completed their training, indicated that coverage of EC in pharmacy education is lacking. Further research could be conducted to assess the coverage of EC in pharmacy training programs and explore ways of strengthening this area of the curriculum, if needed.

Our study has a number of limitations. First, our survey response rate of 14.2% is low and thus our results should be viewed as exploratory. Second, although we administered the survey in both French and English and oversampled pharmacies in Franco-Ontarian communities, we had very few participants in both components who were based in language-minority areas. Future research would benefit from inclusion of these perspectives. Finally, reproductive health is an evolving field. We completed our data collection in the fall of 2015; efforts undertaken in the last 15 months would therefore not be captured in our study.

Despite these limitations, our study offers insights into the knowledge, attitudes, and practices of Ontario pharmacists toward the IUD as EC and points to several avenues for improving access to a full range of contraceptive services. The enthusiasm among pharmacists for the development of a "same day referral" program is encouraging and the facilitators and barriers identified by our interviewees could inform this type of effort. Engaging with a range of stakeholders to build upon these results and explore creative educational, training, and service delivery initiatives appears warranted.

ACKNOWLEDGEMENTS

Andréanne Chaumont received a Queen Elizabeth II Graduate Scholarship in Science and Technology and several grants from the University of Ottawa to support this project. Dr. Foster's 2011-2016 Endowed Chair in Women's Health Research was funded by the Ontario Ministry of Health and Long-Term Care and the funding attached to her Chair covered the costs associated with this study. We are also grateful to the Society of Family Planning for its support of Dr. Foster's mentorship activities. We would like to thank Drs. Raywat Deonandan and Karen Phillips for their feedback during various phases of this project and Dr. Sheila Dunn for providing us with her survey instrument. We are also grateful to the team of volunteers for their efforts. The conclusions and opinions expressed in this article are those of the authors and do not necessarily represent the views of the organizations with which the authors are affiliated or the funders.

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Personal Goals of Women Recently Diagnosed with Breast Cancer: Protocol for a Cohort Study

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ABSTRACT

Objectives: This study aims to identify the personal goals of women with breast cancer, to describe the characteristics of participants' personal goals over four months, and to identify barriers and facilitators to their pursuit.

Methods: This protocol outlines plans to conduct a prospective cohort study. We will recruit women participating in the Ottawa Integrative Cancer Centre's Head Start program (an integrative oncology psychoeducational program in Ottawa, Canada), and those on the program's waiting list if possible. We anticipate a sample size of approximately 18 to 36 women. Prior to the beginning of Head Start, participants will identify their current personal goals and rate them on various dimensions on a questionnaire. At one and three months, participants will re-assess their goals and their goal pursuit. In a one-on-one interview at three months, they will identify barriers and facilitators to the pursuit of their goals. We will analyze quantitative data using descriptive and inferential statistics, and qualitative data using thematic content analysis.

Conclusion: Findings from this study will identify important information about the personal goals of women recently diagnosed with breast cancer that can help to support the process of positive goal adjustment and enhance support to these women.

RÉSUMÉ

Objectifs : Cette étude vise à identifier les objectifs personnels des femmes atteintes d'un cancer du sein, à décrire les caractéristiques des objectifs personnels des participantes sur une période de quatre mois, et à identifier les obstacles et les facilitateurs à leur poursuite.

Méthodes : Ce protocole décrit les plans pour mener une étude de cohorte prospective. Nous recruterons des femmes qui participeront au programme Head Start du Centre de cancérologie intégrative d'Ottawa (un programme psychopédagogique intégratif en oncologie à Ottawa, au Canada) et celles qui sont sur la liste d'attente du programme, si possible. Nous prévoyons un échantillon d'environ 18 à 36 femmes. Avant le début de Head Start, les participantes identifieront leurs objectifs personnels actuels et les noteront sur différentes dimensions dans un questionnaire. À un et trois mois, les participantes réévalueront leurs objectifs et la poursuite de leur objectif. Dans une entrevue individuelle à trois mois, elles identifieront les obstacles et les facilitateurs à la poursuite de leurs objectifs. Nous analyserons les données quantitatives à l'aide de statistiques descriptives et inférentielles, et les données qualitatives à l'aide d'analyses de contenu thématiques.

Conclusion : Les résultats de cette étude permettront d'identifier des informations importantes sur les objectifs personnels des femmes récemment diagnostiquées avec un cancer du sein qui peuvent aider à soutenir le processus d'ajustement positif des objectifs et améliorer le soutien à ces femmes.

Everyday life is characterized by the pursuit of multiple personal goals, such as learning to salsa dance or spending more time with family, which together describe important expressions of life motivations [1]. A personal goal is an individual's cognitive expression of a desired state or process which provides directional motivation towards that state; it defines what individuals do and strive for in everyday life [2,3]. Goals may be described at various levels of aggregation [2]. For example, personal strivings are mid-level goals, which often become the inputs of higher-order goals and life meaning [2,4]. Trying to always say hello to the coffee shop clerk facilitates the higher-order goal of being a good person. Personal projects, a closely related term, are also mid-level, individually defined, characterized by action and shaped by an individual's environment [5-7]. For consistency, we use the term personal goals in the sense of personal projects and personal strivings. Goal-setting theory suggests that conscious goal-setting and motivation is important in determining individual

Keywords: Breast cancer; Personal goals; Goal pursuit; Integrative oncology; Observational study

performance and satisfaction [8]. Diagnosis with a serious illness such as cancer, however, can affect an individual's day-to-day physical resources and time, thus disrupting the pursuit of personal goals [9-11]. Among women with breast cancer, a higher burden of physical symptoms has been associated with a reduced ability to pursue goals, and higher psychological distress [12]. Reducing physical symptoms or distress are common reasons that women with breast cancer seek complementary therapy [13]. Over the past decade, an approach known as integrative oncology, which integrates evidence-based complementary therapies and medical treatment and emphasizes patient-centered care and coordination between providers, has emerged [14]. The Ottawa Integrative Cancer Centre (OICC) practices integrative oncological care, treatment, and research. With community support, the OICC developed and operates the Head Start program, to address the distress expressed by many of their clients recently diagnosed with breast cancer. Funded by Babes4Breasts and free of charge to participants, Head Start offers education, resources, and skills to improve women's knowledge of integrative care options, reduce fear and anxiety, and strengthen their ability to cope with their diagnosis and incorporate life changes associated with living well with cancer.

A study of personal goals, which are expressions of life motivations, among women with breast cancer aligns with integrative oncology's focus on patient-centered care. In our literature search, we identified one published study of personal goals in integrative oncology [15]. Participants in an integrative oncology program in Vancouver, B.C. were asked to identify personal goals related to program participation. The personal goals identified highlighted important motivations related to breast cancer: improved well-being, increased chance of remission, increased physical energy, more effective pain management, and a return to active living [15]. But to design effective interventions that help women with breast cancer set and successfully pursue their goals, we first need to understand whether this population is able to pursue their goals and what factors may facilitate or obstruct that pursuit. In partnership with the OICC, we plan to examine the personal goals of women participating in Head Start in-depth. Our primary objective is to identify the perceived barriers to and facilitators of goal pursuit, including those related to Head Start. The secondary objectives are to describe the characteristics of participants' personal goals (goal content and dimensions) over time and to analyze whether women pursue their most important goals. Goal dimensions are factors which express how women think or feel about their goals (e.g., difficulty, control) [2]. They can be associated with important outcomes: higher goal importance may be associated with better psychological outcomes among people living with cancer, and higher goal stress with worse depressive mood and worse subjective health [10,16]. Towards their program objectives, Head Start works with women on mindfulness, awareness of emotions, identifying social supports, and use of coping mechanisms. Based on the aims and activities of Head Start, we hypothesize that there will be an increase in ratings of self-identity, perceived autonomy, and perceived support from others. In addition, we hypothesize a decrease in feelings of being scared and stressed over time among Head Start participants that will be greater than changes observed within the control group.

By publishing this study protocol, we provide transparency in our study plans and processes. It also enables external assessment of any changes between the protocol and the final study report, guarding against selective outcome reporting and other methodological changes influenced by study data. Finally, it strengthens the protocol by submitting it to the rigor of a peer-review process.

METHODS

Study design

This will be a prospective, observational cohort study of women participating in the OICC's Head Start program and, if available, controls taken from the program's waiting list ("wait-list controls").

Participants and procedures

Eligible individuals must be: either enrolled in one of two upcoming Head Start rounds (May and September 2017), or placed on a waiting list for either of these rounds; aged 18 years or older; female; and experiencing their first cancer diagnosis. They must also have good English comprehension and received a breast cancer diagnosis no more than five months prior to the start of the Head Start round for which they are enrolled or on the waiting list. Participants who are unable to provide informed consent will be excluded.

Recruitment will take place in the eight weeks prior to the first day of each Head Start round. Each Head Start round will last approximately five weeks. For each round, data will be collected at three time points: approximately one to fourteen days pri-

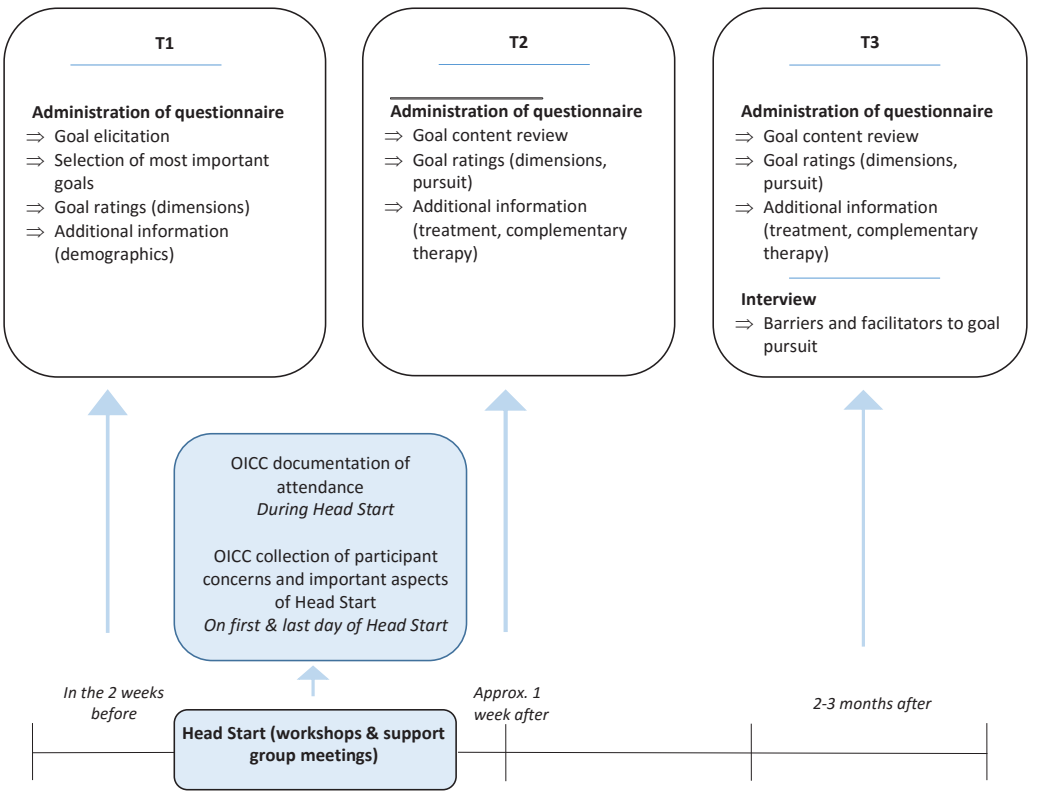

Figure 1. Illustration of study procedures. Illustration of study activities and timelines.

or to Head Start (T1 - baseline), approximately one week after Head Start ends (T2), and approximately two to three months after Head Start ends (T3). Study procedures are illustrated in Figure 1.

Ethics approval was obtained from the Research Ethics Boards of the Ottawa Hospital Science Network (OHSN-REB) and the Canadian College of Naturopathic Medicine. Participants will provide written informed consent consistent with the OHSN-REB's guidelines before taking part in the study.

Recruitment

The OICC will conduct recruitment. Following OICC standard procedure, interested individuals will be assessed for eligibility for Head Start. Eligible women will enroll or be placed on a waiting list if maximum enrollment has been reached. If a woman also meets this study's eligibility criteria, the OICC will inform her of the study. Interested individuals will receive a letter of introduction about the study and the consent form. Study enrollment and consent will be conducted by the primary investigator (i.e. the first author). Recruitment started in May 2017.

Sample size

The anticipated sample size will be 18 to 36, but will depend on the number of women interested in participating in selected Head Start rounds and the availability of a control cohort. This study is primarily concerned with examining the goals of Head Start participants, the "exposed" group. A control cohort will be included only if the following criteria can be met. If maximum enrollment (12 women) in each Head Start round is reached, the OICC places additional eligible individuals on a waiting list. If a minimum of 12 women on the waiting list enroll in this study, a control cohort will be formed. Based on our expectation of the Head Start enrollment process, the "exposed" group will have a maximum of 24 individuals (2 rounds of 12 individuals).

Table 1. Data sources and measurement. Presentation of sources and measurements of data for each variable of interest.

Variable of interest	Source of data	Method of measurement
Participation in Head Start	Head Start attendance records	Yes/no. For "yes", number of workshop days and number of support group meetings attended will be counted
Barriers and facilitators to goal pursuit, including Head Start factors, cancer-related symptoms, treatment factors, and complementary therapy factors	Participants, Head Start client records	Semi-structured, face-to-face interviews (participants); MYCAW data on important treatment aspects (Head Start client records)
Personal goal elicitation	Participants	PPA-based goal elicitation
Personal goal pursuit ratings	Participants	Ratings on a 5-point scale
Personal goal dimensions of: challenge, likelihood of success, autonomy, intention attention, support, time adequacy, self-identity, hopeful, scared, sad, happy, and stressed	Participants	PPA-based goal ratings on a 11-point scale
Demographic variables	Participants	Participant assessment. Categorical: current living situation, highest education level completed, household income (annual, Canadian dollars), breast cancer stage. Continuous: age (years), time since diagnosis (days)
Conventional cancer treatment	Participants	Participant assessment of whether treatment is currently received (y/n)
Complementary therapy	Participants	Participant assessment of whether therapy is currently received (y/n)

MYCAW: Measure Yourself Concerns and Well-Being questionnaire; PPA: Personal Projects Analysis

DATA ELEMENTS AND INSTRUMENTS

Data sources and assessment methods are summarized in Table 1. We will invite participants to complete paper-based questionnaires at T1, T2 and T3 (15 to 25 minutes to complete each). At T3, following completion of the questionnaire, participants will participate in a face-to-face, one-on-one interview (approximately 45 minutes). Interviews will be audio-recorded with participant consent.

Head Start participation

The exposure is Head Start participation: enrollment and attendance in a pre-specified Head Start round (yes/no). Non-participants will be on the waiting list to participate in Head Start, thus forming the wait-list control group for this study. If a spot becomes available in Head Start prior to the first day of the round and a wait-list control becomes a participant in Head

Start, she will be included in the "exposed" cohort rather than the control group. Crossover is not possible after the program starts. We will count the days of Head Start participation in the exposed group using OICC attendance records linked to study records.

Personal goals

To identify personal goals, we will use the Personal Projects Analysis (PPA), a well-established methodological approach developed by Dr. Brian Little for collecting data on personal goals [5]. Personal goals are identified by the participant using his or her own phrasing, but goal dimensions are scored by standard means, allowing for comparison across participants [5]. The PPA allows for the assessment of multiple goals simultaneously and has been used to assess personal goals among a range of populations including people with cancer and people experiencing illness [6,9,17-19]. Consistent with the PPA, at T1, we will ask participants to list up to twelve personal goals, in their own words, over the next three to four months. Participants will then be asked to choose up to six goals among the twelve that are most important to them. At T2, participants will be shown their lists of six important goals from T1 and asked to annotate any changes they wish to make. They may remove or modify existing goals, add new ones, or leave the list as is. This process will be repeated at T3 with a review of the goals identified at T2.

