Bone health in women with premature ovarian insufficiency

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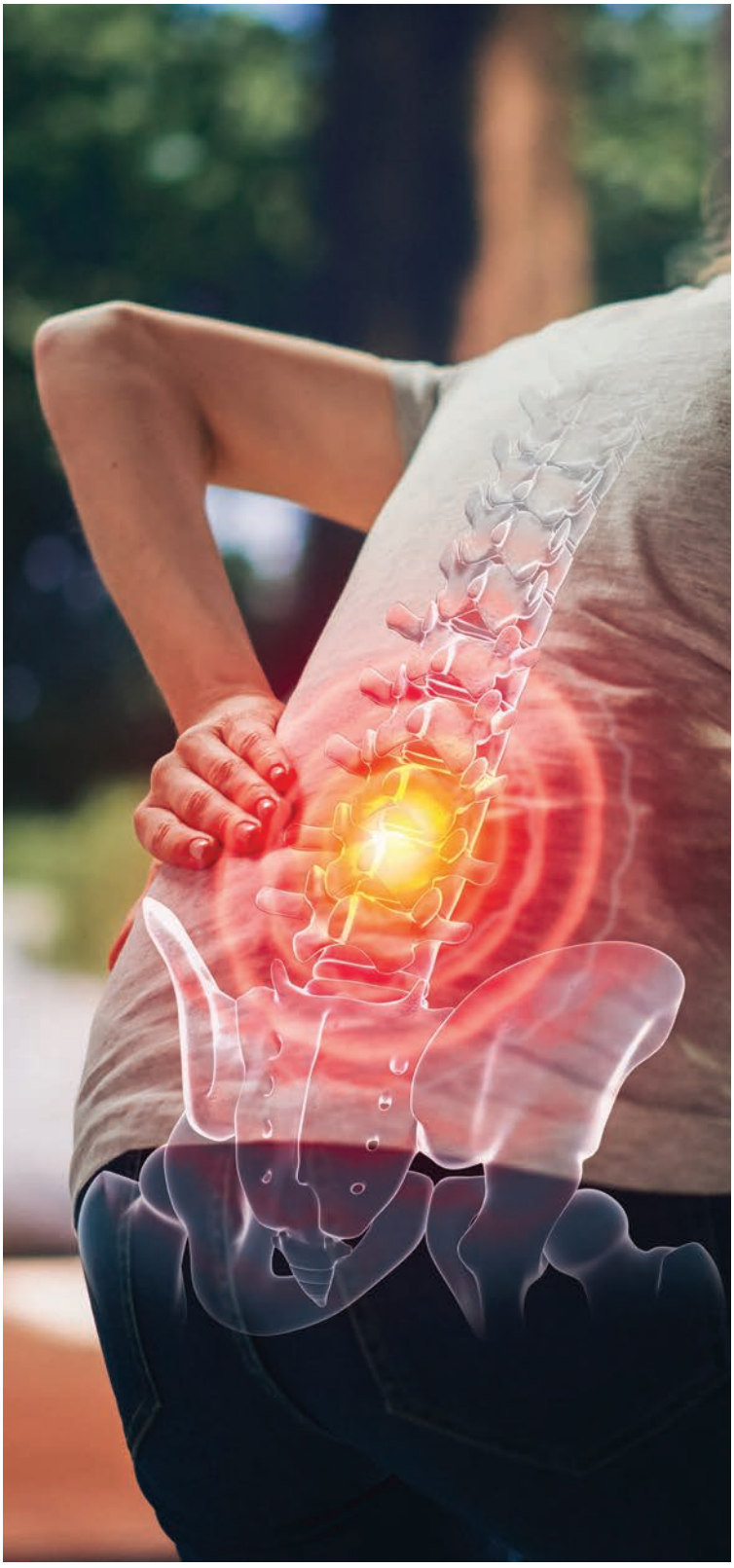
Women with premature ovarian insufficiency (POI) have poor bone health and increased susceptibility to fractures due to a combination of oestrogen deficiency and the presence of POI-associated risk factors. Thorough evaluation and management of bone health are necessary to achieve better skeletal outcomes in these women.

