Canadian Women's Health Today

Vol. 1, Issue 1
Spring 2024

In this issue:

ISSN 2818-1816 (print)
ISSN 2818-1824 (online)

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SERM=selective estrogen receptor modulator

* SMART 2: 12-week, double-blind, placebo-controlled trial in 318 women who had seven moderate to severe hot flashes/day or ≥50/week at baseline. Primary endpoint assessed efficacy of vasomotor symptom relief. Secondary endpoints included: number of mild, moderate, and severe hot flashes, sleep parameters (Medical Outcomes Study [MOS] scale), and overall Menopause-Specific Quality of Life (MENQOL) questionnaire. Mean daily number of moderate and severe hot flashes at baseline: 10.3 for DUAVIVE, 10.5 for placebo.[1,2]

† SMART 1: 24-month, double-blind, placebo- and active-controlled, dose-ranging trial of 3,397 women who were randomized to DUAVIVE (n=433), raloxifene 60 mg, or placebo. Women took calcium and vitamin D (Caltrate 600 + D™) daily. Primary endpoint was the incidence of endometrial hyperplasia; secondary endpoint was the treatment of vasomotor symptoms.[1]

‡ SMART 5: 12-month, double-blind, placebo- and active-controlled trial of 1,843 women who were randomized to DUAVIVE (n=445), conjugated estrogens 0.625 mg/bazedoxifene 20 mg (n=474), bazedoxifene 20 mg (n=230), conjugated estrogens 0.45 mg/medroxyprogesterone acetate 1.5 mg (n=220), or placebo (n=474). Women also took calcium, 600 mg and vitamin D, 400 IU daily.[1]

§ Comparative clinical significance has not been established.

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doi.org/10.58931/cwht.2024.115

About the Author

Wendy L. Whittle, MD, PhD, FRCSC

Dr. Whittle is a Maternal Fetal Medicine specialist at Sinai Health System where she is the Head of the Division of Maternal Fetal Medicine and leads the Prevention of Preterm Birth Program including a dedicated maternal care clinic, an access to tertiary care program for patients at increased risk of extreme preterm birth and participates in studies focused on preterm birth prevention and improved perinatal outcome.

Affiliations: Maternal Fetal Medicine Specialist, Division of Maternal Fetal Medicine/Department of OBGYN; Sinai Health System
Assistant Professor, Department of OBGYN; University of Toronto

A Pragmatic Approach to the Prevention of Preterm Birth

Wendy L. Whittle, MD, PhD, FRCSC

Introduction

Preterm birth (PTB) -delivery before 37 weeks of gestation- occurs in ~8% of Canadian pregnancies, a rate that has remained stable for >20 years.[1] Prematurity remains the leading cause of neonatal mortality- especially at the extreme of viability: 22–26 weeks gestation. Children born prematurely have increased rates of cerebral palsy, global neurodevelopmental impairment, learning disabilities, deafness, vision impairment and behavioural diagnoses.[1] Hospital length of stay and re-admission rates in the first year of life are higher in babies born preterm.[1] The family impact is immeasurable in the domains of mental health diagnoses, financial health, and disordered social interactions.[1] Prematurity has a longitudinal impact on reproductive and public health with an increased risk of occurrence in subsequent pregnancies.[1]

The phenotype of PTB can be described as spontaneous (SPTB) versus iatrogenic or defined by clinical presentation: labor, antepartum hemorrhage, premature ruptured membranes, hypertensive disorder, cervical insufficiency.[2] PTB is best appreciated as a syndrome attributed to one or more contributing underlying pathologies (intrauterine infection, abnormal placentation), one or more identified risk factors (smoking, malnutrition, short interpregnancy interval) and most commonly one or more unknown "idiopathic" influence(s).[2] PTB must be considered a heterogenous condition. It is this heterogeneity which drives frustration in the prevention of PTB. No one intervention has been demonstrated to universally reduce the risk or prevent PTB for all comers. As such, a pragmatic population and individual based strategy for PTB prevention takes on a two-pronged approach. "Primary prevention" is targeted at all pregnant or future pregnant individuals to optimize the gestational age at delivery and "secondary prevention" is targeted at an at-risk population based on maternal health/risk factors, obstetrical history and/or clinical risk factors identified through the course of the pregnancy. The hypothesis underlying this tactic is that the synergistic effect of a multi-modal approach leading to an individualized strategy will best optimize pregnancy outcome: decrease the risk of PTB or at minimum, prolong gestational length.

Prevention starts with pre-pregnancy counselling focussed on maternal health, and lifestyle optimization. Contraceptive counselling and access to safe, low-cost birth control decreases the rate of adolescent pregnancy and its associated risk of PTB.[3,4] Effective post partum contraceptive counselling is important as short

inter-pregnancy interval (<6 months) increases PTB risk (OR 1.45).[3,4] This can be challenging when counselling a patient following a PTB with neonatal death or a previable loss as there is a sense of urgency for the next pregnancy. Pre-pregnancy weight management is important; BMI <20 is associated with increased risk (OR 1.32).[3,4] Obesity (BMI >25) is linked to pregnancy complications associated with PTB including hypertensive disorders, poor fetal growth, congenital malformations, and diabetes.[3,4] Optimizing maternal health conditions such as hypertension, diabetes and anemia improves the risk of PTB. Smoking and recreation drug use doubles the rate of prematurity; smoking cessation, including the use of a substitute nicotine patch, has a well studied benefit.[3,4] As multiple gestations have a mean gestational age of <37 weeks, single embryo transfer at the time of IVF is an important consideration for optimizing outcome. Screening for and managing mental health diagnoses (especially anxiety and depression) and intimate partner violence contribute to risk reduction.[3,4]

Early pregnancy care is critical; it is well recognized in both developing and developed countries that limited, or no antenatal care is associated with PTB. "Mid-wife led continuity of antenatal care models" are associated with reduced rates of PTB, stressing the importance of supportive care for the health and well-being of women through pregnancy.[4] Specialized PTB clinics providing dedicated care for women at risk of PTB have shown a risk reduction and are mechanism to address the emotional, psychosocial stressors of an "at risk pregnancy".[4] Lifestyle and nutrition guidance contribute to pregnancy outcome. A "healthy" dietary pattern higher in fruits, vegetables, legumes, and whole grains is associated with a lower risk of PTB. Micronutrient supplementation with vitamin D, Zinc, DHEA and calcium are associated with pregnancy prolongation and reduction of early PTB.[4] Periodontal disease is associated with prematurity; a dental exam early in pregnancy may be provide benefit on an individual level.[3,4] Screening and treatment for lower genital tract infections (syphilis and vaginal candidiasis) and asymptomatic bacteriuria have well established impact on risk reduction.[3,4] Bacterial vaginosis (BV) is strongly associated with SPTB; diagnosis and management of BV should be part of routine antenatal care. Genital tract colonization with *Ureaplasma* species is associated with PTB and *Ureaplasma* is a commonly isolated bacteria from the amniotic fluid and placenta of patients delivering preterm.[5] There is insufficient evidence to determine if universal screening and treatment of *Ureaplasma* has a beneficial impact on PTB prevention; however, the use of macrolide antibiotics targeted at *Ureaplasma* in pregnancy is safe.[5] Based on an individualized approach focussed on risk factor modification, screening and treatment for *Ureaplasma* may be of benefit, particularly in patients with a history of infection mediated PTB. The use of probiotic(s) to reduce the rates of vaginal infections, in particular BV, is recommended outside of pregnancy; there no evidence that taking probiotics during pregnancy decreases the risk of PTB but could be useful on the individual level for risk reduction.[4,6]

Secondary prevention is targeted at individuals at risk of PTB; these targeted interventions include aspirin (ASA), vaginal progesterone (VP), and cervical cerclage.[4,7,11,12,13] The Aspirin for Evidence-Based Preeclampsia Prevention trial demonstrated that ASA has a significant risk reduction for early onset pre-eclampsia (PET) (<34w gestation) with or without fetal growth restriction. At risk patients can be identified by demographics factors: maternal age >30, BMI >35, IVF achieved pregnancy, twin pregnancy, history of PET and maternal health conditions including chronic hypertension, diabetes, lupus and anti-phospholipid antibody syndrome.[7] The Fetal Medicine Foundation provides an easily accessible online tool for PET prediction at 11–14 weeks' gestation using maternal characteristics, medical and obstetric history, mean arterial blood pressure, uterine artery Doppler ultrasound and serum biomarkers (pregnancy associated placenta protein A and/or placenta like growth factor) which will identify a greater number of patients at risk compared with risk-factor-based screening alone.[7,8] A daily dose of ASA, ideally 150 mg, at night, initiated before 16 weeks' gestation, and maintained until 36 weeks' gestation or birth demonstrates a dramatic decrease in the rate of early onset PET. Although one small study of patients at risk for SPTB did not show benefit of ASA, it should be noted that placenta pathological findings associated with PET (fetal and maternal vascular mal-perfusion, perivillous fibrin deposition, immature, avascular villi) are also associated with SPTB.[9] Based on the beneficial effect of ASA for PET prevention driven by these pathological findings, it is reasonable to

recommend ASA supplement in patients with these placental findings in the subsequent pregnancy.

Natural micronized vaginal progesterone (VP) supplement and cerclage have been hailed as the gold standard interventions to prevent SPTB in at risk individuals.[4,10,11,12,13] The mechanism(s) by which VP prevents SPTB are not clear but may involve the molecular pathways of premature cervical ripening, inhibition of uterine contractility and/or an anti-inflammatory effect on the labor cascade. A comprehensive individual patient data (IPD) meta-analysis makes the following recommendations regarding the use of VP.[10] In patients with a transvaginal sonographic short cervix (<25 mm) identified mid-trimester (18–24 weeks gestation), VP (100–200 mg) continued until term significantly decreased the risk of PTB at <36w gestation and the rate adverse neonatal outcomes associated with prematurity: RDS, composite neonatal morbidity and mortality, low birth weight and NICU admission.[10] In patients with a twin gestation and mid-gestation cervix length <25mm, VP reduces the risk of PTB occurring at <34 weeks gestation and the associated risk of perinatal morbidity.[10] There is no evidence to support VP use in twin or higher-order multifetal gestations in the absence of a short cervix.[4,10]

The role for VP in patients with history of SPTB is controversial. Many small studies strongly support the use of VP in these patients. However, the IPD meta-analysis, with an adjustment for small-study effects, demonstrated a nonsignificant effect of VP in this population.[10] Alternatively, a systematic review and meta-analysis demonstrated an effect of VP on PTB <37 weeks (RR 0.78).[4,11] In addition, no adverse maternal and/or neonatal effects were reported. Given the multifactorial and not well understood etiology of SPTB, the potential benefit on an individual level and its safety profile, the use VP for patients with a history of SPTB should be recommended and is supported by clinical practice guidelines from governing obstetrical societies.

