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Consideration of Use of Semaglutide and Tirzepatide Prior to Pregnancy

Alyse Goldberg, MD, FRCPC

Introduction

In reproductive-age females with elevated body mass index (BMI), weight loss is often recommended independent of their reproductive and family planning goals. However, it is clear that lifestyle methods for losing weight often fall short of achieving and maintaining weight loss. As approaches to addressing obesity and weight optimization evolve beyond the simplistic notion of "eat less and move more," there has been a growing acceptance of weight loss medications as part of comprehensive weight management strategies. It should also be noted that health optimization cannot be solely attributed to reducing BMI or kilograms of body weight. The objective of this paper is not to contribute to the well-established weight stigma in medicine, but rather to highlight a thoughtful approach to the use of weight loss medication in a cohort where the prevalence is expected to rise independent of the indication.

When considering pregnancy and pregnancy health optimization, decreased fertility and increased pregnancy complications have been associated with higher weight.[1] However, the role of weight loss in reversing these associations is less clear. It is possible that the lack of definitive benefits of weight loss is due to inherent challenges of achieving and sustaining significant weight loss. Pharmacological interventions that assist with weight loss may overcome that obstacle in the future. Related to this efficacy, there is an anticipated rise in the use of anti-obesity medication in reproductive age individuals who aim to optimize their weight for many health and non-health-related reasons. Therefore, as a medical community, we need to be thoughtful in advising this population on how to appropriately use and discontinue these medications in relation to reproductive goals.

Use of Anti-Obesity Medications

The approved anti-obesity medications in Canada include orlistat, naltrexone/bupropion, liraglutide, semaglutide, and tirzepatide, and they have been reviewed recently in relation to pre-pregnancy care.[2] As pregnancy is not a state of negative energy balance, weight loss medications do not have a role in pregnancy and should be discontinued prior to it. Metformin is not traditionally considered an anti-obesity agent as its effects on weight loss are less clear.[2]

However, metformin is often first-line adjuvant pharmacotherapy in those with documented insulin resistance, and/or polycystic ovary syndrome in the hope of weight stabilization and anthropometric benefits.[3] There is also experience in using metformin during early and late pregnancy. Thus, there are fewer concerns about pregnancy implications in those who conceive when on that medication.[4] With that in mind, metformin use in this population is less controversial.

The long-acting incretin mimetic medications, including the glucagon-like protein 1 receptor agonist (GLP-1 RA) semaglutide, and the combined GLP-1 RA and gastric inhibitory polypeptide receptor agonist (GIP RA) tirzepatide, have changed the landscape of anti-obesity medications given their observed efficacy in weight reduction. Both GIPs and GLP-1 RAs suppress appetite, slow gastric emptying, and enhance satiety leading to decreased food intake and weight reduction. They also halt the physiologic surge in hunger in response to weight loss that often limits weight loss sustainability.[5,6] Animal studies suggesting teratogenicity, as well as lack of pregnancy safety data, led to the recommendation to discontinue these medications 1-2 months prior to conception.[7,8] This paper aims to describe a practical approach to advising individuals who have been prescribed long-acting incretin-based anti-obesity medication, specifically semaglutide and tirzepatide, who are hoping to conceive.

Expectations of Weight Loss with Anti-Obesity Medication Use Prior to Pregnancy

Weight loss outcomes from semaglutide use were studied in a population with body mass index (BMI) >30 but without Type 2 diabetes (T2DM), in the Semaglutide Treatment Effect in People with Obesity (STEP) trials and found a 15.8% average loss after 68 weeks.[9] Tirzepatide was evaluated in individuals without T2DM and BMI >30 in the SURMOUNT-1 trial, which reported an average change in weight of up to 21% after 68 weeks.[6] Prescribing information, mechanism of action and dose titration are summarized in **Table 1**.

When considering use of anti-obesity medication in reproductive age patients, it is crucial to clarify expectations and implications of weight loss. Weight loss through lifestyle means has been shown to increase chances of spontaneous pregnancy, but has not conclusively demonstrated an increase in pregnancy or live birth rates after fertility intervention.[10] There remains a lack of published data on fertility (either unassisted or assisted) after intervention with semaglutide or tirzepatide, although this data is being collected. Pre-gestational weight loss is associated with fewer complications during fertility intervention, and some reduction in certain pregnancy-related health outcomes (e.g., hypertension and cesarian sections).[10] However, there may also be associated risk of early pregnancy losses.[11]

Expectations of weight regain post-drug cessation were observed in the STEP4 and SURMOUNT-4 trials, where the placebo arm discontinued semaglutide and tirzepatide after 20 or 36 weeks respectively of lead-in treatment with medication. In these studies, the treatment and placebo arm participants continued with monthly counselling, and were prescribed nutritional calorie deficit and weekly exercise requirements, as well as daily diarizing of lifestyle. Despite this, at 8 weeks from randomization to drug continuation vs placebo, the placebo groups did gain weight. However, they remained below their baseline weight.[12,13] These extension studies observing the sustainability of weight loss while taking semaglutide or tirzepatide also revealed that weight regain continued until the end of observation at 66-88 weeks. Upon trial completion, the participants' weight was still below baseline, but the weight regain had not yet plateaued. In counselling patients who need to discontinue these medications, we can acknowledge that weight regain is expected to occur, but the expected degree and/or speed of the regain is not clear, especially in a real-world scenario.

In patients who intend to conceive and discontinue the medication, the recommended 2-month "wash-out" would lead to potential weight regain immediately prior to and in early pregnancy, the impact of which has not been studied. "Excess" weight regain in early pregnancy post-GLP-1 RA discontinuation has been described in a case report[14] in which the authors proposed that the weight rebound after recent medication use was a potential contributor to observed fetal macrosomia. Regaining weight can lead to an overshoot phenomenon, resulting in excess weight gain, changes in body composition, and adverse surrogate markers of cardiometabolic health.[15] It is not clear if these anticipated weight

changes would pose increased risk during early pregnancy negating the same risks that weight loss was intended to improve. To complicate the decision-making process regarding initiating these medications, consideration should be given to availability of the medication given the rolling shortages, as well as the potential for long-term financial implications of these expensive medications that are rarely reimbursed by insurance when there is no T2DM diagnosis.

