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Table of Contents

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The Impact Of Menopause On The Musculoskeletal System: A Practical Overview

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Key Points

- Menopause is associated with a rapid decline in estrogen, which significantly affects bone, joint, and muscle health.
- Bone loss accelerates during the menopause transition, with up to a 10% reduction in spine bone density within the first five years after the final menstrual period.
- Menopausal hormone therapy (MHT) has been shown to be effective in preserving bone density and reducing fracture risk.
- Musculoskeletal symptoms, such as pain, stiffness, and joint discomfort are common and often underrecognized during the menopause transition, sometimes leading to misdiagnosis.
- Foundational strategies for preserving musculoskeletal health during and after menopause include lifestyle interventions such as strength training, balance exercises, and adequate protein and vitamin D intake.

Menopause represents an important phase in a woman's reproductive life, marked by the permanent cessation of menstrual periods, signalling the end of the reproductive years. In North America, the average age of onset is 50.5 years, generally occurring between the ages of 45 and 55.[1] Hormonal fluctuations and symptoms of hypoestrogenism—such as hot flashes, night sweats, mood and cognitive changes—can begin up to 10 years before menopause, during the perimenopausal or menopause transition.[1] These symptoms stem from fluctuations in sex hormones, primarily estrogen, which has receptors distributed throughout the body and impacts nearly every organ system, including the bones, joints, and muscles.[2] In this review, we will summarize the effects of hypoestrogenism on bone, joint, and muscle health during and beyond the menopause transition.

Menstrual Periods (MP) And Bone Health

Estrogen plays a critical role in regulating bone turnover, a process involving osteoclasts and osteoblasts that work within specialized cellular units to maintain bone integrity. Osteoblasts are responsible for bone formation, whereas osteoclasts drive bone resorption.[3] Estrogen suppresses bone resorption by inhibiting osteoclast function. As estrogen levels decline during perimenopause, osteoclast activity increases, leading to accelerated bone resorption, overall bone loss, and weakened bone architecture. In turn, this bone loss increases the risk of osteoporosis and fractures later in life. A rapid phase of bone loss occurs within the one- to two-year period surrounding the final menstrual period (FMP) and continues for three years thereafter.[4] During this period, the bone loss is estimated to occur at an annual rate of 1.8–2.3% at the spine and 1.0–1.4% at the hip. As a result, bone density can decline by up to 10% at the spine and 7% at the hip within the first five years following the FMP.[5] This rapid loss of bone density over a relatively short period of time makes the menopausal transition a crucial window of opportunity for optimizing bone health and implementing preventive strategies to mitigate this loss.

Although osteoporosis often remains asymptomatic, its most serious clinical outcome is fracture. The general management approach for osteoporosis in menopause aims to prevent fractures and maintain bone mineral density (BMD). This involves a combination of pharmacological and non-pharmacological strategies. Pharmacological options are based on a patient risk assessment, commonly using the

Fracture Risk Assessment Tool (FRAX) for risk stratification, and may include the use of bone-sparing medications such as bisphosphonates, receptor activator of nuclear factor kappa b (RANK)-ligand inhibitors (i.e., denosumab), and anabolic agents such as teriparatide and sclerostin inhibitors (romosozumab).[6]

Non-pharmacological management begins with a comprehensive assessment of fall risk, followed by the implementation of preventive measures. Maintaining mobility is essential, and this is best achieved through a combination of balance and muscle-strengthening exercises aiming for ≥ twice weekly, tailored to the individual's needs and physical capacity.[6]

Addressing nutritional deficiencies is also a crucial component of bone health management. Ensuring an adequate intake of calcium, with a target of 1200 mg/day, can be achieved through calcium-rich foods or supplementation.[6] Optimizing vitamin D levels is recommended, with a daily supplement of at least 400 IU/day to achieve serum 25-hydroxyvitamin D levels equal to or greater than 50 nmol/L. However, patients with vitamin D deficiency may require higher doses to reach sufficient levels.[6]

What Is The Role Of Menopausal Hormone Therapy (MHT) In Maintaining Bone Health?

There is robust data supporting the use of MHT for maintaining bone density and reducing fracture risk. MHT has been shown to increase BMD by 6% at the spine, 5% at the total hip, and 4% at the femoral neck compared to placebo.[7] In addition, studies show that MHT can prevent menopausal bone loss, with even low-dose MHT offering protection.[8] With regard to fracture risk, results from the Women's Health Initiative (WHI) study show that MHT reduces the risk of hip fracture by up to 30% and the risk of all fractures by 24%.[7]

While the Canadian-based Society of Obstetrics and Gynecology (SOGC) guidelines on menopause do not recommend using MHT primarily for bone protection, the US-based Menopause Society Guidelines do endorse its use for bone protection.[9,10]

When treating postmenopausal osteoporosis, the most recent Osteoporosis Canada guidelines recommend MHT as an alternative treatment option to bone-sparing medications for postmenopausal females aged <60 years or within 10 years of menopause who are experiencing menopausal symptoms who meet the criteria for treatment of osteoporosis.[6] However, because bone loss occurs with cessation of MHT, patients who discontinue MHT should be monitored and followed in accordance with osteoporosis management guidelines.

MP And Joint Health

Estrogen also plays a critical role in connective tissue cells, including chondrocytes within articular cartilage, and is essential for maintaining the health of joints, ligaments, and muscles.[11] The concept of "arthritis of the menopause" was first described in 1926, and more recently, the term Musculoskeletal Syndrome of Menopause has been introduced to describe the constellation of musculoskeletal signs and symptoms associated with the menopausal transition.[12,13] Polyarticular osteoarthritis (OA) is more prevalent in women over the age of 50 compared to age-matched men, suggesting a potential contributory role of estrogen in this sex-based disparity.[14] Although declining estrogen levels during menopause can contribute to the progression and worsening of OA, they are not the sole factor. Other important contributors include age, prolonged disease duration, and degenerative changes.[15]

Musculoskeletal pain is a common yet underrecognized symptom of menopause, with evidence suggesting that more than 70% of perimenopausal women are affected.[16] Aches and joint stiffness are the most frequently reported musculoskeletal symptoms during the menopausal transition; however, they may not necessarily indicate osteoarthritic disease.[17] Determining the underlying cause of joint pain in postmenopausal women can be challenging, as the menopause era coincides with a rise in the prevalence of chronic rheumatic disorders, including osteoarthritis. Addressing the patient's concern through clinical evaluation for structural damage and ruling out potential pathology is necessary, keeping in mind the role of estrogen deprivation in this population. Notably, studies suggest that up to 40% of women who present with musculoskeletal concerns during the menopause transition have no detectable structural abnormalities, and their symptoms are frequently misdiagnosed as rheumatologic or immunological conditions rather than being attributed to menopause.[16]

What Is The Role Of MHT In Maintaining Joint Health?

MHT has been shown to positively influence musculoskeletal symptoms, as demonstrated by the findings from the WHI study, which found that women receiving MHT reported a reduced incidence of new musculoskeletal concerns, including joint pain, stiffness, general aches, low back pain, and neck discomfort.[18] However, discontinuing MHT can exacerbate musculoskeletal symptoms. A cross-sectional survey of over 9,000 WHI participants revealed that those who experienced abrupt MHT withdrawal following health concerns reported a significant increase in pain and stiffness within 8 to 12 months.[19]

Although numerous studies have demonstrated a relationship between estrogen deficiency and OA, the role of MHT in improving OA symptoms and preventing disease progression remains unclear. Epidemiological evidence suggests that estrogen therapy may exert a greater impact on large joint OA compared to small joint OA.[20] While radiographic studies have indicated a protective impact of MHT on the radiographic identification of OA or its progression, a recent meta-analysis reported a higher rate of knee arthroplasty among individuals treated with MHT.[21,22] However, these findings may have been confounded by the healthy user effect, where women receiving MHT often have better access to healthcare services and are more likely to have good access to healthcare providers, are therefore more likely to be assessed for and treated for OA.