A cervical cerclage, which offers mechanical support to the cervix by placing a suture around the cervix, assumes that such re-enforcement will reduce the rate of SPTB.[4,12,13] A cerclage has also been described as a rescue, emergency surgical intervention to close the cervical os in a patient presenting with an open cervix. A cerclage placed based on a history of SPTB alone (prophylactic) has not been found to be of any benefit except for a modest risk reduction in the context of 3 or more second trimester losses.[4,12] A cerclage placed because of a short mid-gestation cervical length (<25mm) regardless of obstetrical history, significantly reduced the risk of PTB <37 weeks (RR 0.72).[4,12,13] This effectiveness of a cerclage, prophylactic or indicated by cervical length, in twin gestation and higher order multiple gestation has not been proven beneficial and thus should not be routinely recommended.[4,12] A rescue cerclage does prolong gestation and decrease the rate of SPTB, however, there is significant infectious morbidity associated with such intervention and should be used with caution and informed counselling.[4,12,13] It should be noted that a cerclage is a much more invasive and costly intervention compared with VP. A cerclage can impart residual trauma and laceration to the cervix impacting its mechanical function in a subsequent pregnancy. A cerclage does not consider or treat the recognized pathologies triggering a PTB: intrauterine infection and abnormal placentation. A short and/or open cervix in the current or prior pregnancy is not solely attributed to an impaired ability of the ultrastructure of the cervix to withstand the deformative pressures of the increasing uterine muscle bulk and the uterine contents: placenta, amniotic fluid and fetus. Premature cervical ripening is an under appreciated contributor to the shortening of a cervix. In addition, a short cervix may have a secondarily acquired ascending intra-uterine infection, which would contribute to the failure of this intervention. It would be naïve to assume a cerclage alone would be universally effective as is often suggested at the time of a PTB or requested by a patient seeking care after loss.

Unfortunately, there are no studies comparing VP head-to-head with cerclage or studies with VP+cerclage versus placebo. It is intuitive to combine such interventions based on individualized multi-modal approach to a multifactorial diagnosis, recognizing the risk associated with each intervention and counselling to ensure an understanding that no one intervention has been shown to 100% eliminate the chance of a PTB. However, it should be recognized that both VP and cerclage have protective benefit for individuals with a mid-gestation short cervix providing strong rationale for the universal screening of cervix length for all pregnant individuals as a population-based strategy for SPTB prevention. Interventions such as a vaginal pessary, bed rest, home uterine monitoring and the use of tocolytic agents (including VP

in this setting) have no impact on the rate of SPTB and should not part of routine or targeted pregnancy care.

Conclusion

In summary, PTB is a heterogenous condition requiring both population based and individualized prevention strategies. Healthy lifestyle, nutrient supplements, reproductive counselling, psycho-social support, packages of antenatal care, treatment of genital tract infections are population-based strategies for risk reduction.[4,13] Risk factor screening and mid-gestation cervical length assessment to identify an at-risk population for whom the use of VP, aspirin and/or cerclage has proven benefit in the prevention of PTB.[4,10,11,12,13] The national and international rate of PTB has not improved over the past 20 years, proving that these interventions alone are insufficient at eliminating and/or reducing PTB. An improved understanding of the etiology of PTB to drive prevention care is an obstetrical imperative.

Correspondence

Dr. Wendy Whittle
Email: wendy.whittle@sinaihealth.ca

Financial Disclosures

None declared.

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doi.org/10.58931/cwht.2024.116

About the Author

Jaime Reardon, MD, FRCSC

Dr. Jaime Reardon is a general obstetrician/gynecologist practicing in Saint John, New Brunswick with clinical interests in vulvar dermatoses, colposcopy and menopause. She completed a fellowship in Vulvovaginal Health at the University of Toronto in 2023, after completing residency at Western University in London, Ontario in 2022.

Affiliations: Department of Obstetrics & Gynecology, Dalhousie University

2024 Updates to Cervical Cancer Screening in Canada

Jaime Reardon, MD, FRCSC

Introduction

The landscape of cervical cancer screening in Canada is about to undergo a major shift from cytology-based screening to testing directly for the presence of high-risk strains of the human papilloma virus (HPV), the persistence of which is known to be a prerequisite for the development of almost all cases of cervical cancer. In 2018, the World Health Organization declared a call to action for the worldwide elimination of cervical cancer by 2040.[1] Subsequently the Canadian Partnership Against Cancer (CPAC) released an action plan outlining the necessary steps for Canada to reach this goal.[2] One of the 3 major priorities identified in the action plan is the transition to primary HPV testing.[2] This transition from screening to testing represents a major shift in infrastructure and also a shift in mindset for clinicians, policymakers, and the public. To help guide this transition, CPAC has collaborated with the Gynecologic Oncology Society of Canada (GOC) and the Society of Canadian Colposcopists (SCC) to release two open-access, evidence-based guidelines in June 2023. These guidelines address how to manage a positive HPV screening test,[3] and colposcopy in the context of primary HPV-screening.[4] This paper will outline the evolution of cervical cancer screening in Canada along with the rationale behind the transition to HPV testing. Also included is a discussion on the broad recommendations from the 2023 CPAC/GOC/SCC guidelines, as well as recommendations for age and interval of screening and special populations. Readers of this article in e-journal format can access the Canadian Guideline on the Management of a Positive Human Papillomavirus Test and Guidance for Specific Populations here. Readers may also access the 2023 Canadian Colposcopy Guideline: A Risk-Based Approach to Management and Surveillance of Cervical Dysplasia here.

Cervical Cancer Screening in Canada

Most Canadian provinces currently screen for cervical cancer using cytology-based screening, with many, but not all provinces having some type of organized screening program.[5] Screening for cervical cancer with cytology has been used in Canada since the 1940s, with the first organized screening programs in place starting in the 1960s.[6] Cytology-based testing, colloquially referred to as “Pap smears” or “Pap tests,” actually includes two distinct types of tests: the original Papanicolaou smear performed on a glass slide with fixative, and newer liquid-based cytology tests. In the 1980s it was discovered that HPV the causative agent for

cervical cancer; this finding led to the eventual development of HPV vaccines and the ability to test for viral DNA directly.[6] HPV testing is currently available as a follow up test for cytology to varying extents in some Canadian provinces.[5]

HPV DNA Testing

HPV nucleic acid testing has been known to outperform cytology for a number of years, and there have been major Canadian contributions to this research. For example, in 2007, the Canadian Cervical Cancer Screening Trial compared cytology-based testing and HPV DNA testing and showed HPV testing to be more sensitive for the detection of cervical high-grade squamous intraepithelial lesions (HSIL) or cancer (94.6% for HPV testing compared to 55.4% for Pap tests), with a similar specificity (94.1% for HPV testing, 96.8% for Pap tests).[7] Also in the Canadian context, the 2018 HPV FOCAL randomized clinical trial showed a reduced likelihood of HSIL cervical intraepithelial neoplasia grade 3 or worse (CIN3+) when primary HPV screening was used compared to the use of liquid-based cytology.[8] Several randomized controlled trials have provided evidence that HPV testing is also superior to cytology for reducing the incidence of and mortality from cervical cancer.[9] In recent years, a number of countries have implemented primary HPV screening, including the Netherlands and Australia in 2017, followed by the United Kingdom, the United States of America, and Finland.[10] Implementing primary HPV screening by these countries has allowed other countries to observe and learn from their experiences. Some Canadian provinces have already announced plans to transition to primary HPV testing.[2] In May 2023, Prince Edward Island became the first province in Canada to implement primary HPV screening for cervical cancer.[11] As of January 2024, British Columbia announced plans to imminently begin HPV-self swabbing for HPV with a phased plan for implementation of provide-collected primary HPV testing.[12]

The high sensitivity but lower specificity of the HPV test compared with that of the Pap test suggests that a triage test is recommended to improve the performance of the HPV test, and to reduce unnecessary referrals to colposcopy.[13] In Canada, the recommended triage tests are HPV genotyping for high-risk strains, followed by reflex liquid-based cytology.[3] In addition to these, other types of triage tests are actively under investigation.[3,10] As outlined in the 2023 CPAC/GOC/SCC guideline on management of a positive HPV test, if primary HPV testing produces a positive result, genotyping and/or reflex cytology should be performed to determine whether testing should be repeated at a predetermined interval versus direct referral to colposcopy. (**Table 1**)[3] There is currently no recommendation to modify screening based on vaccination history.[3]

Anticipated challenges in the implementation of primary HPV screening include the logistics of such a major shift in established programs, the need to educate clinicians and the public about why the change is recommended, and to manage the anticipated temporary doubling or tripling of colposcopy referrals that has occurred in other jurisdictions in which primary HPV-screening was implemented.[10] In the long-term, primary HPV testing reduces colposcopy referrals. (**Table 1.**)

Age and Interval of Screening with HPV Testing

The characteristics of HPV DNA tests compared to cytology-based tests allows the screening interval between HPV DNA tests to be extended to 5–10 years for the general population compared with the recommended interval of 3 years for cytology-based testing.[13] The 2023 CPAC/GCC/SCC guideline on HPV testing purposely avoids recommending an age at which screening is initiated.[3] This is because the decision should be determined provincially based on local population factors such as age of population, screening and vaccination uptake, as well as available resources.[9,10] HPV infection in young people is common and the virus is commonly cleared from the body. Screening for HPV at a very young age can lead to over-investigation and potentially unnecessary treatments.[10] Since 2013, the Canadian Task Force on Preventive Health Care has recommended initiating cytology-based screening at age 25.[14]; however, a number of provincial screening programs continue to initiate screening at age 21.[5] Other countries have recommended initiating screening at age 30 with intervals of 5–10 years, ending between age 65–74.[10] The World Health Organization recommends starting screening at age 30 for the general population with an interval of 5–10 years between HPV tests if negative.[13] Prince Edward Island chose to begin primary HPV-screening at age 25, with 5-year intervals, with routine

Indications for Referral to Colposcopy
• If positive for HPV 16 or 18, refer to colposcopy (reflex cytology should still be done)
• If positive for "other" high-risk HPV with ASCUS or LSIL reflex cytology, repeat HPV testing at 12 and 24 months and refer to colposcopy if persistently HPV positive at 24 months
• If positive for any genotype of high-risk HPV with high-grade reflex cytology (ASC-H, HSIL, AGC, AIS or suspicious for invasive cancer), refer directly to colposcopy
• If immunocompromised, refer to colposcopy with any genotype of high-risk HPV

Table 1. Indications for referral to colposcopy in the setting of primary HPV screening; *adapted from Zigras et al, 2023*.