Personal goal dimensions

Goal dimensions are "constructs on which goals vary" [2, p.340]. We will examine both cognitive and emotional dimensions—how people think and feel about their goals. Following selection of the six most important goals at T1, participants will rate each of their six goals (scale of 0 to 10) in various dimensions consistent with the PPA (challenge, likelihood of success, autonomy, intention, attention, support, time adequacy, self-identity, hopeful, happy, sad, scared, stressed) [5,20,21]. This process will be repeated at T2 and T3, following goal content review. Participants will rate any new or modified goals identified at T2 as well, but will not rate any goals removed from the list at T2. This process will be repeated at T3 with a review of the goals identified at T2.

Personal goal pursuit

Goal pursuit is defined as actions taken to strive towards goals [2,22]. At T2, participants will assess their pursuit of each of the six important goals identified at T1 (including those removed at T2) by assigning a score on a five-point scale (1 'not at all' to 5 'as much as I could') to the question, "How much did you feel you pursued this project?". At T3, participants will repeat this process for the goals assessed at T2, along with any new goals identified at T2.

Barriers and facilitators of personal goal pursuit

Participants will identify barriers and facilitators during face-to-face interviews at T3. Questions will be open-ended, but participants will also be asked specifically about the role, if any, of Head Start aspects, cancer-related symptoms, cancer treatment, and complementary therapies as barriers or facilitators to goal pursuit.

Additional variables

At T1, we will collect demographic data on: current living situation, highest education level completed, household income, breast cancer stage, age (years, measured at Head Start round start date), and time since diagnosis (days, measured to Head Start round start date). At T2 and T3, we will collect data on whether participants are currently receiving medical treatment for breast cancer, and whether participants are currently receiving complementary therapy (yes/no).

Data on important Head Start program elements will be collected from exposed participants only, using the Measure Yourself Concerns and Well-Being (MYCAW) questionnaire [23]. MYCAW was developed for use by cancer care services including complementary therapy centres to capture outcomes that are important to cancer patients. On the last day of Head Start (approximately one week before T2), the OICC will administer the MYCAW to participants. The MYCAW asks, "Reflecting on your time with the Head Start program, what were the most important aspects for you?" This data will be provided by the OICC to the investigator, with participant consent.

PROTOCOL AMENDMENTS

This protocol reflects amendments that were implemented after completion of the first version of the protocol (November 14, 2016), but prior to participant recruitment and data collection. Due to a delay in starting the study, we replaced an original plan to conduct feasibility testing with more intensive data collection tool development and will recruit participants from two rounds of Head Start instead of three. Protocol amendments are presented in Supplementary File 5.

DATA ANALYSIS

Qualitative analyses

Barriers and facilitators to goal pursuit will be analyzed using inductive content analysis following Braun and Clarke's process guidelines [24]. Important aspects of Head Start from the MYCAW will be analyzed using the same thematic approach.
Goal content will be categorized by: (a) directional motivation (attain, maintain, or avoid); and (b) by themes using directed content analysis [25-27]. Preliminary thematic categories based on life domains suggested by Little will guide analysis, but final categories will be identified in an iterative process as data is analyzed [5].

Quantitative analysis

For the additional variables, we will calculate proportions (%) for categorical variables. For continuous variables, mean and standard deviation (SD), or median and range if data is non-normally distributed, will be used. We will use t-tests and chi-square tests to compare continuous and categorical data, respectively, between study groups (if a control group is formed), with 5% significance. If there are small cell counts, we will use an appropriate non-parametric test, such as the Wilcoxon Rank Sum Test, instead.

We will calculate descriptive statistics on personal goals, each goal dimension, and goal pursuit scores (number and mean/SD or median/range, as appropriate), and on goal content (number and proportion of goals in each thematic category) within groups at each study timepoint. To analyze how personal goals change during the study, we will calculate the mean/SD (or median/range as appropriate) of the number of goals added, removed, and modified at T2 and at T3. We will use T-tests with 5% significance to compare the goal pursuit scores between groups (if a control group is formed).

Sub-group analyses

As this study is exploratory, we will conduct several descriptive sub-analyses to explore possible relationships with goal pursuit. We will calculate mean/SD (or median/range as appropriate) goal pursuit scores for: (a) those undergoing cancer treatment and those who are not at T2 and T3; (b) those receiving complementary therapy and those who are not at T2 and T3; (c) each goal content category; and (d) each goal dimension.

Missing data

The investigator will be nearby during questionnaire completion to answer any questions that may otherwise lead to missing data. We will report the number of missing values for each variable of interest, the reasons for missing values (if known), and the number of missing data for each analysis. We will restrict quantitative analysis to individuals with complete data on variables required for a particular analysis.

Loss to follow up

Dropout may be influenced in some way by cancer (i.e., lack of time due to treatment, or lack of physical capacity due to symptoms), or be related to the exposure, as wait-list controls may feel less support to continue with the study. This study has been designed with a short timeframe to minimize loss to follow-up. Non-responsive participants will be contacted twice before being considered lost to the study.

At study end, we will assess the balance of dropout rates between groups. The analysis will include data collected before participants are lost to follow up. We will report the number of participants lost to follow-up. If differential dropout occurs between T1 and T2, and there are fewer than 12 control group members with data, we will focus on analysis within the exposed group only. If differential dropout occurs between T2 and T3, we will compare groups on goal pursuit at T2, but not at T3.

DISCUSSION

We have a unique opportunity to examine personal goals among women with breast cancer within five months of diagnosis, a critical time psychologically. Following a breast cancer diagnosis, anxiety, depressive symptoms, and emotional distress are common [28-31]. Weisman and Worden found that distress is highest two months into treatment [29].

We anticipate that study results will contribute new knowledge about the personal goal pursuits of women with breast cancer seeking integrative oncology care and the factors that facilitate or obstruct their goal pursuit. Recent studies suggest that people living with cancer adapt their personal goals as they adjust to treatment and survivorship, but the adaptation may be positive or negative. People living with cancer have demonstrated use of a range of strategies to adjust their goals, including aborting a goal and engaging in a new one and aborting a goal without engaging in a new one [9,32,33]. In a 2015 study, a minority of women, following their breast cancer surgery, coped with disruptions in their personal goal pursuit by not taking any actions to overcome goal interference; this response was associated with in-

creased perception of goal unattainability over six months [34]. But positive goal adjustment may have important psychological effects in a cancer context: the ability to disengage from unattainable goals and engage in different goals is positively associated with well-being [35,36]. Understanding more about goal pursuit can inform interventions aiming to support the process of positive goal adjustment.

Our study limitations include a risk of attrition bias, where wait-list controls (if used) may be more likely to drop out than Head Start participants, as discussed. People who face more barriers to goal pursuit (for example, those are heavily affected physically or emotionally by their cancer diagnosis) may also face barriers to study participation, presenting a risk of response bias. The primary data elements will be collected via qualitative interviews and analyzed by a single unblinded researcher. To reduce the possibility of interviewer bias, we will use an interview guide, and interview questions have been reviewed for possible introduction of bias. The researcher will review every interview transcript for possible introduction of bias and adjust questions as needed to reduce bias. Other authors will also periodically review interview transcripts.

CONCLUSION

We anticipate that study findings will identify important information about the personal goals of women recently diagnosed with breast cancer. This information can inform the development of activities to support goal setting and pursuit in Head Start and other integrative oncology programs to enhance support to women recently diagnosed with breast cancer.

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The Effects of Multiple Sclerosis and Disease Modifying Therapy on Pregnancy

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ABSTRACT

Multiple sclerosis (MS) is the most common inflammatory condition of the central nervous system. Disease modifying therapy (DMT) aims to reduce relapse rates and decrease the quantity of lesions in the brain and spinal cord. Since MS is more prevalent in women than men, it is important to be aware of the interplay between MS and pregnancy. As MS can engender sexual dysfunction, primarily in the form of decreased desire and fatigue, it thereby affects conception. Hormonal differences between women with MS compared to women without MS include an increase in follicle-stimulating hormone and luteinizing hormone, and a decrease in testosterone. While fluctuations in estrogen result in a reduction in MS relapse rates during pregnancy, a subsequent increase in the post-partum period is observed. The mechanism of action and side effects of DMTs are described in this paper, including interferon, glatiramer acetate, and some newer medications. Although there are no recommended guidelines on the use of DMTs during pregnancy, it is generally agreed upon to cease their use prior to conception if possible, and the decision to continue a DMT should take into account the benefits to the mother and the risks to the fetus. Comprehending the mechanisms of action and teratogenicity indices of DMTs is crucial in understanding their effects on MS during pregnancy, which is an important aspect of providing health care to women with this condition.

RÉSUMÉ

La sclérose en plaques (SP) est l'affection inflammatoire du système nerveux central la plus commune. Le traitement modificateur de la maladie (DMT, de l'anglais) vise à réduire les taux de poussées et à diminuer le nombre de lésions au cerveau et à la moelle épinière. Comme la SP est plus prévalente chez les femmes que chez les hommes, il est important de reconnaître l'interaction entre la SP et la grossesse. Puisque la SP peut engendrer une dysfonction sexuelle, principalement en raison d'une diminution du désir sexuel et de la fatigue, elle affecte la conception. Les différences hormonales entre les femmes avec la SP et les femmes sans la SP incluent une hausse de l'hormone folliculostimulante et de l'hormone lutéinisante, et une baisse de testostérone. Bien que les fluctuations en œstrogènes entraînent en une réduction des taux de poussées de la SP durant la grossesse, leur augmentation subséquente lors de la période postpartum est observée. Le mécanisme d'action et les effets secondaires des DMTs sont décrits dans cet article, incluant l'interféron, l'acétate de glatiramère, et certains autres nouveaux médicaments. Quoiqu'il n'existe pas de lignes directrices sur l'utilisation des DMTs lors de la grossesse, il est généralement accepté qu'il faut cesser leur utilisation avant la conception si possible, et que la décision de continuer la prise d'un DMT devrait tenir compte des avantages pour la mère et des risques pour le fœtus. La compréhension des mécanismes d'action et des effets tératogènes des DMTs est essentielle pour apprécier leurs effets sur la SP durant la grossesse, ce qui constitue un aspect important dans la prestation des soins de santé aux femmes vivant avec cette maladie.

Multiple sclerosis (MS) is a common inflammatory disorder of the central nervous system (CNS) in which the myelin sheath is targeted and subsequently degraded. In MS, disease modifying therapies (DMT) aim to decrease the relapse rates and decrease the number of lesions in the brain and spinal cord. Several different types of DMTs exist with distinct properties and mechanisms of action. This is beneficial because the clinical course of MS varies from individual to individual, and so treatment must be tailored to each individual's unique disease.

Since the proportion of women with MS is larger than that of men, the concept of managing MS with DMT while also taking into account pregnancy and fertility issues constitutes an important discussion. DMT may be useful for treating MS, but it can have negative effects on a woman if she is pregnant, trying

Keywords: Multiple Sclerosis; Pregnancy; Disease Modifying Therapy; Teratogenicity; Breastfeeding

to become pregnant, or has an unplanned pregnancy while on DMT.

EFFECT OF MS ON PREGNANCY

Sexual Dysfunction

The ability of a woman with MS to become pregnant is affected by her sexual function and desire. Sexual problems in MS patients have been organized into three categories: primary, secondary, and tertiary [1,2]. Primary problems refer to the direct neurological effect that MS has on the patient, including decreased sexual sensation, desire, and vaginal lubrication, as well as autonomic dysregulation and difficulties achieving orgasm [1,2]. Secondary problems refer to the physical changes producing an indirect effect on the patient, including fatigue and muscle weakness [1,2]. Tertiary problems refer to the indirect effect on the patient through emotional, social, and psychological mechanisms, including decreases in confidence and body image, increases in guilt and worry, changes in levels of perceived sexual attractiveness, and depression [1,2]. Although all levels of sexual problems negatively impact quality of life, secondary sexual problems have been found to have the largest influence on sexual dysfunction [3].

Several studies have informed our current understanding of the influencing factors and consequences of sexual dysfunction in women living with MS [1-5]. In 2006, a survey of 4,267 patients with MS living in the United States found that perception of body image worsened if the patient was less educated, female, had a longer disease duration, and a greater degree of disability [4]. Another study found that the number of sexual encounters per week was lower in women with MS compared to the general population [5]. These findings suggest that predictors of sexual dysfunction in women with MS are diverse and multifactorial.

The rate of sexual dysfunction is higher in women with MS than in the general population [6]. A study in Poland interviewed 137 women with MS to assess the women's neurological function [7]. It was found that 82.5% of patients suffered from at least one sexual problem, the most common complaints being decreased desire, arousal dysfunction, and orgasmic dysfunction [7]. In fact, another study has shown that sexual dysfunction has a larger negative effect on mental health than the severity of physical disability due to MS [8]. This detrimental impact on mental health is a concern to women who are, or who plan to become pregnant, as stress and depression can negatively influence a pregnancy and have adverse effects on the fetus.

Hormonal Effects

Endocrinological studies have shown differences in the levels of sex hormones and the gonadotropins that regulate their production between women with MS compared to women of the general population [9]. Significantly higher levels of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) have been recorded, as well as significantly lower levels of estrogen in the early follicular phase of the menstrual cycle [10,11]. This can have an adverse effect, as high FSH levels in the early follicular phase are correlated with a condition of low fertility known as impaired ovarian reserve [10,11].

It has also been recorded that levels of testosterone in women with MS are significantly lower than in women without MS during the follicular and luteal phase [12]. Testosterone plays an important role in the repair of brain lesions and has protective effects against the autoimmune effects of MS [12]. The relationship between testosterone and severity of MS in women is seen in MRI studies, which show an inverse relationship between testosterone levels and the severity of brain lesions [13]. Based on this data, testosterone can be correlated with neuroprotective functions. In addition, an experimental study conducted in Iran in 2010 demonstrated that resistance training in women with MS helps to increase levels of testosterone while simultaneously decreasing cortisol levels, suggesting that exercise is beneficial in multiple ways for women with MS [14].

Effect of Pregnancy on MS

The rate of relapse in women with MS decreases significantly during pregnancy, but subsequently increases in the post-partum period. This is thought to be due to circulating hormone levels. In moderate concentrations, estrogens play a role in cell-mediated immunity, but in high concentrations, such as in pregnancy, estrogens have an anti-inflammatory role [15]. The protective effect that estrogens have on MS during pregnancy is currently being researched as a new treatment route. A pilot study showed a decreased number of enhancing lesions on MRI in women who were taking 8mg of estradiol per day compared to a pre-treatment baseline [16]. Other hormones, such as progesterone, are also being investigated as potential treatments for MS. One study examined the effect of progesterone on experimental autoimmune encephalomyelitis, which is the animal model of MS [17,18]. In this study, mice were given either a progesterone implant or a placebo treatment, and it was

Table 1. Common disease modifying therapies used for patients with multiple sclerosis.

Generic Name	Brand Name	Mechanism of Action	Washout Period (months)	Placental Transfer?	Use in breast-feeding?
Interferon beta	Betaseron®	Modulates the body's immune response through an unknown mechanism [9]	0-1 [23]	Unlikely [23]	Avoid [9]
Glatiramer Acetate	Copaxone®	Activates regulatory T suppressor cells specific for the myelin antigen [9]	0-1 [23]	Unlikely [23]	Avoid [9]
Fingolimod	Gilenya®	Prevents release of lymphocytes from lymph nodes [9]	2 [23]	Crosses [9,23]	Avoid [9,23,31]
Natalizumab	Tysabri®	Inhibits the migration of leukocytes in the CNS by binding against integrin [9]	1-3 [23]	Crosses [9,23]	Avoid [9,23,31]
Mitoxantrone		Inhibits cell synthesis by intercalating DNA and by binding to DNA topoisomerase II to prevent replication of nucleic acids [9]	6 [23]	Unknown, but likely [9,23]	Avoid [23,31]
Dimethyl Fumarate	Tecfidera®	Demonstrates anti-inflammatory and cytoprotective properties through an unknown mechanism [9]	0-1 [23]	Crosses [9]	Avoid [9, 23]
Alemtuzumab	Lemtrada®	Binds an antigen on T cells, natural killer cells, and monocytes, inducing their lysis [9]	3-4 [9,23]	Crosses [9,23]	Avoid [9,23]

found that progesterone reduced disease severity [17,18].