MP And Muscle Health

Estrogen is essential for maintaining skeletal muscle health, as it facilitates the proliferation, differentiation, and regeneration of muscle stem cells.[23] These stem cells, known as satellite cells, reside within skeletal muscle fibers and are vital for muscle proliferation, differentiation, and the maintenance of muscle mass and strength. Estrogen exerts its effects by binding to estrogen receptors on satellite cells, promoting their proliferation and aiding in muscle repair.[23]

Aging and menopause are associated with a progressive decline in muscle mass and function, a condition known as sarcopenia. According to the European Working Group on Sarcopenia in Older People (EWGSOP2), sarcopenia is defined as a progressive and generalized skeletal muscle disorder associated with an increased risk of adverse outcomes, including falls, fractures, physical disability, and mortality.[24] Muscle mass typically begins to decrease around the age of 30, with a further decline of 2–7% per decade, particularly accelerating after the age of 60.[25] Following menopause, muscle mass diminishes at an estimated rate of 0.6% per year.[26]

Symptoms of sarcopenia include a history of falls, gait instability, generalized weakness, decreased walking speed, and challenges in rising from a chair or climbing stairs.[24] Numerous validated screening tools exist for assessing the risk of sarcopenia. The EWGSOP2 endorses the Strength, Assistance in walking, Rise from a chair, Climb stairs, Falls (SARC-F) questionnaire, a straightforward five-item self-reported screening instrument.[25,27]

Several factors contribute to the development of sarcopenia, including inadequate nutrition, especially low protein and vitamin D intake, reduced physical activity, and hormonal shifts during the menopause transition, notably decreases in serum levels of estrogen and testosterone.[28] Additionally, comorbid conditions such as obesity may worsen muscle loss by promoting fat infiltration into muscle tissue and impairing physical function.[29]

Research demonstrates that total energy and protein consumption typically decline during the menopausal transition, underscoring the necessity of dietary optimization for muscle health.[30] Given the increased protein requirements of healthy older adults, the European Society for Clinical Nutrition and Metabolism recommends a daily intake of 1.0–1.2 g/kg body weight/day as optimal for a healthy older individual. This should be tailored according to an individual's nutritional status, physical activity level, disease status, and tolerance.[31] Physical exercise, including both aerobic and resistance training, is suggested as a non-pharmacological approach to counteract sarcopenia induced by estrogen deficiency.[32]

What Is The Role Of MHT In Maintaining Muscle Health?

The effect of MHT on sarcopenia can vary depending on the timing of its initiation during the menopause transition, though overall the research in this area remains limited. Some studies indicate that initiating MHT in early post menopause, rather than late post menopause, is linked to a substantial increase in the number of muscle

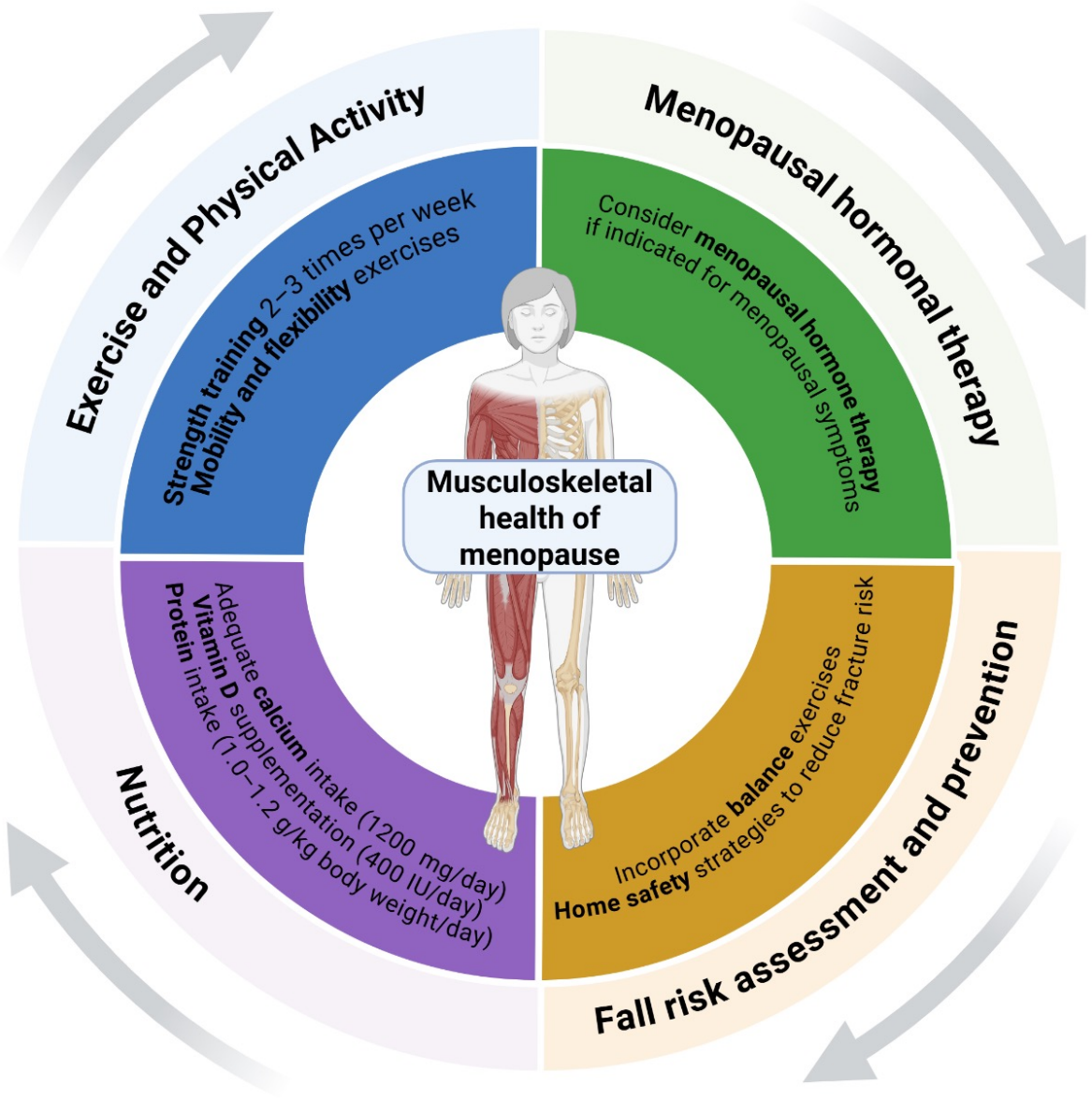

Figure 1. An integrated approach to musculoskeletal health during menopause, emphasizing the role of exercise, hormonal therapy, fall prevention, and nutrition in preserving strength, mobility, and reducing fracture risk.; *created in BioRender. Alshehri, S. (2025) https://BioRender.com/2iazucb.*

satellite cells, along with improvements in muscle strength and mobility.[33]

Conversely, other studies suggest that MHT may not be a reliable intervention for preserving muscle mass.[34] Therefore, when MHT is considered for managing other menopausal symptoms such as hot flashes or night sweating, it may be beneficial to incorporate it into a structured comprehensive plan that includes a nutritional and physical rehabilitation regimen to enhance muscle preservation and function into later life.

Conclusion

In conclusion, musculoskeletal symptoms are frequently experienced during the menopausal transition. Clinicians should address patient concerns and exclude other potential diagnoses while keeping in mind the impact of estrogen deficiency on bone, joint, and muscle health. While MHT may be beneficial in maintaining bone mass and preventing fractures, its impact on joint and muscle health remains less clear. Initiating therapy should be guided by individualized risk

assessment. Additionally, addressing modifiable risk factors, such as optimizing nutritional health and maintaining regular physical activity, can prevent further progression of musculoskeletal concerns **(Figure 1)**. Further studies are necessary to fully understand the role of MHT in musculoskeletal health.