Abbreviations: ASCUS: atypical squamous cells of undetermined significance, **LSIL:** low-grade squamous intraepithelial lesion, **ASC-H:** atypical squamous cells cannot rule out high-grade intraepithelial lesion, **HSIL:** high-grade squamous intraepithelial lesion, **AGC:** atypical glandular cells, **AIS:** adenocarcinoma in situ.

screening finishing at age 65.[11] The Canadian Task Force on Preventive Health Care is expected to make an updated national recommendation in 2025.[15] OncoSim has been developed by the Canadian Partnership Against Cancer to help provinces determine an appropriate age at which to initiate screening for their population. OncoSim is a free online cost-benefit analysis tool designed to help policy-makers estimate the effects of policy change on parameters such as life years and healthcare costs to help make decisions such as when to initiate screening.[2,16] It allows the comparison of cytology versus primary HPV-screening based on different eligibility criteria, participation rates, frequency of screening, and costs to help make public policy decisions such as age to initiate and to discontinue screening in a given population.[2]

Self-Screening Using HPV Testing

One unique possibility with primary HPV testing compared to cytology is the potential for samples to be self-collected. Sample collection can be performed at an office or at home, for example by mail-in programs or home visits.[10] The 2023 CPAC/GOC/SCC guideline on management of a positive HPV test recommends that self-sampling be offered as a method to increase uptake of testing in combination with face-to-face interactions, especially for under-screened populations, and potentially for the general population as well.[3] Self-sampling has been shown to increase participation in screening, be acceptable to participants, yield reliable results, and lead to reasonable attendance at colposcopy follow up.[3,17,18] To be able to perform reflex cytology as the guidelines recommend, if a vaginal self-sample tests positive for HPV, the next step is for a health care provider to collect a liquid-based cytology sample. Participants in the screening program should be aware that a pelvic exam may still be necessary based on the results of the test.

Special Populations

Immunocompromised Individuals: this population has an increased risk of cervical dysplasia and cervical cancer; however, for populations other than those living with human immunodeficiency virus (HIV), evidence is lacking.[19] The 2023 CPAC/GOC/SCC recommends that individuals with certain conditions, including HIV, inflammatory bowel disease or rheumatoid arthritis, if on immunosuppressants, systemic lupus erythematosus (regardless of whether they receive immunosuppressive therapies), and recipients of solid-organ transplants and hematopoietic stem cell transplants be referred directly to colposcopy if they have a positive test result for high-risk HPV, with similar management from colposcopy.[3] More evidence is required to

comment on whether modified screening pathways should otherwise be used.[3] For individuals living with HIV, the WHO suggests starting screening earlier and considering screening every 3–5 years with HPV DNA testing.[13]

After Hysterectomy: HPV vault testing is not recommended after hysterectomy for benign indications if there is no history of cervical dysplasia.[3] If there is a history of cervical dysplasia, HPV testing is used to determine if ongoing surveillance is indicated.[3] The 2023 CPAC/GOC/SCC guideline makes recommendations for the management of those with a low-grade squamous intraepithelial lesion (LSIL) or HSIL found on a hysterectomy specimen, including those with previously treated HSIL and negative or unknown HPV status prior to hysterectomy, hysterectomy performed for adenocarcinoma in situ (AIS), and those with a history of AIS who underwent a hysterectomy for other indications.[3] In most cases, if the HPV test result is negative, no further screening is indicated unless there is a history of AIS for which ongoing surveillance should continue.[3] This is a significant departure from previous cytology-based screening in which an extended duration of yearly Pap tests was recommended for these populations. The guidelines do not address screening after cervical carcinoma and suggest following recommendations consistent with gynecologic oncology.

Under-Screened Populations: CPAC's action plan for eliminating cervical cancer recognizes that under-screened groups must have increased participation in screening to eliminate cervical cancer.[2] Some provinces already have initiatives in place to increase the level of screening in these groups.[5] Offering HPV self-sampling within screening programs should be a consideration for all under-screened groups,[2,3] and has the potential to overcome a variety of barriers to participating in screening.[18]

- **Lesbian, Gay, Bisexual, Transgender, Queer/Questioning, Two Spirit Populations (LGBTQ2S+):** Transmen and women-who-have-sex-with-women are at risk for cervical cancer, though are more likely to have never been screened.[20] Any individual with a cervix who has ever been sexually active should be included in cervical cancer screening. Self-sampling should be offered if preferred by an individual, and providers should be respectful and create safe, inclusive environments for these people.[3]
- **First Nations, Inuit and Metis Populations:** These populations are under-screened. It is crucial to engage them in order to achieve Canada's goal of eliminating cervical cancer by 2040.[10] First Nations people have a higher incidence of cancers, including cervical cancer, and worse cancer-related outcomes.[21] Providers should increase their understanding of these communities, increase cultural safety and trauma-informed care, and offer cultural support and advocacy. Zigras et al. provide some specific suggestions on how providers can increase their understanding of this population.[3] This is another population in which self-screening may be of particular value, although engaging in colposcopy follow up after an abnormal HPV test result may be met with fear and mistrust, which underscores the importance of providers creating a safe environment.[3,21]
- **Those Living in Remote Areas, Immigrants, and Newcomers to Canada:** This is another example of under-served populations with barriers to access in which self-sampling has the potential to improve participation. Implementation of self-sampling access should be prioritized for these populations.[3,10]

Conclusion

The transition to primary HPV testing for cervical cancer secondary prevention is a major step toward reducing, and hopefully eliminating, cervical cancer. Improving HPV immunization rates and follow up of abnormal screening results is also crucial in eliminating cervical cancer.[2] Although some aspects of HPV testing may be faced with hesitation by clinicians and the public, especially the suggested later start for screening and longer screening intervals, HPV testing has a demonstrated capacity to reduce rates of cervical precancers and cancers, and considering the self-sampling option, is potentially less invasive, especially for vulnerable groups.

Correspondence

Jaime Reardon
Email: jaimereardon@gmail.com

Financial Disclosures:

None declared.

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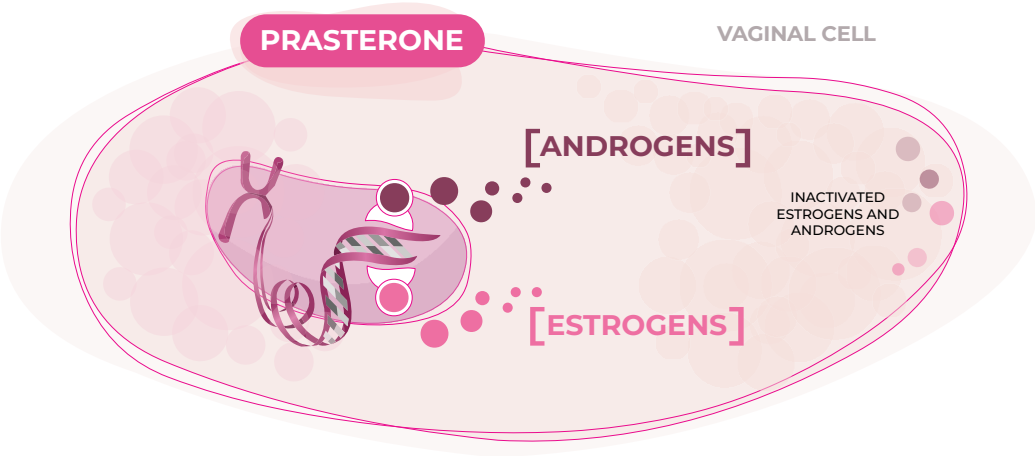

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About the Author

Maria Isidora Yap-Garcia, MD, FPOGS, FPSRM OBGYN, Infertility, Reproductive Medicine & Surgery

Dr. Yap-Garcia obtained her medical degree at the University of Santo Tomas, Faculty of Medicine and Surgery. She later subspecialized in reproductive medicine at the St. Luke's Medical Center, Philippines. In 2018, she did a fellowship in minimally invasive gynecology at the University of Ottawa. Dr. Yap-Garcia's views on endometriosis and PCOS have been shared both locally and internationally via lectures and publications. Her expertise in the role of lifestyle and nutrition in the etiopathogenesis of PCOS has led to her invitation to the Experts Group On Inositol (EGOI) in 2022. She strives to advance the field of reproductive medicine in her country and, as such, is involved in the Philippine guidelines for endometriosis, PCOS, infertility and menopause.

Affiliations: St. Luke's Medical Center College of Medicine William H. Quasha Memorial - Assistant Professor
St. Luke's Medical Center: Department of Obstetrics and Gynecology - Active Consultant
ManilaMed - Medical Center Manila: Reproductive Medicine, Department of Obstetrics and Gynecology - Head of Section
Experts Group on Inositol - Member
Board Treasurer, Philippine Society for Reproductive Medicine
Society memberships: AAGL, Asia-Pacific Initiative on Reproduction

Management of Polycystic Ovarian Syndrome: Looking Beyond the Ovaries

Maria Isidora Yap-Garcia, MD, FPOGS, FPSRM OBGYN, Infertility, Reproductive Medicine & Surgery

The Pathology Behind Polycystic Ovarian Syndrome

There is something remiss in the name polycystic ovarian syndrome (PCOS). It bears the word ovary; however, the ovary is an innocent bystander of a more sinister pathology. The name belies the nature of a disease that is a complex metabolic and reproductive syndrome with sequelae extending beyond ovarian dysfunction.

PCOS is a chronic, life-long illness that affects approximately 1.4 million Canadians.[1] Its inception is thought to begin in utero. Factors such as elevated levels of maternal anti-Müllerian hormone (AMH), endocrine disruptors, growth restriction, and maternal androgen excess generate epigenetic changes that have a life-long, transgenerational impact on the fetus.[2]

Despite its name, PCOS is not just about the ovary. As we are learning more about the disease, it is becoming clear that insulin resistance, rather than a primary ovarian pathology, is the key contributing factor in its pathogenesis. Poor lifestyle choices exacerbate the condition. Insulin plays a key role in androgen production by augmenting luteinizing hormone (LH) stimulation of the ovarian theca cells, and adrenal androgen production. Insulin inhibits the hepatic synthesis of sex hormone-binding globulin, effectively increasing free androgen circulation.