Despite the controversial benefits, some individuals will be seeking weight loss prior to fertility therapy for a variety of reasons, including meeting pre-established BMI cut-offs of outpatient fertility clinics. For individuals undergoing in-vitro fertilization (IVF), but not attempting immediate pregnancy, the timing of discontinuation of the medication is nuanced. There is unlikely to be appreciable risk on stimulated oocytes, as pregnancy concerns are related to organogenesis in pregnancy, and not to effects on the oocyte health. Thus, the decision to continue weekly medication through the oocyte stimulation component of IVF (when embryo transfer is delayed) should be done with input from the physicians who will be organizing the fertility interventions. Importantly, consideration should be given to anesthesia plans, as the current recommendation from American Society of Anesthesiologists Consensus-based Guideline suggests holding GLP-1 RA 1 week prior to procedures requiring sedation, irrespective of the medication indication.[16]

The concerns regarding the teratogenicity of GLP-1 and GIP RA are based on animal studies in which exposed rodent or rabbit offspring had low weight or bone development changes when the mother had active weight loss.[17] Published literature illustrating the pregnancy effects on humans is limited. Given the long half-life of semaglutide and tirzepatide, even discontinuation when pregnancy is confirmed would imply fetal exposure for at least 4-6 weeks gestation. It has been reassuring that, to date, no fetal defects associated with GLP1 RAs have been reported in case reports,[17] supported by a recent review of pregnancies exposed to non-insulin anti-T2DM medication including 461 individuals who had filled prescriptions of semaglutide.[18] Adequate contraception in those actively treated with anti-obesity medication is crucial given the risk of unplanned pregnancy, especially if ovulation is restored with weight loss. Manufacturers of tirzepatide include a warning that oral contraceptive pills may not be absorbed properly, necessitating back-up contraception when initiating and titrating the medication.[7] In the event of conception while taking tirzepatide or semaglutide, the medication should be discontinued, but there is no current recommendation for additional fetal monitoring.

Practical Advice for Pre-Pregnancy Medication Discontinuation

Best practices for discontinuing anti-obesity medications have not been published. After discontinuing GLP-1 or GIP RA medication, there is an expected return of hunger. This may be heightened due to new low weight and a physiological response to return to previous weight set point. It may also be compounded by lower metabolic rate if lean muscle mass loss took place during preceding weight loss. To combat the appetite resurgence, some practitioners hypothesize that gradual reduction of the medication (weaning) may lead to less appreciable appetite resurgence compared to sudden cessation. However, this has not been formally studied. Weaning may inadvertently lead to longer duration of suboptimal dosing, and pregnancy would not be recommended until medication was completely stopped. A preliminary study[19] suggested that using metformin as a "bridge" may assist in halting the degree of weight regain. However, it has not yet been published.

Strategies to support individuals discontinuing incretin mimetics (or any weight loss aid) include:

- Setting expectations: It is important to counsel patients that weight gain has been observed and is expected after medication cessation, based on the given drug's mechanism of action and large clinical studies.
- Emphasizing non-pharmacologic healthy behaviours to reduce weight regain:
    - Nutritional counselling to optimize whole, satiating food with protein and fibre, and to decrease ultra-processed food and liquid calories
    - Resistance training to increase lean body mass
    - Mental health support to assist with thoughts, and behaviour training that reduces high-risk eating behaviours (this may include involvement of a coach/ dietician/behaviour therapist if accessible)

- Gradual dose reduction may ease appetite resurgence but will delay timing of pregnancy
- Trial of metformin use as a "bridge" to slow weight regain (if tolerated)

Conclusion

As there is an anticipated rise in use of semaglutide, tirzepatide, and future versions of long-acting incretin mimetic medications to support weight optimization in reproductive age women, appropriate counselling regarding the risk of pregnancy exposure and management in the peri-partum time is crucial. Discontinuation of these medications is necessary prior to pregnancy but comes with the expectation of weight regain. Non-pharmacologic healthy behaviour optimization should be prioritized during the transition off the medication. Attention should be paid to the implications of rebound weight gain during early pregnancy in order to advise on the future role of the medication in this population.

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Name	Mechanism of Action	Dose	Dosing Titration	Side Effects Management	Safety Concerns/ Contraindications	Duration to Stop Prior to Pregnancy	Observed Weight Loss Post Drug Cessation
Semaglutide	GLP-1 Receptor agonist that leads to appetite suppression and delayed gastric emptying	0.25-2.4 mg subcutaneously weekly	• 0.25 mg/week x 4 weeks, then increased to 0.5 mg/week subcutaneously injected at home • If tolerated, the dose can be increased depending on clinical response and tolerability to 1 mg, 1.7 mg or 2.4 mg and then maintained	Gastrointestinal symptoms, such as: • nausea • vomiting • and constipation. Can be managed with over-the-counter medication (eg. anti-nausea or antacid formulations) or reduction in the dose to balance tolerability and clinical effectiveness.	• Family or personal history of medullary thyroid cancer or multiple endocrine neoplasia type 2 (MEN2) syndrome, pregnancy • Not recommended for pregnancy on lactation	At least 2 months prior to conception[8]	Change in body weight from baseline was -12% at discontinuation after 20 weeks run in At 1 mo post discontinuation change from baseline up to -10% At 4 mo post discontinuation, change in weight was -9% from baseline[12]
Tirzepatide	GIP/GLP-1 Dual Agonist that supresses appetite and delays gastric emptying	5-15 mg subcutaneously weekly	• 2.5 mg/weekly subcutaneous injection and increased to 5 mg after 4 weeks • Further titration by 2.5 mg q4 weeks can be increased to achieve desired effects, up to max dose 15 mg/week			At least 2 months prior to conception[7]	Change in body weight from baseline was -21% at discontinuation after 36 weeks run-in At 1 mo post discontinuation change in weight was -18% from baseline At 4 mo post discontinuation change in weight was -15% from baseline[13]

Table 1. Semaglutide and tirzepatide prescribing information, mechanism of action, and dose titration[8, 12, 7, 13]

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Conversations in Breast Cancer Screening: An Exploration of Age, Density, and Emerging Technologies

Nureen Sumar, MD, MSc, CCFP
Ali Poonja, MD

Introduction

Breast Cancer remains a significant burden in Canada, reflecting global patterns as one of the most common cancers affecting women. In 2023, it was estimated that 26% of all new cancer cases among Canadian women were attributed to breast cancer, contributing to 13% of all cancer deaths in this group.[1] Recent advancements in both detection and treatment of breast cancer have significantly improved cure rates, particularly when breast cancer is detected early. Early-stage breast cancer detected through screening can have a 5-year survival rate of 99%.[2,3] Thus, the quest for early detection through effective and economical screening initiatives is a critical component in minimizing the burden of disease and reducing breast cancer-related mortality.

