Canadian Women's Health Today

Vol. 1, Issue 3
Fall 2024

In this issue:

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

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To contribute to a future issue, email us at info@catalytichealth.com. Submission guidelines and editorial policies are available on the journal website, canadianwomenshealthtoday.com.

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Please consult the Product Monograph at http://pfizer.ca/pm/en/duavive.pdf for important information relating to adverse reactions, drug interactions and dosing information, which have not been discussed in this piece. The Product Monograph is also available by calling 1-800-463-6001.

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.2024.1315

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Imaging Considerations for Adnexal Masses

Tanya Chawla, MD

Background and Clinical Context

Adnexal masses are commonly found during routine imaging of the pelvis and can be seen in up to 4-5% of asymptomatic women undergoing pelvic ultrasound (US).[1] These masses encompass a range of pathologies from both gynecologic and non-gynecologic origins and can either be benign or malignant.

In Canada the lifetime risk for ovarian cancer is 1.7%. There are approximately 3,100 cases per annum in Canada with 2,000 deaths.[2] Despite its low prevalence, ovarian malignancy is a leading cause of death among gynecological malignancies, with a 5-year survival rate of 47%. Imaging plays an integral role in the detection, characterization, and appropriate triage of adnexal masses.

The majority of adnexal masses are benign and can be managed conservatively. For the smaller minority of malignant lesions, accurate characterization with early triage to a gynecological oncology centre has an impact on oncological outcomes, and reduces the risk of re-operation and the time to initiation of adjuvant chemotherapy.[3] Conversely, inappropriate surgical triage of benign masses can have an adverse impact on patient morbidity, compromise fertility, and increase cause-specific death for a variety of conditions, including a range of malignancies and cardiovascular diseases.[4]

Finally, appropriate triage also minimizes the utilization of finite healthcare resources by ensuring that surgery is performed only when it is indicated and avoiding unnecessary follow-ups

and repeated imaging for benign or physiological categories of adnexal lesions.

Ultrasound remains the primary modality used for the characterization and initial assessment of adnexal masses.[5] It is non-invasive, cost effective, and has a high sensitivity and specificity. Transvaginal ultrasound (TVUS) has a sensitivity of 90% and a specificity ranging from 51–97% for detecting malignancies.[6,7]

There has been an increased emphasis on improving the clarity and communication in imaging reports by minimizing the use of ambiguous terminology such as "complex" or "heterogenous" mass, which can be unhelpful to the clinician responsible for triage. Various societies have encouraged the standardized management, reporting, and classification of adnexal masses.[4,7]

The experience and overall expertise of the radiologist performing the US, impacts the accuracy and quality of the assessment. Multiple studies have shown scoring systems using standardized reporting templates and nomenclature can equalize or improve the performance of a novice/relatively inexperienced radiologist to that of a more experienced radiologist.

Role of US; Performance Characteristics

As recommended by multiple guidelines,[5,8] US remains the initial test of choice for assessment. Its numerous benefits include cost effectiveness, safety, patient tolerance, lack of ionizing radiation, wide availability, and the ability to readily discriminate between cystic and solid lesions. Many physiological and benign lesions can be confidently diagnosed by US/TVUS. Additionally, US remains the modality of choice for the routine follow-up of benign lesions, as clearly detailed in the Ovarian-Adnexal Reporting and Data System (O-RADS) management recommendations.

With a sensitivity ranging from 88–100%, a negative ultrasound can confidently exclude malignancy. However, its specificity is variable, ranging from 46–95%, and is dependent on the imaging features and interpretation method.

Data has shown that the pattern recognition approach used by an experienced radiologist/sonographer is one of the most accurate means of discriminating between benign and malignant adnexal masses.[6] However, in real life settings there is a wide variance in the expertise of radiologists who perform and interpret these exams. Maintaining this level of expertise also requires exposure to a broad number and complexity of cases.

What Are We Looking For?

Risk categorization on US relies on the accurate recognition of specific imaging features. A stepwise approach is adopted when evaluating an adnexal finding on US. Benign lesions as well as physiological findings such as follicles or a corpus luteum can be readily characterized by "classic" lexicon features. Any findings outside these categories are classified as "lesions". Further sub-classification requires determining if a lesion is cystic or solid. For cystic lesions, further categorization is based on features such as locularity, mural irregularity, and the characteristics of septations if present. Solid components of cystic lesions include the presence and number of papillary projections (with >4 projections conferring additional risk). For solid lesions, features such as the outer contour (smooth versus irregular), colour score, and shadowing help in assigning a risk category. The presence of ascites and peritoneal nodularity automatically upgrades a lesion to a higher category, unless there is an alternate explanation for the ascites (cardiac failure). In general, increasing soft tissue components and higher vascularity are associated with a higher risk of malignancy. Vascularity is quantified within the solid tissue or wall of a lesion with a colour score ranging from 0 (no flow) to 4 (strong flow).

These findings are then categorized based on menstrual status (pre- or post-menopausal) and lesion size.

What is Standardized Reporting?

Synoptic reporting in radiology is used across a variety of body systems and has eliminated ambiguity in reports, facilitating clear communication, and providing guidance with management.

Several US-based classification systems have been developed for evaluating adnexal masses. These systems rely on morphologic features along with supporting clinical data.

The **IOTA** (**International Ovarian Tumour Analysis**) group conducted the largest study on the sonographic diagnosis and pre-operative classification of adnexal masses. This study paved the way for using standardized terms,

definitions, and measurements for these lesions. In particular, this database helped in testing existing models such as the Risk of Malignancy Index and compiling evidence-based terms and definitions to develop several risk-based models. Of these, the **Simple Rules** and the Assessment of Different NEoplasias in the adnexa (**ADNEX**) **model**[9-11] are the most widely recognized. The IOTA Simple Rules use 10 US features to classify lesions as either benign or malignant. However, approximately 20% of lesions cannot be classified by this method and require additional input such as an evaluation by an expert imager. The Simple Rules have a sensitivity of 91–96% and a specificity of 68–93%. These imaging features have been incorporated into a mathematical model that calculates the likelihood of malignancy. The ADNEX model uses additional information (menopausal status, CA-125 levels, and referral to a tertiary centre) along with 6 US features. It can further stratify risk into categories such as borderline, Stage I vs Stage II-IV malignancy, as well as metastases. With a 10% cut off, it has a sensitivity of 10% and a specificity of 71.3%, outperforming the Simple Rules (AUC 0.92 vs 0.95 for the ADNEX model).

O-RADS[12] was published in 2018 as a lexicon followed by the full system in 2019. This system was developed by a multi-disciplinary team of radiologists, gynecologists, and gynecologic oncologists. It incorporates a standardized lexicon for ovarian and adnexal lesions and provides a numerical score to enable risk assignment based on radiological features to determine the risk of malignancy. O-RADS includes both US and magnetic resonance imaging (MRI) components.

Moreover, it provides evidence-based guidance on management options for each risk category. This system was built on the foundational work of the IOTA group and extrapolated data and US descriptors from those trials to provide the framework for the O-RADS classification. Specifically, data from the IOTA phase 1–3 studies was reflected in this analysis, which included 5905 patients who had pathologically confirmed adnexal lesion(s). The most predictive descriptors identified in the IOTA studies were matched to the O-RADS US terminology.

Terminology such as “unilocular/multi-locular cyst ± solid components” and “mostly solid” were used to define the major categories of the adnexal lesions in O-RADS (See **Table 1**). This approach enabled the unification of a pattern-based approach (seen in North America) with the statistical data obtained from the IOTA studies and was predicated on the prevalence of malignancy in this subgroup of patients.

Numerical Score	Category Risk Assessment	Risk of Malignancy *(% or Range)*
0	Incomplete	NA
1	Physiologic (normal)	0
2	Almost certainly benign	<1%
3	Low risk	1-10%
4	Intermediate risk	10-<50%
5	High risk	≥50%

Table 1. O-RADS v2022 risk assessment categories and risk of malignancy; *adapted from O-RADS US v2022: An Update from the American College of Radiology’s Ovarian-Adnexal Reporting and Data System US Committee.*

How Does O-RADS Work?

O-RADS is divided into 6 risk stratification categories ranging from 0–5. Category 0 applies to an examination that is technically inadequate. Categories 1–5 describe a range of lesions from physiological/normal findings to those with a high risk of malignancy. O-RADS US terminology incorporated the most predictive descriptors from the IOTA data and classifies each descriptor into a risk category. Each risk category is then subsequently assigned a corresponding recommendation for management. Again, this approach facilitates interpretation, but also provides clear guidance for the non-expert clinician/healthcare provider who may be managing or triaging an adnexal mass. The system is designed to be applicable to a general population with an low overall prevalence of malignancy. It is designed to optimize sensitivity at the expense of specificity, given the lethality of ovarian malignancy. Additionally, the number of

false negatives is minimized. Version 2022 of the O-RADS system[13] was introduced to incorporate emerging data and address features that improve specificity for lesions of lower risk.

When and How Should It Be Used?

It is recommended to apply O-RADS to all adnexal masses, whether physiological or otherwise. Certain governing concepts[13] or rules are applied. Note that management guidance is based on patients who are at average risk and asymptomatic. The original IOTA data group, however, included patients who were symptomatic and of high risk. Therefore, the lexicon terminology and categorization apply to these patients, but management recommendations may need to be individualized. While a full description of these rules is beyond the scope of this article, certain broad concepts still apply.