Premature ovarian insufficiency (POI) is the loss of ovarian function before 40 years of age, typically presenting with primary or secondary amenorrhoea or infertility. It is diagnosed by an elevated follicle-stimulating hormone (FSH) level in the menopausal range on two occasions at least four to six weeks apart in a woman under 40 years of age, after more than four months of amenorrhoea or menstrual irregularity. The International Menopause Society guidelines suggest using an FSH level of above 40 IU/L to define the menopausal range, whereas recent guidelines from the European Society of Human Reproduction and Embryology recommend an FSH level above 25 IU/L.[1,2] POI affects 3 to 4% of women worldwide and can be broadly classified into spontaneous and iatrogenic categories (Box 1).[3,4]

Women with POI experience multiple physical and psychological



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consequences, including reproductive manifestations, compromised musculoskeletal health, increased cardiometabolic risk and neurocognitive decline. Importantly, bone loss is the most feared complication in women with POI.[5] The reported prevalence of osteoporosis in women with POI is between 8 and 15%, and fracture risk is increased up to 1.5 times compared with age-matched pre-menopausal women.[6-9] This article focuses on the assessment and management of bone health in women with POI.

Key points

- **Comprehensive screening and evaluation of bone health should be performed at the diagnosis of premature ovarian insufficiency (POI).**
- **Multiple mechanisms contribute to skeletal fragility in women with POI. These include oestrogen deficiency, compromised muscle health and presence of POI-associated risk factors.**
- **Management of bone health requires a multimodal approach, including provision of information, nonpharmacological interventions and use of hormone replacement therapy (HRT) (in the absence of contraindications).**
- **HRT with oestrogen (and progestogen in women with an intact uterus) should be initiated at the diagnosis of POI unless contraindicated (e.g. in women with hormone-sensitive cancers) and continued until the average age of menopause to maximise bone health, alleviate menopausal symptoms and prevent long-term sequelae, such as cardiovascular disease and cognitive impairment.**
- **Women with POI should be referred to a specialist if they require pubertal induction, HRT is contraindicated or they have a history of thrombophilia.**

Diagnosis of osteoporosis

Osteoporosis is characterised by low bone mass or impaired bone quality, leading to an increased risk of fracture. It is routinely diagnosed using dual-energy x-ray absorptiometry (DXA)-derived measures of bone mineral density (BMD) in postmenopausal women and men aged over 50 years. Osteoporosis is diagnosed by a BMD that is 2.5 standard deviations or more below that of a young adult population (T-score ≤–2.5), and osteopenia is defined by a T-score between –2.5 and –1.0.

In younger adults, ambiguity exists regarding the definition of osteoporosis based on BMD. According to the International Society of Clinical Densitometry, low bone mass in premenopausal women is defined by an age- and sex- matched BMD Z-score of less than –2.0.[10] Other expert groups recommend using a BMD T-score of –2.5 or less to diagnose osteoporosis in women under 50 years of age with chronic disorders known to affect bone metabolism, such as POI.[11]

Risk factors for osteoporosis in women with POI

Oestrogen plays a crucial role in defining overall bone structure directly by affecting differentiation, proliferation and activities of various bone cells (Figure 1) and indirectly through its effects on muscle health, leading to an overall increase in bone formation and suppression of bone resorption.[12] Women with POI have compromised muscle structure and function because of oestrogen deficiency and factors specific to the underlying cause of POI (such as radiotherapy, glucocorticoid use, nutritional deficiencies),