However, ongoing dialogue continues within the medical community regarding the optimal timing of screening initiation for women at average risk. Discussion about the appropriate age to discontinue screening is an evolving topic. This conversation is complex and multifaceted, involving careful consideration of the intricate balance between the benefits of early detection, economic implications of population screening, and potential harms such as overdiagnosis and the psychological impact of false positives.[4] Current Canadian guidelines, last updated in 2018, recommended mammography screening every 2–3 years for women aged 50–74 years, reflecting an expert consensus that considers both scientific evidence and population health needs.[5] These guidelines are under revision with an update expected in 2024, while other major organizations have recently published new recommendations, reflecting the value of early detection at a younger age in the effort to minimize cancer deaths.[6]

Additionally, the efficacy of mammography alone as a screening modality in women with dense breast tissue, who constitute up to 43% of the screening population, has come into question.[7,8] This challenge has catalyzed discussion around recommended supplementary screening modalities to improve cancer detection rates in women with dense breast tissue.[9]

This article explores the ongoing discourse on breast cancer screening recommendations for average-risk women, including the age at which to initiate and stop screening, imaging modalities, and emerging technologies.

The Age Dilemma: Evidence, Guidelines, and Ongoing Debate.

When to Initiate Breast Cancer Screening

The optimal age to initiate population screening for breast cancer in Canadians remains a contentious issue within the medical community, with various organizations offering varying recommendations. The 2018 consensus guidelines from the Canadian Task Force on Preventive Health Care (CTFPHC) recommend mammography screening every 2–3 years for women aged 50–74 years who are not at increased risk of breast cancer.[5] These guidelines were independently reviewed using the AGREE II (Appraisal of Guidelines for Research and Evaluation) tool and were found to be of high quality. However, they are currently under review, with an anticipated release in 2024. A recent review of breast cancer screening guidelines highlighted how the current Canadian

recommendations differ from recently updated and comparable screening guidelines.[10]

For example, in the United States, revised recommendations by the American Cancer Society (ACS) recommend that women at average risk should have the option to begin annual mammography at age 40 and should definitely begin by age 45.[11] Early initiation of screening aims to reduce breast cancer mortality by diagnosing breast cancer in its earlier stages, which may be more favourable to treatment. The American College of Radiology (ACR) and the Society of Breast Imaging advocate for annual mammograms starting at age 40, citing significant reductions in mortality and increases in years of life saved.[12] Recent Canadian studies also support early screening. One study concluded that starting mammography at age 40 can significantly decrease breast cancer mortality by enabling earlier diagnosis, where treatment may be more effective.[13] Another study discusses the downstream impacts of organized screening programs in Canada, further advocating for the early initiation of screening.[20]

Arguments for Earlier Screening Initiation at Age 40

Proponents of initiating breast cancer screening at the age of 40 emphasize the potential for early detection to reduce breast cancer mortality by up to 30%.[14] A recent study, which involved hypothetical risk assessments and modelling, found that the age-based strategy detected more breast cancers but led to more false-positive mammograms and benign biopsy results. It went on to show that breast cancer in younger women tends to be more aggressive, highlighting the need for early detection.[15]

Beyond mortality, early and localized detection of breast cancer can improve quality of life by allowing for breast conservation options versus mastectomies, thus potentially having more favourable psychosocial outcomes. Earlier stage cancers may also require less aggressive treatments, which may lead to fewer toxicities and late-effects. Canadian authors have conducted a comprehensive review of important non-mortality metrics and quality indicators that demonstrate alternative considerations in the debate on the age of population screening initiation.[16]

Arguments Against Earlier Age-Based Screening at Age 40

Conversely, concerns about overdiagnosis, the benefits of early diagnosis given treatment advances, and the psychological impacts of false positives are ongoing. Overdiagnosis can lead to unnecessary treatments, which carry significant risks and side effects. Recent expert discussions suggest that a significant proportion of cancers detected through early screening may never become clinically significant.[4] Furthermore, false positives may precipitate anxiety, stress, and invasive procedures.[6]

Economic considerations may also play a role in this debate. Screening younger women for breast cancer more frequently can lead to increased healthcare costs, which may not be proportionate to the benefits in mortality reduction, especially with rapid advancements related to breast cancer diagnosis and treatment. For instance, the United Kingdom's National Health Service (NHS) continues to recommend routine screening at the age of 50, citing a more favourable balance of risks and benefits.[10]

Cessation of Breast Cancer Screening

When to discontinue breast cancer screening is also being debated. Canadian guidelines recommend screening up to age 74, citing insufficient evidence to support screening beyond this age. However, they suggest the decision to continue beyond the age of 74 to be individualized and based on informed discussion, overall health, and patient preferences.[5] The revised ACS guidelines recommend women continue mammography as long as they are in good health and expected to live beyond 10 years.[11]

Older Women: To Screen or Not to Screen?

Proponents of screening cessation as women age cite diminishing returns, suggesting that competing causes of death reduces the relative impact of early detection of breast cancer. Some suggest that continuing mammography beyond the age of 70 does not significantly impact breast cancer mortality and may pose a greater risk of overdiagnosis. Additionally, screening may lead to the detection of slow growing tumours that would not have caused harm within their natural lifespan, possibly resulting in unnecessary treatments and associated morbidity.[17-20]

Conversely, some experts argue that screening should continue for as long as women are in good health with a reasonable

life expectancy, as breast cancer risk increases with age.[12,20,21] A recent study by Lee *et al.* (2023) reports that screening mammography has favourable performance metrics in older women, with benefits outweighing the risk until age 90. Improved sensitivity and specificity lead to fewer false positives. They have also reviewed observational studies that demonstrate screen-detected cancers in older women are found at an earlier cancer stage, making them amenable to less invasive treatments. This highlights the importance of adaptable guidelines and individualized care.[22]

Table 1 provides an overview of access to breast cancer screening across all Canadian provinces and territories, focusing on women aged 40–49 at average risk. Additionally, the table highlights the policies regarding breast density notification.