1. **Applicability criteria:** relevant only to lesions of ovarian or tubal origin. Therefore, if there is a lesion of uncertain origin, (e.g., an exophytic fibroid), O-RADS does not apply. Additional imaging, either with computed tomography (CT) or MRI, may be necessary to determine the compartment of origin. In certain clinical settings (unrelated to malignancy) the O-RADS system does not apply (for instance in the context of pelvic inflammatory disease or an ovarian torsion). In the context of bilateral adnexal masses, each mass is scored independently, with the higher scoring lesion driving the management approach.

2. **Definitions and technique:** the 2022 version has further sub-divided the menopausal status of patients into early and late stages to assist with the management of hemorrhagic cysts. In addition, there is clarification regarding the role of US specialists. The necessity for a TVUS has been negated in this version, as the trans-abdominal technique is considered sufficient when TVUS is either not technically feasible or inadequate in scope.

   Finally, users are encouraged to record 3 dimensions as an average linear dimension to allow an accurate comparison between serial examinations and assess for interval changes.

3. **System use rules:** although O-RADS risk assessment scoring can be applied to the majority of lesions irrespective of patient risk factors and symptoms, management may differ in these clinical scenarios.

Role of MRI Relative to US

Where does MRI fit into the imaging paradigm for risk stratification? There are advantages to imaging adnexal masses on MRI, (discussed below) however, it is also important to acknowledge the resource limitations within the Canadian healthcare system. MRI remains an expensive modality, and access to this resource is limited with long wait times.

MRI offers superior specificity and accuracy compared with US. It not only aids in characterizing benign lesions (in the atypical US scenario), but also provides greater soft tissue contrast and characterization. MRI has a high positive predictive value (PPV) for the exclusion of malignancy (71%) and a high negative predictive value (NPV) (98% vs 99% for US). Similar to US, it is a radiation free modality.

Applying a US-based stratification system allows for accurate classification and risk assignment in the majority of cases. However, 5–25% of lesions remain indeterminate on US.[14] In these circumstances, the PPV for malignancy varies between 7–50%. Additionally, there are circumstances in which US may be limited for technical reasons (e.g., patient habitus, inability to tolerate a TVUS). TVUS is not mandatory for lesion characterization, but it does impact the ability to accurately characterize lesions. When pelvic masses are large (e.g., >10 cm) US may be more limited in determining their origin as well as optimally assessing specific features such as the presence of mural irregularity or nodules. In this setting, MRI allows a clearer assessment. Finally, it is easier to demonstrate vascularity/enhancement in the smaller solid components of cystic lesions with MRI than with ultrasound.

The O-RADS MRI system, developed in tandem with the US-based system, was launched in 2021. Akin to the US-based system, it uses morphologic and functional findings on MRI to assign a risk score for adnexal masses. Further discussion of this topic is beyond the scope of this article.

What is the Role of Other Modalities?

CT plays no role in the work up or characterization of adnexal masses. However, in the setting of a presumed or proven malignant mass, contrast enhanced CT is a first line modality for staging and surgical planning to determine if a patient should be triaged to surgical debulking or neoadjuvant therapy.

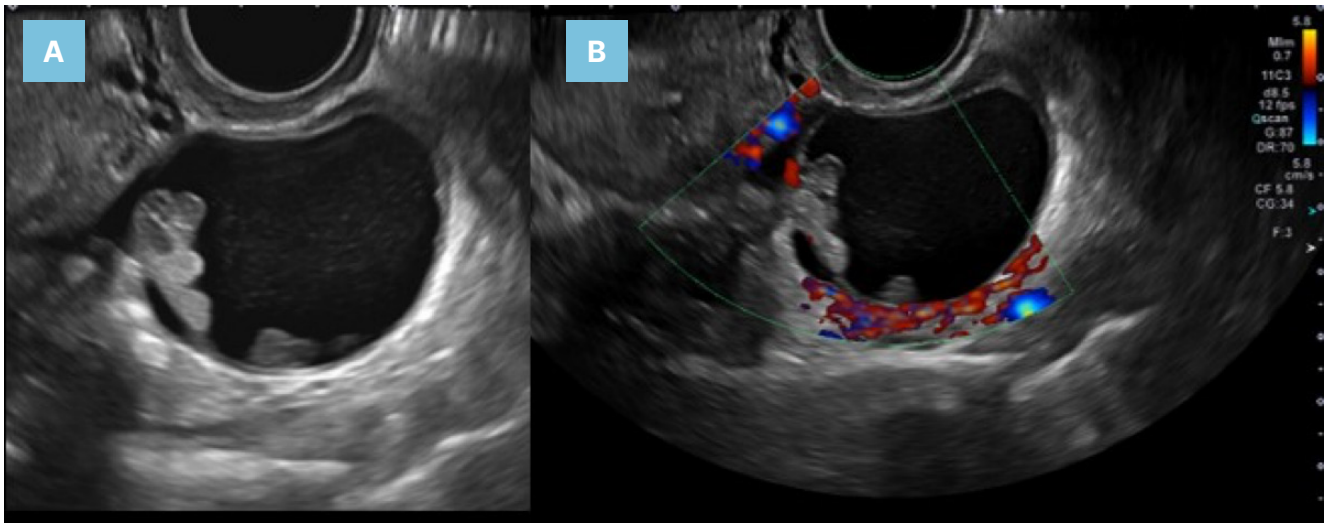
Current Status of O-RADS and Emerging Literature

Since the publication of O-RADS numerous publications and retrospective studies have been conducted in a variety of practice and population settings to assess its performance and accuracy, and to compare it with existing systems. Diagnostic accuracy in these studies has shown an AUC ranging from 0.91–0.98.[15-19] Most studies have shown that O-RADS has a pooled sensitivity and specificity of 95% and 82% on US, and 95% and 90% on MRI, respectively. The majority of these studies have used a cut off of O-RADS category 4 and above for the detection of cancer. These studies all reinforce the significant inter-observer agreement, irrespective of training and/or level of experience. However, in most instances, there was an initial training phase. Studies have also favourably matched the risk of malignancy in most categories, except for O-RADS category 3 and O-RADS category 4, where the malignancy rate is at the lower limit of each category.[16,18]

Take Home Points

Standardized reporting using a classification system is the best method for triaging adnexal masses on imaging. The O-RADS system is highly validated and demonstrates reproducibility and accuracy across a range of studies. Further ongoing refinements to this system are expected to continue improving the specificity and performance in risk categorization.

Locally, our evidence-based review in Ontario endorsed O-RADS as a system for the reporting and management of adnexal masses. Accompanying literature and guidance documents were published to facilitate its adoption in the Canadian healthcare context.



Brief Case Study: 33-year-old patient with dysfunctional uterine bleeding. TVUS greyscale **(A)** and color doppler images **(B)** demonstrate the presence of an adnexal mass measuring 4.8 × 4.8 × 3.4 cm. Utilizing ORADS, this lesion conforms to an ORADS category 5 lesion as it is a unilocular cyst with > 4 papillary projections. Color score is not relevant in this instance. The risk of malignancy is therefore >50%. The patient was triaged to gyne-oncology. Pathology confirmed a borderline serious neoplasm; *courtesy of Tanya Chawla, MD.*

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Financial Disclosures

None declared.

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- Conditions of clinical use, adverse reactions, drug interactions, and dosing instructions.

The Product Monograph is also available by calling Lupin Pharma Canada at 1-844-587-4623.

Reference: 1. Endoceutics, Inc. Intrarosa Product Monograph. September 8, 2023.

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doi.org/10.58931/cwht.2024.1316

Obstructive Sleep Apnea in Women

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Introduction

Obstructive sleep apnea (OSA) is a common disease with a large public health burden.[1] Due to several anatomical and physiological differences, OSA has traditionally thought to be much less common in women than in men. These differences include variations in craniofacial anatomy, sex hormone differences, greater peripheral fat distribution, as well as women having shorter and less collapsible airways and less respiratory drive instability.[2] However the recruitment bias from clinical samples in early studies has fostered this sex difference to an exaggerated degree.

One large community-based sample of adults aged 21–80 indicated a point prevalence of OSA with clinically significant sleepiness of 3–7% in males and 2–5% of females.[3] Another much larger worldwide community study indicated a lifetime prevalence of OSA of 27.3% in men and 22.5% in women in a narrower population aged 30–69.[1] Both studies show an approximate 1:5–1 ratio which is much lower than that of previous studies showing a ratio of 9 or 10:1.[4] In pediatric and elderly populations, the male to female prevalence ratio is close to equal.[5]

Clinical Presentation

Numerous studies have clearly demonstrated that women with OSA are more likely to present with a differential and more nonspecific symptom pattern. While traditionally males present with snoring and apnea, presenting symptoms in women frequently include more non specific symptoms such as fatigue, insomnia, depression, nightmares, nocturia, and use of sleep medications.[6,7]

Due to social stigma, women may have a greater reluctance to present with traditional male OSA symptoms. Women are also less likely to present due to a bed partner noticing symptoms, and their partners are less likely to provide collateral history.[5,8] Even women who present with classic OSA symptoms may not be referred due to lack of clinical suspicion from the physician.[9] Here, we present an approach for the clinician to avoid this scenario.