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Financial Disclosures

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Risk Reduction In Pregnancy: Evidence-Based Use Of Aspirin For Prevention Of Preeclampsia

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Introduction

Preeclampsia is a multisystem disorder that emerges in the second half of pregnancy, characterized by the onset of hypertension and end-organ dysfunction. Globally, hypertensive disorders of pregnancy are the second leading cause of direct maternal death.[1] Preeclampsia alone it is estimated to affect up to 5% of all pregnancies.[2] This condition poses serious risks to both mother and fetus, including increasing the likelihood of complications such as preterm birth, fetal growth restriction, and long-term cardiovascular consequences.

Given the severity of complications associated with preeclampsia, prevention strategies are essential, particularly for individuals at high risk. One of the most well-established interventions is the use of low-dose aspirin, which has been shown to significantly reduce the risk of preeclampsia in select high-risk populations. Leading obstetric organizations, including the Society of Obstetricians and Gynaecologists of Canada (SOGC) and the American College of Obstetricians and Gynecologists (ACOG) have issued guidelines recommending aspirin prophylaxis for individuals with specific risk factors for the development of preeclampsia.[3,4] Despite this, awareness and implementation of these guidelines vary, highlighting the need for continued education and standardization of care.

This article explores the current evidence and guidelines supporting the use of aspirin for preventing preeclampsia. By understanding the benefits of aspirin, identifying appropriate candidates most likely to benefit, and ensuring proper administration, healthcare providers can improve maternal and fetal outcomes and reduce the burden of this serious condition.

Understanding Preeclampsia

Preeclampsia is defined as new-onset hypertension occurring after 20 weeks of gestation, with maternal end-organ dysfunction or uteroplacental insufficiency.[4] Maternal end-organ complications include the central nervous system (e.g., severe headache, eclampsia, stroke, retinal detachment), cardiorespiratory symptoms (e.g., pulmonary edema, myocardial infarction), hematological abnormalities (e.g., thrombocytopenia, coagulopathy), renal impairment (e.g., acute kidney injury, renal failure), and/or hepatic involvement (e.g., Hemolysis, Elevated Liver enzymes, Low Platelet count [HELLP] syndrome, severe liver dysfunction, hepatic hematoma or rupture). Uteroplacental insufficiency may manifest as fetal growth restriction, atypical or abnormal fetal heart rate patterns, oligohydramnios, abnormal Doppler studies, placental abruption, or intrauterine fetal death.[4]

While the underlying etiology of preeclampsia remains unclear, placental dysfunction and maternal cardiovascular maladaptation to pregnancy are recognized as central mechanisms of the disease. The prevailing theory is that defective placental implantation through abnormal trophoblast invasion and abnormal spiral artery remodelling lead to poor placental perfusion. This ischemic environment triggers systemic maternal endothelial dysfunction, inflammation, and an imbalance of vasoactive factors, ultimately leading to the clinical manifestations of preeclampsia.

Several risk factors have been identified that increase the likelihood of developing preeclampsia. Among them, chronic hypertension is considered one of the strongest predictors.[5] Other significant risk factors include advanced maternal age, obesity, diabetes, multiple gestation, use of assisted reproductive technologies, autoimmune

High-risk factors*	Moderate-risk factors**
• History of preeclampsia in a previous pregnancy • Pre-pregnancy body mass index >30 kg/m² • Chronic hypertension • Pre-gestational diabetes mellitus (i.e., type 1 or type 2 diabetes) • Chronic kidney disease • Autoimmune diseases (e.g., systemic lupus erythematosus, antiphospholipid antibody syndrome) • Assisted reproductive technology (e.g., in vitro fertilization)	• Nulliparity • Multiple gestation • Maternal age >40 years • Prior placental abruption • Prior stillbirth • Prior fetal growth restriction

Table 1. Risk factor-based criteria for aspirin use in pregnancy; *courtesy of Mary Alexandra Murphy, MD, MASc, FRCSC and Sebastian Rupert Hobson, MD, PhD, MPH, FRANZOG, FACOG, FRCSC*

* Presence of one is sufficient to recommend aspirin
** Consider aspirin if presence of two or more

disorders, kidney disease, and a personal or family history of preeclampsia.

Preeclampsia is a major contributor to adverse pregnancy outcomes, including preterm birth, fetal growth restriction, and low birth weight.[6] Furthermore, it remains a major cause of direct maternal mortality worldwide, with deaths primarily due to stroke, organ failure, and other complications related to severe hypertensive crises.[1] In addition to its immediate risks, preeclampsia carries long-term implications for both mother and child. Patients with a history of preeclampsia face an increased risk of chronic hypertension, cardiovascular disease, and stroke later in life.[7] Similarly, children born to mothers with preeclampsia may be at higher risk of developing cardiovascular, metabolic, and neurological disorders. Globally, it is estimated that more than 300 million people are at an increased risk of chronic health conditions due to prior exposure to preeclampsia.[8] Given these significant maternal and fetal complications, primary prevention remains a key priority in obstetric care.

The Role Of Aspirin In Preventing Preeclampsia

The preventive use of low-dose aspirin for preeclampsia has been widely studied over several decades. Initial evidence emerged from a 1979 retrospective cohort study, which found that frequent aspirin use during pregnancy was associated with a lower incidence of preeclampsia in primigravidas.[9] This finding led to the hypothesis that platelet activation played a role in the development of preeclampsia, and aspirin, as an antiplatelet agent, could help mitigate this effect.

Aspirin exerts its effects by irreversibly inhibiting cyclooxygenase-1 (COX-1), which reduces thromboxane A2 production, a potent vasoconstrictor and promoter of platelet aggregation.[3] This mechanism ultimately improves placental blood flow and reduces systemic inflammation, both of which contribute to the pathophysiology of preeclampsia.[10] By decreasing placental ischemia and endothelial dysfunction, aspirin may prevent or delay the onset of the disorder in high-risk individuals.

Contemporary evidence supporting the use of aspirin in pregnancy derives from the renowned ASPRE trial, a multicenter, randomized controlled trial that investigated aspirin's role in preventing preeclampsia. The study found that administering low-dose aspirin (150 mg daily) from 11–14 weeks of gestation until 36 weeks in high-risk pregnancies led to a 62% reduction in the incidence of preterm (<37 weeks gestation) preeclampsia compared to placebo.[11] Furthermore, the risk of developing preeclampsia <34 weeks gestation was reduced by 82% in the aspirin group compared to placebo. Additional meta-analyses, including reviews by the United States Preventive Services Task Force (USPSTF), have further confirmed the efficacy of aspirin in reducing the risk of preeclampsia, particularly when started before 16 weeks gestation.[12]

Despite these findings, questions remain regarding the optimal dosage and timing of aspirin administration. These considerations are explored in more detail in the following sections. Current guidelines generally advise starting aspirin before 16 weeks of gestation, as earlier initiation has been associated with greater benefit in some studies.[13] However, patients who present from 16–20 weeks may still derive benefit from daily low-dose aspirin and should be offered therapy when appropriate.[12]

Despite strong evidence supporting aspirin's role in reducing preeclampsia risk, its implementation in clinical practice depends on identifying patients who are most likely to benefit. Given the multifactorial nature of preeclampsia, a risk-based approach is necessary to ensure that aspirin prophylaxis is targeted to those who are most at-risk.

Guidelines For Aspirin Use In Pregnancy

In Canada, the SOGC recommends the use of daily low-dose aspirin (81 or 162 mg) for individuals at high risk of developing preeclampsia, ideally starting before 16 weeks of gestation and continuing until 36 weeks.[4] These recommendations align with international guidelines from organizations such as the ACOG,[3] the USPSTF,[12] and the National Institute for Health and Clinical Excellence (NICE),[14] all of which advocate for a risk-based approach to aspirin prophylaxis. These recommendations are based on extensive research demonstrating that aspirin is most effective when used in high-risk populations and initiated early in pregnancy.