	Women aged 40-49 years can self-refer for a mammogram	Women can self-refer for annual mammograms	All women are directly informed of their breast density	Only women with BI-RADS D density are informed of their density	Only women with BI-RADS D density are invited for annual (instead of biennial) mammography
British Columbia	Yes	No	Yes	No	No
Alberta	Yes with conditions*	Yes with conditions*	Yes	No	No
Saskatchewan	No	No	No	Yes	Yes
Manitoba	No	No	Yes	No	No
Ontario	No	No	No	Yes	Yes
Quebec	No	No	No	No	No
New Brunswick	No	No	Yes	No	No
Nova Scotia	Yes	Yes	Yes	No	No
Prince Edward Island	Yes	Yes	Yes	No	Yes
Newfoundland and Labrador	No	No	No	Yes	Yes
Yukon	Yes	Yes	No	Yes	Yes
Northwest Territories	Yes with conditions*	No	No	Yes	Yes
Nunavut	No	No	No	No	No

*women can self-refer after the first referral is made by the family physician

Table 1: Jurisdictional Screening Access and Breast Density Reporting (Canada); provides an overview of access to breast cancer screening across all Canadian provinces and territories, focusing on women aged 40-49 at average-risk. Some provinces and territories allow for self-referral for mammogram, either directly or after an initial referral by family physician. Additionally, the table highlights the policies regarding breast density notification, including which provinces inform all women of their breast density and which inform only those with BI-RADS (Breast Imaging & Reporting Data System) D density.[6] *Adapted from Yong-Hing CJ et. al, 2023.*

Breast Density and Implications for Mammography

Understanding Breast Density

Breast density refers to the proportion of fibroglandular to fatty tissue in the breast visible on a mammogram. The BI-RADS (Breast Imaging Reporting and Data System) scoring system categorizes breast density into four levels:

- A (almost entirely fatty)
- B (scattered fibroglandular densities)
- C (heterogeneously dense), and
- D (extremely dense)

Women with a BI-RADS score of C or D are considered to have dense breasts.[23,24]

Implications

Dense breasts contain a higher percentage of fibroglandular tissue, which appears white on a mammogram, similar to the appearance of potential tumours, which complicates detection.[7,25] Dense breast tissue not only complicates mammogram readings by obscuring tumours, thereby reducing the sensitivity of mammograms (resulting in lower detection rates), but also independently increases the risk of breast cancer.[23,25,26] These challenges raise the urgency around the need for enhanced screening strategies for women with dense breasts who receive negative mammogram results.

Supplementary imaging for average-risk women with a BI-RADS score of C or D with negative mammography results

To address these challenges, supplementary screening modalities such as ultrasound and magnetic resonance imaging (MRI) are recommended. Canadian guidelines recommend the use of supplemental ultrasound for women with dense breasts following a negative mammogram result. MRI, however, is advised for women with extremely dense breasts or additional risk factors.[7] The DENSE trial in Europe demonstrated that supplemental MRI significantly improved cancer detection rates in women with extremely dense breasts.[9] By comparison, in the USA, the ACR suggests either supplemental MRI or ultrasound for women with dense breasts to improve detection rates.[12]

Current guidelines have adopted recommendations that emphasize a personalized risk assessment to determine the most appropriate screening strategy, balancing the benefits of early detection with the potential harms of overdiagnosis and false positives.

Advanced and Emerging Technologies

Evaluation of advanced imaging techniques such as handheld ultrasound versus automated whole breast ultrasound (AWBUS), digital breast tomosynthesis, and contrast-enhanced mammography are also being explored for their efficacy in improving cancer detection rates.[27] Some provinces have already adopted these advanced technologies. Also emerging in breast cancer screening is the supplementary use of artificial intelligence (AI). AI algorithms may come to play an important role in triaging mammograms, streamlining radiologist workloads, in addition to improving cancer detection rates and diagnostic accuracy.[28]

Thermography

Thermography uses infrared technology to detect heat patterns and vascular flow in breast tissue and has sparked controversial dialogue with respect to its utilization in breast cancer screening. While it offers a non-invasive and radiation-free alternative to mammography, its efficacy has not been established. Studies show variable sensitivity and specificity in the diagnostic accuracy of thermography; however, recent advancements in AI may improve its accuracy. Current evidence strongly suggests that thermography should not replace conventional imaging modalities. However, it may have a utility in underserved areas where access to mammography is limited.[29-31]

Conclusions and Future Directions

Breast cancer remains one of the leading cancers affecting women with a significant population burden. The discourse on breast cancer screening in Canada remains an evolving and rich conversation, centred around when to initiate and cease breast cancer screening, while evaluating benefits, potential harms, risk factors, special populations, rapid advancements in imaging modalities, and cancer therapies. Current Canadian guidelines are under review by the Canadian Task Force for Preventive Health, with an anticipated release of the updated guidelines in 2024. As we await these updates, our focus remains on an evidence-based, individualized, and patient-centric approach that incorporates the importance of early detection in mitigating

breast cancer related morbidity and mortality outcomes, while also mitigating the risks inherent in population screening initiatives.

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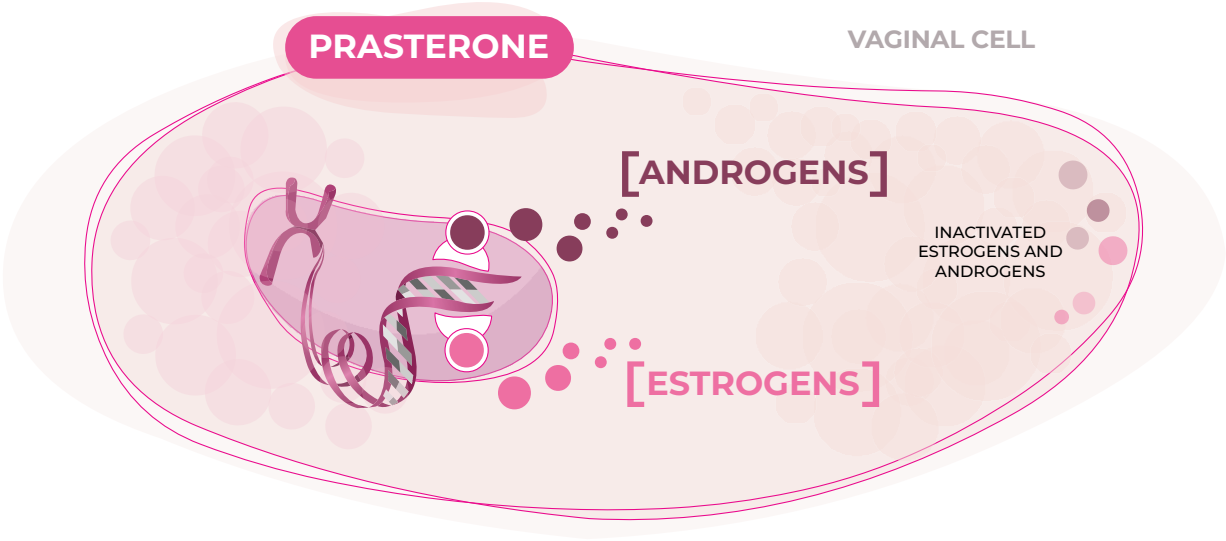

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Dr. Delpero completed her medical training at the University of Toronto including medical school, residency in Obstetrics and Gynecology, and fellowship in vulvovaginal health. During her training she also completed a certificate in health journalism through the Dalla Lana School of Public Health and the Munk School of Global Affairs, and obtained master's in systems leadership and innovation through the Institute for Health Policy, Management and Evaluation. She is currently an assistant professor at the University of Ottawa, where she maintains a general obstetrics practice and a focussed gynecologic practice in vulvar skin disorders, colposcopy and menopause management.