Clinical Sleep Study Features and Outcomes

Polysomnography data have clearly demonstrated that OSA in women is characterized by less snoring, a lower apnea hypopnea index (AHI), less severe apneic episodes, and less pronounced oxygen desaturations. A higher frequency of rapid eye movement (REM)-related OSA, longer sleep time and more disturbed sleep has also been noted.[10,11]

In both genders, fatigue and sleepiness in OSA is well known to correlate poorly to the AHI.[12] Thus, women may be significantly symptomatic with lower levels of traditionally measured disease.[13] Compared to men, women with sleep apnea also use more healthcare resources prior to OSA diagnosis[9] and have a lower level of quality of life that is also independent of the AHI.[14,15]

Outcomes associated with OSA may be different in women as well, with greater prominence of chronic diseases including hypertension, Type 2 diabetes (T2DM), hypothyroidism, and asthma, especially in women with severe OSA.[6,16] Untreated severe OSA in women is also linked to greater healthcare usage, more cardiovascular disease (CVD) and worse health status than men with untreated disease.[11]

The same severity of OSA may also be more deleterious to women than men from a CVD perspective.[11] Women have a higher incidence of REM-related AHI, which can itself be associated with adverse CV outcomes.[17] Additionally, moderate OSA is associated with greater endothelial damage to blood vessels in women than in men.[18]

Women's Health and OSA

Pregnancy

Large meta-analyses indicate that the pooled worldwide lifetime prevalence of OSA in pregnancy is approximately 15–20%, approximately two to three times the baseline prevalence of women of reproductive age.[19,20] This includes both new onset OSA and exacerbated pre-existing disease. Physiological changes such as generalized weight gain, increased uterine/fetal size, mucosal edema, increased rhinitis of the nose, narrowing upper airway diameter, extra pressure on the chest from breast enlargement, as well as elevation of the diaphragm all contribute to reduced lung capacity, increased effort of breathing, and increased oxygen consumption. Hormonal fluctuations affecting respiratory drive, muscle tone and systemic inflammation are also factors increasing the risk and severity of airway collapse.[21,22]

Extensive literature demonstrates a variety of adverse outcomes for women with pre-existing OSA during pregnancy. Significantly, these include both increased overall morbidity and a fivefold increase in the odds of in-hospital mortality, even after adjusting for obesity.[23,24] Additionally, there are increased risks for maternal gestational hypertension/diabetes, preeclampsia, caesarean sections, postoperative wound complication, and more than six times the risk of pulmonary edema.[19] New onset OSA during pregnancy and even snoring were also associated with increased risk of gestational hypertension/diabetes, and preeclampsia.[25]

For the infant, OSA in the mother has also been related to an increased risk for preterm birth, neonatal intensive care unit admission,[19] intrauterine growth restriction, low birth weight,[26] and congenital anomalies.[27]

Sample sizes are very small, but the use of CPAP in pregnancy appears to be well tolerated and may be associated with a reduction in both blood pressure and pre-eclampsia. Maternal CPAP may also improve birthweight and reduce the risk of preterm birth. Further studies are upcoming, but OSA is a clear risk factor for a difficult pregnancy and delivery.[28]

Polycystic Ovary Syndrome (PCOS)

PCOS is an underdiagnosed condition associated with hyperandrogenism, insulin resistance, and central obesity that affects anywhere from 5–15% of women worldwide.[29] One meta-analysis showed that over one-third of women with PCOS had OSA, and the risk of having OSA was almost four times greater in women with PCOS compared to controls.[30]

OSA is also associated with obesity and worse metabolic profiles in women with PCOS; however, the nature of this relationship remains unclear.[31] Nevertheless, given the potential mechanisms and strong comorbidity, clinicians should have a very high index of suspicion of OSA in women with PCOS.

Menopause

Premenopausal protection from OSA is thought to be due to effects of progesterone and estrogen on both overall respiratory stability and peripheral fat distribution.[10] These advantages decline throughout menopause, increasing OSA prevalence 2–3 times in the peri- and post-menopausal period even after adjusting for age and weight.[32,33] To a lesser extent, early and surgical menopause also show an increased risk of OSA,[34] which indicates that OSA increase in menopausal women is likely an interaction between age, weight and various hormonal changes. Studies also indicate that menopause hormonal therapy (MHT) is inconsistent at directly reducing OSA, confirming the role of non hormonal factors.[35] Nonetheless, given the multiple additional benefits to biological and psychological factors in menopause including improved sleep, MHT should always be considered early in the peri-menopausal period.

A Clinical Approach to OSA in Women

Assessment

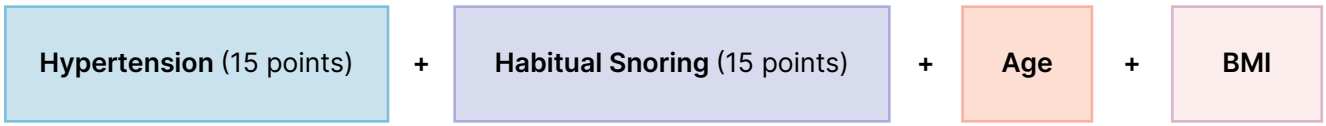
OSA in women can be challenging to diagnose and often may not be the primary issue given the higher rate of comorbidities. Clinicians should have a high index of clinical suspicion for OSA.

Unfortunately, as in many areas of medicine, teaching and clinical guidelines for evaluation and diagnosis of OSA are based on studies of male patients. In particular, OSA should always be considered in women during peri- and post-menopause, during pregnancy, and in patients with PCOS, CVD risk, mood disorders, insomnia, and those taking sleep medications (**Table 1**).

Standard predictive sleep apnea questionnaires are derived from symptom patterns predominantly present in men and

Symptoms	Key Indicators
• Depression • Anxiety • Insomnia • Sleep medication use • Non-specific fatigue • Hypothyroidism	• Peri-post menopause • Pregnancy • PCOS • Metabolic and cardiovascular disease onset (especially hypertension and Type 2 diabetes)

Table 1. Nontraditional symptoms and indicators for OSA screening in women; *courtesy of Atul Khullar, MD, MSc, FRCPC, DABPN (Cert sleep medicine), DABOM, FAASM, and Jennifer Swainson, MD, FRCPC, DABOM.*



Scores exceeding 75 should prompt consideration of OSA screening.

Table 2. Proposed alternative scoring to screen women with OSA; *adapted from Facco, FL et al., 2014.*

alternative predictive scoring for women may be considered when using these.[36,37] A simple, practical four variable model that has been useful in pregnancy (**Table 2**)[38] could potentially be considered for women overall.

Testing and Referrals

Testing and referrals for OSA vary according to jurisdiction, coverage, and availability. In some parts of Canada, sleep apnea must be referred to a sleep centre or for specialist consultation, and in others it is managed by the family physician and a respiratory home care company.

The two current major types of testing include home sleep testing and polysomnography (PSG), which is conducted in a sleep laboratory with more measurements and a greater degree of observation. Though PSG testing is more accurate, home testing is more convenient and available. Remote tracking technology such as watches or phones show promise, but lack clinical validation at this time. Unfortunately, even when referred, only one-half to two-thirds of individuals follow through for testing.[39,40] Therefore, education about the reason for testing and the potential deleterious effects of OSA needs to be part of the patient visit.

Home sleep testing is less likely to pick up the shorter, less pronounced respiratory events and the less severe oxygen desaturations characteristic of OSA in women, which often leads to a missed diagnosis. This is especially true in younger, non-obese women. Under treatment of women can easily occur if an overall AHI from a home study is used. For example, clusters of REM-related apnea, usually only seen accurately on full PSG, can be very fatiguing and are associated with increased cardiac risk. Therefore, home sleep testing can rule in but cannot rule out sleep apnea. Full PSG should be considered in any female patient with a negative home study.

Even if OSA is detected, its clinical severity and implications of untreated disease may be underestimated by the clinician. Canadian insurance companies and some provincial social welfare plans have reinforced this by basing coverage for CPAP treatment on an AHI definition of moderate-to-severe OSA, even though it is clear that mild disease can have deleterious effects, particularly for women.[41]

Given the evolving pathophysiology of OSA over the female life span, repeat testing is often necessary. While there is no consistent guideline for when to repeat sleep testing, it should be

considered when there are new symptoms, significant weight gain, peri- or post-menopausal transitions, or if a number of years have passed. Often patients who did not have significant OSA prior to peri-menopause, develop it in their mid-to-late forties. Disturbed sleep often predates the vasomotor symptoms by months to years. It is important to assess for OSA and other sleep disorders at this time, with strong consideration of MHT therapy.

In terms of pregnancy, time is of the essence. A history of OSA must be reviewed as soon as pregnancy is confirmed. In higher risk patients, testing can be considered as part of preconception counselling. Home studies may be required given limited access to full PSG and treatment may need to be aggressive. One guideline recommended assessment and testing at 12–18 weeks gestation.[40]

Treatment

Proper screening for OSA will yield numerous cases of mild-to-moderate disease. Given that women commonly have a high degree of insomnia and depressive symptoms, OSA may not be the primary clinical focus, but a treatment trial (not purchase) of CPAP or other conservative measures is always reasonable.

Conservative Measures

Weight loss has been shown to improve OSA treatment and some of the newer weight loss drugs have clear effects in improving OSA.[42,43] However, weight loss may be less effective in treating OSA in women than men,[44] perhaps due to differences in peripheral vs. central fat distribution. It is also unclear if there are sex-related differences in OSA improvement with bariatric surgery. Nevertheless, given the multiple other benefits of weight loss, this strategy should be pursued aggressively independent of OSA.

