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# PREMATURE OVARIAN INSUFFICIENCY AFTER BILATERAL OOPHORECTOMY: LONG-TERM SKELETAL OUTCOMES AND FRACTURE RISK

# INSUFICIÊNCIA OVARIANA PREMATURA APÓS OOFORECTOMIA BILATERAL: DESFECHOS ESQUELÉTICOS DE LONGO PRAZO E RISCO DE FRATURAS

# INSUFICIENCIA OVÁRICA PREMATURA DESPUÉS DE OOFORECTOMÍA BILATERAL: RESULTADOS ESQUELÉTICOS A LARGO PLAZO Y RIESGO DE FRACTURAS

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## ABSTRACT

Introduction: Bilateral oophorectomy performed before natural menopause causes an abrupt and permanent reduction in ovarian sex-steroid production. When performed before 40 years of age, it constitutes iatrogenic premature ovarian insufficiency; procedures performed between 40 and 44 years are more accurately classified as early surgical menopause. Estrogen deprivation accelerates bone remodeling, decreases bone mineral density, and may increase lifetime fracture risk. Objective: To evaluate short- and long-term skeletal outcomes after premenopausal bilateral oophorectomy, with emphasis on bone mineral density, bone strength, osteoporosis, fracture risk, and the modifying effect of hormone therapy. Methods: A structured integrative review was conducted using PubMed/MEDLINE and supplementary citation tracking for studies available through August 2026. Cohort studies, controlled longitudinal studies, systematic reviews, meta-analyses, and clinical guidelines evaluating skeletal outcomes after bilateral oophorectomy or risk-reducing salpingo-oophorectomy were considered. Evidence from spontaneous premature ovarian insufficiency was used only as contextual support. Owing to heterogeneity in surgical indications, age, hormone therapy exposure, outcomes, and follow-up duration, findings were synthesized narratively. Results: Prospective cohorts consistently demonstrated accelerated bone loss during the first two to three years after surgery. Lumbar spine bone mineral density generally declined by approximately 3% to 6%, with clinically relevant losses also occurring at the hip and femoral neck. Hormone therapy reduced but did not always eliminate this decline. A nationwide cohort found lower lumbar spine and femoral neck age-adjusted bone density more than 18 years after premenopausal risk-reducing surgery. Fracture results were less consistent. A Danish

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cohort found no statistically significant increase after surgery before age 51, whereas a United States cohort reported higher odds of fractures after oophorectomy before age 46. A recent meta-analysis estimated a modest increase in fracture risk after bilateral oophorectomy compared with ovarian conservation. Conclusion: Accelerated bone loss after premenopausal bilateral oophorectomy is well supported, particularly at the lumbar spine. The magnitude of the long-term fracture risk remains less certain but appears to depend on age at surgery, duration of estrogen deprivation, hormone therapy exposure, cancer treatment, and conventional skeletal risk factors. Early hormone replacement when not contraindicated, baseline bone-density assessment, individualized surveillance, and long-term prevention strategies are essential.

**Keywords:** Premature Ovarian Insufficiency. Oophorectomy. Surgical Menopause. Bone Mineral Density. Osteoporosis. Fractures.