EFFECT OF DMT ON PREGNANCY

A summary of the DMTs described in this article is outlined in Table 1.

Interferon (IFN)

Interferons (IFNs) are endogenous cytokines that modulate the body's immune response. Administration of IFNs or their analogues is a prevalent therapeutic modality in MS, though their effects on fertility and pregnancy are not fully understood [19]. In clinical trials comparing IFN therapy to placebo, IFN did not affect the rate of conception nor the rate of spontaneous abortion [20, 21]. However, IFN exposure was associated with a significantly lower birth weight and preterm birth [22]. The degree and significance of IFN transfer through breast milk has not been established, but it is suggested that IFN be avoided during breast-feeding [23].

Glatiramer Acetate (GA)

GA (trade name Copaxone®) is a mixture of several four amino acid oligomers found in the myelin basic protein (MBP) sequence. It is thought to activate regulatory T-cells that recognize the myelin basic protein antigen. Similar to IFN, GA does not seem to affect the rate of conception nor the rate of spontaneous abortion when compared to women without MS, and no major concerns have been reported when GA has been used in pregnancy [22]. Women who have used GA during breast-feeding report no adverse effects, although it is still recommended to abstain from GA during lactation [24].

Fingolimod

Fingolimod (trade name Gilenya®) acts to reduce the number of lymphocytes present in the central nervous system by preventing their release from lymph nodes. Rat experiments have shown no effect on female fertility upon administration of fingolimod, but they exerted teratogenic effects, the most common being congenital heart defects [9]. The rate of spontaneous abortion in women using fingolimod is higher than that of the general population [25]. Fingolimod has been confirmed to be excreted in breast-milk in rats, and is not recommended during lactation [25].

Natalizumab

Natalizumab (trade name Tysabri®) is a monoclonal antibody against a subunit of the integrin molecule, thereby limiting the migration of leukocytes in the CNS. Although there are no studies of the effects of natalizumab on the fertility of humans, trials in guinea pigs have shown that high doses of natalizumab decrease fertility in females [26]. Reduced fetal survival and significant hematological effects have been seen in animal studies, as well as in children whose mothers took natalizumab in the third trimester of pregnancy [9,27]. Additionally, it has been well established that natalizumab is excreted into breast milk, and is therefore not recommended during lactation [23, 27].

Mitoxantrone

Mitoxantrone inhibits cell synthesis by intercalating between DNA bases and by binding to DNA topoisomerase II to prevent the replication of nucleic acids. The use of mitoxantrone in women has been linked to amenorrhea and a reduced ovarian reserve in multiple studies [9,28]. Furthermore, mitoxantrone has been associated with fetal growth retardation in rats, and has an increased rate of premature delivery in rabbits [9]. Although clinical trials have not been conducted in humans due to the overwhelming contraindications in animal studies, case studies have been reported where women have used mitoxantrone while pregnant. In one case, the use of mitoxantrone until 29 weeks gestation was associated with reduced fetal growth [29]. Due to the negative consequences of mitoxantrone in pregnancy, and due to its excretion into breast milk, its use is contraindicated in pregnancy [29].

Dimethyl Fumarate (DMF)

In MS, the mechanism of action of DMF (trade name Tecfidera®) is not fully understood, but it is believed to have anti-inflammatory and cytoprotective properties. Studies in animals have not demonstrated a decrease in fertility with the use of DMF, but reproductive toxicity has been recorded [9]. Giving DMF to pregnant rats and rabbits during organogenesis resulted in maternal adverse effects and a low fetal weight; but in humans, DMF has not been shown to increase the risk of fetal malformations or the risk of spontaneous abortion [30]. It is currently unknown whether DMF is excreted into breast milk, and it is therefore suggested to refrain from its use during lactation [31].

Alemtuzumab

Alemtuzumab (trade name Lemtrada®) is a humanized monoclonal antibody that reduces the number of CD52 containing T-cells, natural killer cells, and monocytes. Female mice who received alemtuzumab subsequently had decreased fertility and an increase in fetal mortality [9]. Alemtuzumab is also concern-

ing because it can cause thyroid issues, which are especially a hazard in pregnant women, as hypothyroidism increases the rate of miscarriages and fetal malformations [9]. Therefore, the recommended washout period before conception is 3-4 months [23]. Excretion into the breast milk of mice has been reported, and although no information is available regarding excretion into human breast milk, it is advised to avoid alemtuzumab during lactation [23].

CURRENT GUIDELINES

Currently, there are no approved guidelines regarding DMT in pregnant women with MS. However, there are some generalized points that can be made. For each DMT, there is a minimum amount of time that the woman should be off the drug prior to conception [27, 31]. This is called a wash-out period, and the wash-out periods for each drug are outlined in Table 1. Management of MS in the context of a pregnancy must take into consideration the benefits of the DMT to the mother, while keeping in mind the risks to the fetus. If the mother is able to cease her DMT without significant side effects, it is advisable to do so [27,31]. However, if the woman's symptoms are very severe, it may be necessary to continue the DMT during the pregnancy [27,31].

The decision to continue a DMT during a pregnancy should take into account the severity of the disease, the benefits and risks of the DMT, and should entail multiple detailed discussions between the patient and the healthcare provider. However, due to the wide spectrum of disease activity and disease severity among women, there are unfortunately no accepted guidelines on the use of DMT in pregnant women with MS.

CONCLUSION

MS is a complex disease that exerts many effects upon a pregnancy, including sexual dysfunction and hormonal variations. In addition, pregnancy can influence the course of MS in a woman, including reducing the relapse rate intrapartum, and increasing the rate post-partum. Treatment for MS consists of DMT, of which seven different types have been briefly outlined. Although there are no accepted guidelines for the use of DMT in pregnancy, it is advisable to cease the use of DMT prior to conception if at all possible. Understanding the mechanisms of action and teratogenicity profiles of DMTs is important in understanding their effects on MS during pregnancy, which is a crucial aspect of providing health care to women with multiple sclerosis.

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Genito-Pelvic Pain/Penetration Disorder (GPPPD): An Overview of Current Terminology, Etiology, and Treatment

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ABSTRACT

Genito-Pelvic Pain/Penetration Disorder (GPPPD) is a relatively new diagnostic category of female sexual dysfunction, which was introduced during the release of the DSM-5 in 2013. GPPPD reflects the combination of two previous categories of female sexual dysfunction, dyspareunia and vaginismus, into one entity. As such, there is confusion surrounding the proper terminology and diagnostic criteria used when evaluating female sexual or genital pain. This review article attempts to clarify the terminologies used within the medical and scientific community, and provides an overview of current views on etiology and treatment. The likely biological antecedents to genital pain are an exaggerated and prolonged inflammatory response in the vestibular mucosa causing neuroproliferation, and leading to eventual hyperalgesia, allodynia, and pelvic muscle tension in the genital region. These processes interact with psychosocial factors to produce chronic pain. Treatment includes education, CBT, pelvic floor physiotherapy, medical interventions, and surgical interventions, though sexual function may be optimized through a multifaceted approach.

RÉSUMÉ

La Genito-Pelvic Pain/Penetration Disorder (GPPPD) est une catégorie diagnostique relativement récente de la dysfonction sexuelle féminine, qui a été introduite dans le DSM-5 en 2013. La GPPPD reflète la combinaison de deux catégories précédentes de dysfonctionnement sexuel féminin, la dyspareunie et le vaginisme, en une entité. En tant que tel, il existe une confusion entourant la terminologie appropriée et les critères de diagnostique utilisés lors de l'évaluation de la douleur sexuelle ou génitale féminine. Cet article de revue tente de clarifier les terminologies utilisées dans la communauté médicale et scientifique et donne un aperçu des points de vue actuels sur l'étiologie et le traitement. Les antécédents biologiques probables à la douleur génitale sont une réponse inflammatoire exagérée et prolongée dans la muqueuse vestibulaire entraînant une neuroprolifération, et conduisant à une éventuelle hyperalgésie, allodynie et tension musculaire pelvienne dans la région génitale. Ces processus interagissent avec des facteurs psychosociaux pour produire une douleur chronique. Le traitement comprend l'éducation, la TCC, la physiothérapie du plancher pelvien, les interventions médicales et les interventions chirurgicales, bien que la fonction sexuelle puisse être optimisée par une approche multidimensionnelle.

For several years researchers and clinicians have struggled with how to best categorize the various forms of female sexual pain, due in large part to significant overlap in symptomatology and treatment [1]. In 2013, a new diagnostic category of sexual dysfunction was established in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), known as Genito-Pelvic Pain/Penetration Disorder, or GPPPD. This disorder encompasses two previously separate disorders, dyspareunia and vaginismus, into one single diagnostic category defined according to the DSM-5 by persistent or recurrent difficulties in the following criteria:

- Vaginal penetration during intercourse;
- Marked vulvovaginal or pelvic pain during vaginal intercourse or penetration attempts;
- Marked fear or anxiety about vulvovaginal or pelvic pain in anticipation of, during, or as a result of vaginal penetration; and
- Marked tensing or tightening of the pelvic floor muscles during attempted vaginal penetration [2].

Any one of the above criteria must be met for a diagnosis of GPPPD, with at least six months duration and the presence of clinically significant distress. The dysfunction may be lifelong (since the individual became sexually active) or acquired, and is classified as mild, moderate, or severe depending on the extent

Keywords: Sexual Pain; Genito-Pelvic Pain/Penetration Disorder; Dyspareunia; Vaginismus; Vulvodynia; Provoked Vestibulodynia; Sexual Dysfunction

of functional impairment [2,3]. While persons with GPPPD may have a broad range of clinical presentations, the defining feature of the disorder is pain or fear of pain upon sexual genital contact or vaginal penetration. Penetration may refer to entry of a penis, but it can also refer to any other object, making tampon insertion or gynecological exams difficult or impossible [2,3].

In contrast, vulvodynia is a closely related and overlapping term used to describe chronic pain in the vulvar region of at least 3 months duration. It may be generalized or localized to a specific area, and provoked by contact or unprovoked (i.e., spontaneous) [4,5]. Vulvodynia is often associated with GPPPD and sexual pain, though not all cases of GPPPD are necessarily caused by vulvodynia [3]. Vulvodynia is not itself classified as a sexual dysfunction, but is a term used to describe a type of chronic genital pain that is present with or without sexual contact [5]. Table 1 summarizes correct terminology between the two conditions.

There are two main subtypes of vulvodynia: provoked vestibulodynia (PVD), characterized by localized provoked pain at the vaginal vestibule (introitus), and generalized vulvodynia (GVD) characterized by unprovoked, diffuse burning pain throughout the entire vulva [4,5]. PVD is thought to be the most common cause of introital dyspareunia, affecting up to 8% of reproductive age women [6,7]. Recent estimates suggest that 17-19% of American women experience coital pain, though epidemiological data can be difficult to interpret as many women may not discuss these symptoms with their physicians due to fear of embarrassment or stigmatization [3,8].

While dyspareunia and vaginismus were both previously classified as sexual pain disorders in the DSM-IV, they were differentiated by their main clinical features. Dyspareunia was characterized primarily by genital pain during intercourse/penetration, which could be either introital (at the vaginal entrance), deep (deep in the vagina or pelvis), or both [3]. In contrast, vaginismus was characterized by involuntary vaginal muscle spasms which were strong enough to interfere with or prevent intercourse/penetration [3,9].

In clinical practice, however, the disorders were often comorbid or "difficult or nearly impossible" to differentiate: the expectation or fear of genital pain in dyspareunia, for example, may cause involuntary pelvic muscle contraction making intercourse difficult, just as involuntary pelvic muscle contraction in vaginismus may cause genital pain if penetration is attempted [9,10]. Furthermore, vaginal muscle spasm, the defining feature of vaginismus, was not found to be a valid or reliable diagnostic criterion when tested empirically [1,9]. Many researchers felt diagnostic accuracy would be improved through combining both disorders into one unified category. Conversely, some argue that the scope of GPPPD is overly broad and complicates rather than simplifies clinical diagnosis for most practitioners [3,10].

This complication becomes evident when one considers that both vulvodynia and GPPPD are by definition idiopathic, and thus are disorders of exclusion if no medical cause is found [3,5,7]. As specified in the DSM-5 diagnostic criteria, the sexual pain felt in GPPPD cannot be better explained by a medical condition [2]. Similarly, the 2015 Consensus Terminology of Persistent Vulvar Pain and Vulvodynia indicates that vulvodynia must have no clear identifiable cause, otherwise the pain is categorized as persistent vulvar pain [4,5]. Thus, a thorough medical history and exam are essential to rule out potential differential diagnoses that may better explain the woman's pain. In these cases, the treatment of sexual or genital pain would be connected to the management and treatment of her medical diagnosis. However, if the medical cause is successfully treated and the pain has not resolved, a diagnosis of vulvodynia or GPPPD is

Table 1. Correct terminology of sexual/genital pain conditions.

GPPPD	Describes recurrent difficulty/pain on sexual intercourse or penetration attempts, and is classified as a female sexual dysfunction in the DSM-5. May or may not be caused by vulvodynia.
Vulvodynia	Describes idiopathic chronic genital pain localized to the vulva that is present with or without sexual contact. Not classified as a female sexual dysfunction, but can cause or contribute to female sexual dysfunction.

Table 2. Medical conditions associated with/causative of dyspareunia [4,5,19].

Infectious • Recurrent vulvovaginal candidiasis • Sexually transmitted infection (e.g. herpes) • Pelvic inflammatory disease
Inflammatory/Dermatologic • Lichen sclerosus • Lichen planus • Vulvar granuloma fissuratum • Skin allergy (e.g. semen)
Neoplastic • Paget disease • Vulvar interepithelial neoplasm • Pelvic neoplasms (cervical, uterine, ovarian, colon)
Neurologic • Postherpetic neuralgia • Nerve compression or injury (e.g. pudendal nerve, genitofemoral nerve) • Neuroma
Trauma • Female genital cutting • Obstetrical tears / episiotomy scars
Iatrogenic • Post-operative • Chemotherapy, radiation
Hormonal • Vulvovaginal atrophy secondary to decreased sex steroids secondary to: menopause, lactational amenorrhea, anorexia, hyperprolactinemia, oophorectomy
Structural • Endometriosis • Leiomyoma • Ovarian mass • Pelvic adhesions • Congenital abnormalities of the hymen (imperforate hymen, septate hymen) • Vaginal agenesis

appropriate [4]. See Table 2 for possible medical causes of dyspareunia which should be ruled out or treated before considering a diagnosis of GPPPD.

ETIOLOGY

The etiology of GPPPD is multifactorial and complex, in that biological, psychological and relational factors interact to perpetuate and maintain a woman's pain response. What may initially be an adaptive nociceptive response resulting from peripheral tissue damage may gradually shift to a neuropathic and/or inflammatory pain in the absence of acute injury. It is this maladaptive pain that is harmful to sexual functioning, especially with increasing involvement of the central nervous system in pain sensitization [3,11]. Thus, GPPPD should be evaluated from a biopsychosocial perspective, and should never be viewed as a purely psychogenic problem [3,4].

Biological

Mast cell activation signifies the presence of inflammation and has been found in response to mechanical trauma or mucosal damage caused by infections, inadequate lubrication during sexual intercourse, chemical irritation (from soaps, douches, etc.), and allergic reactions [3]. Interestingly, studies evaluating vulvar histology in patients with vulvodynia have found increased inflammatory cell infiltrate in painful regions of the vulvar vestibule, and increased mast cell presence in areas of vestibular pain [4,12].