Positional therapy (i.e., finding ways or devices to reduce supine sleep) is often used to reduce the impact of sleep apnea particularly in patients who have supine predominant OSA. No sex differences have been seen in the limited reports of this treatment.

Continuous Positive Airway Pressure (CPAP)

CPAP is the first-line therapy for moderate-to-severe OSA. Typically, it is delivered as straight pressure, or an automatic range of pressures based on an algorithm in the device that detects airway flow limitations. These automatic algorithms have been designed and tested primarily on uncomplicated male patients with greater flow limitations; therefore, automatic pressure ranges may not be as accurate in treating the characteristics of OSA in women.

On average, women require lower CPAP pressures, so the range of the automatic pressure settings should reflect this. If patients have been diagnosed with a home sleep study, they may need full PSG to correctly set the CPAP if they remain symptomatic with the automatic pressures.

Long-term adherence to CPAP may be limited for multiple physical and social reasons. An estimated 20–50% of patients simply will not or cannot use the machine.[45] Given the higher rates of comorbid insomnia in women than in men, this may need to be treated first or in conjunction with sleep apnea therapy. Short courses of hypnotics can support CPAP adherence and newer agents with superior safety profiles can be considered for long-term usage as necessary. Although younger women in particular are often perceived as less adherent to CPAP,[45] there is no clear overall difference between CPAP compliance and functional outcomes between women and men.

Oral Advancement Therapy (OAT)

OAT is a second-line treatment for OSA that guards against airway collapse by repositioning the jaw and tongue. Women may achieve superior results with OAT treatment given their average lower AHI, smaller necks and reduced upper airway collapse.[46] However, access in Canada is often limited to private plans and frequently requires a prior failure of CPAP therapy.

Airway Surgery

Numerous types of nasal, oropharyngeal and jaw surgeries have been designed as second- or third-line treatment of OSA. No sex differences have been noted in efficacy studies of OSA surgery, but samples are disproportionately male.[21] Newer implanted upper airway stimulators (UAS)[21] for OSA may achieve superior results in females. Again, access to OAS surgery in Canada is quite limited and, to our knowledge, is nonexistent for UAS.

Clinical Takeaways
Always keep a high suspicion of OSA in women.
Depending on the region and resources, home sleep studies may be first-line testing, but they can only rule in and not rule out sleep apnea. They may underestimate and miss disease, especially in younger and non-obese women.
If a high index of suspicion remains with a negative or borderline home study, or the patient is struggling with OSA therapy, refer for full observed polysomnography.
Even with the presence of OSA, other mood, anxiety, or insomnia treatment may take precedence, especially if a trial of CPAP has not been successful
The adverse maternal and fetal health outcomes of OSA in pregnancy are significant. Review of past or evolving OSA should be part of pregnancy risk management.
Women may develop worsened or new onset OSA in peri- and post-menopausal periods; consider reassessment and retesting at times throughout the woman's life.
Although less effective, there are other treatments for OSA besides CPAP, such as oral appliances, surgery, and positional therapy.

Conclusion

Newer, more accurate studies clearly demonstrate that sleep apnea is more common in women than previously believed. It may present with a different symptom pattern than those reflected in traditional teachings on the topic. Women often present with insomnia, fatigue, and depression. During the female life span, the possibility of sleep apnea during pregnancy, and the peri- and post-menopausal periods must be considered. Repeat testing may be required at various phases in a woman's life.

Women are more likely to present with milder objective disease than men and traditional home sleep studies may miss or underestimate clinically significant cases. Full PSG should be considered when there is a high index of suspicion and aggressive symptomatic treatment should be initiated. Research and known data surrounding OSA diagnosis and treatments have been largely based on male populations and further attention and research into this condition in women will help guide best practices.

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Financial disclosures

A.K.: Speaking/Advising: AbbVie, Bausch, Eisai, Idorsia, Lundbeck, Otsuka, Jazz, Elvium, Takeda, CCRN and ICPDHM
J.S.: Speaking/advising: AbbVie, Bausch, Biron, Eisai, Idorsia, Janssen, Lundbeck, Otsuka and NovoNordisk

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doi.org/ 10.58931/cwht.2024.1317

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Menopausal Symptoms in the Workplace and an Update on Treatment Options

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Introduction

Women in midlife comprise an integral component of the Canadian workforce. The Menopause Foundation of Canada (MFC) recently completed a landmark cross-national survey of Canadian women aged 40–60.[1] This study found that 46% of surveyed participants felt unprepared for perimenopause/menopause and that 4 in 10 participants felt their symptoms were undertreated by their healthcare provider. Fewer than 25% of respondents said their family physician proactively discussed menopause with them.

Impact of Menopausal Symptoms in the Workplace

A second survey by the MFC specifically investigated the impact of menopause in the workplace.[2] This survey data is the best representation of the current state of menopausal women in our workforce. The report details that of the 20 million people in the Canadian labour force, one-quarter are women over the age of 40. An analysis of the economic impact data projected $3.5 billion dollars of lost revenue due to unmanaged menopausal symptoms. The MFC's study projected $237 million dollars in annual lost productivity and 540,000 lost days of work due to unmanaged peri-menopausal symptoms. One-third of the women in the menopausal transition reported their symptoms negatively impacted their work performance and one-quarter of respondents hid their symptoms at work. Two-thirds of these women did not feel comfortable speaking to their supervisor about their concerns and 70% of surveyed women were not comfortable speaking with their Human Resources department about their symptoms. This same survey found

Contraindications to Systemic Estrogen	Contraindications to Progestogen
Unexplained abnormal vaginal bleeding	Unexplained abnormal vaginal bleeding
Personal history of breast cancer (independent of receptor status)	Personal history of breast cancer
Personal history of estrogen-dependent malignancy	
Cardiac disease	
History of thromboembolism	
History of stroke	
Active liver disease (excluding fatty liver disease)	
Pregnancy	
History of thrombophilia	

Table 1. Contraindications to menopausal hormone therapy.[3,4]

a 14% drop in the number of employed women between ages 45–55, compared to a 10% decline in male workers. Women are leaving the workforce in the prime of their careers and uncontrolled menopausal symptoms can be a significant factor. Given the magnitude of the impact that midlife women have on the Canadian workforce, Canadian women deserve counselling and up-to-date medical options for management of their symptoms.

Current Treatment Options for Vasomotor Symptoms

Hormone Therapy

Menopausal hormone therapy (MHT) is the first-line treatment option for vasomotor symptoms (hot flashes, night sweats, and resultant sleep disturbance) in women under the age of 60 or within 10 years of a woman's final menstrual period.[3,4] MHT can be delivered via the oral or transdermal route, and is the standard of care for management of vasomotor symptoms barring any specific contraindications (**Table 1**). It is important for providers to note that unlike absolute contraindications such as smoking >35 years of age, migraine, or controlled (medicated) hypertension for combined hormonal contraceptive users, due to a marked dosing difference, these are not considered absolute contraindications to the use of MHT. In general, MHT refers to the use of an estrogen-containing product (which can be used as monotherapy if a woman has had a hysterectomy) and a progestogen for endometrial protection. However, MHT can also include synthetic steroids and the tissue-selective estrogen complex. Historically, providers have followed 5- or 10-year rules and then withdrawn their patients from hormone therapy due to concern for risk. Current major menopause guidelines take into consideration the fact that the average length of the vasomotor experience is approximately 7.4 years and this varies by a person's ethnicity. This information was informed by the Study of Women Across the Nation, or SWAN study.[5] The guidelines agree that there is no maximum length of use of MHT preparations, and that a decision to dose-reduce or cease therapy (either "cold turkey" or via tapering) is a decision that should be made following discussion between a patient and her provider.[3,4]

Risks of hormone therapy when provided to healthy, symptomatic people within this window of safety are considered minimal. Risks of coronary artery disease, stroke, and venous thrombosis in the combined arm of the Women's Health Initiative study (WHI) for women aged 50–59 were 2.5, 2.5 and 5/1000 women, respectively, over 5 years of use. Specific re-analysis of data from the WHI finds a pooled hazard ratio of all-cause mortality for both the estrogen alone and combined estrogen progestin arms in women aged 50-59 to be 0.69 (95% CI, 0.51-0.94) which is reassuring to providers.[6] The main counselling point during the provision of MHT containing estrogen and a progestogen is the association with invasive breast cancer. Breast cancer risk likely depends on several factors including length of use, type of MHT used and individual patient risk factors (most notably menopausal obesity and alcohol consumption).[7] However, the breast cancer risk most often quoted is an excess of 8/10,000 women users of MHT per year which is a finding of all pooled ages, from the WHI study.[8] Our understanding of the association between breast cancer risk and MHT use continues to evolve based on specific preparations. The Post-authorization Safety Study (PASS) on the tissue selective estrogen complex ([TSEC] - containing conjugated estrogens and bazedoxifene) studied more than 75,000 women for up to 5 years (mean follow-up was 22 months). Approximately 18,000 women were studied on the TSEC and 57,000 users of estrogen and progestin MHT were studied. Eighty-eight percent of participants were <60 years of age. The study found no increased risk of breast cancer with TSEC use (RR <1) compared to users of estrogen and a progestin. This same study found lower rates of endometrial cancer and hyperplasia than expected in the population and lower rates of acute cardiovascular events than expected in a comparison untreated population.[9] A large systematic review by Formoso *et al.* in 2016 in the Cochrane database reviewed the association between tibolone use and breast cancer risk. The OR for invasive breast cancer was 0.52 (95% CI 0.21 to 1.25) for tibolone vs placebo.[10]

Women who have undergone total hysterectomy surgery (removal of the uterus and cervix) are candidates for estrogen monotherapy. An important finding from the WHI in the estrogen monotherapy arm for women with a hysterectomy was no increased association with breast cancer.[8] **Table 2a–c** describes current Health Canada approved estrogen options. MHT is a systemic treatment and while it may benefit symptoms of genitourinary syndrome of menopause (GSM), systemic MHT use is not indicated solely for treating GSM in the absence of vasomotor symptoms. GSM refers to the constellation of symptoms including vaginal dryness, dyspareunia, recurrent urinary tract infection, vulvar irritation, and lower urinary tract symptoms.[11,12] This symptom cluster can be extremely symptomatic for many menopausal women and is best treated with local or selective therapies that target the tissues of the bladder, vagina and vulva (**Table 3**). There is no maximum length of use or age limit regarding the use of medications treating GSM, and progestogens are not required for endometrial protection.