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The Three Lichens: A Generalist Approach to Vulvar Skin Conditions

Emily Delpero, MD

Introduction

Vulvar skin complaints represent a significant proportion of visits to family physician, dermatology and gynecology offices. Healthcare training programs place little emphasis on exposure to these conditions, which limits providers' ability to assess and manage them. Increasing the visibility, recognition, and treatment of these conditions serves to improve patient care in Canada.

Lichen Sclerosus

Background

Vulvar lichen sclerosus (vLS) is an autoimmune condition that affects the perineal and perianal skin. It was previously classified as a rare disease which likely represents underestimation and misdiagnosis. More recent estimates indicate its prevalence as 1.7% in a gynecologist's office[1] and 2.4% in a retirement home.[2] This condition is strongly associated with other autoimmune diseases, with one-third of patients having at least one other condition such as Hashimoto's thyroiditis, alopecia areata, and vitiligo.[3]

Currently it takes 5-15 years from onset of symptoms to diagnosis, and while most patients are diagnosed in the pre-pubescent phase of life or in menopause, there is increasing evidence that early signs and symptoms can evolve during reproductive years.[4]

Diagnosis

A diagnosis of vLS can be made based on history and physical examination. While biopsy can offer a definitive diagnosis, not all patients require this intervention. Common symptoms can include pruritus, irritation and pain, dyspareunia with recurrent tearing, and fissuring of the skin. In younger patients, simply having recurrent tearing with intercourse can be the only initial symptom.[5] Some patients might also be asymptomatic. Physical examination signs include evolving ivory white shiny or crinkled patches on the labia and perianal skin, with petechiae and cigarette paper texture changes. These skin changes classically occur in a figure of 8 distribution but

lichen sclerosus (LS) can also arise focally and asymmetrically.

Disease Course

LS is a chronic condition with a relapsing and remitting course throughout a person's lifetime. Progression of disease includes distortion of the vulvar architecture and permanent anatomy changes such as clitoral phimosis, narrowing of the introitus, and lateral and medial agglutination of the labia minora. This can be deeply impactful to daily urinary function and sexual function of patients with vLS. Uncontrolled vLS is also associated with the development of vulvar squamous cell carcinoma in 4-7% of cases.[6]

When to Biopsy

Patients with classic lesions who respond appropriately to therapy do not require a biopsy, but healthcare providers should consider biopsy for definitive diagnosis in the following circumstances:

1. Patient preference
2. Non-classic presentation (i.e., asymptomatic or focal lesions for diagnostic clarification)
3. Any raised, hardened, ulcerated areas (i.e., concern for malignancy)
4. Condition refractory to therapy

Biopsy results can also be misleading and non-specific if an insufficient sample is taken, or if the area is pre-treated with potent steroids. Early vLS can result as non-specific vulvitis or eczema. This author recommends a 4 mm punch biopsy sample directed towards the most prominent area of abnormality.

Treatment

There are three main purposes of treating vLS:

1. Symptom control and quality of life
2. Prevention of ongoing anatomy changes
3. Lower likelihood of progression to vulvar cancer[7]

There is no cure for vLS but the gold standard of therapy is ultra-potent topical steroid ointments.[8] Ointments are preferred over creams for the vulvar skin because creams contain more irritants like alcohol base and can easily be wiped off. The two options available in Canada include clobetasol propionate 0.05% and betamethasone dipropionate 0.05%.

There are slightly different published regimens, but recommended dosing from the British guidelines includes 0.25 g (half a fingertip unit) to affected area nightly for 1 month, then every other night for 1 month, then twice a week.[8]

The role of maintenance therapy is currently under study but is emphasized in order to maintain disease control and address subclinical inflammation.

Some patients may benefit from added topical tacrolimus 0.1% or pimecrolimus 0.1% on days alternating with steroid application. These are considered potentially "steroid sparing" but are less effective than topical steroids at controlling inflammation.[9] Additionally, these options are typically poorly tolerated by patients who often experience burning and irritation after application.

Rare cases that are refractory to topical therapy may require systemic medications that are beyond the scope of this article.

When to Refer

Consider referral to a vulvar skin specialist if there is diagnostic uncertainty (i.e., discrepancy between clinical presentation and histology), concerning and evolving lesions, or if symptoms are refractory to appropriate therapy.

Follow-Up

Initially, patients with vLS should have a skin examination every 6-12 months depending on response to steroids and compliance. Once stable, patients with vLS should have annual skin checks to ensure no new lesions, and be advised to seek medical attention if they evolve into new growths, change in symptoms, or new symptoms refractory to their usual therapy.

Lichen Planus

Vulvar lichen planus (vLP) is a less common autoimmune vulvar dermatosis that can mimic LS. It is diagnosed in the same way, and is characterized more by vulvar burning and irritation than pruritus although both can be present. Classically, patients present with red erosions at the introitus surrounded by white lacy striae and anatomy changes including resorption of the labia minora, clitoral phimosis, and/or narrowing of the introitus. Patients with lichen planus (LP) often have lesions elsewhere, particularly oral erosions. Unlike LS, lichen planus can involve the vaginal mucosa as well and lead to an obliterated or stenosed vaginal canal. Examining patients with vLP does involve a speculum examination to assess for vaginal involvement.[10,11]

Clinically, distinguishing vulvar LS from LP may be challenging, and can be aided by biopsy. However, the principles of treatment are the same. These include a topical steroid taper (using ointment on the vulva, and cream for vaginal involvement) and possibly a steroid-sparing agent depending on symptoms. Similar to vLS, refractory cases may require systemic therapy.