Prolonged tissue damage can lead to mast cell hyperactivation, resulting in over-production of inflammatory molecules and neurotrophins [3]. One such neurotrophin, Nerve Growth Factor (NGF), both has pro-inflammatory roles and induces the proliferation of peripheral nociceptors [11]. Over time, the concentration of mast cells in the inflamed tissue decreases, but there is a corresponding increase in nerve endings resulting in increased sensitivity to painful stimuli (known as hyperalgesia) and causing ordinarily non-painful stimuli to become painful (known as allodynia) [3,11]. Hyperalgesia and allodynia are characteristic of neuropathic pain. Painful stimuli can then cause defensive muscle contraction and eventual hyperactivity and dysfunction [3,4].

Such a mechanism has been proposed in vulvodynia and GPPPD, in which chronic inflammation of the vulvar epithelium (or an abnormal inflammatory response) leads to mast cell hyperactivation, sensitization and proliferation of pain nerve fibres in the area, and resultant pain and hypertonicity of the pelvic floor [3]. In fact, biopsies from the posterior vestibule in vestibulodynia patients confirm the presence of an increased number of free nerve endings when compared to healthy control subjects [13,14]. While nociceptor proliferation has not been found in vulvar tissue samples of patients with generalized vulvodynia, this may be due to a preponderance of research focusing on PVD, and much less on GVD [3].

Some studies suggest that there could be a genetic propensity to develop chronic inflammatory conditions, caused by an abnormal and overactive inflammatory response with a reduced ability to terminate such inflammation. For example, women with vulvodynia are significantly more likely to report other comorbid chronic medical conditions, such as interstitial cystitis, irritable bowel syndrome, and fibromyalgia than those in the general population [3,4]. Women with vulvodynia also seem to react more frequently than control subjects to Candida patch tests, possibly indicating a contact hypersensitivity to the infection [15]. However, more research must be done before suggesting a strong genetic link.

Finally, there is some evidence to suggest that prolonged use of oral combined hormonal contraceptive pills (CHCs) may increase the relative risk of developing PVD due to the resulting decrease in circulating estrogen and testosterone [4,7,10]. This can cause morphologic changes to the vulva, decreasing the size of the clitoris, thickness of the labia and diameter of the introitus, and ultimately rendering the vestibular mucosa more vulnerable to mechanical stress [4,16]. However, CHC use is common in North America, and most women do not go on to develop vulvodynia [4].

Psychosocial

As unwanted pain dampens the sexual response, there may be a progressive withdrawing from sexual interactions [9]. Several controlled studies have shown that women with vulvar pain have a higher incidence of depressive symptoms than controls, and report an increased loss of working days [3,4]. Catastrophizing pain, fear of pain, hypervigilance to pain, low self-efficacy, avoidance, anxiety, and depression may all intensify the experience of pain and perpetuate sexual dysfunction. Conversely, higher self-efficacy (i.e., beliefs that one can successfully manage the pain) may lead to reductions in pain intensity during penetration attempts [17]. Furthermore, pain (and anticipation of pain) reflexively inhibits both mental and physical sexual arousal, thus decreasing vaginal lubrication, vulvar congestion, pelvic muscle relaxation, and sexual pleasure [3]. This makes the vaginal mucosa more susceptible to micro-abrasions and tears, resulting in additional genital pain and inflammation upon penetration attempts.

Women with partners who respond to their sexual pain in a way that facilitates adaptive coping, as opposed to paying excessive attention to the problem or demonstrating hostility, have been found to have higher levels of sexual satisfaction, relationship satisfaction, and lower ratings of pain [4,18]. Thus, the way a partner responds to chronic pain can help or harm the ability to manage painful stimuli. It should be noted here that sexual pain disorders can affect women in same-sex relationships as well, so care should be taken not to assume that sexual pain during penetration is limited to penile-vaginal intercourse within traditional heterosexual relationships.

An understanding of the woman's background, including cultural context, past relationships, sexual education and knowledge of personal anatomy and physiology, may also be important in guiding future discussions of possible cognitions, emotions or behaviours that may be contributing to her pain [9,19]. This is especially relevant if there is significant shame or feelings of inadequacy surrounding sexual functioning, or if there is a history of past sexual or physical abuse.

Unremitting sexual and genital pain can be incredibly disheartening for many women, especially if they feel invalidated by their health care team, by their partners, or by society [4,9]. One study found that fewer than 50% of all women who met criteria for vulvodynia sought treatment, reflecting the apprehension of sufferers to speak about their pain [20]. Additionally, many physicians lack the knowledge to manage sexual pain disorders.

TREATMENT

The aim of treatment is two-fold: (1) to reduce sexual and genital pain, and (2) to restore or improve sexual function [8]. As clinical presentations of GPPPD and vulvodynia can vary widely, treatment should be client-centered and tailored to the unique characteristics of the specific individual undergoing treatment. However, a general guideline to progress from least to most invasive treatment options is usually followed [7,8,19]. As mentioned previously, possible medical causes of pain should be assessed and treated first and foremost, before attempting treatment of idiopathic sexual or genital pain [3].

Non-Medical Approach

Education about vulvar self-care, including avoidance of douches, possible irritants, and allergens, is an important first step for practitioners [8]. Knowledge of genital anatomy and the female sexual response cycle may also be beneficial to facilitate greater understanding of what to expect from sexual encounters and to reduce anxiety [9].

Psychological intervention, often in the form of CBT, aims to explore a woman's thoughts, emotions, behaviours and relationship dynamics associated with the experience of her sexual pain. Thus, maladaptive or unhelpful cognitions that may be perpetuating the physical experience of pain or feelings of fear and anxiety can be identified and replaced with more helpful thoughts [8,19]. This may be undertaken individually, as a couple, or in a group. Research supports the effectiveness of individual CBT, with improvements in pain and sexual function maintained at one year when compared to individual supportive therapy [21]. Similar positive results were found in couple- and group-based CBT [8,19]. One study demonstrated that patients treated with group-CBT had similar self-reported ratings of coital pain at a 2.5-year follow-up when compared to

patients who underwent surgery [22].

Pelvic floor physical therapy, aims to reduce elevated tone or tension in the pelvic floor muscles that are contributing to the experience of sexual pain and making intercourse painful or difficult. This is done through increased awareness of pelvic muscles, improving relaxation techniques, normalizing tone, and providing stretching stimuli at the introitus to gradually reduce anxiety surrounding penetration [8,19]. The approach is often multimodal, and encompasses techniques such as electromyographic biofeedback (EMG), electrical stimulation, manual tissue manipulation, stretching/strengthening exercises, and the use of dilators or accommodators [8-10]. A retrospective study evaluating a pelvic floor physical therapy program found that after an average of 7 sessions, 51.4% of women with PVD had complete or great improvement and 20.0% has moderate improvement in pain at follow-up, with average coital pain intensity ratings decreasing from 8.2 to 3.9 after treatment [23].

As sexual pain disorders involve the interplay between many different though related factors in their onset and progression, an interdisciplinary approach that utilizes a multimodal treatment plan may work best in improving pain scores and sexual function [8,19]. In encompassing the biomedical, cognitive, affective, and relational components of treatment, the unique circumstance of each patient is taken into account and may provide a sense of validation and support. Thus, an integrated approach to treatment will likely produce better outcomes than a single modality alone.

Medical Approach

Anti-nociceptive agents are primarily used when neurogenic pain is suspected [8]. Local anesthetics such as topical lidocaine attempt to block peripheral nerve transmission by acting on sodium channels in nociceptors. However, they have been found to be minimally efficacious, with one study demonstrating only a 20% improvement in pain scores which was not significantly different from placebo [24]. Capsaicin, conversely, decreased pain with intercourse by 95% in one study, though the residual burning sensation was not tolerable as a side effect for many women [8,25]. Botulinum Toxin Type A (Botox) acts at nociceptors to cause local muscle paralysis of 3-6 month duration, making it an appropriate choice for women who have difficulties with pelvic floor hyperactivity causing pain. Several small studies have demonstrated efficacy in improving sexual pain, though larger RCTs should confirm these results before recommendation as a first-line treatment [8,26,27].

Anti-inflammatory agents such as corticosteroids have had only minimal efficacy in treating genital pain, despite increased IL-ß (typically decreased by corticosteroids) being found in the hymenal tissues of women with PVD [8,19]. Cromolyn cream (a mast cell stabilizer), enoxaparin (a low molecular weight heparin), and a skin cream containing lysate of fetal fibroblasts (with anti-inflammatory cytokines) have all undergone RCTs to evaluate the efficacy of possible anti-inflammatory action, with various success [28-30].

As CHCs may contribute to hormonally associated PVD in some women, there is evidence to suggest that topical estradiol and testosterone gels may improve pain scores significantly in such cases [8,10-19]. Vestibular pain scores decreased from 7.5 to 2.0 in a 50-woman, non-placebo-controlled retrospective study for those who developed vulvodynia secondary to CHCs, with treatment using topical 0.03% estradiol and 0.01% testosterone and discontinuation of CHC use [31]. However, more research is needed.

A literature review evaluating the effectiveness of tricyclic antidepressants suggest that they should not be used in the treatment of genital pain due to lack of sufficient evidence [32]. However, a recent small open-label trial of SNRI seemed to reduce pain severity, coital pain, and depression symptoms, though the study was small and non-blinded [33]. Thus, more research into the use of antidepressants as a treatment option is warranted.

Surgical Approach

Vulvar vestibulectomy, or the complete removal of the vestibular mucosa, is a well-established treatment for PVD associated with neuroproliferation [8,19]. While this is the most invasive approach to treatment, the success rates are high, with at least partial relief of sexual pain in 88% of patients and significant relief in 78.5% of patients according to a meta-analysis of 33 previous studies [34]. Of course, as with all invasive procedures, there is a risk of complications such as bleeding, infection, and worsening of pain. However, complications are infrequent, and surgery may prove to be extremely beneficial in managing vestibular pain in women who are resistant to less invasive treatment options [8,19].

CONCLUSION

Recurrent genital and sexual pain is a highly distressing condition encompassed by the diagnoses of vulvodynia and GPPPD. The etiology of sexual pain disorders is complex and involves many interrelated factors that are often difficult to separate within the clinical setting. Nevertheless, effective treatment options are available, generally progressing from least to most invasive. Given the medical, psychological, relational, and cultural connections to the experience of vulvar and sexual pain, a multidisciplinary approach is optimal to achieve the most effective impact on chronic pain symptoms, sexual functioning, relational satisfaction and quality of life. More research in the form of randomized controlled trials is needed to elucidate which medical treatments are effective in long term genital and sexual pain reduction.

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The Modifying Role of Pregnancy on Ophthalmological and Neuro-ophthalmological Diseases

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ABSTRACT

The female visual system experiences a series of physiological modifications during pregnancy, and these changes have profound implications on many general ophthalmological and neuro-ophthalmological disorders, exacerbating some conditions while alleviating others. Patients with open-angle glaucoma experience improved disease states, with accompanying normal visual fields. Uveitis and MS-induced optic neuritis exhibit decreased rates of occurrence. Non-proliferative diabetic retinopathy initially worsens with gestation, eventually improving in the post-partum state with only 5% of cases progressing into the proliferative stage. As for idiopathic intracranial hypertension, existing symptoms worsen during pregnancy. Therapeutic interventions such as immunosuppressants, anti-neoplastic drugs, and steroids administered prophylactically during fetal development may lead to potential teratogenic outcomes manifesting in devastating birth defects and should be administered with caution.

RÉSUMÉ

Le système visuel féminin subit une série de modifications physiologiques pendant la grossesse, et ces changements ont des implications profondes sur de nombreux troubles ophtalmologiques et neuro-ophtalmologiques généraux, exacerbant certaines conditions tout en soulageant d'autres. Les patients atteints de glaucome à angle ouvert ont une amélioration des états pathologiques, accompagnés de champs visuels normaux. L'uvéite et la névrite optique induite par la SEP présentent des taux d'occurrence réduits. La rétinopathie diabétique non proliférative s'aggrave au début avec la gestation, s'améliorant finalement dans l'état post-partum avec seulement 5% des cas progressant dans le stade prolifératif. En ce qui concerne l'hypertension intracrânienne idiopathique, les symptômes existants s'aggravent pendant la grossesse. Les interventions thérapeutiques comme les immunosuppresseurs, les médicaments antinéoplasiques et les stéroïdes administrés de façon prophylactique pendant le développement du fœtus peuvent entraîner des effets tératogènes potentiels se manifestant par des malformations congénitales dévastatrices et doivent être administrés avec prudence.

Pregnancy induces a plethora of physiological changes to a woman's eyes that are often transient but can persist well past the post-partum period [1]. In the anterior segment, there is a temporary reduction in corneal sensitivity in pregnant women from edema-induced corneal thickening [1]. Moreover, a decrease in intra-ocular pressure (IOP) is observed due to increased aqueous outflow, diminished episcleral venous pressures, and reductions in scleral rigidity [1]. Systemically, a pregnant mother's body undergoes immunologic changes, where the maternal immune system is biased towards a TH2 humoral response since TH2 cytokines protect the fetus at the maternal-fetal interface [2]. In addition, T-regulatory cells elevate their activity levels at the maternal-fetal interface, which is essential to achieve adequate immunosuppression to prevent an unwanted attack on the fetus [2]. Due to the aforementioned physiological alterations, certain ocular conditions can be ameliorated while others may be exacerbated (see summary in Table 1). The purpose of this article is to review the modifying role of pregnancy for the most common ophthalmological and neuro-ophthalmological diseases observed in clinical practice: glaucoma, uveitis, diabetic retinopathy, idiopathic intracranial hypertension, and optic neuritis. Approaches and precautions to management will also be provided in light of the potential adverse effects of ocular medications on the mother and developing fetus.

GLAUCOMA

Primary open-angle glaucoma, a disease affecting approximately 2-3% of the population over the age of 40, is often associated with elevated IOP, which ultimately leads to a progressive deterioration of the optic nerve [3]. Though advanced age is a strong risk factor, glaucoma can occasionally be seen

Keywords: Pregnancy; Ophthalmology; Teratogenicity; Neuro-Ophthalmology

Table 1. The effect of pregnancy on common general ophthalmological and neuro-ophthalmological diseases during pregnancy.

Condition	Effects During Pregnancy
Glaucoma	Variable outcome despite ↓IOP during gestation [7]: - 57% reported stable IOPs & normal visual fields - 18% reported visual field loss despite stable IOPs
Uveitis	Decreased rate of uveitis flare-ups [11]
Diabetic Retinopathy	Exacerbation of non-proliferative DR improves by 3rd trimester with 5% risk of progression into proliferative DR [17]
Idiopathic Intracranial Hypertension	No changes to IIH development normally [27] Symptoms may worsen during pregnancy with notable weight gain [28]
Optic Neuritis/Multiple Sclerosis	Disease state improves and ↓ in frequency of MS relapse [46]

in women of childbearing age [3]. These women, for instance, may have previously acquired glaucoma either congenitally, through early childhood (anterior segment dysgenesis or cataract extraction), or from coexisting ocular conditions (uveitis or diabetes) [3].

It is well-evidenced that IOP decreases significantly during pregnancy [1,4]. Glaucoma symptoms such as blurred vision and pressure-induced ocular pain in women with pre-existing primary open-angle glaucoma may demonstrate improvement throughout the later course of gestation, with mean IOP of first trimester patients being 2 mmHg higher than those during the third trimester [5]. IOP reductions can transiently decrease up to 10% for several months post-partum [4]. An interplay of decreased episcleral venous pressures from lowered peripheral vascular resistance, higher aqueous outflow facilitated by hormonal changes in progesterone and relaxin, and the development of mild metabolic acidosis has been proposed as mechanisms for the reduction in IOP [6]. However, the extent to which the decrease in IOP can be protective of glaucoma progression is still highly contentious. The largest retrospective trial examining pregnant women with pre-existing glaucoma reported stable IOPs and visual fields in 57% of eyes, while 18% experienced stable or increase in IOP with progressive visual field loss [7]. This study demonstrated that the course of glaucoma is highly variable despite reductions in IOP. Hence, it is advisable for pregnant patients to receive active monitoring of ocular pressures and visual field deficits.