Non-hormonal Options for Management of Menopause Symptoms

For midlife women who have a contraindication to MHT or a preference to avoid hormonal medications, several medications are used off-label for the management of vasomotor symptoms. These medications are supported by several guidelines; however, as they do not have Health Canada approval for the management of menopausal symptoms, providers should document the reasons why these medications are being prescribed and that they have counselled the patient that they are being used in an off-label fashion.[3,13] Several medications such as clonidine and pregabalin have now been removed from recent guidelines due to lack of efficacy data and possible adverse effects. Important considerations in this category include avoiding oxybutynin in women at risk for cognitive decline and the elderly, and limiting paroxetine use in women on tamoxifen. Venlafaxine is the best-studied non-hormonal agent in the breast cancer survivorship literature (**Table 4**).[13]

The addition of neurokinin B antagonists to the non-hormonal options for menopausal symptoms is an exciting development. This is a novel class of non-hormonal medications with current FDA approval for fezolinetant and elinzanetant which are in advanced development.[14,15] These medications have been studied in clinical trials and have shown improvements in the frequency and severity of vasomotor events.

Estrogen Name *(Generic/Commercial)*	Dosage
17B-estradiol/Estrace	0.5, 1, 2 mg PO OD
Conjugated estrogen (CE)/Premarin	0.3, 0.625, 1.25 mg PO OD
17B-estradiol/Climara	25, 50, 75, 100 mcg patch once weekly
17B-estradiol/Estradot	25, 37.5, 50, 75, 100 mcg patch twice/week
17B-estradiol/Divigel	10, 25, 50, 100 mcg gel applied daily
17B-estradiol/Estrogel 0.06%	2 pumps = 1.5 mg of E2 gel applied daily
17B-estradiol/Oesclim	25, 37.5, 50, 75, 100 mcg patch twice weekly

Table 2a. Estrogen therapy available in Canada (can be used as monotherapy in women who have had a hysterectomy); *courtesy of Kelsey E. Mills, MD, FRCSC, MSc HSEd, MSCP.*

Single Prescription Name *(Generic/Trade)*	Dosage
Conjugated estrogen and bazedoxifene/Duavive	1 tab PO OD (0.45 mg CE and 20 mg bazedoxifene)
Tibolone/Tibella	1 tab PO OD
17B-estradiol and norethindrone acetate (NETA)/Activelle	1 tab PO OD (1 mg estradiol and 0.5 mg of NETA)
17B-estradiol and norethindrone acetate (NETA)/Activelle LD	1 tab PO OD (0.5 mg estradiol and 0.1 mg of NETA)
17B-estradiol and drospirenone/Angeliq	1 tab PO OD (1 mg estradiol and 1 mg drospirenone)
17B-estradiol and micronized progesterone/Bijuva	1 tab PO OD (1 mg estradiol and 100 mg progesterone)
17B-estradiol and levonorgestrel/Climara Pro	1 patch changed weekly (45 mcg estradiol and 15 mcg levonorgestrel)
17B-estradiol and norethindrone acetate (NETA)/Estalis (two dosing options)	1 patch changed twice weekly (50 mcg estradiol and 140 mcg NETA); (50 mcg estradiol and 250 mcg NETA)

Table 2b. Combined estrogen/progestogen and other single-prescription therapies available in Canada (no additional progestogen required for this category); *courtesy of Kelsey E. Mills, MD, FRCSC, MSc HSEd, MSCP.*

Progestogen Name *(Generic/Trade)*	Dosage
Levonorgestrel intrauterine system/Mirena	52 mg intrauterine system (IUS) for 5 years **Note**: Currently the 19 mg IUS is not recommended for endometrial protection
Medroxyprogesterone acetate/Provera	2.5, 5, 10 mg PO OD
Micronized progesterone/Prometrium	100 mg PO/PV OD
Norethindrone acetate/Norlutate	5 mg PO OD
Drospirenone/Slynd	1 tab PO OD
Norethindrone acetate/Movisse	1 tab PO OD

Table 2c. Progestin therapies available in Canada for endometrial protection; *courtesy of Kelsey E. Mills, MD, FRCSC, MSc HSEd, MSCP.*

Medication Name *(Generic/Commercial)*	Dosage
Conjugated estrogen cream (Premarin)	0.5 mg PV x 14 days, then twice weekly
0.1% Estrone cream (Estragyn)	0.5-4 g PV x 14 days then twice weekly
17 B-estradiol suppositories (Vagifem)	10 mcg tab PV x 14 days then twice weekly
17 B-estradiol vaginal ring (Estring)	1 ring PV change q 3 months
17 B-estradiol vaginal suppositories (Imvexxy)	4 or 10 mcg suppository PV x 14 days then twice weekly
Prasterone (Intrarosa)	6.5 mg vaginal ovules PV QHS
Ospemiphene (Osphena) (oral estrogen agonist/antagonist)	60 mg PO OD

Table 3. Genitourinary syndrome of menopause therapies available in Canada; *courtesy of Kelsey E. Mills, MD, FRCSC, MSc HSEd, MSCP.*

Medication Name *(Generic/Commercial)*	Dosage
Paroxetine/Paxil	10–25 mg PO OD
Citalopram/Celexa	10–20 mg PO OD
Escitalopram/Lexipro	10–20 mg PO OD
Desvenlafaxine/Pristiq	25–150 mg PO OD
Venlafaxine/Effexor	37.5–150 mg PO OD
Gabapentin/Neurontin	100–2400 mg PO OD
Oxybutynin/Ditropan	2.5–15 mg XR PO OD

Table 4. Non-hormonal therapies available in Canada for the management of menopausal vasomotor symptoms (all are off-label usage); *courtesy of Kelsey E. Mills, MD, FRCSC, MSc HSEd, MSCP.*

Conclusion

Now, more than ever, the literature is clear that supporting women experiencing menopause by inquiring about and then addressing their symptoms is the standard of care. There are several algorithms for providers that aid in the assessment and treatment of menopausal women.[16,17] Lack of provision of menopausal treatment is resulting in an enormous unmet health need in Canadian women and others experiencing menopause, with very significant health and economic impact. Menopause hormone therapy is the first-line treatment for systemic symptoms, and local or targeted hormonal therapy is the mainstay of GSM therapy. Treatment options exist for women who cannot or will not use MHT and this area of medicine is rapidly evolving. There are many novel hormonal and non-hormonal options either in advanced development or newly brought to market, which increase the range of options available to menopausal women in Canada.

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Financial Disclosures

Speakers bureaus /advisory committees:
Astellas, Abcellera, Biosyent, Knight, Lupin, Duchesnay, Eisai, Pfizer, Bayer.

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doi.org/10.58931/cwht.2024.1318

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The Treatment of Heavy Menstrual Bleeding in 2024

Christine Lett, MD, FRCSC

Introduction

Heavy menstrual bleeding and iron deficiency are both commonly underrecognized and undertreated conditions.[1] In fact, over 2 billion people globally are iron deficient.[2] Iron deficiency disproportionately impacts reproductive-aged women and negatively impacts their quality of life.[2] The most common etiology of iron deficiency anemia in premenopausal women is excessive menstruation.[3] Heavy menstrual bleeding is defined as excessive menstrual blood loss, which interferes with a woman's quality of life.[4] Heavy menstrual bleeding is one of the most common reasons for gynecologic consultation,[4] and impacts one-third of reproductive-aged women. Improving the quality of life for women with heavy menstrual bleeding requires recognizing the condition, identifying its cause, ruling out iron deficiency, and tailoring treatment to reduce menstrual blood loss and replenish iron stores.

Diagnosis and Classification

The diagnosis of heavy menstrual bleeding can be obtained by the patient's history alone. Intermenstrual and postcoital bleeding require investigation to rule out underlying pathology. Postmenopausal bleeding is concerning for underlying malignancy and must be investigated. This article addresses premenopausal bleeding only.