The clinical course of vLP is less well-characterized, therefore the role of maintenance therapy is less robust in LP than LS, as is the link between LP and the evolution of vulvar cancer.[12]

When to Biopsy

If the need arises (similar to the indications highlighted for LS) for diagnosis, consider a biopsy from the edge of the erosion.

When to Refer

The reasons to refer are similar to those for vLS and include diagnostic uncertainty (i.e., discrepancy between clinical presentation and histology), concerning and evolving lesions, or if symptoms are refractory to appropriate therapy.

Lichen Simplex Chronicus

This skin condition affects all people of all ages, and there is an association and overlap with atopic dermatitis. Some patients present with symptoms elsewhere, and some have symptoms only on their vulvar skin. Anogenital lichen simplex chronicus (LSC) is quite common, with a reported prevalence of upwards of 10%.[13]

Clinically, LSC presents as an "itch-scratch cycle". There might be a history of an identifiable trigger (i.e. prior yeast infection, recent shaving, exposure to new soap, or prolonged exposure to damp material), but symptoms of pruritus can also arise spontaneously. Other vulvar dermatoses like LS can predispose to LSC as well. Whatever the cause, the itchy skin is rubbed and scratched, which in turn leads to inflammation and propagates the pruritus. On history, patients might not endorse scratching, but they may be rubbing the skin with a towel after the shower, toilet paper after the bathroom, or at night while they are asleep.

On examination, the vulva can appear symmetrically or focally affected with erythematous, poorly demarcated scaling papules/plaques, epithelial disruption, and lichenification. If the patient has a light skin tone[14], these areas can appear whitened because the thickened skin holds onto moisture. In patients with darker skin tones, the changes can appear hyperpigmented.

A biopsy of the area is often non-specific, and may return demonstrating "psoariasiform dermatitis" which is confusing for clinicians who may in turn diagnose the patient with psoriasis. Distinguishing psoriasis from LSC can be difficult, but patients with vulvar psoriasis will have plaques elsewhere on the body (i.e. scalp), or nail, or joint involvement.[11]

Treatment

Treatment involves several avenues to disrupt the itch-scratch cycle.[11]

1. Counselling patients carefully about vulvar hygiene will help reduce potential contact irritants, and exposure to heat and sweat **(see box on vulvar hygiene tips)**
2. Restore the skin barrier with petrolatum base, coconut oil or zinc ointment
3. Address the inflammation directly with moderate-to-potent steroids. These steroids may need to be used once daily for 1-3 months depending on the severity of initial presentation, then decreased to a PRN basis
    - A common regimen to consider is fluocinonide 0.05% ointment (0.5 of a fingertip unit) nightly for 1-3 months then 2-3 x weekly as needed. Alternatively, one may use desoximetasone 0.25% ointment with the same schedule.
    - If a patient has not improved after 1 month of topical therapy, systemic therapy may be required, or the diagnosis may need to be reconsidered.
4. Finally, patients should be informed that if they do not stop re-traumatizing the skin with scratching or rubbing, the condition will not resolve. If there is concern for nighttime or involuntary scratching, consider a short 1–2-month course of antihistamine at bedtime to reduce the impulse

Follow-Up

In patients with a new diagnosis of LSC, early follow-up at 3-6 months may be required to assess response, compliance with therapy, and to trouble shoot any therapy-related problems. Patient presentations may resolve completely, but if there is an underlying dermatosis (i.e., vLS) further annual follow-up is recommended as discussed above.

Vulvar hygiene tips:

- No soaps/cleansers/douches on the vulva, even "baby soap" or "sensitive skin" soaps
- Use lukewarm water on the vulva
- Avoid cleaning the vulvar skin more than once a day, and avoid scrubbing the skin
- Let the vulvar skin air dry or pat dry
- Avoid tight fitting clothing
- Remove sweaty or wet clothing as soon as possible
- Consider cotton underwear or no underwear at night
- Consider avoidance of pads, or use cotton or hypoallergenic versions

Prescribing Topical Steroids

Healthcare providers, including pharmacists and physicians, are trusted sources of information for patients. Unfortunately, they unwittingly also become sources of steroid phobia and non-compliance.[15] Steroid phobia is defined as "vague negative feelings and beliefs held by patients/caregivers" which are associated with non-compliance, undertreated conditions, reliance on alternative and unproven remedies, or the need to scale to systemic medications which carry their own toxicities. This is best characterized in the field of atopic dermatitis, but it applies to patients with other skin conditions as well.

Safety

When topical steroids are used and monitored appropriately, the risk of side effects is extremely low.[16] For vulvar dermatoses, the impact and harm associated with an undertreated skin condition outweigh the risk of treatment-related adverse events.

Locally, topical steroids may cause skin thinning, telangiectasia, or hypopigmentation (although untreated LS or LP can certainly damage the skin in their own right). There are potential systemic effects of immunosuppression or adrenocortical insufficiency; however, this was found in patients who were using 100 g of ultrapotent topical steroid once-weekly for 1.5 years.[17]

When discussing topical ointment dosing, fingertip units (0.5 g) have been described as: from the end of the finger to the first joint. The vulva requires half of a finger tip unit (0.25 g) to cover its entire surface. Using a topical steroid on the vulva every day for 30 days would translate to a cumulative monthly dose of 7.5 g.

How to Safely and Effectively Prescribe Steroids for Vulvar Skin Conditions

1. Use ointment, not cream
2. Demonstrate to the patient the quantity to use
3. Demonstrate where to apply (i.e. via mirror, diagram, or touch)
4. Explain concerning, albeit unlikely, side effects patients might read or hear about, or be advised of by other people including other physicians and pharmacists. Be careful to place them in the context of how little product the patient will be using.
5. Encourage judicious use. If there is concern of overuse, prescribe 30 g at a time with no refills. This should be sufficient for a 4-month supply for a patient using steroids daily.
6. Follow-up with the patient as required

Other Resources for Healthcare Providers

Useful resources for additional, evidence-based information include:

- The International Society for the Study of Vulvovaginal Diseases (www.issvd.org) a global organization that promotes evidence-based research, publications and conferences.
- Vulva Diaries podcast by Dr. Amanda Selk
- Jill Krapf, MD on Instagram

Conclusion

Various types of vulvar skin conditions occur among a significant proportion of the population, and require treatment on the part of family physicians, dermatologists and gynecologists. This paper highlights the diagnosis, clinical signs and symptoms, and treatment approaches for these conditions with a view toward enhancing healthcare providers' ability to assess and manage them.