**RESUMO**

Introdução: A ooforectomia bilateral realizada antes da menopausa natural causa uma redução abrupta e permanente na produção de esteroides sexuais ovarianos. Quando realizada antes dos 40 anos de idade, constitui insuficiência ovariana prematura iatrogênica; procedimentos realizados entre 40 e 44 anos são mais precisamente classificados como menopausa cirúrgica precoce. A privação estrogênica acelera a remodelação óssea, diminui a densidade mineral óssea e pode aumentar o risco de fraturas ao longo da vida. Objetivo: Avaliar os resultados esqueléticos a curto e longo prazo após ooforectomia bilateral pré-menopáusica, com ênfase em densidade mineral óssea, resistência óssea, osteoporose, risco de fraturas e o efeito modificador da terapia hormonal. Métodos: Uma revisão integrativa estruturada foi conduzida usando PubMed/MEDLINE e rastreamento de citações complementar para estudos disponíveis até agosto de 2026. Foram considerados estudos de coorte, estudos longitudinais controlados, revisões sistemáticas, metanálises e diretrizes clínicas que avaliavam resultados esqueléticos após ooforectomia bilateral ou salpingo-ooforectomia redutora de risco. Evidências de insuficiência ovariana prematura espontânea foram usadas apenas como suporte contextual. Devido à heterogeneidade nas indicações cirúrgicas, idade, exposição à terapia hormonal, desfechos e duração do seguimento, os achados foram sintetizados narrativamente. Resultados: As coortes prospectivas demonstraram consistentemente perda óssea acelerada durante os primeiros dois a três anos após a cirurgia. A densidade mineral óssea da coluna lombar geralmente declined cerca de 3% a 6%, com perdas clinicamente relevantes também ocorrendo na anca e colo femoral. A terapia hormonal reduziu, mas nem sempre eliminou este declínio. Uma coorte nacional encontrou densidade óssea ajustada por idade mais baixa na coluna lombar e colo femoral mais de 18 anos após cirurgia redutora de risco pré-menopáusica. Os resultados de fraturas foram menos consistentes. Uma coorte dinamarquesa não encontrou aumento estatisticamente significativo após cirurgia antes dos 51 anos, enquanto uma coorte dos Estados Unidos relatou maiores chances de fraturas após ooforectomia antes dos 46 anos. Uma metanálise recente estimou um aumento modesto no risco de fraturas após ooforectomia bilateral comparado com conservação ovariana. Conclusão: A perda óssea acelerada após ooforectomia bilateral pré-menopáusica é bem apoiada, particularmente na coluna lombar. A magnitude do risco de fraturas a longo prazo permanece menos certa, mas parece depender da idade na cirurgia, duração da privação estrogênica, exposição à terapia hormonal, tratamento do câncer e fatores de risco esquelético convencionais. A reposição hormonal precoce quando não contraindicada, avaliação basal da densidade óssea, vigilância individualizada e estratégias de prevenção a longo prazo são essenciais.

**Palavras-chave:** Insuficiência Ovariana Prematura. Ooforectomia. Menopausa Cirúrgica. Densidade Mineral Óssea. Osteoporose. Fraturas.

**RESUMEN**

Introducción: La ooforectomía bilateral realizada antes de la menopausia natural causa una reducción abrupta y permanente en la producción de esteroides sexuales ováricos. Cuando se realiza antes de los 40 años de edad, constituye insuficiencia ovárica prematura iatrogénica; los procedimientos realizados entre los 40 y 44 años se clasifican con mayor precisión como menopausia quirúrgica precoz. La privación estrogénica acelera el remodelado óseo, disminuye la densidad mineral ósea y puede aumentar el riesgo de fractura a lo largo de la vida. Objetivo: Evaluar los resultados esqueléticos a corto y largo plazo después de la ooforectomía bilateral premenopáusica, con énfasis en la densidad mineral ósea, la resistencia ósea, la osteoporosis, el riesgo de fractura y el efecto modificador de la terapia hormonal. Métodos: Se realizó una revisión integradora estructurada utilizando PubMed/MEDLINE y rastreo de citas complementario para estudios disponibles hasta agosto de 2026. Se consideraron estudios de cohorte, estudios longitudinales controlados, revisiones sistemáticas, metanálisis y directrices clínicas que evaluaban resultados esqueléticos después de ooforectomía bilateral u ooforectomía salpingo-reductora de riesgo. La evidencia de insuficiencia ovárica prematura espontánea se utilizó únicamente como apoyo contextual. Debido a la heterogeneidad en las indicaciones quirúrgicas, la edad, la exposición a la terapia hormonal, los resultados y la duración del seguimiento, los hallazgos se sintetizaron narrativamente. Resultados: Las cohortes prospectivas demostraron consistentemente pérdida ósea acelerada durante los primeros dos a tres años después de la cirugía. La densidad mineral ósea de la columna lumbar generalmente disminuyó aproximadamente un 3% a 6%, con pérdidas clínicamente relevantes también ocurriendo en la cadera y el cuello femoral. La terapia hormonal redujo pero no siempre eliminó esta disminución. Una cohorte nacional encontró una densidad ósea ajustada por edad más baja en la columna lumbar y el cuello femoral más de 18 años después de la cirugía reductora de riesgo premenopáusica. Los resultados de fractura fueron menos consistentes. Una cohorte danesa no encontró un aumento estadísticamente significativo después de la cirugía antes de los 51 años, mientras que una cohorte de Estados Unidos reportó mayores probabilidades de fracturas después de ooforectomía antes de los 46 años. Un metanálisis reciente estimó un aumento modesto en el riesgo de fractura después de la ooforectomía bilateral en comparación con la conservación ovárica. Conclusión: La pérdida ósea acelerada después de la ooforectomía bilateral premenopáusica está bien establecida, particularmente en la columna lumbar. La magnitud del riesgo de fractura a largo plazo sigue siendo menos cierta pero parece depender de la edad al momento de la cirugía, la duración de la privación estrogénica, la exposición a la terapia hormonal, el tratamiento del cáncer y los factores de riesgo esquelético convencionales. La reposición hormonal temprana cuando no está contraindicada, la evaluación basal de la densidad ósea, la vigilancia individualizada y las estrategias de prevención a largo plazo son esenciales.