Identifying the etiology of heavy menstrual bleeding is important because the cause of the bleeding will determine how best to stop it. The PALM-COEIN classification system is useful for describing the causes of heavy menstrual bleeding.[5] **Table 1** summarizes the PALM-COEIN classification system with suggested investigations and treatments for each cause of heavy menstrual bleeding.

Investigations

Rule out pregnancy

If pregnancy cannot be excluded by the patient's history, a urine or serum beta-human chorionic gonadotropin (BHCG) test is appropriate.

Rule out iron deficiency and anemia

A complete blood count (CBC) and ferritin test should be completed on all patients with heavy menstrual bleeding[6] because of the high prevalence of iron deficiency among reproductive-age women.

	Key Investigations	Treatment Options
Polyp	CBC, iron studies, ultrasound	TXA, iron for ID, polypectomy
Adenomyosis	CBC, iron studies, ultrasound	TXA, iron for ID, hormones, hysterectomy
Leiomyoma	CBC, iron studies, ultrasound	TXA, iron for ID, hormones, myomectomy or hysterectomy
Malignancy and hyperplasia	CBC, iron studies, endometrial biopsy	TXA, iron for ID, hormones, hysterectomy
Coagulopathy	CBC, iron studies, history, special lab tests	TXA, iron for ID, correct coagulopathy, surgery
Ovulatory Dysfunction	CBC, iron studies, history	TXA, iron for ID, hormones
Endometrial	CBC, iron studies, ± endometrial biopsy	TXA, iron for ID, hormones, surgery
Iatrogenic	CBC, iron studies, ultrasound, ± endometrial biopsy	TXA, iron for ID, change hormone therapy, surgery
Not otherwise specified	Etiology not yet understood	TXA, iron for ID

Table 1. Suggested investigations and treatment options by PALM-COEIN classification; *courtesy of Christine Lett, MD, FRCSC.*

Abbreviations: CBC: complete blood count, **TXA:** tranexamic acid, **ID:** iron deficiency, **Hormones:** hormonal suppression of menses

The World Health Organization defines anemia in women as a hemoglobin level <120 g/L.[7] However, this definition of anemia is based on a population sample that includes iron deficient women and is therefore not an ideal value. The target hemoglobin level for optimal health is 140 g/L.[3] Preoperatively, the target hemoglobin level should be ≥130 g/L.[8] Iron deficiency is diagnosed when the ferritin level is <30 ng/mL or the transferrin saturation (TSAT) is <20%.[8] In patients who do not eat meat, adding a vitamin B12 test is appropriate.

Rule out malignancy

Ruling out endometrial hyperplasia and cancer is key for women at risk. Endometrial sampling is indicated for women with the following risks for endometrial cancer: body mass index (BMI) over 30 kg/m^2, nulliparity, diabetes, polycystic ovary syndrome, hereditary cancer syndromes, significant intermenstrual bleeding, failure of medical management, and prolonged periods of amenorrhea.[9] An office endometrial biopsy is the most expeditious way to obtain a tissue diagnosis. While age is also cited as a risk factor for endometrial hyperplasia and cancer, with guidelines recommending endometrial sampling in women over age 40[9] or age 45,[5,10] a Canadian review of endometrial biopsies on women aged 41–49 without other risk factors for endometrial cancer showed no malignancies on biopsy.[11]

Ruling out underlying gastrointestinal (GI) malignancy should also be considered. Bidirectional endoscopy is recommended for asymptomatic premenopausal women with iron deficiency anemia.[12]

Ultrasound

Imaging the uterus is required to rule out structural causes of heavy menstrual bleeding, such as polyps, fibroids, and adenomyosis. Ultrasound is typically the most easily accessible imaging modality. In select cases, hysteroscopy or magnetic resonance imaging (MRI) are required.

Other investigations

The patient's menstrual history may prompt further blood work. For example, when ovulatory dysfunction is suspected by the patient's history, levels of thyroid stimulating hormone (TSH), prolactin, and an androgen panel may be appropriate. If a patient has had heavy menses since menarche or has a family history of a bleeding disorder, a bleeding disorder work-up should be ordered.[13]

The source of iron deficiency is often heavy menstrual bleeding, but there may be another underlying cause for iron deficiency. Ruling out poor nutritional intake, malabsorptive conditions, Celiac disease, and GI malignancy should not be neglected.

Treatment

Medical management is the first line of treatment for managing heavy menstrual bleeding.[9] Many of the medical options listed in **Table 1** are used off-label and they are very effective. Treatment must be tailored to the patient's goals. For example, many hormonal options will prevent pregnancy. My preferred approach for most patients is tranexamic acid (TXA) 1000–1500 mg orally 3 times a day for 5 days with heavy menses because this works immediately with their next menses. I add a levonorgestrel intrauterine system (LNG IUS) if pregnancy is not desired. Recognizing and replacing iron deficiency will further improve her quality of life. Anemia should be corrected before proceeding with surgical management.

Tranexamic acid

TXA is an antifibrinolytic medication that reduces menstrual blood loss by 40% to 59% from baseline.[9] TXA can safely be prescribed for most women because absolute contraindications are rare.[14] Some women find TXA adequate for symptom control. For those who choose other medical or surgical management options, I recommend using TXA with menses until the chosen treatment option is effective. All other medical treatment options often take at least 1–3 months to improve menstrual blood loss, and surgical wait times can be even longer.

TXA has been extensively studied in diverse patient populations. There is controversy about the risk of venous thromboembolism (VTE) with TXA treatment. There is no increased risk of VTE when TXA is used in postpartum hemorrhage or when it is given within 3 hours of trauma.[15] However, an increased risk of VTE was observed with TXA use in acute GI bleeds.[16] One population study of women who filled a prescription for TXA demonstrated a very small increased risk of VTE, with a number needed to harm per 5 days of treatment of 1 in 78,549.[17] It is postulated that heavy menstrual bleeding itself is a risk factor for VTE.[9,18] In addition, a recent study demonstrates that iron deficiency anemia is a risk factor for VTE.[19] My interpretation is that women with heavy menstrual bleeding are at risk for VTE because of iron deficiency anemia, and therefore, reducing the bleeding with TXA is key to preventing further iron loss and the associated risk of thrombosis from iron deficiency.

There is a theoretical concern that the use of TXA with combined hormonal contraceptives (CHC) increases the risk of VTE because of one case report of coronary artery thrombosis with the combination of these medications.[20] The absolute risk of VTE in CHC users is 9–10/10,000 woman years, double the baseline risk of 1–5/10,000 woman years among non-CHC users, while the risk of VTE with the combination of CHC and TXA is unknown.[21] Among postpartum women, who have a 300/10,000 woman year risk of VTE,[21] given TXA in the setting of postpartum hemorrhage, there was reassuringly no increased risk of VTE.[22] Based on this data, I confidently use TXA and CHC concomitantly.

Hormonal suppression

Hormonal suppression of menses has been well described elsewhere[9]; therefore, a detailed discussion is beyond the scope of this review. The 2 mechanisms of action, hormonal-induced thinning of the endometrium, and suppression of ovulation, both result in reducing menstrual blood loss. Because the LNG IUS has the advantage of

fewer systemic adverse effects than other options for hormonal suppression of menses, along with an up to 85% reduction in menstrual blood loss, I offer this option as a first line treatment to most patients. The National Institute for Health and Care Excellence (NICE) recommends the LNG IUS as a first line treatment option for women without identified pathology, with fibroids less than 3 cm in diameter, and for those with adenomyosis.[4]

When regular cyclic bleeding is desired, combined hormonal contraception (CHC) is prescribed in a cyclic regimen. I typically start with a monophasic pill containing 30 mcg of ethinyl estradiol. Once cycle control is acceptable with cyclic use, an extended cycle regimen can be trialled. My experience is that bothersome breakthrough bleeding is more common with low-dose CHC or when an extended cycle regimen is initiated.

Fibroids are a common cause of heavy menstrual bleeding and can be managed with all forms of hormonal suppression of menses. Three classes of hormonal treatment for fibroid-associated heavy menstrual bleeding deserve mention. Ulipristal acetate, a selective progesterone receptor modulator, is no longer available due to reports of liver failure. When surgery is planned for fibroids, pretreatment with a gonadotropin-releasing hormone (GnRH) agonist, leuprolide acetate, should be considered.[23] A new class of medication, GnRH receptor antagonists, work by competitively binding to pituitary GnRH receptors, blocking endogenous GnRH signalling, which leads to reversible, dose-dependent, decreases in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) concentrations. Relugolix CT, a GnRH antagonist, includes 1 mg of estradiol and 0.5 mg of norethindrone acetate as add-back therapy. The purpose of this add-back therapy is to mitigate the adverse effects of hypothalamic hypogonadism.

Surgery

In general, surgery is reserved for patients who experience a failure of medical management. First line treatment with surgery may be required in some cases. For example, symptomatic endometrial polyps and submucous fibroids often require hysteroscopic surgery for symptom control. Hysterectomy provides definitive management for heavy menstrual bleeding. Opportunistic salpingectomy should be offered at the time of hysterectomy, and hysterectomy should be performed vaginally or laparoscopically whenever technically feasible.[23] Oophorectomy should not be done in premenopausal women in the absence of malignancy.[23]

Multiple national and international guidelines strongly recommend that anemia be corrected before surgery.[8,23-25] Anemic patients have a significantly increased risk of adverse perioperative outcomes, including surgical site infection, VTE, major bleeding, and end-organ dysfunction such as cardiovascular, respiratory, and renal dysfunction. Patients with preoperative anemia also have an increased risk of perioperative death. Anemia should be identified and corrected before surgery is performed.