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Endometriosis: A Narrative Review

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Introduction

Although much progress has been made since endometriosis was first scientifically described centuries ago, numerous unanswered questions still surround this chronic, inflammatory condition.[1] For instance, one theory on the pathogenesis of endometriosis suggests that the condition begins from retrograde menstrual flow implanting on surfaces in the abdomen and pelvis (Samson's theory), which is a logical mechanism given the high rates of endometriosis in patients with obstructive anomalies of the lower genital tract and significant retrograde flow. This explanation has many shortcomings however, as retrograde menstruation occurs more commonly than the reported 10% prevalence of endometriosis. Additionally, endometriosis lesions can be found in areas quite remote from the pelvis, such as the thoracic cavity. As such, research has been increasingly focused on identifying immune, genetic, and local environmental factors that likely play critical roles in the development of endometriosis. This growth of benign endometrial-like tissue outside of the uterus can sometimes be asymptomatic, but it can also cause debilitating pain, infertility, ovarian cysts (endometriomas), and can invade surrounding organs such as the bowel or bladder. There are three main phenotypes of endometriosis: superficial lesions, deeply infiltrating endometriosis (including nodules), and ovarian endometriomas.

While the exact etiology may be obscure, the societal and economic impacts of this condition are undeniable. Patients diagnosed with endometriosis are at a significantly higher risk of absenteeism from work or school, lower quality of life, chronic pelvic pain, and are more likely to receive a mental health diagnosis such as depression or anxiety.[2,3] Apart from direct and indirect incurred costs to patients (estimated at approximately $5000 per patient annually), at a national level the economic burden of endometriosis exceeds $2 billion annually in Canada, and approaches $80 billion in the USA.[4,5]

Diagnosis

The difficulty in diagnosing endometriosis is two-fold. Firstly, abnormally painful periods, the hallmark of endometriosis, are commonly normalized or discounted by patients or physicians; this can result in a lengthy delay both in seeking and obtaining a diagnosis that can range from 4–11 years.[6] Secondly, in the absence of endometriomas, imaging for endometriosis is extremely dependent on how the radiological exam is performed and on the interpretation of the images. Apart from imaging, endometriosis can be diagnosed during surgery, however, current guidelines and societies uniformly recommend against diagnostic laparoscopy for the sole purpose of establishing a diagnosis.[7,8] In appropriate patients, a presumptive diagnosis based on a patient's history and physical exam findings can safely expedite clinical management and improve patient symptoms.

Ultrasound

Transvaginal ultrasound typically can detect ovarian endometriomas, with their pathognomonic ground-glass contents, absence of flow within these lesions, and ovaries which are abnormally adherent to one-another ("kissing ovaries"). More subtle signs such as the sliding-sign (assessing the mobility of the uterus and vagina against the rectosigmoid) or the presence of bowel, bladder or uterosacral nodules require more specific expertise not widely available in the community. The overall sensitivity of ultrasound to detect endometriosis ranges from 80–90%, with a specificity of approximately 90%; however, for deep disease (including bowel nodules and ovarian endometriomas) the sensitivity and specificity exceed 90%.[9-11]

Magnetic Resonance Imaging

Compared to ultrasound, magnetic resonance imaging (MRI) has the advantage of visualizing extrapelvic disease (i.e. lower lung fields, diaphragm, abdomen, and bowel lesions beyond the reach of pelvic ultrasound) and does

not rely on the sonographer's dynamic use of the ultrasound probe to generate images. If advanced ultrasound is not available, MRI may improve the accessibility of diagnostic imaging for patients. For deep disease, MRI has a sensitivity and specificity of approximately 94% and 77%, respectively. Classically, T2-hypointense lesions, occasionally with T1-hyperintense spots, signal nodules of endometriosis. Besides its diagnostic role, MRI can also help with operative planning, such as the need for colorectal resection or urological procedures if surgery for endometriosis is being considered.

Molecular Testing

Novel tests are currently under development for the diagnosis of endometriosis using salivary micro-ribonucleic acid (miRNA) signatures. Although these tests have shown promising preliminary results, with a sensitivity and specificity of >95%, these remain investigational and are not yet available for commercial use.[12,13]

Treatment of Endometriosis

The approach to managing endometriosis hinges on whether the patient's main concern is pain, fertility, or both. Apart from the significant impact on quality of life that endometriosis can cause, there are no immediate health concerns unless the endometriosis is compromising another organ such as the bowel or the urinary tract. As such, treatment must be guided by the patient's priorities, keeping in mind that asymptomatic endometriosis generally does not require intervention.

Pain: Non-Surgical Management

Non-pharmacological options for managing the pain associated with endometriosis include an anti-inflammatory diet, mindfulness, and pelvic physiotherapy, the latter of which has significant benefits for chronic pelvic pain as well as dyspareunia.[14] First-line pharmacological management of endometriosis-associated pain typically starts with non-hormonal options such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs), which can be taken as needed, whether during menstruation or otherwise.

Hormonal treatments for endometriosis aim to suppress menstruation and shift the balance toward progestogens from estrogen, which is the dominant hormone driving this condition. Combined hormonal contraceptives (administered either orally, transdermally, or via vaginal ring) are a popular and simple option. These contraceptives are recommended to be taken continuously (without a break for a period) in order to maximize their efficacy for endometriosis-associated pain. Progestin only options, whether approved for contraception (i.e. norethindrone, drospirenone, depot medroxyprogesterone acetate, or levonorgestrel intrauterine system) or not (i.e. norethindrone acetate, or dienogest), have all shown efficacy in treating endometriosis associated pain.[15,16] Dienogest, a synthetic fourth-generation progestin, remains a popular first-line choice for endometriosis owing to its excellent oral bioavailability and tolerability, absence of systemic androgenic effects, and a comparable reduction in pain when evaluated against a gonadotropin releasing hormone agonist (GnRH agonist).[17,18]

GnRH agonists suppress menstruation centrally and induce a temporary menopausal state. Leuprolide acetate and triptorelin pamoate are two commonly used preparations in Canada that are administered as intramuscular injections, either monthly or every 3 months depending on the dose prescribed. An initial flare effect is possible if these GnRH agonists are administered in the follicular phase, therefore timing the injection after ovulation but before menses is preferable. To avoid a flare in the follicular phase, a 5-day course of low dose aromatase inhibitor (e.g. letrozole 2.5 mg by mouth daily) can be used.[19]

Side-effects of GnRH agonist therapy are significant, including hot flashes, mood changes, and decreased bone density with prolonged use. As such, a low dose hormonal replacement, similar to what is used in menopausal women, may be employed as an "add-back" therapy to improve tolerability while still benefiting from globally reduced systemic estrogen. Add-back therapy is recommended if treatment duration exceeds 6-months in order to protect bone density, or earlier to mitigate the side-effects of treatment. Novel oral GnRH antagonists have also been developed either combined with "add-back" therapy (relugolix/estradiol/norethindrone acetate – Myfembree®) or without combined "add-back" therapy (elagolix sodium – Orilissa®). These treatments have proven efficacy for mild-to-moderate symptoms of endometriosis.