1. Causes and associations of premature ovarian insufficiency (POI)

Spontaneous POI

- Idiopathic – most common cause of spontaneous POI
- Genetic causes (10% of cases of POI)
  - Turner syndrome (45X0): most common genetic cause
  - fragile X pre-mutation *(FMR1)*
  - other: *FOXL2, NR5A1, BMP15, FSHR, Gs alpha* genes
- Autoimmune association (20% of cases of POI)
  - Addison's disease
  - autoimmune polyendocrine syndromes 1 and 2
  - autoimmune hypothyroidism
  - other autoimmune conditions: coeliac disease, type 1 diabetes mellitus, myasthenia gravis, systemic lupus erythematosus, thrombocytopenic purpura, vitiligo, alopecia, pernicious anaemia, rheumatoid arthritis, Crohn's disease, Sjögren's syndrome, primary biliary cirrhosis
- Inborn error of metabolism (rare causes of POI)
  - galactosaemia
- Infectious causes
  - mumps oophoritis
  - associated infectious conditions: HIV infection, tuberculosis, malaria, shigellosis, herpes zoster, cytomegalovirus
- Environmental associations
  - smoking: associated with earlier onset of menopause

Iatrogenic POI

- Chemotherapy – particularly use of alkylating agents and dependent on cumulative dose
- Radiotherapy – dependent on cumulative dose and field of exposure
- Bilateral oophorectomy
- Other pelvic surgery has been associated with early age of menopause or reduced ovarian reserve
  - single oophorectomy, hysterectomy, uterine artery emolisation, bilateral ovarian surgery for cysts or endometriosis

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causing defective muscle-bone interaction and mechanical loading leading to bone loss.[12,13] Additionally, oestrogen is crucial in bone mass accrual during pubertal development, and hence bone loss can be more pronounced in women with an early age of POI onset (puberty or adolescence) because of insufficient peak bone mass accrual. In adult women with POI, premature bone loss caused by accelerated bone resorption may be the primary mechanism for low BMD.

Moreover, autoimmune conditions commonly associated with POI, such as coeliac disease, inflammatory bowel disease, Addison's disease, type 1 diabetes mellitus and thyroid disorders, as well as chemotherapy- and radiotherapy-associated toxic effects on bone, can have additional detrimental effects on skeletal health (Figure 2).

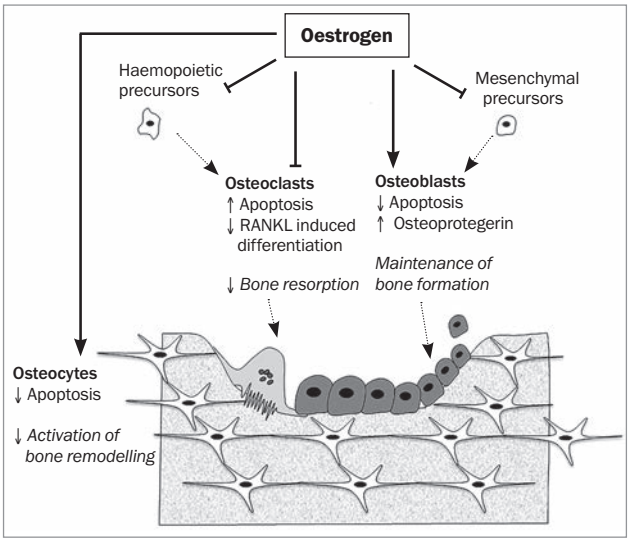

Figure 1. The effects of oestrogen on bone cells. Oestrogen protects against bone loss by restraining the rate of bone remodelling by inhibiting birth and differentiation of osteoclast and osteoblast progenitors, and by promoting maintenance of bone formation through its proapoptotic effect on osteoclasts and antiapoptotic effect on osteoblasts and osteocytes. Arrowheads = stimulatory effects; bars = inhibitory effects.

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In summary, hypoestrogenism is the major risk factor for low bone mass and susceptibility to fractures in women with POI because of decreased bone accrual, failure to attain peak bone mass as well as increased bone loss, leading to an overall decline in bone health. However, other POI-associated risk factors and traditional osteoporosis risk factors may also contribute to bone loss.

Assessment of bone health

Bone health should be assessed at the diagnosis of POI and then monitored during follow up. A detailed clinical assessment is required, followed by investigations such as dual-energy x-ray absorptiometry (DXA) and blood and urine biochemistry (Flowchart).[14] Fracture risk assessment tools, such as FRAX that helps determine an individual's 10-year probability of hip or other major osteoporotic fracture (lumbar spine, humerus or wrist), are not validated for use in women under 40 years of age.