The management of open-angle glaucoma during pregnancy presents a multitude of ethical and legal challenges. One questionnaire conducted by Vaideanu and Fraser [8] revealed that 31% of ophthalmologists are uncertain of how to handle such cases while only 26% reported having treated pregnant women. Presently, only the FDA category B agent, brimonidine, an α2 agonist, is considered safe and based solely from experimental animal studies [6]. Other foundational medications for glaucoma, including beta blockers, carbonic anhydrase inhibitors, and prostaglandin analogues, present uncertain safety risks and potential adverse effects in human and animal trials [9] (see Table 2 for a list of teratogenic effects from ocular medications). Laser trabeculoplasty may be a feasible alternative to the use of medications for the treatment of glaucoma during pregnancy, with the drawback of prolonged time to therapeutic onset and reduced efficacy in younger patients [9]. Surgical intervention may be warranted following persistent relapse after conventional medical and laser therapy.

UVEITIS

Uveitis involves inflammation of the uvea, consisting of the iris, ciliary body, and choroid [10]. The estimated prevalence of uveitis is 120 adults out of 100,000, representing 10% of irreversible blindness [10].

Research has demonstrated that the probability of uveitis flare-ups was reduced during pregnancy in comparison to 3 months prior to pregnancy and 6 months post-partum [11]. Furthermore, one retrospective chart review by Chiam et al. [12] showed that in 47 patients with a history of non-infectious

Table 2. The teratogenic effects of known pharmacological interventions for common general ophthalmological and neuro-ophthalmological conditions.

Condition	Therapeutic Interventions	Teratogenicity
Glaucoma	Brimonidine (α2 agonist)	Safe to administer based solely on animal studies [6]
	Prostaglandin analogues	Uncertain safety risks from human & animal trials [9]
	Timolol (β-blocker)	Risks of infantile apnea, cardiac arrhythmia [52]
	Brinzolamide (Carbonic anhydrase inhibitor)	↓ fetal body weight [53]
Uveitis	Methotrexate (folic acid antagonist)	Skull defect, CNS abnormality, limb, GI, and cardiopulmonary defects [54]
	Cyclophosphamide (Antineoplastic)	Potential ear and eye abnormalities Absent thumb and cleft palate [55]
	Mycophenolate mofetil (Immunosuppressant)	Microtia, cleft palate, heart defects and diaphragmatic hernia [15]
		May contribute to risks of prematurity [12]
	Azathioprine (Immunosuppressant)	May contribute to risks of prematurity [56]
	Cyclosporine (Immunosuppressant)	
Diabetic Retinopathy	Ranibizumab (Antibody Fab fragment, Anti-VEGF)	Low risks of fetal skeletal defects at specific dosage [57]
	Aflibercept (Anti-VEGF)	Potential risks of fetal malformation [57]

uveitis, the course of uveitis changed during different stages of pregnancy, falling starting from second trimester and reaching a nadir in third trimester. However, the severity of uveitis flare-ups (as quantified by cell count in the anterior chamber) did not differ between the pregnant versus non-pregnant period [13]. The primary explanation for the quiescence in rate of flare-up is that pregnancy promotes anti-inflammatory cytokines, thus inhibiting the cell-mediated autoimmunity against the semiallogeneic fetus [14]. Recent evidence by Chan el al. [14] has also suggested that elevated levels of estrogen and progesterone can aid the immune process in upregulating Th2-associated cytokines (IL4, IL5 and IL10) and downregulating Th1-mediated immunity (interferon gamma, IL12 and P40), both of which are predominantly involved in non-infectious uveitis. Moreover, increased activity of factors such as regulatory T cells, immunosuppressive cytokines, alpha-fetoprotein, and melanocyte-stimulating hormone have been shown to interact with Th2-mediated immunity in a multifactorial manner [14]. Interestingly, these immunosuppressive effects are typically reversed within one to two months post-partum [14].

The management of non-infectious uveitis involves the use of immunosuppressive agents which may exert adverse effects on the fetus [15]. The majority of these medications, including

methotrexate, cyclophosphamide, and mycophenolate mofetil (MMF), are not recommended for use during pregnancy due to potential teratogenic risks [15]. Furthermore, there is limited evidence for the use of monoclonoal antibody biologics such as rituximab and infliximab, and interleukin-1 receptor antagonist anakinra, but immunosuppressive agents such as azathioprine and cyclosporine may be administered under careful surveillance [16]. As advised by Wakefield et al. in a review of the management of uveitis during pregnancy [16], expected mothers should be counselled on the risks of infertility, miscarriage, and potential teratogenicity of immunosuppressive medications, so that treatment can be tailored by evaluating the risk of harm for both the mother and child.

DIABETIC RETINOPATHY

Diabetic retinopathy (DR) is a common microvascular complication from diabetes involving vasodegenerative changes that eventually result in areas of retinal ischemia [17]. This condition is one of the leading causes of preventable blindness in the working population (between 24 and 64 years) with a prevalence of 35% in patients with diabetes [17]. DR has been shown to be aggravated by pregnancy and the risk for progression has been associated with poor metabolic control at conception, severity of retinopathy at baseline, longer duration of diabetes, and coexisting hypertension [17]. DR is often classified into two types, non-proliferative DR representing background retinopathy and fluid leakage from vessels, and proliferative DR involving neovascularization [17].

Interestingly, studies have consistently demonstrated that approximately half of patients with non-proliferative DR experience symptom exacerbations that improve by the third trimester and post-partum, with 5% transitioning into proliferative DR [17-20]. According to the Diabetes Control and Complications Trial [19], pregnant women treated for diabetes were at 2.48 higher risk of exacerbations of their background retinopathy in comparison to non-pregnant women.

Despite some studies citing exacerbations of DR following strict glycemic control [21,22], maintaining a normal blood glucose level in long-term follow-up is considered beneficial. Specifically, the normalization of glycemic levels has been linked with successful pregnancies as high levels of glucose can be teratogenic to the fetus, resulting in 39% of preterm deliveries and 9% of intrauterine growth restrictions [21]. Laser therapy such as pan-retinal photocoagulation (PRP) is an effective mainstay of therapy, eliminating proliferative DR as a previously labeled contraindication for pregnancy [17]. Recently, anti-VEGF factors such as ranibizumab and Aflibercept have emerged as effective alternative therapies for DR [17]. In fact, evidence suggests the use of bevacizumab (an anti-VEFT factor) in combination with PRP was effective in the regression of new vessels and improvement of macular edema in patients with DR [20]. Nevertheless, prompt detection and treatment of proliferative DR is crucial. One study demonstrated that in a group of 81 patients with proliferative DR not treated prior to pregnancy, 47 (58%) progressed, while in a group of 35 patients who had received laser photocoagulation prior to pregnancy, only 9 (26%) progressed, suggesting that prepartum examination and management can be favourable on the outcome of proliferative DR [18]. Additionally, the use of scatter laser treatment is indicated during pregnancy in the presence of active neovascularization to prevent the development of vitreous haemorrhage in the second stage of labour [18]. Overall, young women with diabetes should be counselled and managed prior to their pregnancy with regular ophthalmological evaluations for continual monitoring [17].

IDIOPATHIC INTRACRANIAL HYPERTENSION (IIH)

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri, is a condition of unknown etiology characterized by increased intracranial pressure without hydrocephalus or mass lesion, and with normal cerebrospinal fluid (CSF) composition [23]. IIH predominantly affects obese women of childbearing age, with a prevalence of 19.3 per 100,000 [24]. The pathogenesis of IIH has not been fully elucidated, but is thought to be caused by disordered CSF dynamics [25]. Common symptoms include headaches and visual disturbances, including transient visual obscuration, visual field loss, and reduction of central visual acuity [26].

A study conducted by Digre et al. summarizing 109 cases of IIH established that this condition does not exhibit increased rate of occurrence in pregnant patients than in the non-pregnant counterparts of comparable age [27]. However, in agreement with the association between weight gain and IIH [28], symptoms of existing IIH tend to worsen during pregnancy. As demonstrated by Koontz et al. [29], 4 out of 9 pregnant women reported that their headaches intensified, with one of them experiencing increased loss of visual acuity simultaneously. In addition, in their study of 11 pregnancies, Katz et al. [30] showed that symptoms of IIH, including headache and visual changes, were exacerbated in 9 pregnancies. Fortunately, many studies

have shown that, with proper management, the symptoms of IIH improve or resolve rapidly post-partum or after termination of pregnancy [29-31]. Moreover, the outcome of visual acuity and visual field of pregnant women with IIH is similar to that of the non-pregnant patients [31].

In general, treatment of IIH is similar for both non-pregnant and pregnant patients and is aimed at alleviating symptoms- mainly headache and visual obscuration- and preserving vision as blindness may develop in 10% of pregnant patients [32]. Given the strong association between weight gain and IIH, limiting weight gain to 20lbs and a nonketogenic diet are recommended for weight control [31,33]. Among the available diuretics, loops and thiazide diuretics should be avoided due to their adverse effects on the fetus, while acetazolamide, a carbonic anhydrase inhibitor capable of reducing intracranial pressure can be used after 20 weeks of gestation [34]. Steroids have undesirable side effects such as weight gain, hyperglycemia, and disruption of fetal development, and are therefore only indicated in acute settings to treat significant visual decline [23,33]. As for the analgesics available to treat headaches, meperidine and acetaminophen with codeine are recommended for short-term use, while propranolol and topiramate can be used prophylactically for severe intractable headache [33]. If vision continues to deteriorate despite the aforementioned medical therapies, surgical procedures must be considered, which include optic nerve sheath fenestration or decompression, and CSF shunts [23].

OPTIC NEURITIS AND MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an autoimmune disorder causing demyelination of nerve cells [35]. Optic neuritis, a condition where destruction of myelin sheath of the optic nerve causes acute, usually monocular vision loss, is highly associated with MS [35,36]. Two-thirds of cases of optic neuritis occur in women and it typically develops in patients between the ages of 20 to 40 [37-39]. The incidence of optic neuritis is greatest in countries of higher latitude such as the U.S., where annual incidence is estimated to be as high as 6.4 per 100,000 [35,40]. Common symptoms include a decline in vision typically over a 7 to 10-day period and painful ocular movement in the affected eye [41,42].

Due to the immunosuppressive state of pregnancy, disease activity and frequency of MS relapses decrease [46]. This finding was most clearly demonstrated in a large-scale prospective study which included 269 pregnancies in 254 women with MS [46]. Relapse rate was lower throughout pregnancy and fell substantially during the third trimester, reaching 30% of the pre-pregnancy state [46]. This suppression of MS relapse during pregnancy has been substantiated in other prospective clinical trials and MRI data [43-45]. During the first 3 months of post-partum period, multiple studies have shown that rate of exacerbation rebounds may exceed the pre-pregnancy levels, further underlying the protective role of pregnancy [37, 33, 46, 47].

Caution should be exerted when treating pregnant MS patients, as many medications may have adverse effects on the fetus. Among the disease-modifying agents, which are aimed at reducing the number of relapses, glatiramer acetate is considered most favorable as there was no association found with low birth weight, congenital anomaly, premature birth, or spontaneous abortion in a recent systematic review of 97 cases [48]. However, other disease-modifying drugs- including interferon-beta, natalizumab, fingolimod, mitoxantrone, and teriflunomide-- are found to cause one or more of the following: preterm birth, spontaneous abortion, fetal hematological abnormalities, congenital anomalies [49, 50]. Standard symptomatic treatment for acute relapse is high-dose glucocorticoids given daily for 3 to 7 days [51]. There have been reports that steroids increase risk of cleft palate and lower birth weight in the first trimester, but it is generally safe for short-term use in second and third trimesters [51].

CONCLUSION

Pre-existing general ophthalmological and neuro-ophthalmological conditions may be exacerbated or ameliorated due to a variety of physiological changes induced during pregnancy. Diseases that tend to worsen with gestation include diabetic retinopathy and IIH, whereas glaucoma, uveitis, and MS-induced optic neuritis may improve. Treatment of most of these diseases is similar to that for the non-pregnant patients, although one should take into consideration the teratogenic profile of the treatment and conduct therapy with caution. Through familiarity with these possible neuro-ophthalmological changes and the available treatment options, physicians will be able to provide better eye care for their pregnant patients.

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Preterm Birth: An Inflammatory Syndrome, Not Just A Myometrial Disorder

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ABSTRACT

Preterm birth (PTB) is the leading cause of neonatal mortality and morbidity. Although the severity of neonatal outcomes is inversely correlated with gestational age, all PTBs can lead to potentially life-threatening neonatal outcomes and major lifelong health complications. Because advances in neonatal care have substantially decreased neonatal mortality, the incidence of PTB and its complications is unabatedly rising. PTB currently affects more than 10% of births worldwide, with similar numbers in developed countries. Correspondingly, improving neonatal outcome is a key objective of the World Health Organization. The recently approved (in Europe) tocolytics drug, Atosiban, used to prolong preterm gestation, has not been shown to improve neonatal outcome, nor have other tocolytic agents used in clinic. Thus, PTB remains an unmet medical need. Recent evidence shows that most, if not all, PTBs are associated with (overt or occult) inflammatory processes in gestational tissues, independent of infection. Pro-inflammatory cytokines are produced from maternal and fetal cells in response to sterile or infectious stressors. These seem to orchestrate a multi-tissue response including myometrial contractility, cervical ripening, and weakening/rupture of fetal membranes, leading to the onset of preterm labor. This integrated system might have been conserved through mammalian evolution due to increased maternal and/or fetal survival when gestation is terminated in specific settings, such as infection. Hence, inflammation may be a common pathway to the numerous aetiologies of PTB. Most importantly, recent evidence suggests that inflammation is transmitted to the fetus, thereby inducing organ injuries that may underlie the development of major neonatal diseases. Targeting inflammation prenatally instead of myometrial contraction could be a more successful and safe approach for the management of PTB, as suggested by recent animal studies.

RÉSUMÉ

La naissance prématurée est la principale cause de mortalité et de morbidité néonatale. Bien que la sévérité des issus néonataux soit inversement corrélée avec l'âge gestationnel à la naissance, toutes les naissances prématurées peuvent mener à des issus néonataux potentiellement mortels et à des complications avec répercussions s'échelonnant sur toute la vie. Étant donné que la mortalité néonatale a considérablement diminuée avec les récentes avancées en néonatalogie, l'incidence de la naissance prématurée et de ses complications sont en hausse. La naissance prématurée affecte présentement plus de 10% des naissances à travers le monde, avec des taux similaires dans les pays développés. Conséquemment, d'améliorer l'issu néonatal est un objectif clé de l'Organisation Mondiale de la Santé. Le tocolytique Atosiban récemment approuvé (en Europe) pour prolonger les gestations prématurées n'a pas démontré d'efficacité pour améliorer les issus néonataux, tout comme les autres tocolytiques utilisés en clinique, et la naissance prématurée demeure un besoin médical non-atteint. Des données récentes démontrent que la plupart, sinon toutes les naissances prématurées sont associées avec des processus inflammatoires (francs ou silencieux) dans les tissus gestationnels, indépendamment de l'infection. Les cytokines pro-inflammatoires sont produites dans les cellules maternelles et fœtales en réponse à des stresseurs stériles ou infectieux, et semblent orchestrer une réponse multi-tissulaire incluant la contractilité myométriale, la préparation cervicale, et l'affaiblissement/rupture des membranes fœtales, menant au commencement du travail préterme. Ce système intégré pourrait avoir été conservé durant l'évolution mammifère à cause d'une survie accrue de la mère et/ou du fœtus lorsque la gestation est terminée dans un contexte spécifique, comme l'infection. Donc, l'inflammation pourrait constituer une voie commune finale pour les nombreuses causes de la naissance prématurée. De façon importante, des données récentes suggèrent que cette inflammation est transmise au fœtus et en retour induit des dommages aux organes qui pourraient sous-tendre le développement de maladies néonatales majeures. De cibler l'inflammation en prénatal plutôt que les contractions myométriales pourrait constituer une approche sécuritaire et plus efficace, comme suggéré par de récentes études animales.