Criteria For Aspirin Prophylaxis

Risk assessment for preeclampsia is based on a combination of pre-pregnancy demographics, pre-existing medical conditions, previous pregnancy complications, and current pregnancy features. Based on recommendations from the International Society for the Study of Hypertension in Pregnancy, the SOGC classifies risk factors into high-risk and moderate-risk categories to guide aspirin use,[4] as outlined in **Table 1**.

Given Canada's diverse population, it is important to recognize disparities in maternal health outcomes. Studies indicate that individuals of African, South Asian, and Indigenous backgrounds may have an elevated risk of hypertensive disorders in pregnancy. Some guidelines consider racial disparities along with other sociodemographic factors (e.g., low socioeconomic status) as moderate-risk factors for preeclampsia.[3] Ensuring equitable access to aspirin prophylaxis is essential to improving maternal and neonatal outcomes across the country and for all.

Dosing Recommendations

Canadian guidelines currently lack consensus regarding the recommended dose of aspirin for preeclampsia prevention. Traditionally, it was believed that a higher daily dose of aspirin, such as 162 mg or similar, would maximize effectiveness, whereas a lower daily dose of 81 mg or similar would maximize maternal safety. However, a recent large cohort study by Kupka *et al*.[15] compared daily doses of 150-160 mg versus 75 mg during pregnancy for preeclampsia prevention and showed no significant differences in preeclampsia incidence or adverse bleeding outcomes. These findings suggest that both dosing strategies may be appropriate. Clinicians should consider individual patient characteristics, risk profiles, and tolerance when selecting the most suitable dosage. Additionally, practical considerations such as cost, pill burden, and availability may influence decision-making regarding dose selection.

Safety And Contraindications

Low-dose aspirin is considered safe and well-tolerated in pregnancy. Large-scale studies have not shown an increased risk of congenital anomalies, excessive bleeding at delivery, or other major complications when taken at recommended doses.[16] However, aspirin should be avoided in individuals with the following conditions:

- Known allergy or hypersensitivity to aspirin
- Active peptic ulcer disease or gastrointestinal bleeding
- Severe bleeding disorders
- Any contraindication to aspirin therapy, such as contraindication to NSAIDs, severe renal or hepatic disease, and gout

Practical Considerations For Healthcare Providers

To effectively reduce the incidence of preeclampsia, early identification of at-risk patients is essential. Healthcare providers should conduct a comprehensive risk assessment at the first prenatal visit to determine which patients qualify for aspirin prophylaxis. The SOGC recommends a multifactorial screening approach,

which combines maternal history, biophysical markers, and biochemical tests to improve early detection of preeclampsia risk.[4]

Screening And Risk Assessment

All pregnant patients should be screened for preeclampsia risk factors between 11–14 weeks gestation. Where available, the SOGC endorses the use of combined first-trimester screening algorithms that integrate:

- Maternal risk factors (as outlined in **Table 1**)
- Mean arterial pressure (measured at the first prenatal visit)
- Uterine artery Doppler studies (assessment of placental blood flow)
- Biochemical markers (e.g., placental growth factor, pregnancy-associated plasma protein-A)

Studies have shown that using this multifactorial approach, when available, is more effective than relying on clinical history alone for identifying individuals at high risk for preterm preeclampsia.[4,11] This method allows for more precise risk stratification, ensuring aspirin is prescribed to those most likely to benefit. At the very least, risk factor assessment should be conducted at the first antenatal visit.

For individuals at high risk, aspirin prophylaxis should be initiated before 16 weeks of gestation and continue until 36 weeks. Given the multifactorial nature of preeclampsia, a tailored, patient-centred approach is necessary.

Counselling Patients On Aspirin Use

Clear, evidence-based counselling can improve adherence to aspirin prophylaxis. Many patients have concerns about taking medication during pregnancy, and addressing misconceptions is crucial. Key points to emphasize include:

- Aspirin is safe in pregnancy and does not increase the risk of congenital anomalies.[3]
- Aspirin does not cause excessive bleeding at delivery when taken at recommended doses.[16]
- Low-dose aspirin significantly reduces the risk of preeclampsia, particularly in those with high-risk factors.[11]
- As a good practice point, aspirin administration is generally suspended during episodes of antepartum hemorrhage and resumed based on the advice of the most responsible pregnancy care provider.

Shared decision-making is essential, ensuring that patients are well-informed and comfortable with their treatment plan.

Addressing Barriers To Access

Despite strong recommendations, some patients may face barriers to accessing aspirin prophylaxis, including financial constraints, lack of awareness, or limited access to prenatal care. In Canada, efforts should be made to improve accessibility, particularly for individuals from underserved communities, including Indigenous, Black, and low-income communities. Incorporating aspirin prescribing into standard prenatal care protocols can help bridge these gaps.

By prioritizing early risk screening, proactive counselling, and equitable access, healthcare providers play a key role in the effective implementation of aspirin prophylaxis. These efforts are essential to reducing the burden of preeclampsia and improving maternal and fetal outcomes.

Conclusion

Preeclampsia remains a serious threat to maternal and perinatal health in Canada and worldwide, contributing to acute complications, such as seizures, stroke, and maternal death as well as long-term health risks for both mother and child. Given its complex pathophysiology and the limited treatment options once it develops, prevention is critical.

Low-dose aspirin has emerged as a safe, low-cost, and highly-effective evidence-based intervention to reduce the risk of preeclampsia in high-risk pregnancies. Large trials, such as the ASPRE study, have demonstrated its effectiveness, especially when started early in pregnancy. Reflecting this evidence, many guidelines, including those from the SOGC, recommend early screening using multifactorial risk assessment tools to identify candidates for aspirin prophylaxis.

For healthcare providers, the opportunity lies in early identification, patient-centred counselling, and equitable implementation of care. As clinical tools and risk prediction models continue to evolve, integrating these strategies into routine prenatal care can lead to significant improvements in maternal and fetal outcomes.

Continued research, education, and supportive health policies will be key to ensure that all pregnant individuals at risk have access to preventive strategies like aspirin.

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When You Don't Look But You Do Find: Pragmatic Approach To Management Of Asymptomatic Endometrial Thickening In Postmenopausal Patients

Olga Bougie, MD, FRCSC, MPH

Introduction

The endometrium varies in thickness through the menstrual cycle, largely in response to estrogen and progesterone stimulation. Following menopause, the endometrium should remain homogenously atrophied due to the relatively low circulating levels of estrogen. In postmenopausal women, the endometrium is considered thickened when it measures greater than 5 mm.[1] Measuring endometrial thickness includes assessing the width of the anterior and posterior layers of the endometrium made on the midline sagittal image obtained by transvaginal ultrasound. The principal objective of investigating a thickened endometrial lining is to diagnose endometrial hyperplasia or cancer. Patients who experience postmenopausal bleeding and are found to have an endometrial thickness greater than 5 mm necessitate endometrial sampling. However, whether endometrial sampling is required in the absence of symptoms, namely postmenopausal bleeding, is a more nuanced clinical decision. This article provides an approach to evaluating patients presenting with asymptomatic endometrial thickening, including a review of guidelines for when further testing is warranted. It will specifically address unique populations, namely patients using menopausal hormonal therapies as well as those on tamoxifen.