**Palabras clave:** Insuficiencia Ovárica Prematura. Ooforectomía. Menopausia Quirúrgica. Densidad Mineral Ósea. Osteoporosis. Fracturas.

## 1 INTRODUCTION

Premature ovarian insufficiency (POI) is defined as loss of ovarian activity before 40 years of age and is characterized by menstrual disturbance, reduced estrogen production, and elevated gonadotropin concentrations. Menopause occurring between 40 and 44 years is generally classified as early menopause. Bilateral oophorectomy (BO) before these age thresholds produces an immediate and permanent iatrogenic form of ovarian insufficiency, unlike spontaneous POI, in which intermittent ovarian activity may occasionally persist. The broader term premenopausal bilateral oophorectomy (PBO) includes procedures performed before natural menopause, even when surgery occurs after 40 years of age.[1]

The abrupt hormonal transition produced by surgery differs biologically from natural menopause. Natural menopause is preceded by a gradual reduction in ovarian function, whereas BO causes an immediate decline in circulating estrogen, progesterone, and ovarian androgens. Estrogen deficiency increases osteoclast formation and survival, promotes inflammatory signaling, and produces an imbalance in which bone resorption exceeds bone formation. Trabecular-rich structures, particularly the lumbar spine, are affected early, while prolonged estrogen deprivation contributes to cortical thinning, increased porosity, and deterioration of bone strength.[2]

BO may be performed for ovarian malignancy, severe endometriosis, benign ovarian disease, torsion, or as part of hysterectomy. Another major indication is risk-reducing salpingo-oophorectomy (RRSO) in women with pathogenic variants associated with hereditary ovarian cancer. RRSO substantially reduces ovarian and fallopian tube cancer risk in carriers of BRCA1 or BRCA2 pathogenic variants and may reduce mortality.[3] Its oncological benefit must therefore be distinguished from the long-term consequences of ovarian hormone deprivation. Skeletal risk does not ordinarily negate a compelling cancer-prevention indication, but it must be incorporated into preoperative counseling and postoperative follow-up.

An earlier systematic review identified a consistent association between surgical menopause and reduced bone mineral density (BMD), while evidence for clinical fractures remained inconclusive.[4] This difference is important because BMD is an intermediate skeletal outcome rather than a direct measure of fracture incidence. Fractures generally occur decades after the initial hormonal exposure and are influenced by aging, falls, body composition, smoking, physical activity, vitamin D status, medication use, and comorbidities.

Consequently, short prospective studies can identify rapid bone loss but cannot determine lifetime fracture risk.

Evidence from women with spontaneous POI or early menopause provides relevant context, although it cannot be considered equivalent to surgical evidence. In a 23-year Australian longitudinal cohort, women with menopause before 45 years had higher adjusted odds of osteoporosis and fractures than women with menopause at the usual age. Menopausal hormone therapy initiated before or near study entry was associated with a lower combined risk of osteoporosis and fracture.[5] However, the investigators could not distinguish surgical from spontaneous causes, and self-reported menopausal age introduced potential misclassification.

Clarification of these outcomes is clinically relevant because women undergoing early BO may live for several decades with estrogen deficiency. The present review evaluates the temporal pattern of bone loss, persistence of skeletal deficits, risk of osteoporosis and fractures, protective effect of hormone therapy, and practical implications for surveillance and prevention.