Keywords: Preterm birth; Tocolytics; Neonatal morbidity; Inflammation; Chorioamnionitis; Interleukin-1

Each year, approximately 15 million babies worldwide (more than one in 10 births) are born preterm (<37 weeks of gestation) [1,2]. Preterm birth (PTB) rates are increasing in most countries, with the highest reported in the USA, Africa and Southeast Asia [1]. Prematurity is currently the leading cause of neonatal mortality and the second most frequent cause of death after pneumonia among children under 5 years old [3]. Thus, the global burden of PTB on maternal and child health calls for an urgent need to develop effective preventive and treatment strategies to reduce the incidence of PTB.

PTB can be medically indicated (iatrogenic) or spontaneous. In high income countries, about one third of pregnancies are interrupted for maternal or fetal indications, such as preeclampsia and diabetes [4,5]. About 70% of PTBs follow spontaneous labor, with membranes either intact or prematurely ruptured. PTBs can also be subdivided based on gestational age, into extreme preterm (<28 weeks, accounting for 5%), severe preterm (28-31 weeks, 20%), moderate preterm (32-33 weeks, 20%) and late preterm (34-36 weeks, 60-70%) [5].

PTB is now viewed as a complex syndrome arising from multiple mechanisms, such as inflammation or infection, uteroplacental ischemia or hemorrhage, uterine overdistension and stress [2]. Several maternal or fetal risk factors have been linked to PTB. Maternal characteristics include previous preterm deliveries, multiple gestation, extremes in maternal age and BMI, race, and low socioeconomic and educational status. Nutritional status during pregnancy may also affect birth outcomes [2]. Common fetal conditions associated with PTB birth are small-for-gestational-age birth, fetal distress and congenital malformations [6].

Preterm infants are delivered at a time when organ development is still ongoing. Ensuing immaturity of many organ systems at birth put newborns at a greater risk of neonatal complications, most commonly bronchopulmonary dysplasia, necrotizing enterocolitis, periventricular leukomalacia and retinopathy of prematurity [7]. Inflammation and oxidative stress have been proposed as major contributors to these diseases [8]. The current pharmacological approach for PTB aims at prolonging gestation to gain enough time for administration of corticosteroids for lung maturation. However, simply prolonging gestation has shown no improvement in short- and long-term neonatal outcome. Although major advances in perinatal care over the last few decades have improved the survival of preterm babies, recent epidemiological studies show an increased risk of chronic disorders in adulthood following PTB, including hypertension, diabetes and obesity [5]. Clearly, treating PTB as a myometrial disorder has not been effective. A wide body of evidence indicates that in utero inflammation is present in most PTB, especially extreme and severe PTB, independent of infection [9]. Most importantly, maternal in utero inflammation can reach the fetus and induce a fetal inflammatory response syndrome [10], with major implications for neonatal outcomes. Therefore, an emerging paradigm in preclinical research is to target cytokines and other inflammatory factors that are implicated in both PTB and fetal/neonatal organ injuries, using prenatal delivery of candidate drugs.

This review will summarize the candidate drugs used to prolong gestation in case of spontaneous PTB, and review the recent data on the role of inflammation and anti-inflammatory drug candidates in PTB and associated neonatal complications.

PHARMACOLOGICAL APPROCHES IN THE TREATMENT OF PTB

Most therapeutic agents for PTB are designed to target the myometrium in order to arrest or delay labor in symptomatic (laboring) women. These agents are referred to as tocolytics (from the Greek tokos, childbirth; and lytic, dissolving) and represent the mainstay of treatment to prolong gestation in order to gain sufficient time for administration of corticosteroids (to accelerate lung maturation and surfactant production) or transport to a tertiary care unit. Because tocolytics have numerous side effects and have not been shown to improve neonatal outcome, some clinicians prefer not to use them, especially in case of late PTB. The first clinical trials of tocolytics began in the late 1960s and 1970s [11]. Since then, numerous tocolytic candidates have been used, most of them off-label (e.g. indomethacin). Out of all the therapeutic molecules employed to prolong gestation, only progesterone has been used in asymptomatic (non-laboring) women at risk of PTB. Progesterone and the most used tocolytics will be reviewed in this section.

Ritodrine

Numerous β-mimetics have been used as tocolytics (e.g. terbutaline, ritodrine, salbutamol), but the most used is ritodrine [11]. β-mimetics bind and activate β-adrenergic receptors on myometrial cells. β-adrenergic receptors are Gs protein-coupled receptors and therefore activate adenylyl cyclase-induced production of AMPc, in turn reducing intracellular Ca++ levels

Table 1. Most used therapeutic molecules for the treatment and prevention of PTB.

Therapeutic agents	Mechanism of action	Efficacy	Adverse effect profile	RCTs[a] and meta-analysis
Ritodrine	β_2-adrenergic agonist: ↑cAMP (G_s); ↓ intracellular Ca^+ ↓ MLCK activation in myocytes	- Prolong gestation for 48h vs placebo - Elicits no improvement of perinatal outcome	High frequency of potentially life-threatening maternal and fetal side effects including: palpitations, tremor, nausea, headaches, and chest pain [72].	[12]
Nifedipine	Calcium channel blocker	- More effective than ritodrine to prolong gestation - Decreases rates of severe neonatal morbidity	Fewer maternal side effects than ritodrine. Includes: flushing, headache, dizziness, nausea and transient hypotension. Possible neonatal side effects include: tachycardia, hypoglycemia and hypocalcemia.	[14,15]
Atosiban	Oxytocin receptor antagonist	As effective as ritodrine to prolong gestation	Lower side-effect profile than ritodrine and most tocolytics.	[20]
Magnesium sulphate	Competes with Ca^{++} for entry into the cell; Blocks calmodulin-induced activation of MLCK	Not more effective than placebo	Lower side-effect profile than most other tocolytic agents.	[18]
Indomethacin	COX-2 inhibitor: ↓ $PGF_{2\alpha}$ ↓PGE_2	Insufficient level of evidence for firm conclusions	Major side effects on fetal kidney development and cardiovascular system	[25]
Vaginal progesterone prophylaxis	Promotes uterine quiescence	Insufficient level of evidence for firm conclusions	Lower side-effect profile than most tocolytic agents.	[28,29]
17α-hydroxyprogesterone caproate prophylaxis [synthetic progestin]	Promotes uterine quiescence	Insufficient level of evidence for firm conclusions	Lower side-effect profile than most tocolytic agents. Its use has been associated with increased incidence of gestational diabetes	[73]

[a]RCT: randomized control trials.

Table 2. Anti-inflammatory agents in preclinical testing for the prevention of PTB.

Therapeutic agent	Inflammatory target	Mechanism of action	Reference
Resveratrol	Macrophage	Activates sirtuin-1 and NAD+-dependant deacetylase	[74-77]
Tregs	T-cells	Regulates inflammatory cells	[78]
15-epi-lipoxin A4	Neutrophils	Modulates leukotrienes derived from arachidonic acid	[65]
Anakinra	IL-1 receptor	Competitively inhibits the receptor	[28, 61]
101.10	IL-1 receptor	Non-competitively inhibits the receptor	[62, 68]

and promoting the inactivation of myosin light-chain kinases (MLCK; a group of enzymes important for contraction) in myometrial smooth muscle cells [11].

Several randomized control trials (RCTs) and meta-analyses concur to the efficacy of ritodrine to prolong gestation by at least 48h [12,13]. However, there is no evidence for improvement of neonatal outcomes [12]. The current rationale for using ritodrine (and other tocolytics) is to gain enough time for corticosteroid action to kick in and transfer to a tertiary care facility. However, ritodrine (and other β-mimetics) also interact with cells other than myometrial tissue, resulting in maternal and fetal adverse effects (see Table 1). Since other similarly effective tocolytics have been shown to cause less significant side effects, ritodrine is no longer marketed in the USA [11].

Nifedipine

Calcium is an essential signal transducer of pro-contractile intracellular targets by binding to and activating calmodulin. The resulting complex activates MLCK, in turn promoting actomyosin interaction and contraction. Nifedipine blocks calcium channels, thereby reducing intracellular calcium levels and reducing actomyosin activity in smooth muscle cells. A meta-analysis published in 2002 showed that if calcium channel blockers were administered before 34 weeks of gestation, they could prolong gestation by 7 days [14]. This is a much longer period of time than is provided by β-mimetics. Calcium channel blockers, specifically nifedipine, have also been shown to have fewer side effects and a lower neonatal morbidity rate [15]. However, nifedipine is associated with higher rates of adverse effects in women with cardiovascular disease, congenital cardiac malformations or pulmonary hypertension [15,16].

Atosiban

Atosiban is the first drug to be developed for preterm labor (as opposed to already existing drugs used off-label) and is largely used in Europe. It is the first member of a new class of tocolytics, the oxytocin receptor antagonists. When oxytocin binds to its receptor in the myometrium, it activates the phospholipase C/inositol 1,4,5-trisphosphate pathway, leading to the release of intracellular calcium which causes contractions. Atosiban inhibits this pathway, thereby preventing myometrial contractions [17].

In a large multi-centre RCT, atosiban was found to be as effective as β-mimetics in prolonging gestation, with fewer side effects than β-mimetics [18]. However, in a large placebo-controlled RCT in the USA, numerous hurdles were encountered. Most significantly, there was bias distribution of pregnant women in the two treatment groups, leading to a significantly higher number of women at low gestational age (<26 weeks) being placed in the atosiban group. In this subgroup, the mortality was significantly higher than in those treated with β-mimetics. However, in the subgroup that delivered >28 weeks, atosiban was more effective than placebo to prolong gestation [19]. Because the data of women that delivered <26 weeks were inconclusive and other reasons, FDA has not yet approved the use of atosiban. Atosiban is currently the most used tocolytics drug in Europe, however [11]. Numerous new oxytocin receptor antagonists are being considered for acute tocolysis (e.g. barusiban).

Magnesium sulfate

Magnesium is a divalent cation that competes with Ca++ for: 1) entry into the cell via calcium channels, and 2) binding to calmodulin (which precedes MLCK activation). Based on this

rationale, magnesium sulphate is used as a tocolytic agent, but it lost popularity after numerous RCTs and meta-analyses revealed its inefficacy to prolong gestation and an increased risk of fetal and neonatal mortality [20]. Because of the withdrawal of β-mimetics from the American market and the failure of atosiban to obtain FDA approval, magnesium sulfate has been used extensively in the USA as a first-line tocolytic [11]. Magnesium sulfate is still used antenatally for its neuroprotective effects on the progeny [21]; however, this topic seems to be controversial and possibly depends on different pregnancy settings [22].

Indomethacin

Indomethacin is a non-steroidal, anti-inflammatory drug that reversibly inhibits cyclo-oxygenase 2 (COX-2), thereby inhibiting the production of uterotonic prostaglandins. Indomethacin is widely used in Canada for acute tocolysis. Although it has been shown to prolong gestation [23], its prolonged use (>48h) has been associated with severe neonatal complications, including premature closure of ductus arteriosus, renal toxicity, necrotizing enterocolitis, intraventricular hemorrhage, and periventricular leukomalacia [24] . It therefore must be used with utmost caution. There is currently no evidence that indomethacin has any advantage as a first-line tocolytic over calcium channel blockers or oxytocin antagonists, each of which have better side effect profile [25].

Progesterone

Progesterone maintains uterine quiescence in numerous species. In humans, it is thought to do so by inhibiting inflammation-induced activation of the uterus (as discussed in the next section). Prophylactic use of progesterone in women at risk of PTB appears to have few, if any, side effects. However, its efficacy is controversial. In 2003, two RCTs reported that the use of daily vaginal progesterone administered between week 24 and 33 in high-risk pregnant women [26] or of daily 17α-hydroxyprogesterone caproate (slightly different pharmacological properties) administered between week 16 and 36 [27] decreased the rate of preterm deliveries. However, a recent multi-centre, placebo-controlled, double-blind RCT found no significant difference between vaginal progesterone prophylaxis and placebo in decreasing rates of PTB or improving outcomes at 2 years of age [28]. Because progesterone is safe and may be effective in some patients, many obstetricians use it as prophylaxis therapy to prevent PTB. However, the use of progesterone as an acute tocolytic was unsuccessful [29].

Summary

Given the large amount of data available and the range of evidence for each specific treatment, choosing the correct agent may be puzzling even for an experienced clinician. In the current state of knowledge, it is probably reasonable to administer a tocolytic agent in order to gain sufficient time for corticosteroids treatment and transfer to tertiary care unit. Calcium channel blockers and oxytocin receptor antagonists appear effective and present a more beneficial side effect profile than other candidates. Progesterone might be effective to prevent the onset of preterm labor in specific populations, and its prophylactic administration is safe. Although the use of these strategies has had some advantages, none of the agents available are associated with significant improvement of neonatal outcome. Hence, there is still room for improvement. Recent research efforts have been directed at preventing preterm birth by targeting earlier and upstream events in the cascade leading to PTB. In the next section, we will discuss how inflammation activates the pregnant uterus weeks to months before preterm labor, and how inflammatory mediators can be targeted to improve neonatal outcomes.

INFLAMMATION IN PRETERM BIRTH

Inflammation plays a crucial role in the onset of preterm labor and is involved in >60% of extreme PTB (<28 weeks of gestation) [2,30]. Activation of pro-inflammatory cytokines and chemokines at the maternal/fetal interface is associated with PTB [31] and conversely, suppression of inflammation using different agents prevents PTB in numerous animal models [32]. In murine models (hemochorial placentation akin to humans), the intrauterine inflammatory response has been shown to reach the fetal compartment, possibly though a cytokine chain reaction. This induces severe injuries to the fetal organs that begin in utero and persist into adulthood [16]. The inflammatory response begins with bacteria or stressed cells that induce release of small motives (Pathogen/Danger-Associated Molecular Patterns) that are recognized by Toll-like receptors (TLR; receptors part of the innate immune system) expressed throughout gestational tissues. This leads to the production of pro-inflammatory cytokines and chemokines [33], extravasation of myeloid and lymphoid inflammatory cells (mostly neutrophils and monocytes/macrophages), and eventually, activation of many uterine activation proteins (UAPs). These UAPs promote cervical ripening, fetal membrane weakening, contractions and labor [34-36]. Importantly, data show that this inflammatory response does not resolve with birth [16], which may explain the

inefficacy of tocolytics at improving neonatal outcomes.

Interleukin (IL)-1β is a key pro-inflammatory cytokine that has been strongly linked to PTB [37]. Its production is triggered by activation of TLRs via sterile or non-sterile pathways (as mentioned), and it generates a complete inflammatory response (e.g. as seen in the context of an infection) through binding to its ubiquitously expressed receptor IL-1RI. Correspondingly, a single 1μg administration of IL-1β to pregnant mice is sufficient to cause chorioamnionitis and PTB [38]. Other important inflammatory mediators include tumor necrosis factor (TNF)α and IL-6.

Perinatal injuries related to inflammation

Following PTB induced by chorioamnionitis, preterm infants often develop a fetal inflammatory response syndrome (FIRS), exposing many organs to environmental insults and therefore resulting in severe morbidities [10,30]. In this section, we will focus on perinatal injuries to organs that are the most vulnerable to inflammation: the lungs, the brain, the gastro-intestinal (GI) tract and the heart.