Diagnostic Criteria for Polycystic Ovary Syndrome			
Rotterdam Criteria	**Two (2) of clinical and/or biochemical hyperandrogenism, oligo- or anovulation, or polycystic ovaries on ultrasound**		
Hyperandrogenism (HA) (Clinical* and/or Biochemical)	Elevated Calculated free testosterone	Free androgen	calculated bioavailable testosterone
Oligo-ovulation or anovulation (OM)	>1 to >3 years postmenarche: **<21 or >45 days**	3 yyears postmenarche to perimenopause: **<21 or >35 days or <8 cycles per year**	1 year postmenarche: **>90 days for any one cycle**
Polycystic ovarian morphology features (PCOM)	Transvaginal is the preferred approach only for women >8 years from menarche.	Transducers with a **frequency bandwidth that includes 8 MHz**	follicle number **per ovary of ≥20 and/or** an **ovarian volume ≥10 ml** on either ovary

Table 1. The Rotterdam Criteria.[4]

*Using the Modified Ferriman-Gallwey system

Consequently, elevated insulin levels lead to gonadotropin imbalances (LH>FSH) which result in ovulatory dysfunction and hyperandrogenism.[3]

Diagnosing Polycystic Ovarian Syndrome

Based on the Rotterdam criteria, there are four PCOS phenotypes that rely on permutations of three criteria: **1)** hyperandrogenism (clinical or biochemical), **2)** irregular cycles, and **3)** polycystic ovarian morphology as observed on ultrasound. The Rotterdam criteria is distinct from other PCOS criteria, because the diagnosis can be made even in the absence of hyperandrogenism or ovulatory dysfunction. Owing to its simplicity, the Rotterdam criteria is the most utilized criterion for diagnosing PCOS worldwide.[2] The Rotterdam criteria are presented in **Table 1**.

Diagnosing PCOS differs for adolescents. First, the definition of oligomenorrhea depends on how remote one is from menarche. Because of the immaturity of the hypothalamic-pituitary-ovarian axis, the absence of menses for up to 90 days remains within the bounds of normal in the year following menarche. Within 1–3 years from menarche, amenorrhea with an interval of up to 45 days is considered normal. However, in women who are 3 years post-menarche, an amenorrhea with an interval of more than 35 days is considered prolonged.

Polycystic ovarian (PCO) morphology is defined as an ovary with ≥20 follicles and/or an ovarian volume of ≥10 mL as seen on ultrasound (8 mHz bandwidth). In adolescents, the diagnosis does not depend on ovarian morphology. Instead, the diagnosis mainly considers the presence of hyperandrogenism and oligomenorrhea. In addition, ultrasound is generally only useful 8 years after menarche.[4]

An accurate measure of biochemical hyperandrogenism uses either calculated free testosterone, free androgen index (FAI), or calculated bioavailable testosterone. One challenge is the limited availability of high-quality assays for these measures. Alternatively, androstenedione or dehydroepandrostenedione sulfate (DHEAS) may be used as measures of biochemical hyperandrogenism. Clinically, hirsutism is a reliable marker for hyperandrogenism, and the Modified Ferriman-Gallwey scoring system is one of the most common methods of assessment. While the published cut-off score for hirsutism is >7, this value varies depending on ethnicity, with east

Asians having a lower cut-off score compared to South Asian and Middle Eastern women. Another reliable clinical marker of hyperandrogenism is androgenetic alopecia. Take note that female pattern hair loss is characterized by anterior hairline sparing, which differs from male pattern hair loss that occurs at the vertex and frontotemporal regions.[5]

There is emerging evidence that Anti-Müllerian Hormone (AMH) can be used as a marker for PCOS. AMH levels for PCOS are generally higher (>3.8 ng/mL), however, cut-off values have not been standardized.[6]

Considering that the sequelae of unchecked hyperglycemia are potentially life-threatening, there is a need to screen for insulin dysfunction. In women with PCOS, glycemic status should be reassessed every one to three years. The gold standard for diagnosing insulin resistance is the glucose clamp. This method relies on dynamic testing after a glucose load. Because dynamic testing is cumbersome and viable alternatives exist, its use has largely been relegated to research.[4,7] The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) is a popular diagnostic test. Unfortunately, its mainstream use is limited by a lack of standardization among different centres. The 75g Oral Glucose Tolerance Test (OGTT) is a reliable method of testing because of its availability, practicality, and standardization.[8] Fasting insulin is also useful because it has been shown to correlate well with other metabolic parameters.[9]

The following routine screening for women with PCOS is recommended: cardiovascular disease risk, endometrial pathology (hyperplasia or cancer), obstructive sleep apnea, and mental health disorders. Cardiovascular disease screening is advised every 6–12 months and should include the following: determination of body mass index (BMI), waist circumference, blood pressure, lipid profile, and an evaluation of lifestyle risk factors such as smoking and sedentary behaviours. A detailed menstrual history should be directed toward ruling out abnormal uterine bleeding or prolonged amenorrhea—both of which are suggestive of unopposed estrogen on the endometrium. Obesity is another risk factor for endometrial cancer that should be documented on the first visit. If these risk factors are present, an endometrial biopsy may be warranted, particularly in women who are over the age of 40 years.[10] Another important risk factor for cardiovascular disease is obstructive sleep apnea. Screening is recommended in women with PCOS because they are more likely to develop obstructive sleep apnea. The Berlin Questionnaire is a practical method of screening those at risk of obstructive sleep apnea, and if positive, the patient should be referred for specialist care. In addition, anxiety, depression, psychosexual disorders, and eating disorders are significantly more common in women with PCOS and, likewise, must be screened for at the first visit.[4]

Therapeutic strategies

PCOS may not have manifested as a disease in the past. It may be an ancestral adaptive response to an environment where food scarcity and fear of predation kept humans mobile and lean. Our ancestral past set the stage for evolution favouring the promotion of traits of PCOS. Lower conception rates due to infrequent ovulation and sustained high levels of AMH allowed for better child spacing and a longer reproductive career. Enhanced energy storage and insulin resistance provided stable glucose levels in times of starvation. Increased physical activity counteracted the elevated blood glucose levels caused by insulin insensitivity. Hyperandrogenism fostered increased muscle mass and aggressiveness that were advantages for ancient survival.[11] Unfortunately, the modern environment has engendered maladaptation to the survival benefit of insulin resistance, resulting in a “devolution” into the pathology known as PCOS today.

The impact of lifestyle interventions on the reproductive endocrine profile are not as intuitive as their established benefit on the metabolic profile. One prospective study looked at women with PCOS who underwent a lifestyle regimen in addition to their usual care. Overall, lifestyle intervention showed statistical improvements on the levels of follicle-stimulating hormone (FSH), sex hormone binding globulin (SHBG), FAI, and clinical improvement in hirsutism.[12]

As ubiquitous as the term “lifestyle intervention” is, precise recommendations for diet and exercise are difficult to find. Various diets (Keto diet, intermittent fasting, the Atkin’s diet, among others) have been recommended for women with PCOS, and most are considered effective for short-term weight loss—the commonality among them being hypocaloric intake (1500 kCal/day or a 500 kCal/day deficit). To maintain long-term adherence to an eating

plan with a healthy balance, a good strategy is to include nutritionists in the care team. Regarding exercise regimens, there is likewise no specific recommendation. Instead, women with PCOS are advised to perform moderate intensity exercise for at least 150 minutes/week. Brisk walking for 30 minutes, 5 times a week is a practical example of such a regimen.[4]

Hyperandrogenism

Combined hormonal contraceptives (CHCs) provide non-contraceptive benefits for women with PCOS. When choosing the right CHC, it is helpful to consider its progestin component, since not all progestins are considered equal. Given the metabolic profile of women with PCOS, cardiovascular friendly options (with anti-mineralocorticoid activity, without glucocorticoid activity, and natural estrogen preparations) are preferred. Another factor to be considered is the anti-androgenic component of the CHC. Cyproterone acetate (CPA) was once considered a first-line choice owing to its strong anti-androgenic properties. Unfortunately, CPA is paired with higher levels of ethinyl estradiol which, in turn, can increase the atherogenic and thromboembolic potential. CPA also enhances glucocorticoid activity, making it less cardiovascular-friendly than other CHCs. Third generation CHCs contain low-dose estrogen preparations and are considered safer for obese/overweight women.[13]

Anti-androgens such as spironolactone, finasteride, and flutamide are part of the armamentarium for hyperandrogenism. The use of flutamide, however, is limited because of the potential for liver toxicity. Anti-androgens are not recommended for women seeking fertility because of their potential for teratogenicity. In fact, in women being treated for hyperandrogenism, contraception forms part of the therapeutic goals. This adds another dimension to the importance of CHCs in the treatment of PCOS.[13]

Hyperinsulinemia

The use of metformin in managing PCOS is backed up by robust data. Metformin inhibits gluconeogenesis and promotes peripheral glucose uptake. The overall effect is lower levels of glucose in the bloodstream owing to enhanced cellular uptake. Unfortunately, in some patients, compliance with metformin is limited by its gastrointestinal side effects.[14]

Thiazolidinediones, particularly pioglitazone, can be used in patients with PCOS. Pioglitazone is a peroxisome proliferator-activated receptor gamma (PPAR-γ) agonist that indirectly ameliorates peripheral insulin resistance and reduces androgen synthesis in the ovaries.[15] Glucagon-like peptide 1 (GLP-1) analogs function as an incretin mimetic that directly increases pancreatic insulin secretion in response to food intake. One of the major limitations of GLP-1 is the mode of delivery (injectable). In addition, similar to metformin, GLP-1 causes significant gastrointestinal symptoms. Despite these limitations, the use of GLP-1 has been steadily on the rise due to its marked effectiveness for weight control.[2] (See **Table 2** for information on insulin sensitizers.)

Infertility

Though arguably more important, less attention is given to lifestyle therapy in women wishing to achieve a pregnancy. The periconceptional period is a stage in which environmental endocrine disruptors and other exposures can critically affect the fetus. These are important counselling pearls because the effects are far-reaching and potentially trans-generational. Counselling should also underscore that gestational diabetes mellitus (GDM), pregnancy related hypertension, preterm delivery, and babies who are small and large for gestational age are possible sequelae of PCOS and poor lifestyle choices.

Ovulation induction is the major therapeutic focus in the treatment of women with PCOS. For ovulation induction, letrozole is considered a first-line treatment.[5] It is an aromatase inhibitor that works peripherally; therefore, it mimics the natural tendency of the menstrual cycle for monofollicular development. In contrast, clomiphene citrate, because of its central mechanism of action, induces polyfollicular development. Another advantage of letrozole over clomiphene citrate is its promotion of normal endometrial proliferation. Letrozole may also improve the quality and quantity of the oocytes because the transient build-up of androgens favours improved gonadotropin receptivity. These physiologic advantages have shown clinical implications. Compared to clomiphene citrate, letrozole significantly improves ovulation and live birth rates.[16] Clomiphene citrate is no longer available in Canada.