## 2 OBJECTIVES

### 2.1 PRIMARY OBJECTIVE

To evaluate the association between bilateral oophorectomy performed before natural menopause and long-term skeletal outcomes, including BMD loss, osteoporosis, and clinical fractures.

### 2.2 SECONDARY OBJECTIVES

1. To characterize the magnitude and anatomical distribution of bone loss after surgery.
2. To assess changes in bone strength, microarchitecture, and bone-turnover markers.
3. To determine whether age at surgery modifies subsequent skeletal risk.
4. To evaluate whether hormone therapy prevents or attenuates postoperative bone loss.
5. To examine the consistency of evidence relating PBO to fragility fractures.
6. To summarize recommendations for BMD assessment, surveillance, lifestyle intervention, and pharmacological prevention.

## 3 METHODOLOGY

### 3.1 STUDY DESIGN

A structured integrative literature review was undertaken. The review was designed to differentiate direct evidence from women undergoing PBO or RRSO from contextual evidence involving spontaneous POI, early natural menopause, or postmenopausal oophorectomy.

### 3.2 SEARCH STRATEGY

PubMed/MEDLINE was searched from database inception through August 31, 2026. Reference lists of eligible articles, systematic reviews, clinical guidelines, and international consensus statements were also examined. Search terms combined concepts related to “bilateral oophorectomy,” “bilateral salpingo-oophorectomy,” “risk-reducing salpingo-oophorectomy,” “surgical menopause,” “premature ovarian insufficiency,” “bone mineral density,” “osteoporosis,” “bone strength,” “bone turnover,” “fragility fracture,” and “hormone therapy.”

### 3.3 ELIGIBILITY CRITERIA

Eligible publications included adult women undergoing removal of both ovaries before natural menopause and reported at least one skeletal outcome. Outcomes of interest were lumbar spine, total hip, or femoral neck BMD; bone microarchitecture or estimated strength; bone-turnover markers; osteopenia; osteoporosis; vertebral or nonvertebral fractures; and fracture-risk estimates.

Prospective and retrospective cohorts, controlled longitudinal studies, systematic reviews, meta-analyses, and evidence-based guidelines were considered. Studies exclusively evaluating unilateral oophorectomy, animal models, isolated case reports, or postoperative outcomes without skeletal assessment were excluded. Studies of spontaneous POI were retained only when they clarified long-term risk or treatment principles.

### 3.4 DATA SYNTHESIS

Study design, sample size, menopausal status, surgical indication, comparator, follow-up, hormone exposure, skeletal measurement, and quantitative results were extracted. Effects are presented as mean percentage changes, hazard ratios (HRs), odds ratios (ORs), relative risks (RRs), and 95% confidence intervals (CIs).

A new meta-analysis was not performed because the studies differed substantially in age at surgery, oncological history, comparator definition, hormone exposure, follow-up, and fracture ascertainment. Reports derived from overlapping populations were interpreted as related evidence rather than independent confirmation.

### 3.5 EVIDENCE APPRAISAL

Methodological appraisal focused on selection bias, baseline group differences, age at surgery, confounding by indication, cancer treatment, hormone therapy exposure, adherence, outcome ascertainment, attrition, and duration of follow-up. Greater weight was given to prospective controlled studies for BMD change and to large registry-based cohorts for fracture outcomes.

## 4 RESULTS

### 4.1 CHARACTERISTICS OF THE EVIDENCE

The direct evidence was dominated by observational studies of women carrying hereditary cancer-associated pathogenic variants and undergoing RRSO. These studies provided detailed serial dual-energy X-ray absorptiometry (DXA) measurements but generally had modest samples and limited fracture follow-up. Larger population cohorts provided fracture outcomes but had less precise information regarding menopausal status, hormone formulation, dose, duration, and adherence.

The principal studies and their quantitative findings are summarized below.