Apart from the novel GnRH antagonists, all of the above hormonal preparations have also shown efficacy in reducing ovarian endometrioma

diameter or volume over time, as well as reducing the risk of recurrence of endometriomas and pelvic pain after surgery.[20-22] Other medications that were previously used to treat endometriosis, such as danazol and aromatase inhibitors, have generally, fallen out of favour due to poor tolerability.

Pain: Surgical Management

Surgery generally carries more risks than medical management, and many patients may experience a significant improvement in their symptoms with medication such that they decide against surgery altogether, making medical management a compelling first-line option. Nonetheless, surgery for endometriosis associated pain can be offered with or without an initial course of medical therapy based on patients' informed decision making. Additionally, regarding patients with large endometriomas, significant visible pathology on imaging, or impingement on the urinary or digestive tract, surgery may be the most effective treatment option.

Without any clear signs of endometriosis on imaging, a laparoscopy may still be offered with the goal of both identifying and treating lesions of endometriosis, if found. Patients with pelvic pain in the absence of endometriosis, and a negative laparoscopy (i.e. no lesions identified) may warrant a referral to a pain centre.

Discussing surgery for endometriosis with patients requires consideration of many variables such as the desire for future childbearing, anticipated years remaining until menopause, and any site-specific symptoms (such as dyschezia or hematuria). Pre-operative planning and obtaining a thorough, informed consent, are of paramount importance to avoid patients undergoing a suboptimal or incomplete surgery.

There are two described approaches to managing lesions of endometriosis: ablation (typically electrosurgical, CO2 laser, or plasma-jet destruction of the lesion *in situ*) and excision (removal of the entire lesion). Excision tends to be favoured by experts on the grounds that it may reduce the risk of future recurrence, which is supported by studies that have shown a lower likelihood of requiring additional therapies post-operatively, and greater improvements in pain and dyspareunia compared to ablation.[23-26] In addition, ablation is not always possible, especially when lesions are deep or nodular and involve other organs. That being said, excision of lesions can be technically challenging due to the location and depth of the invasion, particularly when in close proximity to structures such as the ureters, pelvic nerves, or bowel.

When deep disease is suspected, referral to an appropriate surgical specialist is important to ensure that a complete excision can be safely performed. For instance, patients with endometriomas are significantly more likely to have an obliterated cul-de-sac and rectosigmoid disease, and therefore may be best served with a specialist in gynecologic surgery.[27]

The goal of surgery is to restore anatomy and excise all visible traces of endometriosis. This may necessitate excision of the pelvic side-walls, uterosacral ligaments, peritoneum, and endometriomas. Incidental discovery of damaged Fallopian tubes occurs not infrequently in these patients and the management of these damaged tubes (either to remove or preserve) should be pre-emptively discussed during the consent process to ensure the patient's wishes are respected. Endometriosis may also affect the ureter, the bladder, the bowel (including the appendix), and the diaphragm; therefore, a thorough evaluation and consent process pre-operatively are imperative to ensure that screening for such lesions has occurred and that a discussion regarding the surgical plan and possible involvement of other surgical specialists at the time of surgery has been fully developed.

Two final special populations are those amenable to hysterectomy and those approaching or in menopause for whom a bilateral oophorectomy can be considered. Concomitantly performing a hysterectomy during a surgery for excision of endometriosis significantly increases the chances of improving a patient's pain symptoms after surgery and decreases the risk of requiring reintervention.[28,29] These benefits are balanced by an incrementally increased surgical risk (i.e. vault related complications) and potential regret – as such, the decision to proceed with a hysterectomy should not be taken lightly. Bilateral oophorectomy has previously been shown to improve patients' symptoms and reduce the risk of endometriosis recurrence; however, the implications of surgical menopause (if relevant) must be explored.[30] Consideration of unilateral oophorectomy if there is significant ovarian disease with a healthy contralateral ovary may also be an appropriate option.

Fertility

Surgery for endometriosis in the context of fertility remains controversial and a heavily

debated field of research. While there is evidence that surgery for deeply infiltrating endometriosis may assist with natural pregnancy rates, any manipulation of the ovaries for endometriomas (whether cystectomy, cyst drainage with sclerotherapy, or cyst ablation) negatively affects the ovarian reserve to varying degrees.[31,32] For those undergoing assisted reproduction with in vitro fertilization (IVF), the role of surgery is controversial, with some studies showing a benefit in the live birth rate while others do not. A recent systematic review and meta-analysis conducted in 2021 did favour surgery for improving IVF outcomes; however, robust randomized controlled trials are lacking.[33] Surgery before IVF does clearly confer an advantage in the clinical pregnancy rate in two specific scenarios. Firstly, if the patient has abnormal Fallopian tubes (e.g., hydrosalpinx), surgery to clip or remove these tubes may improve implantation rates.[34] Secondly, due to severe anatomic distortion from endometriosis or large endometriomas, healthy ovarian tissue may be inaccessible at the time of ovarian stimulation and egg collection. In such instances, surgery may be beneficial to improve access to ovarian tissue for IVF. Surgery may also be offered prior to ovarian stimulation to improve tolerability of the exogenous hormones during IVF cycles, as endometriosis symptoms often worsen during IVF protocols.

Conclusion

Endometriosis is a common condition with widespread consequences on a patient's quality of life, mental health, reproductive health, and ultimately on society at large. Detection and diagnosis remain challenging, and treatment strategies, whether medical or surgical, depend on patients' priorities and symptoms. An empiric diagnosis and medical management is a reasonable approach for the appropriate patient. In addition, referral to a surgical specialist is recommended should surgery be desired. Research is warranted to facilitate earlier diagnosis, to improve our understanding of the differences between the three phenotypes of endometriosis, and to better clarify the association between lesions and symptoms.

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