Use of Insulin-sensitizing agents for Infertile Patients with PCOS			
Insulin-sensitizer	**Dosage**	**Mode of action**	**Issues**
Metfomin	Usual dose: 500 mg TID	Inhibits hepatic gluconeogenesis and promotes skeletal muscle glucose uptake. Helps regulate menses and decreases androgens.	**PROS:** Backed up by existing national and international guidelines due to robust evidence. **CON:** Gastrointestinal side-effects affect tolerbility.
Thiazolidinediones (TZD)	Pioglitazone: 30-45 mg/day	PPAR-γ agonist that ameliorates peripheral insulin resitance indirectly and can decrease androgen synthesis in ovaries.	May cause weight gain, some association with bladder cancer but not backed up by recent data.
Glucagon-like peptide 1 (GLP-1) analogs	Liraglutide SQ 18 µg BID Semaglutide SQ 1 mg/week	Incretin mimetic; increases insulin secretion from the pancreas in response to ingested food. Improves menstrual frequency and hyper-androgenemia in obese women.	**PROS:** Improves glycemic control, insulin resistance and weight loss. **CON:** Injectable medication.
Inositol	Myo Inositol: 2000 mg BID D-Chiro Inositol: 50 mg BID	Acts as a second messanger increasing the cellular uptake of glucose. In the ovary it acts as a second messenger for FSH.	**PROS:** Very favourable safety profile. **CONS:** Evidence is from smaller scale studies.

Table 2. Insulin Sensitizers.[2,14,15,17]

Future Directions

The inositols are gaining recognition as a therapy for PCOS. In the latest European guideline, Myo-inositol (MI), initially classified as an experimental therapy, is included in the recommendations for the treatment of PCOS.[4] This recommendation is based on clinical evidence for metabolic benefits and some studies have provided evidence for improved ovulation, decreased hirsutism, and weight reduction, all while reporting limited harm. This favourable benefit-to-risk ratio is logical given that inositol is a naturally occurring molecule found ubiquitously in nature. Once considered a B vitamin (Vitamin B8), inositol is found in many plant-based foods. It is also present in animal tissues, and once it was discovered to be copiously produced in the body, inositol was declassified as a vitamin.

The most common biologically active inositols are MI and d-chiro-inositol (DCI). MI, the most abundant isomer, acts as a second messenger to several endocrine signals including insulin, FSH, and thyroid stimulating hormone. Conversely, DCI is produced from MI via a unidirectional, insulin-dependent reaction. With insulin signalling, DCI facilitates glycogen formation thereby reducing the circulating levels of glucose. Simply put, MI promotes glucose uptake, while DCI promotes storage.

Insulin insensitivity, common in women with PCOS, dampens the production of DCI in the peripheral organs. Interestingly, this does not apply to all tissues of the body.[17] Here lies the key to understanding the role of the inositols in regulating critical reproductive endocrine processes.

Overall, DCI levels are reduced in PCOS women, while counterintuitively, there are copious amounts of DCI in their ovarian follicular fluid. This is thought to be due to the ovary, which never becomes insulin resistant—a phenomenon called the "ovarian paradox." In the ovary, MI acts as a second messenger to FSH in the granulosa cells and potentiates the production of estrogen. DCI acts in the theca cells by converting cholesterol to androgens. In the granulosa cells, DCI acts as an aromatase inhibitor. Therefore, with continual insulin stimulation, an androgen build up occurs. The resulting hyperandrogenism likewise affects the FSH receptors in the granulosa cells resulting in a relative decrease in estrogen. The end effect is the arrest of follicular growth, which is observed as polycystic appearing ovaries.[18]

Because the in-vitro fertilization (IVF) process provides us a glimpse of the markers of fertility, it is interesting to observe the effects of inositol supplementation during the stimulation cycle. An early prospective observational study by Chiu et al looked at MI and estradiol levels in follicular fluid and compared the quality of embryos treated with MI. They found that higher levels of follicular MI can be a surrogate marker for embryo quality.[19] Another paper showed that MI lowers usage of gonadotropins, stimulation days, and the risk of ovarian hyperstimulation.[20] In addition, emerging evidence suggests that follicular MI improves clinical pregnancy rates.[21]

Women with PCOS are at risk for GDM, which is fairly common in North America, with a prevalence of approximately 7%.[22] Since MI supplementation is considered safe for pregnant women, several studies have evaluated its effect on women at risk for GDM (strong family history of type 2 DM). The findings demonstrate that MI supplementation at a dosage of 4 g/day significantly decreases the prevalence of GDM. Moreover, supplementation has been shown to improve secondary outcomes such as insulin therapy, prevalence of polyhydramnios, and neonatal hyperglycemia.[23]

Summary

PCOS is a life-long metabolic, and endocrine condition. Hyperandrogenism and insulin resistance jointly contribute to PCOS, which, when unchecked, increases the risk of metabolic disease, cardiovascular disease, mental health issues, and endometrial cancer. Contrary to the simplicity of its name, the pathophysiology of PCOS is complex, and extends well beyond the morphology of the ovary. The treatment approach is therefore multifaceted and anchored to healthy lifestyle choices. Therapy depends on the goals of the patient, and can include treatment of infertility, alleviation of hyperandrogenism, weight loss, and/or good glycemic control. Pharmacologic therapies are available to treat the above symptoms. Finally, nutraceuticals, such as the inositols, are gaining legitimacy as treatment options for PCOS.

Correspondence

Maria Isidora Yap-Garcia
Email: marisyap@hotmail.com

Financial Disclosures

None declared.

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doi.org/10.58931/cwht.2024.118

About the Author

Konia Trouton, BSc, MD, CCFP, MPH, FCFP

Dr. Trouton is a Clinical Professor in the Department of Family Practice at UBC, and a Clinical Associate in Women's College Hospital in Toronto, Ontario. She completed medical training at the Queen's University in 1990, residency in Calgary and holds a Masters of Public Health from Harvard. Over the last 30 years, she has worked in at least 2 provinces on a regular basis, including various family planning clinics in BC, Alberta, Ontario, and New Brunswick. In addition to clinical work, she participates in many research and teaching initiatives in contraception and abortion care. For the last 20 years, she was based in Victoria, BC where she founded the Vancouver Island Women's Clinic in 2003. She recently relocated to Toronto to be closer to family and works in the community and hospital.

Affiliations: Clinical Professor, Department of Family Practice UBC, Vancouver, BC
Clinical Associate, Women's College Hospital, Toronto, ON

New Options in Contraception

Konia Trouton, BSc, MD, CCFP, MPH, FCFP

Introduction

In the last few years, more contraceptive options have been introduced into Canada, expanding choice for our patients. Patients and clinicians have experienced changes in how health care is accessed and delivered. For patients, this includes an increased use of the internet and social media as sources of information. Also included are changes to insurance coverage for contraception, such as provincial coverage for some (British Columbia, Quebec and Manitoba), and private insurance offered through school or an employer. In 2015 the cost of universal coverage of contraception in Canada was $157 million, while the cost to provide health care for unintended pregnancies was $320 million, providing a strong economic argument for this change.[1] For clinicians, the pandemic provided an opportunity for many to switch to increase the use of virtual care options, and toward efficiencies in practice.

Contraceptive consultation is generally focused on reaching shared goals of care with patients. While the immediate goal is to prevent pregnancy, the other goal is to prevent dissatisfaction and discontinuation of the method. Regarding the choice of contraceptive method, patients value choice, effectiveness, side effects, ease of use, as well as availability and cost, interference with the sexual experience, and interaction with health care professionals.[2,3] Best practice, therefore, requires that the clinician understands the priorities of the patient, including if or when pregnancy is desired, and also whether a long acting (clinician dependent) or a short acting (user dependent) method is preferred.

Updates on Long Term Reversible Contraceptives

When cost is not an option, over 75% of individuals opt for long-acting reversible contraception (LARC), strongly preferring the option of a very reliable method that does not require self-administration/application and that can be in place for 3 or more years.[4] Evidence shows that discontinuation rates are significantly lower with LARC than with short acting reversible contraception.[5] In particular, for teens aged 14–19 years, discontinuation is only 19% for LARC compared to 56% for short acting methods.[6] It was estimated that if 10% of people in Canada switched from short term methods to LARC, health care savings would be approximately $35 million annually in 2015, and the potential savings would likely be greater now.[1]

Intrauterine Contraceptive	Duration of Use *(Years)*	COVID	Strength *(mg/day LNG) (surface area of Cu)*	Length *(mm)*	Width *(mm)*
		LNG IUDs			
Kyleena (LNGIUS 12)	5	**5**	9 average mcg/day	30	28
Mirena (LNGIUS 20)	5	7	14 average mcg/day	32	32
		Copper IUDs			
Flexis-T 300	5	5	**300mm²**	28	23
Flexis-T 300+	5	5	**300mm²**	32	28
Flexis-T 380+ (sleeves)	5 (12)	**12**	380mm²	32	28
Liberte UT 380 Standard	5	**7**	380mm²	35.4	32
Liberte UT 380 Short	5	**7**	380mm²	28.4	32
Liberte TT 380 Standard (cuffs)	10 (12)	**12**	380mm²	34	29.9
Liberte TT 380 Short (sleeves)	5	**12**	380mm²	29.5	23.2
Mona Lisa 10 (sleeves)	10 (12)	**12**	380mm²	35.85	31.85
Mona Lisa 5 Standard	5	**7**	380mm²	31.9	31.8
Mona Lisa N (ST 300)	3 (5)	**5**	**300mm²**	29	23
Mona Lisa 5 Mini (380)	5	**7**	380mm²	24	30

Table 1. Canadian Intrauterine Contraceptives. Sizes of each IUD available in Canada, with the additional blue column showing a summary of the SOGC 2020 Guidance Document for duration of use.[12]

Today in Canada, the LARC family includes 11 copper intrauterine devices (IUDs), approved for 3 to 10 years of use depending on the type, and two levonorgestrel intrauterine systems (IUS), approved for 5 to 8 years. In 2020, the 3-year single rod sub-dermal implant (SDI) was approved for use in Canada. With the addition of this implant, choosing a LARC will depend on the bleeding profile and the desired location of the implant. LARC methods are highly effective and require a trained clinician for their insertion and removal. As such, they are sometimes termed a "set and forget" option.[7] There is also evidence that the use of methods such as IUD and IUS reduce the risk of endometrial cancer.[8]

1) Copper IUD

The copper IUD is the most effective non-hormonal method of contraception. A patient may strongly consider a copper IUD if they prefer not to use any hormones, owing to either prior poor experiences, personal preference, or a desire to be more aware of their inherent biological rhythm. They also may prefer to have a monthly menstrual cycle that is not induced by medication yet have the benefit of a LARC.