History and examination

Detailed clinical history taking and physical examination should be performed in women with POI, taking into consideration POI-associated risk factors for low bone density, as well as traditional risk factors for osteoporosis (see Flowchart).

Pathology tests

Bone-specific pathology tests, including serum biochemistry tests, measurement of calcium, phosphate and 25-hydroxyvitamin D

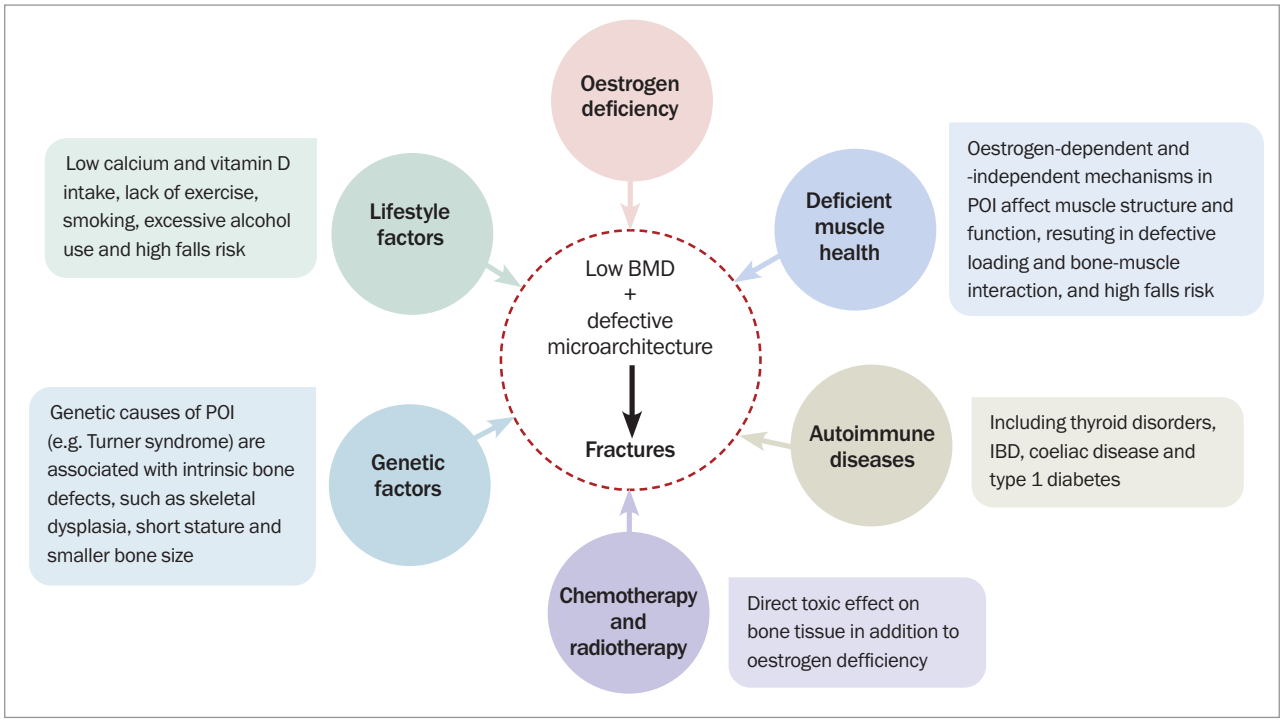

Figure 2. Mechanisms of skeletal fragility in premature ovarian insufficiency (POI).
Abbreviations: BMD = bone mineral density; IBD = inflammatory bowel disease.

levels, and liver and renal function tests, should be performed at the initial assessment of women with POI. If there is evidence of a low bone density or history of fractures, consider further biochemical evaluation for other secondary causes of osteoporosis in young adults, such as hyperparathyroidism, coeliac disease and thyroid disorders (Flowchart). Measurement of bone turnover markers, such as C-terminal telopeptide of type 1 collagen and procollagen type I N-propeptide, may be useful in monitoring drug response and adherence to osteoporosis therapies.