Lungs

As the newborn is separated from the maternal womb, its tiny lungs have to take on gas exchange while still in the developing stage. Immaturity of the lungs at birth can lead to respiratory distress syndrome (RDS), a main cause of neonatal mortality and morbidity [39]. Interestingly, many studies show that intrauterine inflammation has a positive impact on RDS, diminishing its incidence by accelerating lung maturation and surfactant production [40-42]. However, chorioamnionitis induces fetal lung inflammation [43] and increases the risk of bronchopulmonary dysplasia, an alveolar and vascular malformation and dysfunction [41]. Resulting decreased lung function often leads to airway obstruction persisting until adulthood, as well as impaired development of other organs due to a lack of oxygen delivery [44].

Brain

The developing brain in preterm newborns has been shown to be sensitive to inflammatory insults [45]. The white matter is particularly vulnerable to ischemia and injury because of the very low pressure of perfusion [46]. Ischemia and intrauterine inflammation may cause premature differentiation of the oligodendrocytes, thereby increasing vulnerability to fatal insults [47]. Correspondingly, chorioamnionitis predisposes preterm neonates to periventricular leukomalacia [48], periventricular hemorrhagic infarction [49], cerebral palsy [50], and to many other permanent cerebral deficits such as chronic epilepsy and intellectual disability [45,51]. Moreover, inflammation and infection are independently linked to neonatal encephalopathy, one of the most prevalent causes of child mortality [52]. Overall, the brain is vulnerable to inflammation, which is a major concern when addressing prematurity and its outcomes.

Gastro-intestinal tract

Intestinal complications associated with PTB are a major source of admission to the neonatal intensive care unit (NICU) [53]. It was shown in the fetal sheep that IL-1 plays a key role in bowel inflammation by causing damage to the gut mucosae [54]. In the preterm infant, perinatal development of necrotizing enterocolitis and spontaneous intestinal perforation was also linked to inflammation [55].

Heart

Inflammation has also been shown to play a role in in prematurity-related cardiac conditions. Exposing lambs to lipopolysaccharides (LPS, a TLR4 agonist) during gestation caused alterations of the cardiac tissue and function [56]. Some evidence has linked chorioamnionitis and patent ductus arteriosus, a prevalent cardiac defect in preterm newborns, but it is still controversial due to conflicting studies [57,58]. Inflammation and prematurity also seem to be involved in the development of arteriosclerosis and cardiovascular disease later in life [59]. Therefore, inflammation may impact fetal heart development, but the exact mechanism by which it does so has yet to be conclusively defined.

CURRENT PRECLINICAL TRIALS TARGETING INFLAMMATION IN PTB

Given the important role of inflammation in PTB and its consequences on fetal development, modulation of pro-inflammatory mediators has been tested in recent preclinical studies. A short review of the ongoing preclinical advances targeting inflammation in PTB follows (summarized in Table 2).

Resveratrol

Resveratrol is a natural polyphenol capable of reducing LPS-induced PTB to 36% (versus 85% without drug) and stillbirth to 34% (versus 62% without drug) when administered orally to pregnant mice [60]. The mechanism of action suggested is downregulation of the expression of pro-inflammatory mediators such as iNOS and COX-2, and suppression of the produc-

tion of eicosanoids such as prostaglandins. Although promise has been shown in murine models, clinical translation might not give the same results, as many human trials with progesterone have failed to curb PTB [28,61,62].

Tregs

Regulatory T cells (Tregs) are a subpopulation of CD4+ T cells that downregulate inflammation and play a role in maternal immune tolerance to the fetus [63]. Adoptive transfer of Tregs is a technique where healthy Tregs are transferred to a receiver to alleviate inflammatory syndromes [64]. When tested on a mouse model of PTB induced with LPS, preterm birth was not prevented. However, there was a reduction in pro-inflammatory markers in the fetus's brain, suggesting the use of Tregs may have a protective effect in the context of inflammatory PTB.

Lipoxins

Arachidonic acid derived leukotrienes have a pro-inflammatory role in stimulating the adhesion and degranulation of neutrophils [65]. Lipoxins are eicosanoids that modulate leukotriene-mediated interactions between the endothelium and neutrophils [65]. A recent study showed that when administered during gestation, a lipoxin analogue named 15-epi-lipoxin A4 demonstrated great anti-inflammatory potency [66]. Intra-peritoneal injections during gestation of 15-epi-lipoxin A4 reduced the mortality rate of pups; yet it was inefficient in delaying LPS-induced PTB [67]. Pro-inflammatory markers IL-1β, IL-6 and TNFα were not downregulated and the anti-inflammatory cytokine IL-10 was not upregulated, indicating that lipoxins might intervene too far downstream (late) in the inflammatory signaling pathway leading up to preterm labor.

IL-1RI inhibitors

The pro-inflammatory cytokine IL-1β is a main component of the inflammatory reaction leading to PTB. Therefore, inhibitors of the IL-1RI have been used to try and curb the inflammatory process. The commercially available drug anakinra (Kineret) competitively blocks the receptor and inhibits all of its intracellular pathways [68]. While it does not prevent PTB, it has been proven efficient to protect the fetal brain from inflammatory damage [69]. More recently, a small all-d peptide, 101.10, was designed to partially inhibit IL-1RI without blocking important pathways for cytoprotection [70]. Pre-clinical murine studies have been tremendously promising, as it prevents PTB and protects the fetus from multisystemic perinatal injuries [16,71]. This encouraging finding indicates IL-1β is a good pharmacological target to curb inflammation at the beginning of its cascade, therefore protecting the fetus from inflammation-associated damages.

CONCLUSION

PTB is a common complication of gestation and represents a major social and economic burden worldwide. Tocolytics can prolong gestation but they have not been shown to improve neonatal outcomes. In clinical settings, preterm neonates are treated postnatally, but most neonatal pathophysiological processes are initiated in utero. New preclinical research points to a promising role of anti-inflammatory agents in improving neonatal outcomes, especially when administered antenatally. Notably, a novel IL-1 antagonist termed 101.10 seems safe and effective in preventing chorioamnionitis-induced perinatal brain, lung, and intestine injuries. In addition to the need of improving existing therapies, further research is warranted to develop specific diagnostic tests and biomarkers to identify women at risk of preterm birth.

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Opioid Replacement In Pregnant Mothers With Opioid Use Disorder and Fetal Neurodevelopment: A Review

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ABSTRACT

This paper reviews the published literature regarding neurodevelopmental outcomes in neonates following in utero exposure to opioids. We have summarized available clinical and experimental data. Overall, clinical data is limited and equivocal with most studies showing no significant neurodevelopmental impairments in infants and children exposed to opioids in utero. Various outcome measures assessed language, communication, cognitive, psychomotor, and behavioural outcomes. The equivocality of the data may be a result of the complexity of the cohort and the inability to disentangle the effect of the opioids from the multiple comorbidities. Results from experimental data show that all opioids cross the placental barrier. Mouse studies show biochemical and neurophysiological changes, leading to long-term effects on learning and memory. Some data also suggests that epigenetic and imprinting changes in the central nervous system of mice may lead to multigenerational effects of opioid exposure. Ultimately, the benefits of opioid replacement therapy outweigh its risks, but it should be done in the context of a broader biopsychosocial risk reduction approach. Promoting mother-child bonding and care through skin-to-skin contact, rooming-in, and breastfeeding can reduce severity of neonatal abstinence syndrome and improve outcomes. This cohort of women and children requires advocacy for comprehensive multidisciplinary care.

RÉSUMÉ

Cet article passe en revue la littérature publiée concernant les résultats neurodéveloppementaux chez les nouveau-nés après exposition in utero aux opioïdes. Nous avons résumé les données cliniques et expérimentales disponibles. Dans l'ensemble, les données cliniques sont limitées et équivoques, avec la plupart des études ne montrant aucune déficience neurodéveloppementale significative chez les nourrissons et les enfants exposés aux opioïdes in utero. Diverses mesures de résultats ont évalué les résultats linguistiques, de communication, cognitifs, psychomoteurs et comportementaux. L'équivocité des données peut être le résultat de la complexité de la cohorte et de l'incapacité à démêler l'effet des opioïdes des multiples comorbidités. Les résultats des données expérimentales montrent que tous les opioïdes traversent la barrière placentaire. Les études sur la souris montrent des changements biochimiques et neurophysiologiques, conduisant à des effets à long terme sur l'apprentissage et la mémoire. Certaines données suggèrent également que les changements épigénétiques et d'empreinte dans le système nerveux central des souris peuvent conduire à des effets multigénérationnels de l'exposition aux opioïdes. En fin de compte, les avantages de la thérapie de substitution aux opioïdes l'emportent sur ses risques, mais cela devrait être fait dans le contexte d'une approche plus large de réduction des risques biopsychosociaux. La promotion des liens et des soins entre la mère et l'enfant par le contact peau à peau, l'accoutumance et l'allaitement peut réduire la gravité du syndrome d'abstinence néonatale et améliorer les résultats. Cette cohorte de femmes et d'enfants a besoin de plaidoyer pour des soins multidisciplinaires complets.

Opioid use disorder has become increasingly prevalent worldwide and thus is a topic of public concern [1]. Concomitantly, this is resulting in increased rates of opioid use in pregnancy [2]. The number of infants born to opioid dependent women in Ontario has increased from 46 to almost 800 between 2002 and 2014 [2]. The Society of Obstetrics and Gynaecology of Canada (SOGC) recommends opioid replacement therapy in pregnancy to avoid withdrawal and illicit substance abuse [3,4]. The SOGC cites benefits of opioid replacement during pregnancy such as increased birth weight, longer gestation, improved prenatal care, more infants being discharged in the care of their mothers, and decreased complications [3,4].

Opioid replacement can be carried out with full agonist therapy (methadone), partial agonist therapy (buprenorphine), or combined partial agonist and antagonist therapy (buprenorphine plus naloxone) [3,4]. In longitudinal studies looking at develop-

Keywords: Opioid use disorder; Opioid replacement; Methadone; Buprenorphine; Neurodevelopment; Outcome studies

mental outcomes, it is difficult to separate effects of opioid exposure from comorbidities existing in this population including poverty, malnutrition, and co-infection (such as with Hepatitis B and C and HIV) [3,5]. Despite the potential effects of opioid replacement on fetal neurodevelopment, the risk of the mother experiencing withdrawal or relapse of illicit drug use when replacement is not provided carries greater morbidity; thus, replacement is recommended [3,4].

Infants exposed to opioids in utero either through illicit use or medical opioid replacement can experience withdrawal symptoms. The manifestation of these withdrawal symptoms in the neonate is referred to as neonatal abstinence syndrome (NAS) [6]. The symptoms of NAS include features of hyperactivity of the central and autonomic nervous system [6]. Hyperactivity of the central nervous system results in symptoms such as jitteriness and tremors. Hyperactivity of the autonomic nervous system results in symptoms such as sweating and mottling of the skin and enteric symptoms such as vomiting and diarrhea. NAS severity is graded with a validated clinical tool, called the Modified Finnegan Scoring System and is managed by pharmacological treatment with oral morphine or methadone [6].

Here, we will review literature on neurodevelopmental outcomes of neonates with in utero exposure to opioids. We note that neonatal abstinence syndrome can also affect fetal neurodevelopment. We will focus on the effects of opioids themselves on the developing brain. We will first review the clinical data (outcome studies) of in utero opioid exposure. We will then discuss the limitations of such studies. Next, we will review existing basic scientific data and summarize what this data suggests in terms of potential (perhaps more subtle) consequences that we should be mindful of.

CLINICAL DATA

Overall, the majority of data that is older than a decade suggests that there is no significant long-term neurodevelopmental effect of in utero opioid exposure [4]. Recent data is slightly more equivocal, with various levels of deficit being documented in opioid exposed cohorts on general developmental scales (such as the Bayley Scale of Infant Development), motor delays, and changes in Electroencephalographic (EEG) responses to auditory stimulation. These changes were seen in infancy and in some studies, they persisted into toddlerhood [7]. In contrast, one large epidemiological study showed that language development and communication skills were not affected in 3-year-old children who were exposed to analgesic opioid in pregnancy [8]. A meta-analysis published in 2014 aggregated five case-controlled observational studies that compared opioid exposed to non-exposed children, using various quantitative psychometric tests [9]. All five studies involved populations living in urban, low socioeconomic communities. For the sake of the meta-analysis, the outcomes of the tests were grouped into one of three domains: cognitive, psychomotor and behavioural. The meta-analysis found no statistically significant impairment in cognitive, psychomotor, or observed behavioural outcomes in infants and pre-school children exposed to opioids in utero. However, there was a trend to impaired outcomes in all domains [9].

Another group of investigators attempted to examine correlates of neurodevelopment measured in utero [10,11]. This was accomplished by assessing the relationship between fetal movement and the integration of movement with cardiac regulation, as measured by Doppler. The authors found that towards the end of gestation, there were reductions in intrauterine fetal movement in fetuses of mothers receiving buprenorphine. They also found a reduction in the coupling of cardiac activity with fetal movement at peak buprenorphine levels (2.5 hours following the daily dose) when compared to trough buprenorphine levels (measurements taken immediately prior to the daily dose) [10,11]. The authors consider the evolving ability of a developing fetus to match cardiac rate to activity level as a form of neurodevelopment and thus question whether opioids could impact neurodevelopment more broadly.

LIMITATIONS

Mothers and neonates with opioid exposure in pregnancy have multiple co-morbidities and are therefore very complex. These comorbidities include food insecurity, lack of access to care, additional drug and alcohol dependencies, mental health conditions, exposure to trauma, victimization and violence, malnutrition, and infection. This makes it extremely difficult to disentangle where the risk to neurodevelopment lies [7]. Authors have suggested that sociodemographic factors and effects of the care-taking environment may be more important determinants of developmental outcomes than the biological effects of opioid exposure. These authors have emphasized the need for interventions that support the parent and enrich the child's environment [5,12,13].

Another limitation of clinical studies is that opioid doses vary widely, which makes it difficult to generalize a given study. Accurate quantification of illegal opioid use is very difficult, and in studies of patients receiving medical replacement, it is difficult to account for potential illicit use during the study interval.

EXPERIMENTAL DATA

Evidence that opioids cross the placenta

All opioid replacement regimens are known to cross the placenta. Malek et al. reviewed the pharmacology of the interaction of opioids with the placenta [14]. The studies they reviewed included analyses of metabolites within maternal blood and umbilical cords (fetal blood) of mothers exposed to opioids, as well as experiments employing in vitro perfused placental explants. All methodologies suggested that opioids, including morphine, and synthetic opioids (such as fentanyl) can cross the placenta [14].

Mouse data of anatomical CNS variations in mice exposed antenatally to opioids

One elegant and carefully designed experiment demonstrated that mice exposed to morphine prenatally showed early postnatal biochemical and physiological changes, which correlated with changes in learning and memory at older ages [15]. The authors compared total protein and protein phosphorylation levels between the hippocampus of mice that had been exposed to morphine in utero with unexposed controls. They found evidence of altered expression of markers known to be associated with signaling through the N-methyl-D-aspartate receptor (NMDAR), which plays an important role in learning, memory, and development. This included reduced level of a protein called PSD-95, which complexes with the NMDAR, and mediates signaling as well as decreased phosphorylation of the cAMP responsive element binding protein (CREB) at serine 133. CREB is an NMDA activated transcription factor involved in learning and memory. The change in PSD-95 levels was seen at day 14 of life but normalized at later time points [15].

The results also showed that neurophysiological changes were taking place in those mice exposed to morphine in utero [15]. Hippocampal neurons of these mice showed decreased long-term depression of excitatory post-synaptic potentials following a stimulatory voltage pulse, thus showing reduction in a form of synaptic plasticity — a cellular correlate of learning. This study also found persistent long-standing changes in memory and learning. Mice exposed to morphine in utero had impaired performance on the water maze task, which is a classical test of spatial learning and memory. This effect was only seen in the first 2 days of testing and on consecutive days the mice did catch up to their respective controls [15].