In Canada 11 distinct types of copper IUDs have regulatory approval, requiring one of three insertion methods. Sizes differ slightly, as well as the approved duration of use as illustrated in **Table 1**. Choosing which copper IUD to use is often a clinician preference based on the familiarity with one particular insertion method; however, there is strong evidence for the use of a smaller frame copper IUD for nulliparous patients. A large trial that included 927 nulliparous participants compared their experience with 2 IUDs: a 24 mm x 30 mm device or a

32 mm x 36 mm device. The study demonstrated that those who received the smaller frame copper IUD had significantly less bleeding, pain and expulsion.[9] This trial's findings underscore the necessity that clinicians become familiar with all insertion techniques because pelvic pain and bleeding are common reasons for discontinuation of a copper IUD. Clinicians can play a role to minimize these issues, by selecting the appropriate type of copper IUD and by addressing myths and misconceptions.[10]

2) Levonorgestrel IUS

Many patients seek a reduction or elimination of bleeding in addition to the longer term and superior efficacy of the IUD, and this is accomplished with the addition of levonorgestrel (LNG) in various doses. While products with three different doses of LNG have been approved, only two are currently available in Canada. These include the LNG 19.5mg (containing 19.5 mg of LNG that releases 12 µg /24 hours) and the LNG-IUS 52mg (containing 52 mg of LNG that releases 20 µg /24 hours). Notably, there is currently no generic LNG IUS available in Canada. The LNG-IUS devices work by releasing LNG, a type of progestin, into the uterus, which allows for thickening of the mucous in the cervix, thus preventing sperm from penetrating. Ovulation is generally not suppressed. The implication of this is that some patients will occasionally notice cyclical changes at the time of ovulation. Return to fertility with discontinuation of this method is therefore immediate.

The LNG-IUS 19.5 mg is designed with a slightly smaller plastic frame as noted in **Table 1** and has a small silver ring at the cross junction of the T shape. This design allows for more accurate detection and localization by ultrasound. The LNG-IUS 19.5 mg is approved for use of up to 5 years, and there is no evidence for extended use beyond that time period. Those considering use of the LNG IUS 19.5 mg should be aware of possible irregular spotting, and/or small withdrawal bleeding.

The LNG-IUS 52 mg has been available for a longer period of time compared with the other LNG-IUS devices. The relative bleeding suppression achieved by each LNG-IUS over a 2 year period is illustrated in **Figure 1**. Since 2021, in Canada, the LNG-IUS 52 mg has been indicated for the treatment of idiopathic menorrhagia following an appropriate diagnostic investigation in women who accept the contraceptive effects.[11] Endometrial biopsy, if required, can be performed with the LNG-IUS in situ.

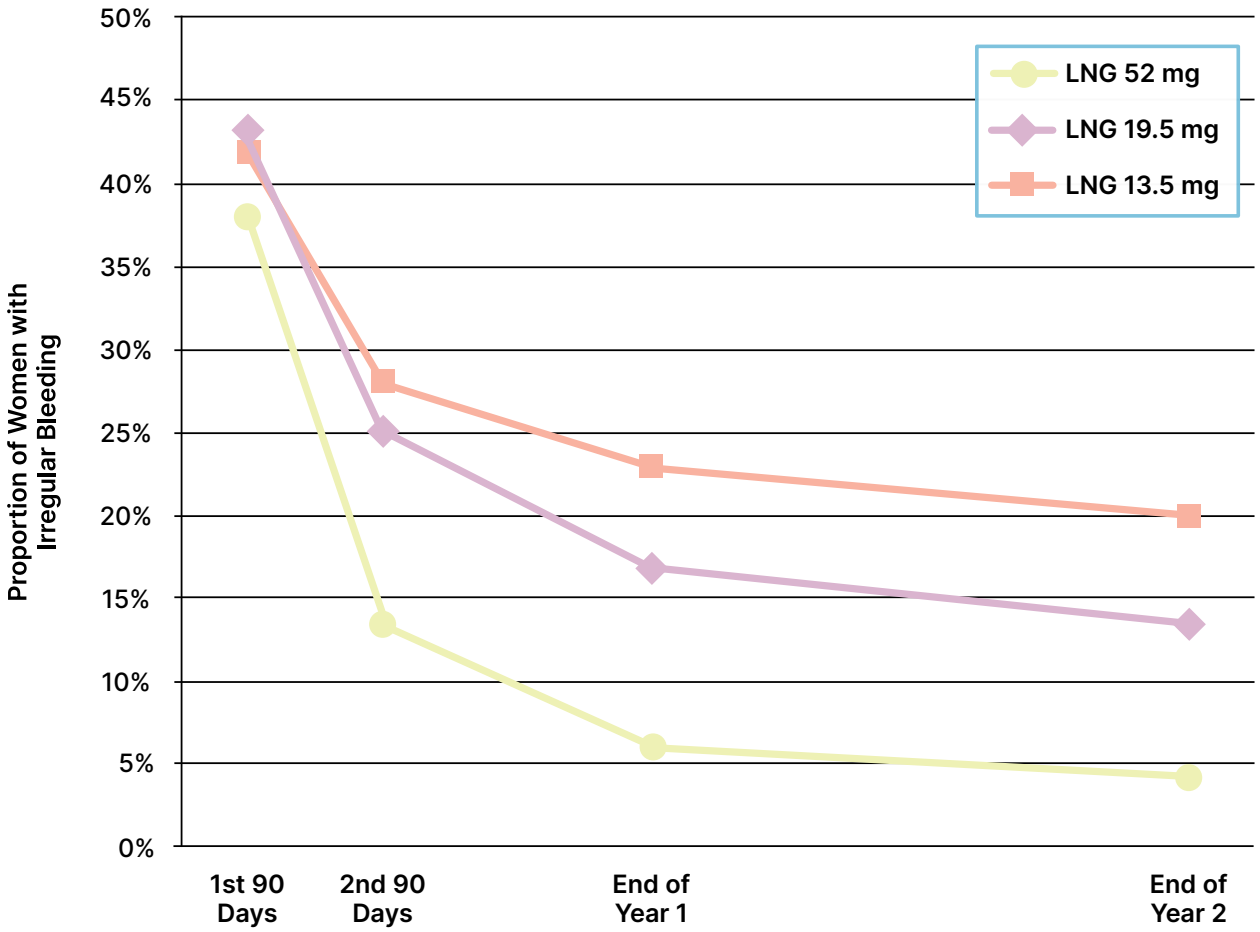
There is good evidence supporting some off label uses of the LNG-IUS 52 mg. For example, during the pandemic, several studies were conducted that reviewed the clinical use of both the copper IUD and the LNG-IUS 52 mg. These studies confirmed that the copper IUD and the LNG-IUS 52 mg can be safely used beyond the time approved . The Society of Obstetricians and Gynecologists of Canada Guidance Document supports use of the LNG-IUS 52 mg up to 7 years.[12] These off label but evidence based guidelines are illustrated in a separate column in **Table 1**. Another off label use of the LNG-IUS 52 mg includes use within 5 days as a post coital contraceptive with a success rate equivalent to the use of a copper IUD. In the randomized non-inferiority trial that included 317 participants who received an LNG-IUS 52 mg and 321 participants who received a copper T380A, only one pregnancy occurred.[13] These findings offer reassurance for clinicians about both the timing of insertion and use of the LNG-IUS 52 mg.

Clinicians will be reassured to know that on February 18, 2024, Health Canada approved the LNG-IUS 52 mg for 8 years for contraception[14], supporting previous findings and recommendations.

3) Subdermal Implant

As of September 2020, patients in Canada have access to the subdermal implant (SDI) as an additional contraceptive option. By December 2021, 2740 clinicians in Canada had been effectively trained in its insertion and removal via a virtual simulation-based training program.[15] Patients can consult their clinician with the aim of having a longer-term contraception method that does not involve undressing or a vaginal examination. They may want a method that suppresses their menstrual period and is safe, especially if fertility in the future is a consideration.[16]

The SDI is effective for 3 years and has a Pearl Index slightly superior to that of the LNG-IUS, and even to that of tubal ligation or vasectomy.[17] The SDI contains etonogestrel, which is an active metabolite of desogestrel. The contraceptive effect of etonogestrel is through inhibition of ovulation, though it also causes changes in the cervical mucus. The etonogestrel in the SDI is encapsulated in ethylene vinyl acetate and is impregnated with barium sulphate so that



LNG-IUS type	1st 90 days	2nd (90 Days)	End of Year 1	End of Year 2
LNG-IUS 52 mg	648 (38.1%) [n=1700]	220 (13.6%) [n=1621]	89 (6.1%) [n=1448]	52 (4.4%) [n=1178]
LNG-IUS 19.5 mg	665 (42.5%) [n=1566]	377 (25.0%) [n=1511]	226 (16.5%) [n=1371]	(14%)
LNG-13.5 mg*	643 (42.0%) [n=1531]	415 (28.1%) [n=1475]	300 (22.6%) [n=1329]	(20%)
		p-values		
52 mg vs 19.5 mg	0.01	<0.0001	<0.0001	--
52 mg vs 13.5 mg	0.03	<0.0001	<0.0001	--
19.5 mg vs 13.5 mg	0.8	0.051	<0.0001	--

Figure 1. Relative bleeding suppression achieved by each LNG-IUS; *adapted from Goldthwaite et al, 2019.*

it is radio-opaque.[18] This means that any imaging modality will be able to identify it, especially in the instances in which the implant is embedded too deeply and must be located prior to removal. In general, imaging is not needed, because the rod is superficially identified immediately after insertion and prior to removal/replacement by palpation and is typically located over the triceps muscle of the non-dominant arm.

While the effectiveness and insertion procedure of the SDI are appealing, patients should be advised that the likelihood of irregular bleeding is higher compared with any of the LNG-IUS devices. There are few direct comparison studies between the SDI and the LNG-IUS. For instance, a large study conducted in 38 centres in 6 countries enrolled 766 patients to compare their 12-month experiences with the SDI and the LNG-IUS 8 (containing 13.5mg of LNG that releases 8 µg /24 hours).[19] Note that the LNG-IUS 8 is no longer available in Canada; however, what the report concludes is that 12-month discontinuation rates were 26.8% in the SDI group compared with 19.6% in the LNG-IUS 8 group, mainly because of increased irregular bleeding patterns. The relative suppression of bleeding between the etonogestrel implant (ENG) and the LNG-8 at each 90 day interval is illustrated in **Figure 2**.

Clinicians considering adding the SDI to their practice will find the insertion process similar to other dermatological procedures. The implant comes contained in an insertion device; however, clinicians need to prepare by landmarking the area and injecting local anesthetic. Following insertion, the site must be covered with a band aid or steri strips and pressure dressing applied. Removal of the device can be slightly more challenging than insertion, requiring a 2 mm incision to access the device and slide it out. This is then closed with steri strips. . Removal of deeply embedded and non-palpable implants (which occur in 1% of patients) should not be attempted in the office; rather, consultation with experts is prudent.[18]

A 2-rod SDI is available in some countries that uses levonorgestrel rather than etonogestel as the type of progesterone. These are non-radio opaque rods and can be left in place for 5 years, rather than 3 years. The insertion device is different, and while clinicians in Canada are not likely to insert a device that is not approved, they may be required to remove the device. Once the device is removed, the return to fertility is rapid, thus patients can be advised that within 24 hours, fertility returns to baseline. Implants can, however, be used back-to-back, indefinitely.