Imaging

DXA-derived BMD remains the gold standard for assessing skeletal strength and is widely available, noninvasive and inexpensive. An initial DXA scan is indicated at the initial diagnosis of POI and, if osteoporosis or low bone mass is diagnosed, a repeat DXA scan at two to five years should be considered.

Although DXA-derived BMD strongly correlates with the risk of fracture in older populations, it has limitations in younger women with POI. In women with short stature, delayed bone age or smaller bone size, such as Turner syndrome (the most common genetic cause of POI), DXA underestimates BMD. Moreover, BMD only partly explains skeletal fragility, as a substantial proportion of patients experience fracture despite a normal BMD. Compromised bone microarchitecture can lead to skeletal fragility but is not assessed by routine DXA scans.

Advanced techniques to assess bone strength, geometry and microarchitecture, such as trabecular bone score, advanced hip analysis, peripheral quantitative CT, high-resolution peripheral quantitative CT and quantitative ultrasound, are currently being investigated. A recent study found that a low trabecular bone score was more common in women with POI than in healthy premenopausal women.[15] These emerging techniques may be useful adjunctive tools in the assessment of fracture risk; however, they require further validation, and DXA remains the gold standard imaging tool for investigating osteoporosis.

In case of any bony tenderness or back pain, further evaluation with spinal x-rays to exclude fractures should be performed.

Management

Management of bone health encompasses nonpharmacological measures, pharmacological interventions and treatment of comorbidities that may affect bone health (Flowchart).[14,16] However, a formal appraisal of guidelines for bone health showed variable quality and recommendations and a variable consensus on the optimal hormone replacement therapy (HRT) regimen and DXA screening and monitoring.[14] Providing information to women is an integral part of management (Box 2); lack of knowledge on bone health is associated with suboptimal health-related behaviours.[17]

Nonpharmacological measures

Routine lifestyle measures to maintain adequate nutrition, a healthy body mass index, calcium intake and vitamin D status and

MANAGEMENT ALGORITHM FOR BONE HEALTH IN WOMEN WITH PREMATURE OVARIAN INSUFFICIENCY (POI)[14]

Woman is diagnosed with POI

Initial bone health evaluation
History and examination

Potential risk factors for low BMD in women with POI
- Primary amenorrhoea
- Longer duration of POI
- >1 year delay in diagnosis
- Age <20 years at onset of irregular menses
- Childhood cancer survivors with hypogonadism and:
  - hypothyroidism and growth hormone deficiency
  - previous treatment with chemotherapy, glucocorticoids (higher cumulative dose)
  - cranial irradiation
  - Caucasian ethnicity

General risk factors for low BMD*

Nonmodifiable
- Age
- Prior fragility fracture
- Family history of osteoporosis
- Parental history of fracture

Modifiable and lifestyle
- Height loss >3 cm
- Multiple falls
- Low physical activity or immobility
- Low body weight (body mass index <18 kg/m^2)
- Low muscle mass and strength
- Poor balance
- Vitamin D insufficiency
- Protein or calcium undernutrition
- Smoking
- Alcohol >2 standard drinks/day

Diseases associated with low BMD ± POI
- Rheumatoid arthritis
- Hyperthyroidism
- Hyperparathyroidism
- Chronic kidney disease
- Coeliac disease or malabsorption
- Diabetes mellitus
- Myeloma or MGUS
- Bone marrow/organ transplant
- HIV infection
- Depression

Medications associated with low BMD
- Glucocorticoids
- Excess thyroid hormone replacement
- Aromatase inhibitors

Pathology and imaging

Blood and urine tests
- Measurement of UEC, CMP, TSH and 25-hydroxyvitamin D levels and LFTs
- Bone turnover markers: not currently recommended for routine use
- If reduced bone mass is present, also consider the following: measurement of serum PTH levels, coeliac serology, serum electrophoresis and measurement of 24-hour urine calcium excretion