**Table 1**

*Characteristics of the evidence*

| Study | Design and sample | Comparison and follow-up | Principal skeletal findings |
|---|---|---|---|
| Kotsopoulos et al., 2019[6] | Retrospective cohort of 95 BRCA1/2 carriers with preoperative and postoperative DXA; 50 were premenopausal | Mean follow-up of 22 months | In premenopausal women, annual BMD change was −3.45% at the lumbar spine (95% CI −4.61 to −2.29), −2.85% at the femoral neck (95% CI −3.79 to −1.91), and −2.24% at the total hip (95% CI −3.11 to −1.38). Hormone therapy reduced spine loss from −4.69% to −2.00%. |
| Jiang et al., 2021, What Happens After Menopause study[7] | Prospective controlled cohort: 30 women undergoing premenopausal RRSO and 42 controls | 24 months | Surgery was associated with a 4.7% decline in lumbar spine BMD and a 12.1% reduction in estimated tibial bending stiffness. Without hormone therapy, spine, hip, and femoral-neck BMD declined by 5.8%, 5.2%, and 6.0%, respectively. |
| Chan et al., 2023, Prospective Research of Outcomes after Salpingo-oophorectomy study[8] | Prospective cohort of 91 BRCA1/2 carriers: 40 RRSO and 51 ovarian-conservation controls | 12 and 36 months | At 36 months, BMD declined by 5.71% at the spine and 5.19% at the hip after RRSO. Differences from controls were −7.06% at the spine (95% CI −11.01 to −3.11) and −5.14% at the hip (95% CI −8.11 to −2.16). Hormone therapy mitigated but did not eliminate loss. |
| Hueg et al., 2023[9] | Danish Nurse Cohort: 25,853 women, including 1,938 with BO; 419 underwent surgery before age 51 | Registry follow-up through 2018 | BO before age 51 was not significantly associated with any fragility fracture: adjusted HR 1.12 (95% CI 0.91–1.39). Associations with hip, vertebral, and forearm fractures were also nonsignificant. |
| Mielke et al., 2023[10] | Long-term cohort of 514 women: 274 with PBO and 240 referents | Median of 22 years after surgery or index date | PBO before age 46 was associated with higher odds of recorded bone fractures: OR 2.86 (95% CI 1.17–6.98). The association was not significant for surgery at 46–49 years. |
| Beekman et al., 2025[11] | Nationwide cross-sectional cohort of 721 high-risk women: 493 premenopausal RRSO at ≤45 years and 228 postmenopausal RRSO at ≥54 years | Median 18.1 years after premenopausal RRSO | Premenopausal RRSO was associated with lower lumbar spine and femoral-neck Z-scores: adjusted coefficients −0.88 and −0.51, respectively. Risk of a Z-score ≤−1.0 was higher at the spine (RR 2.35; 95% CI 1.26–4.40) and femoral neck (RR 1.84; 95% CI 1.08–3.13). |
| Islam et al., 2025[12] | Systematic review of 29 studies; 19 included in meta-analyses | BO versus ovarian conservation or other surgical comparators | BO was associated with a modest increase in fractures compared with no oophorectomy: RR 1.17 (95% CI 1.03–1.33). The pooled osteoporosis estimate was RR 1.46 (95% CI 0.94–2.27). Hysterectomy with BO did not increase fracture risk compared with hysterectomy alone: RR 0.99 (95% CI 0.83–1.18). |

| Study | Design and sample | Comparison and follow-up | Principal skeletal findings |
|---|---|---|---|
| De Vincentis et al., 2026[13] | Prospective observational study of 104 women divided into RRSO without hormone therapy, RRSO with therapy, natural menopause, and fertile-control groups | Baseline assessment approximately 2.85 years after RRSO and reassessment after 18 months | Untreated RRSO was associated with a more pronounced lumbar spine BMD decline than natural menopause and a higher calculated fracture risk than fertile controls. The hormone-treated group was small but suggested attenuation of deterioration. |
| Jones et al., 2024[5] | Contextual 23-year cohort of 8,603 women; 610 had POI or early menopause | POI/early menopause versus menopause at ≥45 years | POI/early menopause was associated with osteoporosis (OR 1.37; 95% CI 1.07–1.77) and fractures (OR 1.45; 95% CI 1.15–1.81). Early hormone therapy was protective against the combined outcome (OR 0.65; 95% CI 0.45–0.96). Causes of early menopause were not separated. |

Source: Prepared by the authors.