Another study showed region-specific changes in the quantities of a specific class of neuron (defined by its expression of the calcium binding protein Calbindin D28-k) in the offspring of mice exposed to morphine throughout gestation [16]. The study looked at expression of Calbindin D-28k in the cingulate cortex, parietal cortex, and hippocampus of opioid exposed versus unexposed neonatal mice. The study found that in certain cortical layers, expression was increased whereas in others it was decreased by opioid exposure. These changes were not seen when adult mice were exposed to opioids. This suggests that immature neurons in the mouse brain have specific sensitivities to opioid exposure during development, which could theoretically affect learning, behaviour, or mood later in life. There is also evidence that maternal exposure to morphine prior to conception, even if there is no fetal exposure in the pregnancy itself, could have biological effects on the fetus. One study showed that when morphine was administered to female rats for five weeks, and then discontinued 4 weeks prior to mating, the offspring showed increased levels of hippocampal tumor necrosis factor alpha (TNFα) and decreased levels of the S100B protein [17]. Hippocampal TNFα has been shown in previous studies to alter memory performance in rats with chronic morphine exposure [18]. S100B protein is mainly expressed by astrocytes, a glial cell, and plays a role in neuro-inflammation and response to CNS damage.

Epigenetic and imprinting changes in the CNS lead to long-term consequences

Human studies have established that epigenetic changes in the promoter of the mu opioid receptor (OPRM1), which is the main site of action of opioids, exist in adults with opioid use disorder [19,20]. This was demonstrated by showing a higher frequency of methylation of certain cytosine residues within the OPMR1 promoter, part of CpG islands, which are areas on the DNA subjected to epigenetic control by methylation. This epigenetic change has been postulated as a potential mechanism contributing to tolerance and addiction. A group of investigators showed similar higher levels of methylation on the OPMR1 promoter in the saliva and blood of infants with neonatal abstinence syndrome. However, the study could not determine whether the epigenetic change was a pre-existing risk factor or

a change caused by the opioid exposure itself [21].

Animal experiments have suggested that exposure to morphine can cause multigenerational inherited effects. Byrnes et al. showed that when adolescent female mice were exposed to morphine prior to conception, the first generation (F1) and even second generation (F2) offspring showed behavioral and endocrine changes and accompanying molecular changes within the nucleus accumbens [22]. The nucleus accumbens is a dopaminergic system in the basal forebrain that is central to the reward circuit and is integrally implicated in addiction neuroscience. The authors used the locomotor sensitization assay, which is an established behavioural assay wherein animals that are chronically exposed to addictive drugs such as cocaine show hyperactivity following an acute challenge. The study showed that first and second generation progeny of female mice that were given morphine prior to conception show diminished locomotor sensitization in response to a dopamine agonist, quinprole, This was accompanied by reduced corticosteroid release which is mediated through the nucleus accumbens. They also found upregulation of mRNA expression of the kappa opioid receptor and the D2 dopamine receptor in the nucleus accumbens of the F1 and F2 female progeny. This heritability suggests an epigenetic mechanism whereby changes in genomic regulation (such as chromatin methylation or histone modification) are transmitted across generations [22].

As a caveat, we note that extrapolating such results from mouse to human is controversial. For example, the behavioural effects of epigenetic changes are likely to be much stronger in mice than humans, as behaviour in humans is, in general, less deterministic.

CLINICAL APPLICATIONS

Opioid replacement during pregnancy is currently indicated as part of a realistic risk reduction approach. Uniformly, published consensus statements and practice-guidelines state that the potential risk of in utero opioid replacement is strongly outweighed by its benefits [3,4,6]. These benefits include improved prenatal care, longer gestation, and reduced incidences of fetal demise, placental abruption and fetal passage of meconium [3,4]. In addition, untreated opioid use disorder is associated with high-risk activities such as prostitution, which expose women to violence, STIs and potential legal consequences [3]. Opioid replacement has also been shown to increase the rate of newborns remaining in the care of their mothers [4].

Long term follow-up and careful studies of language cognition and communication are required. This will help optimize management to ensure the best possible outcome. A potential, but not well-studied, alternative to opioid replacement is supervised withdrawal. This approach is not currently supported because it is associated with high relapse rates (to illicit opioid use) and poorer overall outcomes [3]. A recent study in Northern Ontario at the Meno Ya Win Health Centre in Sioux Lookout demonstrated that narcotic tapering with long-acting morphine preparations can be safely conducted in pregnancy and is associated with significantly lower incidences of NAS [23]. More studies are needed to assess whether supervised withdrawal may have a role, for example, in remote communities where there is no access to a methadone replacement program and where obtaining funding and supply for buprenorphine may be challenging.

As opioid replacement is a harm reduction strategy, it should be part of a comprehensive approach that provides supportive care to the mother, child, and family in order to optimize outcomes. Immediately following birth, skin-to-skin contact is protective against NAS [24]. Enabling a mother to room-in with her newborn while the newborn is getting advanced care or monitoring has also been shown to lower the incidence of NAS [24,25]. Providing maternal support to improve rates and duration of breastfeeding is also important, because evidence shows that breastfeeding not only decreases severity of NAS but also reduces maternal stress and enhances maternal confidence and mother-child bonding [6]. Ongoing medical and social support assistance to the family should include chemical dependency and relapse prevention programs [6], nutritional and financial support [26], and screening and support for co-occurring mental health conditions, trauma, and victimization [3]. Preventive interventions that provide enriched environments and high-quality care for infants and children are beneficial to neurodevelopmental outcome [12].

CONCLUSION

Clinical literature strongly supports opioid replacement in pregnancy for mothers with opioid use disorder and this approach is recommended by most professional guidelines. Opioid replacement prevents withdrawal and relapse and increases participation in antenatal care. Clinical experience and the studies conducted show that the benefits of opioid replacement outweigh its risks and that there are no major short-term developmental risks to the neonate. Careful epidemiological and ex-

perimental data, however, suggests that there could be subtler neurodevelopmental consequences that merit further study. Opioid replacement is part of a risk reduction strategy and the child's longer-term outcome can address social, psychological and physical injustices and comorbidities experienced by this vulnerable and precious population.

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Observing the Status of Women Through Health System Interactions

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ABSTRACT

This elective report provides an overview of the challenges women in Bolivia face when accessing care for reproductive health reasons. The perspectives provided in this paper are from the viewpoint of a Canadian medical student, after completing a 4-week elective in obstetrics and gynecology. Examples within obstetrics, gynecology, and obstetrical violence are used to provide insight into personal reflections regarding the status of women, observed during clinical encounters with patients and staff in a women's hospital.

RÉSUMÉ

Ce rapport de stage fournit un aperçu des défis auxquels sont confrontées les femmes en Bolivie lorsqu'elles accèdent à des soins pour des raisons de santé génésique. Les points de vue présentés dans ce document sont du point de vue d'une étudiante en médecine canadienne, après avoir terminé un stage de quatre semaines en obstétrique et en gynécologie. Des exemples d'obstétrique, de gynécologie et de violence obstétricale sont utilisés pour donner un aperçu des réflexions personnelles concernant la condition de la femme, observées lors des rencontres cliniques avec les patients et le personnel d'un hôpital pour femmes.

I arrived at the entrance of a woman's hospital in Bolivia with baggage. Metaphorically speaking, I arrived with my values, my opinions, and my experiences. Prior to my elective, as I was beginning to establish a foundation in health advocacy by learning to harness my skills and competencies, I found myself questioning our roles in health advocacy beyond our national borders. I wanted to ensure I was taking an ethical approach to this elective. My objectives were to observe and learn, not to teach. I came equipped with my own supplies and prophylaxis to minimize the 'medical footprint' I was to leave behind. My work was cemented in the notion of health as a human right, which included the right to quality health services. I recognized my limitations as a medical student, and refused to advance my technical skills at the expense of a patient and their safety.

My approach to this elective stemmed from my interest in a holistic approach to healthcare for a vulnerable population: women. Bolivia harbours one of the highest maternal mortality rates in Latin America [1]. I completed my elective at a tertiary-level hospital dedicated to women's health, where I hoped to acquire knowledge on the triumphs and tribulations facing women regarding their reproductive care.

OBSTETRICS

The emergency department was set up to maximize efficiency. Protocol disallowed family from entering the department and accompanying women during labour and delivery. This protocol is contrary to what I have observed in Canada, where labouring women are often accompanied by their partners or other support systems. The delivery room had four beds with cracks in the synthetic materials covering the thin padding; each bed was adorned by stirrups and separated by a curtain. Women were triaged, then escorted to either the dilation or pre-operative rooms for monitoring, or to a room designated for manual vacuum aspiration.

Systemically, Bolivia has public and private health centres. In private clinics, women with the ability to pay can deliver their babies in private rooms, in the presence of their loved ones. At this public hospital, family members waited outside, often spending the night on plastic benches or on the cobblestone.

Each vaginal delivery had a synchronicity to it. The patient was ushered from the dilation room onto a gurney, and helped onto the delivery table. A roll of cotton covered in paper packaging was placed under the patient's neck. She was ordered to rest her legs onto the stirrups, and position her hands around the

Keywords: Bolivia; Obstetrics; Gynecology; Reproductive Health; International Elective

vertical metal bars currently supporting her bent knees. After she delivered, it was time to lower the head of the bed, unroll the packaged cotton, and place it between her legs, and remove her legs from the stirrups. Epidurals were only provided to women undergoing a caesarean section, demonstrating the differences in pain management options compared to Canada and perhaps explained by disparities in resource availability, feasibility, and accessibility.

GYNECOLOGY

My first day at the hospital coincided with the first day of the staff strike. Mattresses were placed on the floor of the hospital entrance. I would often hear protestors chanting for better working conditions and benefits. Various women's health services were temporarily unavailable. The strike ended less than two weeks later, and external consultations resumed.

Although I witnessed the stagnation of health services when non-physicians went on strike, I also observed physicians go on strike. I was scheduled to work with a physician in external consultations one morning. I arrived to an empty waiting area. The physician cancelled his clinic, as he was on strike. This cancellation meant that many women would not be receiving their Papanicolaou smears. When he resumed clinical duties the following day, I saw women in their forties come for their first Papanicolaou smears.

Unfortunately, many cases are lost to follow-up, where patients do not return within the recommended timeframe. Although Bolivian and Canadian health systems strive to screen women for cervical cancer within suggested periods, I noticed that the average age at first presentation for cervical cancer screening was older in Bolivia than in Canada. A medical student highlighted the fact that the limited primary healthcare system stems from the notion that the presence of symptoms is what drives people to seek medical attention; thus, preventative medicine is neglected for more symptomatic presentations.

VIOLENCE AGAINST WOMEN IN HOSPITALS

Actions of abuse or disrespect by health professionals prenatally, during labour and delivery, or postnatally in facility-based childbirths is known as obstetrical violence [2]. My first experiences witnessing obstetrical violence occurred during this elective, and I realized how unprepared I was to challenge these violations as a foreign medical student and health advocate.

Discrimination from physicians was often in the form of verbal comments. I was rounding with a physician in the post-operative wing. If a patient had six or more children, the physician said they needed to 'ligate themselves', or that they 'needed to be more responsible'. These comments placed blame on women for their family size. Restrictions in reproductive health exist in Bolivia and produce barriers for women to ascertain their reproductive health rights. There were no conversations about the root causes of unwanted pregnancies in Bolivia, nor about the targeting of social inequalities, and gender-based violence that engender these outcomes.

Furthermore, a vulnerable sub-population are adolescent mothers. I interacted daily with adolescent patients, many of whom delivered their babies by caesarean section. To demonstrate the pervasiveness of adolescent pregnancies in Bolivia, the adolescent fertility rate, for women aged 15-19, was 70 births per 1,000 women in 2015. Canada's adolescent fertility rate in the same year was 9 births per 1,000 women [3].

I recall standing by a patient's bedside. The mother was holding her newborn, and the doctor turned to me and asked, "How old do you think she is?" The patient looked down, and I sensed sadness and shame. I believed that the emphasis made by the physician on her young age was afflicting her emotionally. I felt uncomfortable wearing my white coat, as I thought that this piece of fabric was engendering negative emotions in a patient based on the judgements of other providers at her expense. The most challenging experiences occurred when health professionals neglected the compassionate art of medicine for a more discriminatory approach to patient interactions. This incident was not an isolated event during my elective. These experiences provided insight into the treatment of a vulnerable population of women. My intentions are not to subject the health system, nor its members to scrutiny; however, I believe that treating patients in a humanistic matter is ethical, irrespective of national borders.

Obstetrical violence is not isolated to a specific country. Reports have also been published on cases of obstetrical violence in North America [4]. As health advocates, our role is to challenge systemic abuses and injustices faced by our patients, and by society. Although I felt unprepared to exercise my role as a health advocate in a foreign country, this elective has provided me with the opportunity to grow and expand my competencies as a future advocate in both national and international areas. I

hope to incorporate health advocacy as a cornerstone to my future practice. No country is immune to the tyranny of injustice, and with human rights transcending international borders, individuals can advocate at both national and international levels when done professionally and ethically.

FINAL REFLECTIONS

Reflections from my elective that I hold dear are not merely the techniques I observed nor the medical vocabulary I acquired. Rather, it is the privilege of being granted insight into women's health services in a system different from my own. The macrosystemic effects on the status of women percolate down all echelons of civil society and infiltrate into the care provided to women. I realized that concepts surrounding women's reproductive health in Bolivia are not openly discussed. And as a result, many of the abuses and realities surrounding reproductive health remain untold.

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In the twenty-first century alone, we have seen incredible evolution in the field of surgery and transplantation. Innovative surgical and medical imaging, implementation of robotics and artificial intelligence, and better understanding of the immunological aspects of transplant engraftment and rejection have played important roles in enhancing access to treatment and patient outcomes. However, scientific and clinical challenges remain and warrant discussion by scientists, medical professionals, stakeholders, and policy makers.

Issue 8.1 of the UOJM is therefore intended to explore the advancements and challenges in the field of surgery and transplantation, the development of relevant techniques and technology, and the translational impact on patient care, Canadian healthcare policy, and clinical collaboration. The submission deadline for our Spring issue is March 1, 2018 at 11:59PM. High-quality writing will be recognized with an honorarium award. Submissions can be made online and questions can be directed to contact@uojm.ca.

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Appel de soumissions

Le Journal de Médecine de l'Université d'Ottawa (JMUO) est une revue à comité de lecture publiée par des étudiants diplômés et des étudiants en médecine de la Faculté de médecine. Le JMUO est la seule revue médicale institutionnelle bilingue au Canada, accueillant des présentations de haute qualité en anglais ou en français. Les articles acceptés comprennent la recherche originale, les critiques et la pratique clinique, les nouvelles et les commentaires, les rapports de cas, les rapports facultatifs, et les entrevues. Le JMUO accepte actuellement des soumissions pour notre prochain numéro du printemps 2018 : Chirurgie et transplantation.

Au XXIe siècle seulement, nous avons vu une évolution incroyable dans le domaine de la chirurgie et de la transplantation. L'imagerie chirurgicale et médicale innovante, la mise en œuvre de la robotique et de l'intelligence artificielle, ainsi qu'une meilleure compréhension des aspects immunologiques de la greffe ont joué un rôle important dans l'amélioration de l'accès au traitement et aux patients. Cependant, des défis scientifiques et cliniques demeurent et méritent d'être débattus par les scientifiques, les professionnels de la santé, les intervenants et les décideurs.

Le numéro 8.1 de l'UOJM vise donc à explorer les progrès et les défis dans le domaine de la chirurgie et de la transplantation, le développement de techniques et de technologies pertinentes et leur impact sur les soins aux patients, la politique de santé canadienne et la collaboration clinique. La date limite de soumission de notre numéro du printemps est le 1er mars 2018 à 23h59. L'écriture de haute qualité sera récompensée par un prix d'honneur. Les soumissions peuvent être faites en ligne et les questions peuvent être adressées à contact@uojm.ca.

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