Imaging
- DXA: indicated at initial diagnosis for all women with POI. A Z-score <–2 defines low bone mass and T-scores ≤–2.5 may be used to define osteoporosis[2,11]
- Plain imaging: lateral radiographs of lumbar and thoracic spine or DXA-based vertebral fracture assessment should be considered on an individual basis particularly if there are concerns about height loss, back pain, chronic diseases associated with low BMD and current or past glucocorticoid use

Management

Maintain healthy lifestyle
- Weight-bearing exercise
- Avoidance of smoking
- Maintenance of normal body weight
- Balanced diet containing the recommended intake of calcium and vitamin D – dietary supplements may be required if inadequate intake
- Avoid excess alcohol

Hormone replacement therapy
- Offer oestrogen replacement therapy to all women diagnosed with POI unless contraindicated
- Both HRT and COCP are appropriate but COCP has less favourable effects on bone protection. HRT containing 17 beta-oestradiol, also known as estradiol, is preferred for oestrogen replacement
- Give combined treatment with progesterone to women with intact uterus.
- Consider patient preference for route and method of administration as well as contraceptive needs
- Continue HRT until at least the time of anticipated natural menopause (about 50 years of age), then reassess

Antiresorptive therapy
- Other pharmacological treatments, including bisphosphonates, should only be considered with advice from an osteoporosis specialist

Education
- Provision of information

Ongoing monitoring

Subsequent assessment of bone health
- If BMD is normal and adequate systemic oestrogen replacement is commenced, the value of repeated DXA scan is low
- If a diagnosis of low bone mass is made and oestrogen replacement or other therapy initiated, repeat DXA in 2 to 5 years

Specialist referral
- A decrease in BMD on subsequent scans (bone loss >5% or >0.05 g/cm^2) should prompt review of oestrogen replacement therapy and other potential factors. Review by an osteoporosis specialist may be appropriate
- Development of a fragility fracture should prompt referral of the patient to an osteoporosis specialist

Abbreviations: BMD = bone mineral density; CMP = calcium, magnesium, phosphate; COCP = combined oral contraceptive pill; DXA = dual-energy x-ray absorptiometry; FRAX = fracture risk assessment tool; HRT = hormone replacement therapy; LFT = liver function tests; MGUS = monoclonal gammopathy of undetermined significance; PTH = parathyroid hormone; TSH = thyroid stimulating hormone; UEC = urea, electrolytes, creatinine.

* FRAX risk calculator is not validated for use in women <40 years.

Modified from: Kiriakova V, Somarajah G, Milat F, et al. Maturitas 2019; 128: 70-80.[14]

high-intensity progressive resistance training should be adopted to optimise bone health. Women should be counselled on smoking cessation and avoiding excess alcohol. Furthermore, coexisting causes of secondary osteoporosis should be diagnosed and appropriately managed as ongoing disease activity contributes to ongoing bone loss or inadequate treatment responses.[18]

Pharmacological interventions

HRT with oestrogen (with added progestogen in women with an intact uterus) should be initiated at the time of POI diagnosis unless contraindicated (e.g. in women with hormone-sensitive cancers) and continued until the average age of menopause.[2] This not only improves skeletal outcomes but also helps alleviate menopausal symptoms, prevents long-term sequelae, such as cardiovascular disease and cognitive impairment, and is required for pubertal induction.[19]

The use of HRT has been shown to maintain or increase lumbar spine, femoral neck and hip BMD compared with placebo; however, the optimal dose and formulation is still debated.[20] A recent observational study showed an increase in spine BMD in women with POI taking continuous combined oral contraceptive pills (COCPs) or high-dose HRT; the BMD response in the low-dose HRT or no therapy groups were inferior to the former two groups in the study.[21] These findings were corroborated in a systematic review and suggest that continuous COCP or HRT containing at least 2 mg oral estradiol are required for bone health, whereas low-dose HRT, cyclical COCPs or no treatment are associated with unfavourable bone outcomes.[22] Additionally, the cause of POI also impacts BMD response to HRT. Bisphosphonate therapy is more effective than HRT for women with iatrogenic POI following allogeneic stem cell transplantation.[23]

Nevertheless, when selecting HRT, an individual's preference should be considered to ensure compliance, as nonadherence to HRT can compromise bone health. Transdermal HRT is preferred in women with risk factors for venous thromboembolism or stroke, as oral HRT preparations have a higher risk of hypercoagulability than transdermal preparations because of hepatic first-pass effects, which cause altered production of hepatic coagulation proteins.[24] Continuous COCP may be noninferior to traditional HRT regimens and may be preferred by women with POI, as this provides a more 'peer similar' and socially acceptable option.