## 4.2 EARLY POSTOPERATIVE BONE LOSS

The most consistent finding was rapid BMD loss during the first two to three years after surgery. In the Kotsopoulos cohort, premenopausal participants lost approximately 3.5% of lumbar spine BMD per year, with simultaneous reductions at the femoral neck and total hip.[6] The larger reduction at the spine is biologically plausible because trabecular bone has a greater remodeling surface and responds rapidly to estrogen withdrawal.

The prospective What Happens After Menopause (WHAM) study extended these findings beyond conventional DXA measurements. At 24 months, RRSO was associated not only with lower lumbar spine BMD but also with reduced cortical volumetric density and estimated tibial bending stiffness.[7] Among women who did not use hormone therapy, losses approached 6% at the spine and femoral neck. This indicates that surgical menopause affects both mineral density and biomechanical competence.

The Prospective Research of Outcomes after Salpingo-oophorectomy (PROSper) study provided a contemporaneous ovarian-conservation comparator.[8] BMD remained relatively stable in women who retained their ovaries but declined progressively after RRSO. By 36 months, between-group differences exceeded 7% at the spine and 5% at the hip. These differences are clinically relevant because they occurred in women who were still young and therefore had a long remaining period during which additional age-related bone loss could accumulate.

### 4.3 LONG-TERM PERSISTENCE OF SKELETAL DEFICITS

The Dutch nationwide cohort provided evidence that early postoperative changes may not be completely recovered. More than 18 years after premenopausal RRSO, women continued to have lower age-adjusted BMD at the lumbar spine and femoral neck than women who underwent RRSO after natural menopause.[11] A history of hormone therapy was associated with higher BMD, but treatment timing, cumulative duration, adherence, and dose varied.

The study was cross-sectional and the comparison groups differed substantially in age. Age-adjusted Z-scores reduced but could not eliminate this problem. In the overlapping subgroup aged 60–70 years, the prevalence of osteopenia or osteoporosis was not significantly different between groups. Nevertheless, the persistent Z-score deficit supports the interpretation that early estrogen deprivation can leave a measurable skeletal legacy.

The 2026 prospective study also found continued lumbar spine deterioration in women who underwent RRSO and did not receive hormone therapy.[13] Because its baseline assessment occurred almost three years after surgery, the study mainly evaluated continued decline rather than the initial period of maximum bone loss. Its small hormone-treated group and nonrandom treatment selection limit causal interpretation.

### 4.4 FRACTURE OUTCOMES

Fracture evidence was less consistent than BMD evidence. In the Danish Nurse Cohort, PBO defined by surgery before age 51 was not associated with a statistically significant increase in fragility fractures.[9] The adjusted estimate for any fracture was 1.12, but its CI included both no effect and a clinically relevant increase. Only 419 women underwent BO before age 51, and age below 51 was an imperfect proxy for true premenopausal status. Registry data also could not directly confirm the trauma mechanism of every fracture.

Conversely, the Mayo Clinic cohort found nearly threefold higher odds of documented fractures among women undergoing PBO before age 46.[10] No corresponding association was demonstrated for surgery at 46–49 years. This age gradient supports a possible biological effect of longer estrogen deprivation, but the estimate was imprecise, with a wide CI, and fracture type and trauma severity were not the primary focus of the study.

The 2025 meta-analysis provided a larger summary estimate, showing a 17% relative increase in fractures after BO compared with no oophorectomy.[12] However, moderate-to-high heterogeneity was present, and many component studies inadequately characterized age at

surgery, indication, hormone therapy, hysterectomy, or bone-active medication use. Moreover, the absence of increased fracture risk when hysterectomy with BO was compared with hysterectomy alone suggests that comparator selection and underlying surgical indications materially affect results.

### 4.5 EFFECT OF HORMONE THERAPY

Across the longitudinal cohorts, hormone therapy (HT) consistently reduced postoperative bone loss. In the Kotsopoulos study, HT users had substantially less lumbar spine and hip loss than nonusers.[6] In the WHAM study, HT prevented most hip, cortical-density, and estimated-strength losses, although lumbar spine BMD still declined by 2.3% over 24 months.[7] Similarly, PROSper participants using hormones experienced smaller reductions, but spine and hip BMD remained below baseline at 36 months.[8]

These results do not demonstrate that HT is ineffective. Residual loss may reflect delayed initiation, inadequate replacement dose, inconsistent adherence, treatment interruption, or bone loss occurring between surgery and treatment commencement. The observational allocation of HT also creates confounding because women with previous breast cancer, greater comorbidity, or higher baseline risk may be less likely to receive systemic hormones.