Updates in Short Term Reversible Contraception

1) New Progesterone Only Pill

Progesterone-only pills (POP) are considered safe and can be appropriately prescribed in a virtual health consultation with minimal risk. The contraindications for POPs are limited and rare. International medical eligibility criteria can be consulted to verify the contraindications.[20] The contraindications include personal history of breast cancer, malabsorptive bariatric procedures, hepatocellular adenoma, and systemic lupus erythematosus with positive antiphospholipid antibodies, as well as ischemic heart disease or stroke. Those taking medications such as certain anticonvulsants or rifampin should neither initiate nor continue taking a POP. However, POPs are appropriate for most people, particularly those who have contraindications to the use of estrogen, such as people with hypertension, those who do not tolerate estrogen, smokers over the age of 35, or those who are breastfeeding exclusively.

For many years, the POP available in Canada contained 0.35 mg daily of norethindrone, which works primarily by thickening the cervical mucus to inhibit sperm penetration. Norethindrone also lowers the midcycle LH and FSH peaks, slows the movement of the ovum through the fallopian tubes, and alters the endometrium with suppression of ovulation in approximately half of users.[21] For patients, the benefit of taking a POP is reduction in bleeding and suppression or elimination of menstrual periods. While this POP is effective for contraception, it has a short half life, and therefore must be taken every 24 hours. The clinical guidelines for POPs that indicate a “three-hour window” of tolerance before back-up contraception should be used have been recently reviewed.[22] These guidelines are primarily based on one study that Cox et al. conducted in 1968 that included 6 women using megestrol acetate (0.5 mg), which is a progestin no longer sold as an oral contraceptive for humans.[23] The study found that megestrol acetate did not lead to any ovulation suppression. The median Pearl index for most POPs is higher than for combined oral contraceptive pills (COCP), which means that there is generally a higher risk of pregnancy.

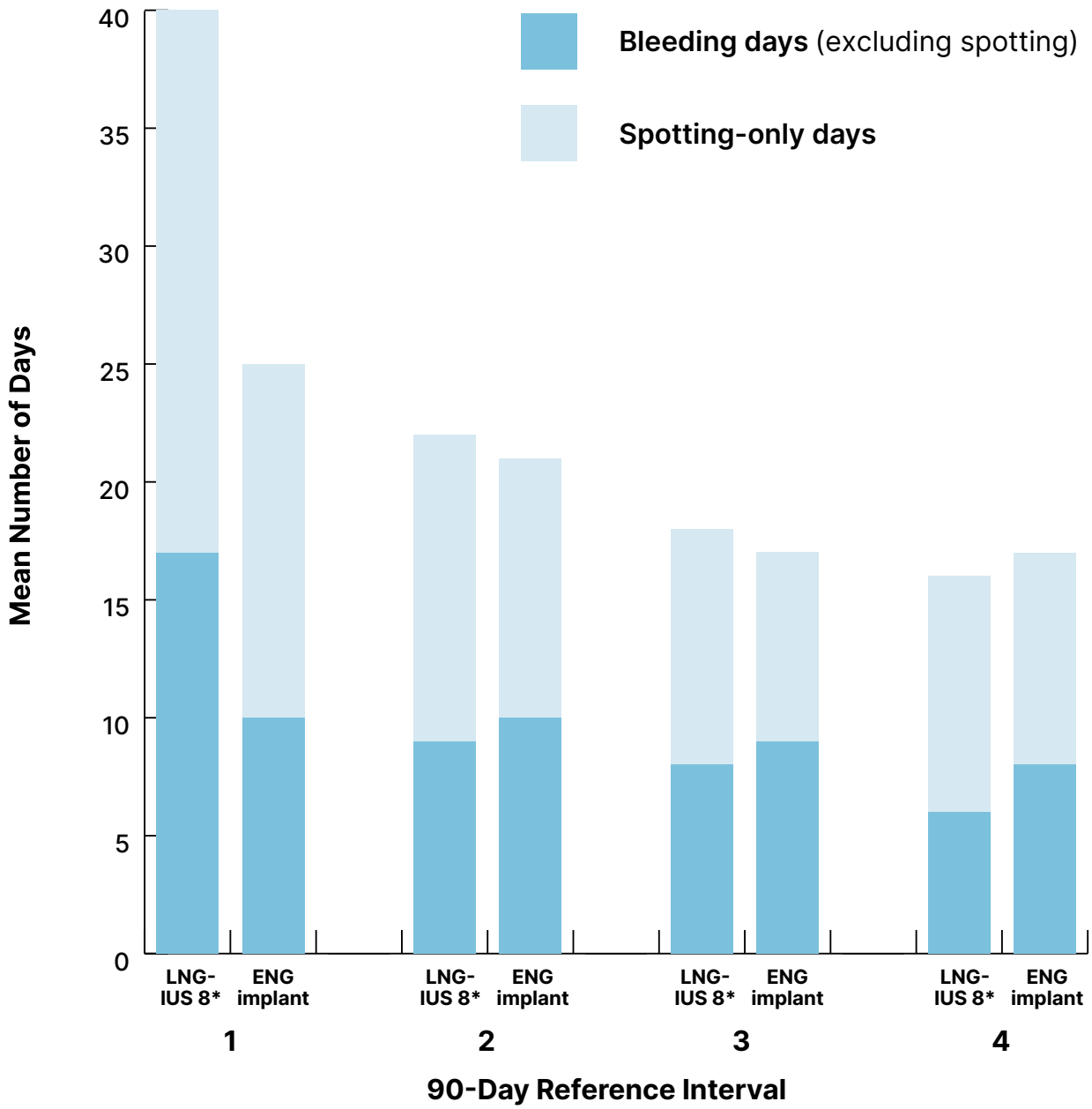


Figure 2. Relative suppression of bleeding between the etonogestrel implant (ENG) and the LNG-8, which is no longer available in Canada; *adapted from Apter et al, 2016.*

Mean number of bleeding and spotting days by 90-day reference intervals (modified intention-to treat set) in the LNG-IUS 8 and ENG implant groups. The numbers of bleeding and spotting days were not recorded at baseline. Modified intention-to-treat set: all women for whom at least one placement/insertion attempt was made. ENG = etonogestrel; LNG-IUS 8 = levonorgestrel intrauterine system total content 13.5 mg (average, ~8 µg/24 hours during the first year).

Abbreviations: LNG-IUS: levonorgestrel intrauterine system; **ENG:** etonogestrel

*LNG-IUS 8, marketed as *Jaydess*, is no longer available in Canada.

However, a new POP is as effective as COCPs, and has an equivalent Pearl Index. This POP was recently approved in Canada and contains a different progestin (4 mg of drospirenone) that has a long half life. This POP is packaged with 24 active treatment days followed by 4 placebo tablets. The primary mechanism of action is suppression of ovulation, and in studies,[24] despite the 4-day hormone-free period and multiple intentional 24-hour delays in tablet intake, ovulation inhibition was maintained. This option should be considered for most patients desiring or requiring a POP.

2) New Considerations in Combined Oral Estrogen and Progesterone Pills

Many patients do well on a COCP, because the addition of estrogen to the progestin base allows the lining of the uterus to thicken and stabilize, leading to a more regulated and predicable withdrawal bleed, (or menstrual period), when the estrogen is discontinued for a few days. Estrogens reduce both follicle development and secretion of FSH, leading to ovulation inhibition. Various products have adjusted both the amount and duration of the estrogen contained in the COCP to address the reasons for discontinuation. Until recently, the only estrogen available in COCPs in Canada has been ethinyl estradiol, which is metabolized by the cells and has systemic effects on the bone, breast and uterus—all organs that have estrogen receptors. COCPs available in Canada contain different types and quantities of progestins.

Patients may experience challenges finding a suitable COCP with no side effects, such as unwanted bleeding, spotting or break-through-bleeding, or adverse impacts on mood. For example, satisfaction rates with COCP use can be as low as 55%.[25] However, clinicians may be less aware of this because discontinuation of any pill does not require a clinical visit. Patients may subsequently seek medical attention for a pregnancy termination, or with a mis-timed pregnancy, or for the use of over-the-counter agents such as the morning after pill. Adjusting the amount of ethinyl estradiol from 10 mcg to 35 mcg has been one option to address the side effects of bleeding.

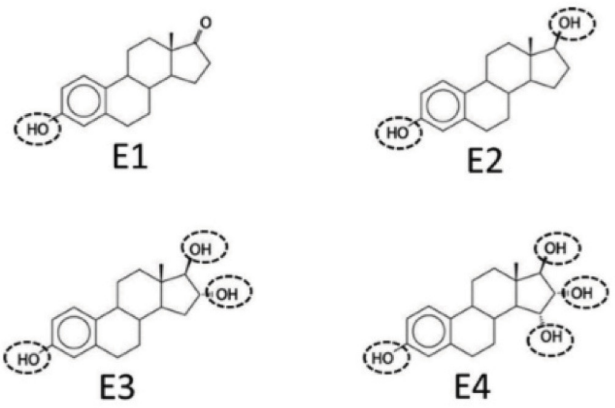


Figure 3. Comparison of naturally occurring estrogens. Molecular structures of estrone (E1), estradiol (E2), estriol (E3) and estetrol (E4). The dashed line cirlces depict -OH groups; *adapted from Grandi et al, 2020*.

The novel estrogen, estetrol (E4), recently approved in Canada, is a promising alternative for patients because of its tolerability and safety profile.[26] E4 is a naturally occurring estrogen and is an estrogen with selective activity in tissues. **Figure 3**[27] shows the chemical configuration of all four naturally occurring estrogens. It has minimal impact on triglycerides and breast stimulation, and has minimal impact on hepatic metabolism, while continuing to have estrogenic effects on the uterovaginal tissues, bone and brain. E4 is made from a plant source, which may be important to some patients. It occurs naturally in the human body, during fetal development.

A trial looked at COCPs that combined E4 with both LNG and drospirenone at various doses to optimize bleeding patterns, cycle control, and satisfaction.[28] As a result, the optimum combination was found to be drospirenone at a dose of 3 mg, administered in a regimen of 24 active days followed by 4 inactive days. The trials have shown a statistically significant improvement in favourable bleeding patterns, high levels of user acceptability, and effective control of body weight. Long term results regarding venous thromboembolism risk are being tracked; although initial clinical results suggest a lower rate of VTE, this needs to be confirmed with larger studies. Therefore, at present, clinicians should follow established contraindications for COCPs when recommending this new option to patients.[29]

Conclusion

Selecting a contraceptive method requires increasingly focused discussions to establish reproductive health goals and to consider broader health care considerations. Patients are equal partners in collating relevant information for decision making. In the last few years, the introduction of additional information and products for both long-term and short-term contraceptive use has expanded options, and improved safety. There is reason for optimism that there will be a reduction in the burden and cost of unplanned pregnancies. Crucially, universal coverage of contraception will allow patient choice to become a reality in Canada.