Spontaneous ovulation and conception can occur in 5% of women with POI;[25] therefore, appropriate contraceptive options should be discussed with women not desiring pregnancy. Transdermal oestrogen combined with the levonorgestrel intrauterine device is a useful regimen providing contraception, symptom management and prevention of long-term sequelae of hypoestrogenism. Continuous or long cycles of COCP can be prescribed to prevent periods of symptomatic oestrogen deprivation. Women considering pregnancy should be informed regarding possible bone loss during pregnancy and breastfeeding, and the importance of maintaining healthy nutrition and exercise.

2. Online resources on premature ovarian insufficiency

Resources for clinicians

- **Spontaneous premature ovarian insufficiency**
  www.menopause.org.au/hp/information-sheets/spontaneous-premature-ovarian-insufficiency
- **Early menopause due to chemotherapy and radiotherapy**
  www.menopause.org.au/hp/information-sheets/early-menopause-due-to-chemotherapy-radiotherapy
- **Premature ovarian insufficiency: an International Menopause Society White Paper**
  www.imsociety.org/statements/position-papers-and-consensus-statements/

Resource for consumers

- **Ask Early Menopause**
  www.askearlymenopause.org and a free App 'AskEarlyMenopause' that includes bone health information

Specialist management is recommended for women with POI who require pubertal induction, in whom HRT is contraindicated or who have a history of thrombophilia. Additionally, the use of HRT is controversial in women with iatrogenic POI in the context of risk-reducing bilateral salpingo-oophorectomy for *BRCA1* mutation and in the absence of breast cancer. Limited data suggest that oestrogen-only HRT does not increase the risk of breast cancer.[26,27] Women with low bone mass, osteoporosis or evidence of significant declines in bone mass on serial DXA scans should be referred to an osteoporosis specialist for consideration of other osteoporosis-specific pharmacological therapies such as bisphosphonates. Limited literature exists on the clinical use of denosumab, raloxifene and tibolone in this group of women, whereas anabolic agents such as romosozumab and teriparatide have not been trialled in women with POI. Teriparatide has been shown to be efficacious in young premenopausal women with idiopathic osteoporosis, medication-induced amenorrhoea, anorexia nervosa, pregnancy, lactation-associated osteoporosis and glucocorticoid-induced osteoporosis, and may prove useful in women with POI.[28-32]

The desire for future pregnancy must be considered in women in whom osteoporosis-specific treatment is indicated. Although the chance of spontaneous pregnancy in women with POI is low, many will achieve pregnancy with a donor egg and, thus, the potential impact of bone-specific therapies needs to be recognised. Safety data in humans for bisphosphonates are limited, and nonexistent for teriparatide and denosumab. Bisphosphonates accumulate in the maternal skeleton, cross the placenta, accumulate in the fetal skeleton and cause toxic effects in pregnant rats, hence should be used with caution in women planning pregnancy.[33-35] An oral bisphosphonate such as risedronate may be preferable over an intravenous bisphosphonate or alendronate due to its

3. A case of spontaneous premature ovarian insufficiency

Case scenario

Natalie is a 19-year-old woman who was diagnosed with spontaneous premature ovarian insufficiency (POI) at 17 years of age, in the context of delayed puberty and primary amenorrhoea. Her follicle-stimulating hormone levels were elevated on two occasions at 32.5 U/L, her oestradiol level was low at 18 pmol/L and total and free testosterone levels were normal. A POI screen showed normal karyotype, negative FMR mutation testing, negative coeliac serology and adrenal antibody screen, and normal renal, liver and thyroid function. Her initial dual energy x-ray absorptiometry (DXA) scan showed a lumbar spine and hip bone mineral density (BMD) Z-scores of –2.4 and +0.6, respectively, consistent with low bone mass at the spine.