- Increasing age
- Obesity
- Diabetes
- Hypertension
- Polycystic ovarian syndrome
- Tamoxifen use
- Unopposed estrogen use
- Nulliparity
- Prolonged menstrual history (early menarche, late menopause)
- Genetic predisposition (i.e., Lynch syndrome)

Table 1. Risk factors for endometrial cancer; *courtesy of Olga Bougie, MD, FRCSC, MPH*

Differential Diagnosis Of Endometrial Thickness

Although the primary goal of investigating asymptomatic endometrial thickening is to exclude a malignant process, it is helpful to consider the different diagnoses of this finding. Most common causes of endometrial thickness include endometrial polyps, submucosal fibroids, intrauterine adhesions or septum, adenomyosis, proliferative endometrium, endometrial hyperplasia, and endometrial cancer. Additional ultrasound descriptors, such as whether the thickening is global or focal, the presence of fluid collections, increased vascularity, and the identification of a feeding vessel are all valuable features to help tailor the differential diagnosis and direct further investigations.

Certain sonographic features may be highly suspicious for an endometrial polyp, such as a hyperechoic focal endometrial mass with or without vascularity and distortion of the endometrial contour. The application of power doppler on transvaginal ultrasound, as well as the use of 3D imaging, may aid diagnostic accuracy. Saline-infused sonohysterography provides high diagnostic accuracy. Alternatively, hysteroscopy can offer concurrent diagnosis and treatment. The risk of malignancy within an endometrial polyp is estimated to be between 0.5% and 3.4-5.4% in high risk populations.[2] The strongest risk factors for malignancy in endometrial polyps are age greater than 60 years, postmenopausal status, and the presence of bleeding.[3,4] Other risk factors include polyp size, obesity, hypertension, and diabetes mellitus.[3,4]

Endometrial histopathological assessment can yield a number of findings including atrophic endometrium, proliferative endometrium, secretory endometrium, polyps, endometritis, endometrial hyperplasia, and cancer. While proliferative endometrium is generally regarded as a benign entity, this pathological finding is associated with an 11.9% risk of developing endometrial cancer in postmenopausal patients, compared to a 2.9% risk of cancer in those with atrophic endometrium.[5] Proliferative endometrium typically develops from unopposed estrogen stimulation and should prompt an evaluation to identify and address the underlying cause. Ongoing monitoring through repeat endometrial sampling should be considered in patients with this diagnosis. Although not standard practice, progesterone treatment may be considered in certain high risk patients on an individualized basis to reverse proliferative endometrium and prevent further development of endometrial hyperplasia or cancer.

Etiology Of Endometrial Cancer

Endometrial cancer is the most common gynecologic malignancy in developed countries, and its incidence continues to rise. There are 2 main subtypes of endometrial cancer: endometrioid, accounting for 80% of the cases, and non-endometrioid.[6] Endometrioid cancers arise from endometrial hyperplasia due to overstimulation of the endometrial lining from estrogen. Non-endometrioid cancer subtypes do not have a precursor and importantly may not result in a thickened endometrium. In the postmenopausal population, over 90% of patients who are ultimately diagnosed with endometrial cancer will experience bleeding.[7] Although we typically aim to diagnose and treat cancer early, it is unclear whether diagnosing endometrial cancer in asymptomatic patients provides a survival advantage.[8] Current guidelines recommend offering treatment to patients at the time of diagnosis. The main risk factors for endometrioid typical cancers are related to estrogen stimulation and include obesity, metabolic syndrome (diabetes, polycystic ovarian syndrome,

hypertension), tamoxifen use, and nulliparity **(Table 1)**. While more than 50% of all cancers are attributable to obesity, endometrial cancer has the strongest associated risk with this diagnosis. Patients with a normal body mass index (BMI) carry a 3% lifetime risk of developing endometrial cancer; however, for every 5-unit increase in BMI, the risk of developing cancer increases by 50%.[9]

Approach To Evaluation Of Thickened Endometrial Lining

Depending on the baseline characteristics of the population studied, up to 3-15% of postmenopausal women will have asymptomatic endometrial thickness. If this finding is noted on a CT scan, an ultrasound should be performed to confirm it.

A concerted effort has been made to determine the optimum cutoff for further testing, primarily through endometrial sampling, in this clinical presentation. It is estimated that the risk of cancer in patients without postmenopausal bleeding is 0.002% when the endometrium is ≤11 mm in thickness and 6.7% when it exceeds 11 mm. This distinction is similar to the risk stratification in patients with postmenopausal bleeding, where a ≤5mm cut off is used to determine the need for endometrial sampling. Increased vascularity observed on ultrasound has been associated with increased risks of endometrial hyperplasia or cancer.[10] Upon a comprehensive review of the evidence, the Society of Obstetricians and Gynecologists of Canada recommends that patients found to have endometrial thickening of ≥11 mm, or concerning sonographic features such as increased vascularity, heterogeneity, or fluid collection, should be considered for further investigations or be referred to a gynecologist.[11]

Endometrial Sampling

Endometrial sampling can be obtained using a pipelle biopsy, generally performed in an outpatient clinic setting or through dilation and curettage. Although an endometrial pipelle biopsy is a blind procedure, it has a high diagnostic accuracy for endometrial cancer (99.6% sensitivity), particularly in postmenopausal women. However, up to 20% of postmenopausal women will have an inadequate sample collected through office endometrial sampling. As such, office endometrial biopsy is considered a reliable and accurate test for diagnosing endometrial cancer, provided that the endometrial thickness is global in nature on ultrasound assessment and an adequate sample is obtained for histological evaluation. If an inadequate sample is obtained, monitoring and repeating imaging in approximately 4 months, or proceeding with further testing such as hysteroscopy and endometrial curettage can be considered. This decision is typically individualized for each patient, depending on their risk of endometrial pathology versus surgical risks. In cases where a stenotic cervix prevents obtaining office endometrial sampling, a similar balance of risks must be evaluated. Although prostaglandin E1 (misoprostol) pre-treatment is often employed in this setting to help with cervical dilation, there is no evidence to support its benefits prior to office endometrial biopsy.[12,13] A number of operative techniques may be used to safely access the endometrial cavity in individuals with a stenotic cervix, if necessary.

Directed hysteroscopic evaluation and sampling can be considered when focal endometrial thickness is identified on ultrasound, other ultrasound features suggest the presence of an endometrial polyp or distinct lesion, or when an inadequate sample is obtained from an office biopsy.[2] Hysteroscopic evaluation can be performed in an ambulatory setting, thereby decreasing the risk of anesthetic complications.

Specific Populations

Tamoxifen

Tamoxifen use is associated with a significant increase in endometrial cancer and endometrial hyperplasia, which is dose dependant. A systematic review of 26 studies, including 44,980 tamoxifen users and 193,414 non-tamoxifen users demonstrated a relative risk of 2.03 (95% confidence interval: 1.68–2.45; I^2: 76%) for endometrial cancer diagnosis in the tamoxifen group.[14]

There is a significant increase in endometrial thickness observed in patients using tamoxifen, with up to 70% of postmenopausal patients having an endometrial thickness greater than 5 mm while on this medication.[15] Additionally, the endometrium of patients on tamoxifen is often described as irregular and containing multiple cystic areas. Increased endometrial thickening is associated with a higher risk of bleeding. Endometrial polyps are the most common endometrial pathology

diagnosed in postmenopausal patients using tamoxifen, with a rate of 8–36.0%.[16]

Currently, there is a lack of evidence to support routine screening in the population.[17] Patients using tamoxifen should be counselled regarding the risks to the endometrium and to report any vaginal bleeding, which should be promptly investigated.

Menopausal Hormonal Treatment

Systemic estrogen use is associated with increased endometrial thickness, as well as the development of endometrial hyperplasia and cancer. A Cochrane review concluded that there is no clinically significant increased risk of endometrial thickness or endometrial pathology diagnosis with the use of combined estrogen and progesterone treatment, whether in continuous or sequential regimens.[18] The use of a tissue selective estrogen complex combination product containing CEE 0.45/bazedoxefine 20 mg daily has not been associated with a significant increase in endometrial thickness or hyperplasia.[19] Treating genitourinary symptoms of menopause with vaginal preparations of estradiol, conjugated equine estrogen or estrone, DHEA, or testosterone have not demonstrated an impact on the endometrium.[20]

Conclusion

Endometrial thickness greater than 5 mm is common in postmenopausal patients. The primary goal of assessment in this situation is to exclude endometrial cancer or hyperplasia, which are currently on the rise. Major risk factors for endometrial cancer include obesity, metabolic syndrome, and a history of anovulation. The majority of patients (>90%) with endometrial cancer will present with vaginal bleeding, at which point endometrial sampling should be performed.