### 4.6 CERTAINTY OF EVIDENCE

Confidence is moderate that PBO causes clinically relevant short-term BMD loss and that HT attenuates this effect. Confidence is lower regarding long-term osteoporosis and low regarding the precise magnitude of fracture risk. No adequately powered randomized trial has assessed fracture prevention specifically after PBO, and withholding physiologic hormone replacement for prolonged periods from young women without contraindications would present ethical difficulties.

## 5 DISCUSSION

The evidence establishes a clear distinction between an early structural outcome and a delayed clinical outcome. Accelerated BMD loss begins soon after BO and is demonstrable within 12 months. Clinical fractures, however, result from the cumulative interaction of bone strength, aging, falls, physical function, medication exposure, and comorbid disease. A young woman may therefore experience substantial BMD loss while her absolute 10-year fracture

risk remains low. The consequences of that loss may not become apparent until several decades later.

The lumbar spine appears particularly vulnerable during the initial postoperative period. The predominance of trabecular bone and its higher remodeling rate explain the early response to estrogen withdrawal. Hip and femoral-neck losses become increasingly important because they are strongly associated with disability and mortality in older age. The WHAM findings further indicate that DXA does not capture the entire skeletal effect, as cortical density and estimated mechanical strength may deteriorate even when areal BMD changes appear modest.[7]

The apparently contradictory fracture studies should not be reduced to a conclusion that surgery either definitively causes or does not cause fractures. The Danish cohort had robust registry follow-up but a relatively small early-surgery subgroup and imprecise classification of menopausal status.[9] The Mayo cohort more clearly separated age at surgery but used a broad fracture outcome and produced a wide CI.[10] The pooled RR of 1.17 suggests a modest average association, but an average estimate may obscure greater risk among women undergoing surgery at very young ages, remaining untreated, or receiving additional skeletal insults.[12]

Age at surgery is likely one of the most important modifiers. Removal of both ovaries at 35 years produces approximately 15 additional years of estrogen deprivation before the average age of natural menopause. The same procedure at 49 years produces a much shorter hormonal deficit. This difference is consistent with the increased fracture odds after surgery before 46 years in the Mayo cohort and the persistent BMD deficit following RRSO at 45 years or younger in the Dutch cohort.[10,11]

Cancer history complicates interpretation. Many RRSO cohorts include women previously treated for breast cancer. Chemotherapy may induce ovarian failure before surgery, glucocorticoids may affect bone remodeling, and aromatase inhibitors can cause additional bone loss. Women with a previous hormone-sensitive malignancy may also be unable to use systemic estrogen. Consequently, untreated women may differ systematically from HT users in both baseline risk and treatment exposure.

Current international guidance recommends HT until approximately the usual age of natural menopause for most women with POI or early surgical menopause who do not have a contraindication.[1] When the uterus is present, adequate progestogen is required to protect the endometrium. After hysterectomy, estrogen-only therapy can usually be considered.

Treatment should be understood as replacement of hormones lost prematurely rather than as elective extension of exposure beyond the usual menopausal age.

For carriers of BRCA1 or BRCA2 pathogenic variants without a personal history of breast cancer, international consensus supports offering HT after premenopausal RRSO and individualizing continuation as the woman approaches the usual menopausal age.[14] Available evidence has not demonstrated that short-term HT eliminates the cancer-risk reduction provided by RRSO, although treatment decisions must consider the specific pathogenic variant, breast history, mastectomy status, uterus, symptoms, thromboembolic risk, and patient preferences.

Systemic HT is generally not recommended after hormone-sensitive breast cancer without multidisciplinary assessment.[14,15] These women require particular attention to DXA surveillance, vitamin D status, exercise, fall prevention, and oncology-compatible osteoporosis therapies. The inability to use estrogen does not justify therapeutic inaction; it instead changes the preventive strategy.