Iron supplementation

Oral iron salts are the first line treatment for the management of iron deficiency and anemia.[26] There are 3 iron salts used in supplements: ferrous gluconate, ferrous sulphate, and ferrous fumarate, which all can be dispensed as 300 mg tablets. Each formulation contains a different amount of elemental iron, with ferrous fumarate containing the most elemental iron (100 mg per tablet). Oral iron should be taken daily, or every other day, on an empty stomach. Vitamin C supplementation does not enhance iron absorption in healthy individuals.[27] A repeat hemoglobin level should be ordered 4 weeks after initiating oral iron therapy. An appropriate response to oral iron supplementation is demonstrated when the hemoglobin level increases by 20 g/L over a period of 4 weeks for anemic patients. Oral iron supplementation is required for at least 3 months after achieving a normal hemoglobin level to replenish iron stores.

Intravenous iron provides a rapid replenishment of iron stores. Four formulations are available in Canada. Sodium ferric gluconate complex in sucrose injection (Ferrlecit®) is used in dialysis patients. Iron sucrose (Venofer®) has been available and used for decades, but its use is off-label outside the context of chronic renal disease. The maximum one-time dosing of iron sucrose in my centre is 300 mg, per infusion, administered over 90 minutes. Newer iron formulations safely provide larger doses of iron at once over a shorter infusion period. Ferric derisomaltose (Monoferric®) is approved to treat iron deficiency anemia in adults and is dosed at 1000 mg or 1500 mg per infusion, administered over 20–30 minutes (Monoferric monograph).[28] Ferric carboxymaltose (Ferinject®) is approved to treat iron deficiency anemia in pediatric and adult

patients and is expected to be on the Canadian market by the end of 2024. A maximum adult dose is 1000 mg per infusion, administered over 15 minutes. Ferric carboxymaltose is associated with transient hypophosphatemia in 45% of patients, which can be managed expectantly for most patients.[29]

The indications for intravenous iron in anemic women include:[8,26]

1. Oral iron supplementation is not tolerated, typically due to GI side effects
2. Lack of response to oral iron supplementation, <20 g/L hemoglobin level increase over a period of 4 weeks
3. Profound anemia (hemoglobin level <80 g/L)
4. Anemia and surgery planned within 8 weeks

Accessing intravenous iron differs between institutions. Becoming familiar with arranging intravenous iron in your area will expedite your patient's care.

Conclusion

Heavy menstrual bleeding and iron deficiency are very common conditions, but neither condition is normal, and both negatively impact a woman's quality of life. In reproductive-aged women, iron deficiency is frequently due to menstrual blood loss. The first line of management for heavy menstrual bleeding is medical treatment. A two-pronged approach is required to successfully manage iron deficiency in heavy menstrual bleeding, stop the excess bleeding, and replace iron stores.

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Financial Disclosures

None declared.

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doi.org/10.58931/cwht.2024.1319

Hot Topics in Postpartum: Why the Six-week Visit is Outdated

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Introduction

Gone are the days of the single six-week postpartum visit. Research has shown that healthcare, both physical and mental, must be more robust and comprehensive to adequately address the changes that occur and the ensuing challenges that transpire when welcoming a baby into the world.[1] In this paper, the words woman and mother include all pregnant people and those who give birth.

Why Should We Care?

Postpartum depression/anxiety/psychosis (which we will call Perinatal Mood and Anxiety Disorders [PMAD]) is very common. It occurs in 14–20% of women in high-income countries.[2] Of those pregnant people who get PMAD, one-third have pre-pregnancy psychiatric diagnoses, which can be exacerbated in the perinatal period. One-third develop PMAD during the pregnancy, and one-third present in the postpartum period, which can even extend to one year after birth.

PMAD is a disorder with a large spectrum ranging from "the baby blues" to postpartum psychosis. In recent years, it has become apparent that anxiety disorder may be even more prevalent than major depressive disorder.[3] Mortality in patients with PMAD is significantly higher than in their unaffected sisters.[2] The risk of death in the first year postpartum, primarily from suicide and accidents, carries a higher mortality than the risk of hypertensive disorders of pregnancy and postpartum hemorrhage combined.

Review of Three Cases

You are meeting three new prenatal patients in your clinic today.

Devi is a 20-year-old refugee claimant who just arrived in Canada and is in your clinic for her first prenatal visit at 26 weeks. The interpreter tells you she was forced to flee India because she and her husband married for love. When her husband's family found out that she was pregnant, they threatened her life and the baby. The refugee aid organization has arranged welfare and health benefits through the Federal Blue Cross program. Her husband cannot obtain a visa because of the current tensions between Canada and India. In your clinic, she is weepy and withdrawn.

The next patient is Martha, a 41-year-old litigation lawyer in a prestigious law firm. Her husband is a vice president of finance in a multinational business. They have been trying to have a baby for the past three years and Martha has undergone four cycles of IVF. She is now 12 weeks pregnant. She called for the appointment and asked if it was possible to come in before eight a.m. or after six p.m. After fifteen minutes in the waiting room, she asked your receptionist why you were late. On questioning, there is a history of endometriosis and anorexia as a teen. She is still very careful about her weight and fitness. Her husband joins the visit via Zoom from Paris, and they are thrilled to see their live active baby on point of care ultrasound (POCUS).

Finally (almost an hour late), you see Emily, a 29-year-old G2P1 with a 10-month-old baby you delivered. This pregnancy was unexpected, but Emily is happy to be pregnant again. Grateful to have a relatively simple visit, you hurry through it.

What Are the Risk Factors for PMAD in These Three Cases? How Can You Help Prevent its Development?

The most obvious risk factors are present in the first case. Devi is young, a new immigrant, socioeconomically vulnerable, has inadequate support, and will likely be a single parent.[4] Most importantly, perhaps, she is already depressed. In this situation the most appropriate thing to do is "call in the cavalry!" An immediate referral to social services, particularly those aiding refugee

claimants, is essential. They may help her find an ethical immigration lawyer to expedite her husband's admission to Canada. A referral to perinatal psychiatry/mental health services can be life-saving.

Martha also has multiple risk factors for PMAD. As an older pregnant person with a history of infertility, she is at higher risk.[4] Her personal history of anorexia nervosa may indicate that the bodily changes in pregnancy could trigger a recurrence of her psychiatric issues. Her personality and life experience have led her to believe that she can control everything, and this perfectionism can be a challenge when faced with the inherently uncontrollable nature of pregnancy, birth and the postpartum period.

To help protect her from possible PMAD, she should take some time to prepare for this pregnancy by participating in prenatal classes, ideally in a group setting where she could make contact with other pregnant women. She would also benefit by being referred to a reliable and trusted doula.[5]

Emily's risk factors are perhaps fewer than those of the first two patients, except for the unplanned pregnancy and a short interpregnancy interval.[4]

Other risk factors for PMAD include intimate partner violence, relationship dissatisfaction and LGBTQS+ identity. A personal history of mental health disorders and a family history of PMAD are also red flags. Nonetheless, risk factors are not the only important element in these cases: the perinatal period is an opportunity for primary prevention in psychiatry.[4]

Thirty-week Follow-up Visit

At the 30-week follow-up, you have some news to communicate to Martha. At 28 weeks, you were concerned that her symphysis-fundal height was not growing appropriately. An ultrasound has now shown her baby growing at the 8th percentile. The dopplers are normal. Her glucose tolerance test (GTT) is also positive.

You recommend that Martha decrease her workload from 60 hours/week and that she work from home when possible. You also inform her that she needs to be closely followed by the gestational diabetes and high-risk pregnancy clinic, which involves repeated visits and ultrasounds. Martha is distraught. This was not the plan! She bursts into tears in the office and leaves.

Devi, on the other hand, is looking much better than previously. The perinatal psychiatry team is following her. She has been placed on sertraline and is attending psycho-education groups. She attends prenatal classes at the community health centre and is linked with the public health nurse. She is obtaining food support from welfare and the community group she has joined.

She has met with an immigration lawyer. Although you have written letters supporting her husband's visa request, they are not optimistic he can arrive in Canada before the birth. Despite this, she smiles shyly during the visit. She "WhatsApps" with her husband while you examine her, and he is loving, supportive, and excited to see his baby on the ultrasound screen.

Emily is next. At her last visit, she complained about how exhausting her life was now that her baby was teething and waking her up at night. As she has not been able to return to work as planned, her husband has taken a second part-time job, and she is responsible for everything at home.

At her second trimester blood tests, her TSH, CBC and ferritin were checked. She was euthyroid, but her Hgb was 89 g/L with a ferritin of 5 mcg/L. It's no surprise that she was exhausted. You initially administered an oral iron replacement, which gave her constipation and cramps. You now arrange for IV iron, which should improve her fatigue. However, she is not the cheery person she was during her last pregnancy. You reassure her that the iron will help both physically and emotionally since optimizing the physical health of pregnant women can help prevent PMAD.[6]

Birth

Martha is the first to give birth. She has been working from home and has accepted that she must transfer many files to her home office. She is now taking insulin for her gestational diabetes. Her baby hovers around the 6th percentile, but the dopplers remain normal. At her 36-week visit, she complains of a headache with flashing lights in her vision. Her blood pressure is 150/95. Martha is diagnosed with HELLP syndrome with platelets of 45,000. Induction is initiated. Her husband Paul, who is in New York for a meeting, rushes to the airport.