Correspondence

Konia Trouton
Email: konia.trouton@wchospital.ca

Financial Disclosures

Clinical Advisory Boards: Bayer, Organon, and Celopharma.
Speaking: Bayer, Organon, Celopharma, Searchlight Pharma.

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doi.org/10.58931/cwht.2024.119

About the Author

Laurie Betito, PhD

Dr. Laurie Betito is a clinical psychologist with a specialty in sexual wellness and has been a practicing psychotherapist for over 35 years. For the last three decades she has been doing radio and television, dispensing sex and relationship advice. For 22 years she was the host of the nightly Canadian syndicated show *Passion*. She is a regular contributor to various magazines, newspapers and television shows. Dr. Laurie is also President of the Sexual Health Network of Quebec and Past President of the Canadian Sex Research Forum. She is the author of *The Sex Bible for People Over 50* and the Director of the Pornhub Sexual Wellness Center, an online sexual health information platform. Dr. Laurie has also done two TEDx talks on the subject of sexuality. Her weekly podcast "Passion with Dr. Laurie and Jon Pole" is available on all platforms.

Understanding Female Sexual Dysfunction

Laurie Betito, PhD

Introduction

Sexuality is an integral part of our human existence. It is more than a source of pleasure—it is a source of fulfillment, emotional connection, intimacy and empowerment. Unfortunately, for many women worldwide, a satisfying and fulfilling sex life is thwarted by sexual dysfunction. Female sexual dysfunction (FSD) is an all too common and often very distressing condition that encompasses a wide range of difficulties, and affects women of all ages and backgrounds. This condition is characterized by a persistent or recurrent inability to achieve sexual satisfaction, causing the woman distress. This is a complex issue as the causes can be quite varied and sometimes elusive. The contributing factors we evaluate include physical (hormones, chronic illnesses, medication side effects), psychological (anxiety, depression, stress, relationship issues) and social (cultural or religious beliefs). Women who experience FSD are often distressed, experiencing relationship strain as a result, and their overall quality of life is impacted. This is a topic that is still shrouded in shame and stigma, leaving many women unable to discuss or uncomfortable discussing their difficulties even with healthcare professionals. We need to empower women with knowledge, encourage them to discuss their sexuality, and provide help and support. As health professionals, we need to play our part in the destigmatization and normalization of sexual wellness.

Evaluating Female Sexual Dysfunction

Evaluating FSD involves a comprehensive assessment of the physical, emotional, relational and psychological factors that may be contributing to the dysfunction. In addition to a medical history and a physical examination, healthcare providers can use standardized questionnaires to understand and diagnose the particular area of difficulty.[1,2]

The Female Sexual Function Index (FSFI) is the most widely used tool for assessing sexual health in women, and for readers of this article in e-journal format, the FSFI can be found here. It is a self-reporting measure that asks questions about desire, arousal, lubrication, orgasm, sexual satisfaction, and pain.[2] This tool is a great beginning to initiating the conversation about sexual wellness and evaluating the specific areas of distress. If time is a constraint, focusing on the

following elements will provide an overview of the problem and will help you refer the patient to the appropriate healthcare professional:

1. **Sexual activity:** Is the patient sexually active (self or partnered)?
2. **Response:** Do they have desire? Do they experience arousal and/or orgasm? Do they experience pain?
3. **Onset:** Is it lifelong/acquired? Is it gradual or sudden?
4. **Pattern:** Is it situational or global?
5. **About the partner:** Any sexual concerns or problems in the partner?
6. **Impact of the problem** on patient's life/relationship
7. **Previous intervention:** Has the patient received treatment for the problem? If so, was it effective?
8. **Motivation for seeking help now?**

Using this index systematically during a wellness checkup is recommended and lets the patient know that the provider is open to discussing sexual issues.

Categorization

FSD can be categorized following the human sexual response cycle[3]: desire disorders, arousal disorders and orgasmic disorders. Pain disorders should also be included.

Hypoactive Sexual Desire Disorder (HSDD) is now categorized in the DSM-54 as Female Sexual Interest/Arousal Disorder. This is a common sexual dysfunction, defined by a complete lack of or significant reduction in sexual interest or/and arousal. Symptoms to investigate include the absence of interest in sex; the absence of sexual thoughts; lack of initiating partnered sex; little or no sexual excitement or pleasure during sexual activity; little to no arousal to sexual cues; and a lack of genital sensation during sexual stimulation. The symptoms must persist for a minimum of six months and result in distress for the patient. This last element of distress is a vital component in the assessment of FSD (in fact, this was only added in the DSM-IV in 1994).[5] It is also important to note that traditional models typically posit that sexual desire is spontaneous. However, this framework often fails to align with the experiences of many women regarding their sexual response. As a result, definitions of desire dysfunctions tend to presuppose a baseline of spontaneous sexual desire, which has led to many women being erroneously labeled as dysfunctional.

Sexual arousal disorder is characterized by persistent difficulty in becoming sexually aroused or maintaining arousal during sexual activity resulting in distress to the patient. It is important to assess the context by asking if this is specific to certain sexual situations (partnered sex, solo sex) or specific partners; if this is a new condition, and if so, what else is occurring in the person's life (or relationship) that may be contributing to the issue. Assessing changes in the patient's psychological state (including stress, anxiety, trauma) that may also contribute to the issue is important as is the societal/cultural context the patient is influenced by. We also want to assess if lack of arousal is due to low desire and/or sexual pain.

Orgasmic disorder, also known as anorgasmia or inhibited orgasm, is characterized by the difficulty or inability to achieve orgasm despite adequate sexual stimulation and arousal, causing the patient distress and frustration. Orgasmic disorders may be due to psychological factors such as anxiety, body image issues, stress, history of trauma, and relationship issues. It may also be a result of prescription medications.

Sexual aversion disorder is a much less common sexual dysfunction, characterized by a strong aversion to or avoidance of sexual activity altogether. The etiology may be very similar to that of the other dysfunctions discussed above.

Treatment for the above disorders depends on their etiology, which is why it is crucial to conduct a thorough evaluation of the person's medical history; trauma history; relationship dynamics; cultural context; belief system; and degree of sexual knowledge/experience. It is also important to assess if the problem is global or situational, primary or secondary. For example, if the problem only occurs in certain situations, it is most likely a psychological/relational issue rather than a medical issue. If it is secondary (developed over time), we must assess changes in the patient's life, relationship or medical situation.

Treatment often involves a combination of approaches including psychotherapy, sex therapy,

lifestyle changes, or medication in certain cases. Therapy can include "prescriptions" such as exploring sexual techniques; sensate focus exercises such as self-stimulation (often with clitoral stimulators) to get to know one's body; working on body image issues; psychotherapy with a focus on healing trauma; treating underlying anxiety or depression; couple therapy to address relationship issues; teaching mindfulness techniques to learn how to be present sexually and others. If the problem is hormonal, hormone replacement therapies should be considered (estrogen or testosterone replacement). If the problem is due to a medication side effect, we would consider changing the medication to one with less sexual side effects (for example, adding Wellbutrin to a patient on an SSRI may counter the side effect of low desire).[6]

Unfortunately, to date, there are few efficient medications for the treatment of low desire or arousal disorders. There is still quite a bit of controversy over the use of such medications considering that female sexuality is quite complex, with multiple factors at play that cannot be remedied by medication alone, especially concerning desire. Filbanserin is an oral medication that is FDA and Health Canada approved for the treatment of hypoactive sexual desire disorder (HSDD) in pre and postmenopausal women. It is thought to work by affecting neurotransmitters in the brain. However, there are many reported side effects and its efficacy is questionable.[7] At the present time, testosterone replacement therapy is sometimes used off label as a treatment for FSD. However, it is not approved by either the FDA nor Health Canada for this use due to the uncertainty around both efficacy and long-term safety. Furthermore, there does not seem to be any consensus on what constitutes androgen insufficiency in women. For these reasons, it is not further explored in this article.[8,9]

Sexual pain disorders are conditions that cause pain during sexual activity. They can involve pain during intercourse (dyspareunia), persistent genital pain (vulvodynia) and vaginismus.

Dyspareunia is a condition marked by persistent or recurring genital pain that occurs before, during or after sexual intercourse. It can originate from factors like inadequate lubrication; injury; inflammation; infection; skin conditions; structural issues or vaginismus.

Vaginismus is a syndrome characterized by involuntary spasms of the vaginal muscles that hinder penetration, or make it completely impossible for the insertion of even a tampon or finger.

Vulvodynia is a pain condition whereby women experience sensations of burning and soreness in the vulval area, especially when the area is touched, even lightly. It is considered a form of localized, provoked vulvodynia when it is specific to touch. When the pain is continuous it is considered unprovoked vulvodynia. The pain is often described as burning; irritation; stinging; rawness; soreness; or sharp, knife-like pain. It can be felt in a very specific spot (like the vestibule), the clitoris or the entire genital area.[7]

Female sexual pain disorders can greatly affect a woman's health, self-esteem, relationships, quality of life, and work productivity. It is uncertain if sexual pain should be classified as a sexual disorder, a pain disorder or both.[10] The causes of these disorders vary from straightforward anatomical issues or infection to intricate biopsychosocial factors. Identifying the exact cause of pain can be difficult as a woman may experience more than one underlying cause.

Avenues to explore in determining the etiology of genital pain include: skin conditions; sexually transmitted infections; yeast or bacterial infection; vulvar growths; and genitourinary syndrome of menopause. Unfortunately, sometimes the exact cause is difficult to determine as there may be no visible sign. One line of thinking is that there is damage or irritation to the nerves that transmit pain from the vulva. Researchers also consider an increase in nerve fibre density in the vulvar vestibule as a potential factor.[11]

Therapies for sexual pain disorders may include topical hormone therapies for GSM; pelvic floor physiotherapy which has robust, evidence-based support and is considered a first-line treatment[12]; local anesthetics for temporary relief; nerve block injections to the area; pain management therapies such as biofeedback, talk therapy and sex therapy (individual/couple); or surgery of the vestibule tissue.

Needless to say, treatment strategies should be tailored to address each patient's unique requirements and may involve a combination of approaches.

Conclusion

FSD is an often distressing condition that encompasses a wide range of difficulties. It affects women of all ages and backgrounds, with significant physical and psychological repercussions. It is incumbent on healthcare professionals to provide women with FSD information and knowledge, encourage them to discuss their sexuality, and provide them assistance and support. Healthcare professionals have an important role to play in destigmatizing and normalizing sexual wellness.

Correspondence

Dr. Laurie Betito
Email: laurie@drlaurie.com

Financial Disclosures

None declared.

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Canadian Women's Health Today
Science for the Real World

canadianwomenshealthtoday.com

Canadian Women's Health Today is published three times per year
in English. (ISSN 2818-1816) under the terms of the

Vol. 1, Issue 1

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