DXA should be obtained at diagnosis of POI or soon after premenopausal RRSO.[1,14] When initial BMD is normal and adequate HT is initiated and maintained, repeating DXA within five years may offer limited value. Women with low BMD, rapid decline, treatment contraindications, previous fragility fractures, or additional risk factors generally require reassessment at shorter intervals, commonly every one to three years. Measurements should preferably be performed on the same device, with attention to least significant change rather than isolated numerical variation.

The Fracture Risk Assessment Tool (FRAX) may supplement evaluation in women older than 40 years, but it should not be interpreted in isolation. FRAX estimates 10-year risk and may therefore classify a young woman as low risk despite a substantial lifetime exposure to surgical estrogen deprivation. Age at surgery, baseline BMD, rate of decline, falls, previous fractures, cancer treatment, low body weight, smoking, glucocorticoid use, and family history remain essential to clinical judgment.

Preventive counseling should include resistance training, weight-bearing aerobic activity, balance exercise, smoking cessation, limitation of excessive alcohol intake, and maintenance of adequate protein, calcium, and vitamin D intake. Supplementation should correct dietary insufficiency or documented deficiency rather than replace a balanced diet. Secondary causes of low BMD—including thyroid dysfunction, hyperparathyroidism,

malabsorption, renal disease, and medication exposure—should be investigated when clinically indicated.

Bisphosphonates, denosumab, or anabolic agents should not automatically replace HT in young women with surgical POI. These medications may be appropriate in established osteoporosis, fragility fracture, continuing bone loss despite adequate replacement, or when HT is contraindicated. Selection should involve a bone-health specialist, particularly when future pregnancy remains possible, because some agents have prolonged skeletal retention or require carefully planned discontinuation.

The decision to remove normal ovaries during surgery for benign disease should include the long-term skeletal consequences of premature hormone deprivation. Ovarian conservation and removal of the fallopian tubes alone are different strategies and should not be treated as equivalent to BO. Conversely, when RRSO is recommended because of a high inherited cancer risk, the evidence supports proceeding at the appropriate oncological age while establishing a preventive bone-health plan before surgery.

The principal limitations of the evidence are the absence of randomized fracture trials, small samples in detailed DXA cohorts, heterogeneous definitions of premenopause, incomplete HT information, and confounding by cancer treatment. Many studies also combine women undergoing surgery before 40, between 40 and 45, and near the usual menopausal age. Future studies should stratify these groups, prospectively document hormone formulation and adherence, obtain preoperative DXA measurements, and ascertain low-trauma fractures through validated clinical records.

## 6 CONCLUSION

Premenopausal bilateral oophorectomy causes rapid and clinically relevant bone loss, particularly at the lumbar spine. Prospective studies also demonstrate deterioration at the hip, femoral neck, and cortical bone, as well as reductions in estimated mechanical strength. These effects are greatest during the first years after surgery and may remain detectable decades later.

The association with clinical fractures is less certain than the association with BMD loss. Individual cohorts have produced both neutral and positive findings, while pooled evidence suggests a modest increase in fracture risk. The risk is unlikely to be uniform and appears greater when surgery occurs at a younger age and estrogen deprivation remains untreated for longer.

Hormone therapy attenuates postoperative bone loss and should generally be offered until approximately the usual age of natural menopause when no contraindication exists. It may not completely prevent skeletal deterioration, particularly when initiation is delayed or adherence is incomplete. Decisions in women with hereditary cancer susceptibility or previous breast cancer require individualized gynecological, oncological, and endocrinological assessment.

Bone-health management should begin at or before surgery. Baseline DXA, assessment of conventional risk factors, adequate calcium and vitamin D, resistance and weight-bearing exercise, smoking cessation, and individualized repeat imaging constitute the foundation of prevention. Women with low BMD, fragility fractures, contraindications to hormone therapy, or continued loss require specialist evaluation for bone-specific medication.

Surgical menopause should be regarded as a lifelong skeletal exposure rather than a transient postoperative condition. Future research must link accurately documented age at surgery and hormone exposure with decades-long fracture ascertainment. Until these data are available, the most defensible clinical approach is early prevention, sustained surveillance proportional to individual risk, and avoidance of unnecessary bilateral oophorectomy in premenopausal women without a compelling indication.

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