If patients present with an incidental finding of endometrial thickness and deny vaginal bleeding, referral to a gynecologist or endometrial sampling should be performed when the endometrial thickness exceeds 11 mm or if concerning features are noted on ultrasound.

Although patients using tamoxifen are at an increased risk of endometrial pathologies, there is currently insufficient evidence to support routine sonographic screening.

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Analgesia For Office Gynecology

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Introduction

Intrauterine device (IUD) insertion and endometrial biopsy are two common and essential procedures routinely performed in office-based gynecology. IUDs offer highly effective contraception and also serve as important treatments for dysmenorrhea, abnormal uterine bleeding, and endometrial hyperplasia or cancer. Endometrial biopsy remains a first-line diagnostic tool for evaluating abnormal uterine bleeding. Despite their utility, both procedures are often associated with moderate to severe pain,[1] which can discourage patients from pursuing them. As patient comfort becomes an increasing priority for both patients and providers, clinicians should become familiar with the effective analgesic strategies available in this setting.

Nonpharmacological Interventions

Clinicians are encouraged to provide a trauma-informed and individualized approach to care, through grounding their practice in the key principles of patient respect, autonomy, informed consent, and shared decision making.[1] Pre-procedure counselling is recommended to obtain a comprehensive patient history, review expectations, explore non-pharmacologic and pharmacologic comfort measures, and establish rapport.[2] Furthermore, screening patients for risk factors associated with an increasingly painful experience can help clinicians individualize counselling. For example, nulliparity, dysmenorrhea, history of trauma, prior loop electrosurgical excision procedure, anxiety or mood disorder, and younger age are associated with potentially more painful IUD insertions.[1,3] As such, these patients would be most likely to benefit from pain management interventions.

Dialogue

Deliberate and careful language selection is critical. Implementing "verbal analgesia" through a calming and comforting tone characterized by soft, slow, and low-pitched speech has been shown to provide analgesic effects comparable to oral tramadol during IUD placement in nulliparous patients.[1,2,4] Patients may benefit from distraction through casual conversation during procedures.[1,2] Moreover, frequent verbal check-ins with the patient to assess comfort, offering breaks (for example between IUD removal and insertion), and ensuring consent is maintained are essential.[1]

Environment

Patient comfort and safety can be enhanced by modifying the environment to individual preferences using evidence-based interventions such as dimming room lighting, playing music, regulating room temperature (for example cooling fan/cold towels on forehead or warm towels/heating pads on abdomen), acupressure, aromatherapy with lavender or peppermint, and incorporating breathing techniques.[1,2,5,6] Implementing these simple strategies can help create an ideal clinical environment.

Equipment

Procedural equipment should be selected in a patient-centred manner. For example, a Pederson speculum is preferred for nulliparous patients provided it allows sufficient visualization.[1] The use of a water-based lubricant is recommended during speculum use and does not interfere with cervical screening.[7] To further reduce discomfort, consider using the narrowest available uterine sound (e.g., plastic sound, endometrial pipelle) as well as a single-tooth tenaculum or Allis clamp with a one-notch closure.[1]

Oral Analgesics

There are mixed results regarding the efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) in reducing pain for patients undergoing in-office gynecologic procedures. A recent systematic review and meta-analysis found that NSAIDs alone, regardless of type

or dose, were not effective at reducing pain during IUD insertions.[8] Similar results were found for patients undergoing in-office endometrial biopsies.[9] However, a double-blind randomized controlled trial (RCT) concluded that oral ketorolac resulted in decreased pain during IUD deployment compared to placebo (4.2 vs. 5.7, *P* = 0.031), overall pain score (3.6 vs. 4.9, *P* = 0.047), and pain 10 minutes following the procedure (1.1 vs. 2.5, *P* = 0.007).[10] While NSAIDs alone may not effectively address pain during the procedure, they are appropriate for managing post procedure pain.[3] As such, premedication with an NSAID prior to IUD insertion or endometrial biopsy is recommended, particularly as part of a multimodal pain management strategy.[1] For some patients, opioid analgesics may also be considered. Among opioids, tramadol is the most commonly used for in-office gynecologic procedures and has demonstrated greater efficacy than naproxen.[2,11] However, if an opioid is being considered, providing adequate counselling regarding associated risks and safety precautions (for example, avoidance of benzodiazepines or alcohol, ensuring a safe ride home) is required.

Options include:

- Ketorolac 20 mg orally, taken 1-2 hours before the procedure.[1,8,10,*]
- Naproxen 500 mg orally, taken 1-2 hours before the procedure[1,2]
- Ibuprofen 800 mg orally, taken 1-2 hours before the procedure.[1]
- Tramadol 50 mg orally, taken 30-60 minutes before the procedure.[2]

* Ketorolac 20 mg orally may offer superior pain relief compared with other NSAIDs[8]

Oral Anxiolytics

Benzodiazepines may be a reasonable option for specific patients experiencing high anxiety related to gynecologic procedures. Careful and appropriate patient selection is critical due to special considerations associated with benzodiazepines (i.e., controlled drug and substance). As with opioids, patients should receive counselling regarding side effects and the importance of arranging a safe ride home.

Options include:

- Midazolam 10 mg orally, taken 30-60 minutes before the procedure.[1,*]
- Lorazepam 1-2 mg sublingual, taken 20-30 minutes before the procedure.[1]
- Diazepam 5-10 mg orally, taken 1-1.5 hours before the procedure.[1]

* Midazolam is preferred due to its favourable safety profile, rapid onset, and short half-life compared to alternative benzodiazepines[1]

Topical Analgesics

Topical analgesics, such as lidocaine-prilocaine cream (EMLA®) and 10% lidocaine spray applied to the cervix have been shown to reduce pain with IUD procedures, endometrial biopsies, and office hysteroscopies.[1-3,9,12] Moreover, these agents have also shown superior pain relief compared to NSAIDs such as naproxen or ibuprofen.[8] In a double-blind, placebo-controlled RCT, 10% lidocaine spray reduced pain during IUD procedures, specifically during tenaculum placement (mean pain score 0.75 vs. 2.0, *P* = <0.001), uterine sounding (2.30 vs. 4.10, *P* = <0.001), and IUD insertion (2.95 vs. 5.00, *P* = 0.002).[13] A systematic review and meta-analysis found that lidocaine-prilocaine cream was the most effective option for reducing IUD-insertion related pain.[8] Compared with placebo, lidocaine-prilocaine cream resulted in reduced pain during tenaculum application (mean difference [MD] -2.38; 95% confidence interval [CI]; 4.07 to 2.38) and IUD insertion (MD 2.76; 95% CI; 4.61 to 0.91).[8] While topical 2% lidocaine gel administered intravaginally or to the cervix is generally not effective, it may still offer a practical option for self-administration by patients with a history of trauma, vestibulodynia, or pelvic pain, particularly to reduce discomfort associated during speculum and/or tenaculum placement.[1,2]

Options include:

- EMLA® cream (e.g., 2.5% lidocaine/2.5% prilocaine): apply 4-5 g to the cervix and cervical canal 5-7 minutes before the procedure.[1,14]
- Lidocaine 10% spray: administer via four sprays (each delivering 10 mg, for a total of 40 mg/mL/spray) to the cervix and toward the cervical canal 3 minutes before the procedure.[1,13,15]