After a few hours, her doctor decides to perform an emergency C-section because of recurrent decelerations. Martha's husband enters

into the labour and delivery room as Martha is being transferred to the operating room. He has many questions, but everyone is too busy to respond, and he receives very few answers. Martha is upset and somewhat confused but knows she needs to have this C-section now. The C-section proceeds and a 2.3 kg baby boy is born and transferred to the NICU. Paul is frightened to see how tiny and frail the baby appears and how hard everyone seems to be working on him. He was not prepared for the amount of blood and the seeming chaos. Once the baby is stabilized, the neonatologist and nurse debrief with him, and he proceeds to the recovery room to check on his wife.

Devi goes into labour at 39 weeks. She is accompanied in labour by her friend, who speaks some English. Her daughter is born after an uneventful labour. Devi is happy; her husband on the phone encourages her and supports her as much as possible from far away. She returns home with a plan for early follow-up visits from the public health nurse and follow-up by psychiatry. Her social worker has found her a place to live in a collective building for young mothers where she will receive support.

Emily arrives in active labour at 40 weeks, rushing through the door to triage, screaming. At her first examination she is 9 cm dilated with bulging membranes. Her water breaks and Emily delivers precipitously in triage into the hands of a medical student. She has a third-degree tear.

Postpartum

Emily is alone in her apartment. Her husband returned to work after only five days because his employer refused to recognize his paternity leave. In their precarious financial position, he cannot risk being fired. Her mother, who lives in another province, is still working but has arranged to take a two-week vacation in a few weeks to give Emily a hand. But for now, Emily is alone with her sixteen-month-old and her newborn. She is standing in her kitchen, leaking tears, milk, blood, and urine. Whenever she falls asleep, she is awakened by nightmares of her birthing experience, remembering how frightened she was. Like many in Canada now, she has no family doctor. Her postpartum visit is in four weeks.

Martha and baby Michael are now home. Michael spent a few weeks in the NICU. Martha worked very hard with the NICU lactation consultant to establish a milk supply. Michael has grown well but continues to require supplementary formula feeds. Paul has arranged for maternity nurses to provide nursing coverage both day and night because he is obsessed with the memories of how close he came to losing them both. He wonders if he is going crazy when he has flashbacks that awaken him from sleep.[7]

The night nurse encourages Martha to leave the baby with her "so she can get sleep and recover." Every time Martha awakens and goes to see Michael, the nurse says that she has just given him a bottle. During the day, she feels almost shut out as the nurse holds Michael the whole time. She feels incompetent. She starts thinking about going back to work soon because, at least there, she knows what she is doing. She is teary and lonely.

Devi is adjusting well to her new life. The support in her building complex is helping her learn skills as a mother. She has other people to talk to, and the mothers laugh and hold each other's babies. Soon, she can start language classes while her baby is cared for in the complex's nursery. She is happy, except for her deep longing to be reunited with the man she loves.

Antidepressants in Pregnancy

There is growing evidence that depression is harmful to the developing fetus. Having a depressed mother can cause epigenetic changes in the offspring that make them more prone to depression themselves and less socially open and communicative.[8] Researchers and clinicians alike realize that what happens in the womb can last a lifetime.[9]

Given the burden of PMAD in our society, the use of antidepressants in the perinatal period is well studied. Most currently used antidepressants are considered safe in pregnancy and breastfeeding. Sertraline and paroxetine have the least penetrance across the placenta and in breast milk. While some withdrawal symptoms have been reported, breastfeeding mitigates these effects as there is a naturally slow withdrawal as the baby grows.[10]

Zuranolone, a new drug that may change the way we manage PMAD, is available in the United States but is not yet approved in Canada.[11]

Discipline	Sample Topics
Nurse	Safe sleep routines, normal crying behaviour
Lactation consultant	Latch techniques, pumping/storing milk
Kinesiologist/physiotherapist	Pelvic floor health, diastasis recti exercises
Psychologist	Destigmatization, bonding activities
Social worker	Setting limits, self-identity
Pharmacist	Baby first aid, safe pharmaceuticals
Occupational therapist	Reactivation strategies, organizational tools
Nutritionist	Energizing foods, meal preparation strategies

Table 1. Model for multidisciplinary postpartum care; *courtesy of Perle Feldman, MDCM, FCFP, MHPE and Judy Hagshi, MD, CCFP.*

Multidisciplinary Care: Optimizing the Postpartum Course

Many experts now believe that postpartum care must be multidisciplinary to provide new parents with the skills, education and confidence to navigate the daunting task of raising a child in the modern world (**Table 1**).[1]

Why have things changed so much? The answer is twofold: first, we no longer live near or with extended family, where new parents absorb child-rearing skills by osmosis. Historically, parents welcomed new babies into multigenerational homes. These homes can be considered the prototype for a multidisciplinary support program.

In the above scenario, grandparents are awake in the middle of the night to help support a new mother or soothe a colicky baby. Aunts know the special care recipe to nourish a new mother and improve her milk supply. Cousins are great at occupying older siblings so the mother can rest. For some lucky new parents, a grandparent may move in for a few weeks, thus allowing the age-old practice of the 40-day postpartum confinement.[1] For many, however, there is no one to teach new mothers and fathers parenting skills due to minimal access to support services.

The second answer is more ominous. Life in the 21st century results in many parents entering parenthood with their own pre-existing challenges and vulnerabilities. While the incidence of PMAD is rising, so is the incidence of major depression in young adults before they even become parents. Setting up families for success right from the beginning has a cumulative effect on the family's life and beyond.

The links between poor coping and bonding at birth, to physical and mental health issues in the child, are well established.[9,12] Furthermore, when the birthing parent suffers from PMAD, the incidence of a depressive disorder is elevated in the partner, resulting in worse child outcomes.[3] We need to be careful not to blame parents for future health problems while realizing that breaking the cycle of depression and poor resilience can have effects that will echo down through generations.[8,13]

It Takes a Village

What should the postpartum evaluation encompass? Let's look at it from the perspective of a day in Devi, Martha, and Emily's lives. Babies require round-the-clock care, and poor parental sleep ensues. Emily could not ask too much of her husband during the overnight hours as he was

the only breadwinner and was already working two jobs outside the home.

While pregnant women are valued in our society, once the baby is born, new mothers take on enormous levels of responsibility with very little support. Implementing occupational therapy strategies such as prioritizing rest, outsourcing tasks, and restructuring routines can help ease the load.[14]

Many birthing women encounter breastfeeding difficulties. Martha had several strikes against breastfeeding success right from the beginning since she was separated from Michael while he spent time in the NICU. When a new mother cannot feed her baby or can only feed with pain, this reinforces the narrative that she isn't a good mother.[10]

We need to make lactation support easily accessible. Simple latch adjustments early in the postpartum stage can make an enormous difference in the long run. Furthermore, successful breastfeeding has even been postulated as a protective measure against PMAD.[10] Martha received these services in the NICU, but a lactation consultant who can provide latch adjustments should be publicly funded for everyone.[13]

Unfortunately, many women suffer from urinary control issues in the postpartum period[15] but do not address the issue directly with their healthcare provider. Both Devi and Emily were experiencing urine leakage every time they coughed or laughed. Given her language difficulties and shy nature, Devi couldn't even imagine discussing these issues with the other women in the complex. Emily was too isolated and overwhelmed and didn't know where to seek help.

The postpartum assessment must explicitly ask about and manage these incontinence issues. Ideally, the interventions of a provider adept in pelvic floor exercises would also be part of the prenatal care. But at the very least, support should be easy to access following delivery.[15]

The Ideal Scenario

Currently partners have more parental leave than in the past, but typically it lasts for just a few weeks. Eventually, the partner returns to their routine and the onus is on the birthing parent. If prenatal risk factors are present, the risk of PMAD is higher, but anyone and everyone is at risk. Many aspects of daily survival can be troubling, from interrupted sleep to integrating siblings and setting limits. All of these require psychoeducation and skills building.[1]

However, why should clinicians wait for symptoms? A structured support group comprising a range of clinicians providing evidence-based interventions[13] could prevent many incidents of PMAD and screen for severe disease. All of these primary prevention evaluations should be community-based, should not require heroic efforts to source, or cost enormous funds to realize.

The Fourth Trimester

Devi received extensive support from the public health nurse. However, Martha and Emily flew "under the radar" and were not targeted for supplementary intervention. Fortunately, a weekly postpartum psychoeducational group, dubbed "The Fourth Trimester" is being piloted at the hospital where Martha and Emily delivered. The group is run by a nurse practitioner adept at mental health interventions. Partners are welcome, and Paul joins Martha and Michael when he is in town.

Every week, a guest practitioner presents their area of expertise. The pelvic floor physiotherapist discusses incontinence and diastasis recti exercises. The lactation consultant monitors the participants and adjusts or supervises the latch. The psychologist discusses attachment theory and intergenerational trauma. The women learn together and from each other.

Conclusion

Building healthy families is an objective of women's health. Effective, structured postpartum care is a key to achieving that goal.

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Financial Disclosures

J.H.: None declared.
P.F.: None declared.

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Canadian Women's Health Today
Science for the Real World

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Vol. 1, Issue 3

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