Management

She was referred to an endocrine specialist for pubertal induction. As recommended, she was initially started on low-dose oestrogen to mimic natural puberty and avoid potential side effects (e.g. nausea, mastalgia) with a higher oestrogen dose. The oestrogen dose was gradually increased to 2 mg daily to ensure adequate breast and uterine development and optimal bone mass accrual. Cyclical norethisterone was added two years later. After two years of combined cyclical hormone replacement therapy, her BMD improved 6.3% at the spine with a Z-score of –2.0 and her hip BMD remained stable.

The timely initiation of hormone replacement therapy in this case facilitated the late peak bone mass accrual, as reflected in the improvement in BMD.

4. A case of iatrogenic premature ovarian insufficiency

Case scenario

Kathleen is a 33-year-old woman who had iatrogenic premature ovarian insufficiency (POI) in the setting of hormone-sensitive breast cancer treated with wide local excision, radiotherapy, chemotherapy and endocrine therapy with exemestane and goserelin. She had minimal vasomotor symptoms; however, the initial dual-energy x-ray absorptiometry (DXA) scan showed spine bone mineral density (BMD) T-score and Z-score of –1.7 and –1.2, respectively. Left hip BMD T-score and Z-score were –0.3 and +0.2, respectively.

Initial laboratory investigations showed elevated bone turnover activity (alkaline phosphatase level 178 U/L) and normal 25-hydroxyvitamin D (84 nmol/L), calcium and phosphate levels. Urine biochemistry testing showed mild hypercalciuria at 9.28 mmol/day.

Management

Hormone replacement therapy (HRT) was contraindicated in the setting of hormone-sensitive malignancy. She was started on hydrochlorothiazide to minimise hypercalciuria, and advised to optimise dietary calcium and vitamin D levels and engage in regular exercise. However, a DXA scan 12 months later showed significant reduction in spine BMD of 7.3%, with a T-score and Z-score of –2.6 and 2.1, respectively.

Because of bone loss in the context of ovarian suppression therapy (aromatase inhibitor), she was started on zoledronic acid infusions under the care of her endocrinologist. Repeat DXA showed a 7.7% improvement in spine BMD and stable left hip BMD.

Screening and treatment of modifiable risk factors, in conjunction with close bone health monitoring and prompt initiation of antiresorptive treatment, are necessary for women with POI and contraindications to HRT to prevent adverse skeletal outcomes.

Aromatase inhibitors are perilous for bone health in premenopausal women and their use results in significant BMD loss and deterioration of cortical and trabecular microstructure.[36] Specific osteoporosis guidelines are available and specialist input is recommended for women receiving aromatase inhibitors.[37]

shorter half-life in women with osteoporosis and high fracture risk who are intending pregnancy. However, it is recommended to withdraw bisphosphonate therapy for at least 12 months before pregnancy/conception.[24] Specialist review by a physician with expertise in osteoporosis is recommended for these women. Denosumab and teriparatide are not recommended for use in pregnant women, as adverse events have been observed in animal studies.

A management algorithm for bone health in women with POI is outlined in the Flowchart. The case studies discuss specific management of bone health in women with POI (Box 3 and Box 4).[36,37]

Conclusion

Poor bone health is common in women with POI, with loss of oestrogen a major risk factor for fragility, fractures, morbidity and mortality. Management to prevent premature and accelerated bone loss involves careful evaluation, optimisation of risk factors, regular surveillance of bone health, timely initiation of HRT (if not contraindicated) or antiresorptive drugs and provision of information. Future studies are needed to evaluate modern diagnostic techniques for assessment of bone health and determine the optimal HRT regimen to preserve bone health. ET

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A list of references is included in the online version of this article (www.endocrinologytoday.com.au).

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