Paracervical And Intracervical Blocks

Paracervical and intracervical blocks with lidocaine may provide effective analgesia across various pain points associated with IUD insertion and endometrial biopsy.[1-3] Paracervical blocks are placed in the cervico-vaginal junction, whereas

intracervical blocks are injected directly into the cervical tissue. Some clinicians may prefer administration of an intracervical block due to perceived ease, safety, and reproducibility.[16] However, there is more evidence supporting paracervical block for pain reduction. Paracervical blocks are more effective at reducing pain during IUD insertion compared with NSAIDs and topical lidocaine application.[3,17] A recent double-blind RCT showed that a 1% lidocaine paracervical block significantly reduced pain across all pain points compared to control (tapping the cervix). The reduction was especially notable in nulliparous patients, with pain scores significantly lower during tenaculum placement (0 vs. 3, P <0.05), uterine sounding (5 vs. 6, P <0.05), IUD deployment (5.5 vs. 7, P <0.05), and overall pain (40 vs. 60, P <0.05).[18] Additionally, patient satisfaction was higher among those who received a paracervical block, with 85% reporting satisfaction compared to 65% in the control group. Importantly, patients rated the pain associated with a paracervical block as a mean of one out of 10 (range 0-1). As such, injection-related pain should not deter clinicians from offering paracervical blocks. For endometrial biopsies, most studies show some analgesic benefit of paracervical blocks; however, intrauterine anesthetics may be more effective.[9,19]

Options include:

- **Paracervical Block:** Administer 10-20 mL of 1% or 2% lidocaine with or without 2 mL of sodium bicarbonate as a buffer. Injections should be made bilaterally at 1/2/4 and 8/10/11 o'clock positions at the cervicovaginal junction, to a depth of more than 1 cm before placement of the tenaculum.[1,2,20]
- **Intracervical Block:** Inject 3.6 mL of 1% or 2% lidocaine, with or without 2 mL of sodium bicarbonate buffer, directly at the tenaculum site.[1,16] Alternatively, inject 4 mL of 2% lidocaine directly into the cervical stroma at 3, 6, 9, and 12 o'clock positions before tenaculum placement.[1]

Intrauterine Anesthesia

Intrauterine anesthetic agents instilled through the cervix and into the endometrial cavity provide effective analgesia during procedures such as IUD insertion, endometrial biopsy, and endometrial aspiration biopsy using low-pressure suction.[9,19,21] For example, a double-blind, multi-centre, RCT found that intrauterine instillation of 10 mL mepivicaine (20 mg/mL) significantly reduced pain in nulliparous women undergoing IUD insertion compared to placebo, reducing mean visual analogue scale (VAS) pain scores by 13.3 mm on a 100 mm scale (95% CI 5.75 to 20.87; P = <0.001).[21] For endometrial biopsies, a systematic review showed that intrauterine lidocaine reduced pain relative to control (MD 1.31; 95% CI 2.70 to 0.09; P = 0.07).[19] However, the use of intrauterine anesthesia may be limited by the availability of necessary equipment as well as the technical expertise required for administration.

Options include:

- **Mepivicaine 20 mg/ml:** Instill 10 mL through a hydrosonography catheter 2 minutes before the procedure.[1,21]
- **Lidocaine 2%:** Slowly instill 5 mL over 5 minutes through a feeding catheter placed 2-3 cm distal to the endocervix in the endometrial cavity.[20]

Inhaled Anesthesia

Methoxyflurane (Penthrox®) is a self-administered inhaled analgesic/anxiolytic with few side effects and contraindications, a very short half-life, and high patient satisfaction. In small studies, methoxyflurane has been shown to significantly reduce intraprocedural pain and enhance patient satisfaction during outpatient hysteroscopy and intrauterine procedures, such as endometrial biopsy or IUD insertion/removal.[22,23] In a double-blind RCT assessing the efficacy of methoxyflurane on diagnostic hysteroscopy, methoxyflurane was associated with a mean pain score reduction of 11.5 mm/100 mm in the VAS compared to placebo (95% CI 0.08 to 22.95; P = 0.05).[24] While research specific to gynecologic procedures is limited, methoxyflurane yields promising analgesic results across other disciplines.[22] For example, methoxyflurane has been associated with pain reduction among emergency department patients undergoing a variety of procedures.[25] As such, further exploration into its effectiveness for managing pain during in-office gynecologic procedures is warranted.

Nitrous oxide is another short-acting inhaled analgesic/anxiolytic that is frequently used in office-based dental procedures. Unlike methoxyflurane, administration of nitrous oxide requires additional equipment (gas tank, tubing, and a mask/nasal prongs). In a double-blind RCT comparing nitrous oxide to oxygen in nulliparous patients undergoing IUD insertion, no statistically

significant reduction in pain was observed.[26] Further studies are needed prior to recommending nitrous oxide as an effective option for office-based gynecology procedures.

Options include:

- **Methoxyflurane (Penthrox®):** Administer 20 inhalations (10 inhalations with diluter hole closed) prior to the procedure and intermittent inhalations throughout the procedure as needed.

Misoprostol

Misoprostol is not considered an effective analgesic for IUD procedures or endometrial biopsies.[8,9] Moreover, it may be associated with increased cramping and subsequent higher pain levels during IUD procedures.[2] However, misoprostol may be a reasonable option for patients at risk for failed or challenging insertions where cervical softening may be helpful (e.g., cervical stenosis).[1]

Options include:

- **Misoprostol:** Administering 400 mcg buccally or vaginally 3-4 hours before the procedure may be helpful.[1]

Conclusion

Care providers should be well-versed about the full range of pain management strategies available for office-based gynecologic procedures. Taking the time to discuss these options with patients can significantly enhance their overall experience and increase the acceptability and uptake of these important interventions.

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How To Tackle Sleep Concerns In Peri-And Post-Menopausal Women

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Introduction

Sleep concerns represent a common symptom of menopause, affecting approximately half of women during perimenopause and postmenopause. Often, sleep difficulties increase throughout the menopausal transition, particularly when not assessed and treated early on. Recent Canadian data highlights an increased risk among women for insomnia, more daytime sleepiness, and elevated rates of sleep-related conditions such as obstructive sleep apnea (OSA), REM sleep behaviour disorder, and restless leg syndrome.[1] The etiology of poor sleep in this population is multi-factorial. While vasomotor symptoms (VMS) such as hot flashes and night sweats contribute to sleep disturbance, other contributing factors include hormonal changes, comorbidities, chronic pain, and age-related changes in circadian rhythm. A range of helpful options are available, including lifestyle and behavioural approaches and pharmacotherapy, which can ameliorate sleep quality to improve the lives of women during this important transition and thereafter.

Hormone Changes And Sleep Disturbances

Fluctuations and subsequent declines in estrogen and progesterone during perimenopause and following menopause play a central role in sleep disturbances. Estradiol, a primary and active form of estrogen in the body, fluctuates unpredictably during perimenopause, sometimes with significant rises followed by extended periods of decline. This hormone plays a critical role in regulating neurotransmitters such as serotonin, which is essential for maintaining healthy sleep cycles.[2] As estrogen levels decrease, serotonin levels become dysregulated, often leading to longer sleep onset times, more frequent nighttime awakenings, and reduced time spent in deep and restorative sleep.[3,4]

Progesterone, a hormone secreted by the ovaries, also plays a key role in sleep regulation. One of its metabolites, allopregnanolone, functions as a neurosteroid by binding to gamma-animobutyric acid (GABA)-A receptors in the brain, exerting a calming effect. As progesterone levels decline, many women may experience heightened emotional sensitivity or feelings of being overwhelmed. A study conducted by Andréen et al. (2006) identified a bimodal relationship between serum allopregnanolone concentration and mood in postmenopausal women. The study revealed that women experienced the highest levels of negative mood when allopregnanolone concentrations were within a specific range (1.5–2 nmol/L), suggesting that even slight hormonal imbalances can have measurable emotional consequences.[5] In a study conducted by Babalonis et al. (2011), healthy premenopausal women were given oral progesterone at doses of 100 mg and 200 mg. The researchers observed significant sedative effects, particularly when the hormone was taken with a moderate-fat snack to enhance bioavailability.[6] These findings suggest that progesterone naturally facilitates sleep onset and maintenance. As progesterone levels decline during menopause, the loss of its sedative influence likely contributes to symptoms of insomnia and non-restorative sleep. Melatonin is another important hormone that regulates the body's internal clock and prepares the brain for sleep. During the menopausal transition, perimenopause, melatonin production starts to decline, especially at night, resulting in delayed sleep onset, reduced sleep depth, and more frequent awakenings throughout the night.[7] the combined decline of estrogen, progesterone, and melatonin during menopause creates an environment that disrupts circadian rhythm alignment and weakens sleep quality. Low-dose melatonin supplementation (0.3-1 mg) may help improve sleep timing and quality without notable adverse effects.[7] While melatonin is not a cure-

all, its role in synchronizing circadian rhythms and supporting sleep patterns suggests it could be a valuable tool for menopausal women experiencing sleep difficulties. Understanding how hormonal shifts affect the body during menopause helps clarify why sleep disturbances and fatigue are common during this stage of life.

Poor sleep quality among menopausal women can worsen quality of life by increasing the risk of physical and emotional impairment. In addition, negative associations with physical health have been reported, such as an increased risk of heart disease, hypertension, and carotid atherosclerosis. Longitudinal data demonstrates that midlife women experiencing chronic sleep disturbances during the menopause transition may be at greater risk for cardiovascular disease. Findings from the Study of Women's Health Across the Nation (SWAN) revealed that shorter sleep duration and poorer subjective sleep quality were associated with increased carotid intima-media thickness and greater plaque buildup, which are early indicators of atherosclerosis, even after accounting for factors such as hot flashes, estradiol levels, and other cardiovascular risk factors.[8] Additional evidence connects short sleep duration and poor sleep efficiency to elevated blood pressure and a greater likelihood of developing hypertension. According to research by Maas and Franke (2009), the years surrounding menopause are associated with a sharp rise in blood pressure and a higher prevalence of hypertension, partly due to hormonal changes that also influence sleep quality. Poor sleep can elevate sympathetic nervous system activity, making it more difficult for the body to regulate blood pressure. As hypertension is one of the most critical cardiovascular risk factors after menopause, addressing sleep problems during this period is crucial for protecting long-term heart health.[9]

Postmenopausal women are also at increased risk for OSA and sleep-onset insomnia disorder compared with premenopausal and perimenopausal women. Studies show that between 47% and 67% of postmenopausal women may develop OSA, which is higher than rates observed in premenopausal women.[10] Progesterone normally supports breathing by stimulating airway muscles and enhancing the tone of muscles such as the genioglossus, which helps reduce the risk of airway collapse. Estrogen supports this effect by contributing to neuromuscular control of the airway. As women transition through menopause, declining levels of both hormones weaken these protective mechanisms. This hormonal shift increases upper airway resistance, contributing to the higher prevalence of OSA in postmenopausal women.[11]

Treatment

Both pharmacological and non-pharmacological approaches have shown effectiveness in addressing sleep disturbances in this population. However, prior to implementing any of those strategies, the basics of sleep hygiene must be considered. Those going through the menopause transition should aim to maintain a consistent bedtime routine. The bedroom should be reserved solely for sleep and intimacy. Additionally, substances that can negatively impact sleep, such as alcohol, caffeine, or cannabis, should be limited, and if consumed, done so well in advance of bedtime. Screen time should cease one hour prior to going to bed as the blue light emitted from smartphones and other devices activates the brain and interferes with the body's ability to release melatonin. A sleep routine that includes progressive muscle relaxation, body scans, or mindfulness meditation can also improve the ability to fall asleep and improve overall sleep quality.

Non-pharmacological approaches for sleep disturbances include exercise, cognitive behavioural therapy (CBT), sleep restriction therapy (SRT), stimulus control therapy, and mindfulness or relaxation therapy. Cognitive behavioural therapy for insomnia (CBT-I) typically combines several psychotherapeutic techniques and behavioural interventions. It may incorporate SRT, stimulus control therapy, sleep hygiene, and relaxation therapy.[12] These approaches are purported to work by altering dysfunctional beliefs about sleep, providing education, reducing maladaptive behaviours that contribute to sleep issues, and attenuating both cognitive and autonomic arousal levels. The current clinical practice guidelines from the American College of Physicians recommend CBT-I as the first-line treatment for adults with chronic insomnia.[13] Despite this, qualitative studies show that practitioners still tend to rely on pharmacological interventions. This is reflected in the 30-fold increase in prescriptions for non-benzodiazepine sedative hypnotics (e.g., Zolpidem and Zopiclone, referred to as Z-drugs) between 1994 and 2007.[14]

Medications used for the treatment of typical menopause symptoms can also help improve

sleep quality. Both oral and transdermal hormone therapies have demonstrated effectiveness in improving sleep quality and sleep satisfaction. Transdermal hormone treatment can effectively treat sleep disturbances, reduce the number of minutes awake, and decrease the number of nighttime awakenings in perimenopausal women compared to oral hormone treatments.[15] Regular use of transdermal estradiol and progesterone during the perimenopausal and early postmenopausal period can reduce the time it takes to fall asleep and decrease the frequency of nighttime awakenings.

Although pharmacological interventions such as hormone therapy and hypnotics have shown some effectiveness in treating menopause-related sleep disruption and chronic insomnia, some women are hesitant because of potential adverse effects. Furthermore, some women are unable to use these medications because of contraindications, interactions with other medications, and increased risk of falls. A newer class of medications, known as dual orexin receptor antagonists (DORAs), offers a promising alternative which can mitigate some of these risks. Unlike traditional GABA sedatives (i.e., benzodiazepines and Z-drugs) which focus on sleep-promoting systems, DORAs work by targeting wake-promoting systems. This is a novel approach for treating insomnia and sleep disturbances, as it focuses on reducing the drive to stay awake, rather than increasing the drive to sleep. DORAs can impact wakefulness by antagonizing the orexin receptors 1 and 2 (OXR1 and OXR2), preventing activation by orexin neuropeptides and thereby decrease the wake drive, and in turn, allow sleep to occur. With their distinct mechanisms of action and shorter terminal half-lives, the safety profile of the DORAs is better in terms of reduced fall risk and improved safety for driving.

Not all postmenopausal women want to employ pharmacotherapy. For these women, high doses of valerian root can lead to improved sleep quality.[16] Another less commonly used herbal supplement is black cohosh, which has been shown to improve both subjective sleep quality and objective measures such as sleep efficiency and awakenings after sleep onset. However, it must be noted that safety data on black cohosh remains limited, so caution is necessary when considering its use.[17]

Lastly, physical activity and exercise should be considered as they have been shown to improve sleep in both perimenopausal and postmenopausal women. These benefits are thought to occur through several mechanisms, including reduced depression and anxiety, improved thermoregulation, elevation of cytokines, optimized neurochemistry, and improved circadian rhythm regulation. A wide range of physical activities can improve sleep. Practices such as yoga, low and moderate intensity exercise, Pilates, walking, and strength training have all been shown to improve sleep outcomes.

Conclusion

Sleep disturbances are common during the menopause transition, often caused by hormonal changes, shifts in circadian rhythms, and other medical or emotional factors. These sleep challenges can affect nearly every part of a woman's health, from mood and memory to heart and metabolic function. Understanding what drives these disruptions is an essential step in offering meaningful support. While some women benefit from medications or hormone therapy, many also find relief through changes in daily habits, stress management, and sleep routines. There is no one-size-fits-all solution but recognizing sleep as a core part of menopause care is essential. Prioritizing sleep health can lead to meaningful improvements in comfort, wellbeing, and overall quality of life.

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