젊은 여성의 골다공증과 골감소증: 어떻게 대처하나?

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Premenopausal osteoporosis

- **Definition**
  - history of low trauma fracture
  - only after excluding osteomalacia & other causes of pathologic fracture (eg, malignancy, AVN, fibrous dysplasia, other bone lesion)

- **Lower BMD & fracture**
  - in cross-sectional studies
  - few longitudinal prospective studies
  - predictive relationship is unclear
    - : FRAX - only for ≥ 40 yo
    - : DXA - not sole guide for diagnosis or treatment of osteoporosis
      - not recommended as screening

Cohen A, Endocrinol Metab Clin N Am 2017

DXA in premenopausal women

- **ISCD**
  - **Z scores rather than T scores at the lumbar spine, hip, forearm**
  - **Z score ≤ -2.0: “below the expected range for age” (vs. within~)**
  - **Diagnosis based on BMD T score: should NOT be applied in preMP**
  - **Without fragility fracture or secondary cause, osteoporosis should NOT be diagnosed on DXA**

- **IOF**
  - **Z score ≤ -2.0: low bone mass in children, adolescents, those under 20y, some over 20y**
  - **recommends use of T score in age 20-50y**

- **USPSTF**
  - **NOT recommended BMD screening in healthy preMP women with no risk factors for osteoporosis**

Low bone mass in young women

- **Idiopathic low BMD**
- **Secondary causes of osteoporosis**
- **Associated with pregnancy and lactation**

Idiopathic low BMD

- **BMD depends primarily on achievement of peak bone mass**
  - **at least 90% by the late teen years**
  - **gender, ethnicity, body size, menarchal age, region of bone**
  - **negative impact by genetic predisposition, illness or medication**

- **Idiopathic low bone density**
  - **likely to have abnormal bone microarchitecture (c/w osteoporosis)**
  - **should NOT be treated!**
    - **(1) currently available data do not allow using BMD by DXA to predict fracture risk in premenopausal women**
    - **(2) fracture risk depends greatly on age**
    - **(3) few studies have addressed risks and benefits of osteoporosis drugs in premenopausal women**

Secondary causes

Cause or contributor to osteoporosis & fractures

Lifestyle factors		
Alcohol abuse	Excessive thinness	Excess Vitamin A
Frequent falling	High salt intake	Immobilization
Inadequate physical activity	Low calcium intake	Smoking (active or passive)
Vitamin D insufficiency		
Genetic diseases		
Cystic fibrosis	Ehlers-Danlos	Gaucher's disease
Glycogen storage diseases	Hemochromatosis	Homocystinuria
Hypophosphatasia	Marfan syndrome	Menkes steely hair syndrome
Osteogenesis imperfecta	Parental history of hip fracture	Porphyria
Riley-Day syndrome		

Secondary causes

Cause or contributor to osteoporosis & fractures

Hypogonadal states		
Androgen insensitivity	Anorexia nervosa	Athletic amenorrhea
Hyperprolactinemia	Panhypopituitarism	Premature menopause (<40 yrs)
Turner's & Klinefelter's syndromes		
Endocrine disorders		
Central obesity	Cushing's syndrome	Diabetes mellitus (Types 1 & 2)
Hyperparathyroidism	Thyrotoxicosis	
Gastrointestinal disorders		
Celiac disease	Gastric bypass	Gastrointestinal surgery
Inflammatory bowel disease	Malabsorption	Pancreatic disease
Primary biliary cirrhosis		
Hematologic disorders		
Hemophilia	Leukemia and lymphomas	Monoclonal gammopathies
Multiple myeloma	Sickle cell disease	Systemic mastocytosis
Thalassemia		

Secondary causes

Cause or contributor to osteoporosis & fractures

Rheumatologic and autoimmune diseases		
Ankylosing spondylitis	Other rheumatic and autoimmune diseases	
Rheumatoid arthritis	Systemic lupus	
Neurological and musculoskeletal risk factors		
Epilepsy	Multiple sclerosis	Muscular dystrophy
Parkinson's disease	Spinal cord injury	Stroke
Miscellaneous conditions and diseases		
AIDS/HIV	Alcoholism	Amyloidosis
Chronic metabolic acidosis	Chronic obstructive lung disease	Congestive heart failure
Depression	End stage renal disease	Hypercalciuria
Idiopathic scoliosis	Post-transplant bone disease	Sarcoidosis
Weight loss		
Medications		
Aluminum (in antacids)	Anticoagulants (heparin)	Anticonvulsants
Aromatase inhibitors	Barbiturates	Cancer chemotherapeutic drugs
Depo-medroxyprogesterone (premenopausal contraception)	Glucocorticoids (≥ 5 mg/d prednisone or equivalent for ≥ 3 months)	GnRH (Gonadotropin releasing hormone) agonists
Lithium Cyclosporine A and tacrolimus	Methotrexate	Parental nutrition
Proton pump inhibitors	Selective serotonin reuptake inhibitors	
Tamoxifen® (premenopausal use)	Thiazolidinediones (such as Actos® and Avandia®)	Thyroid hormones (in excess)

Secondary causes

Exclusion of secondary causes

Consider the Following Diagnostic Studies for Secondary Causes of Osteoporosis
Blood or Serum
Complete blood count (CBC)
Chemistry levels (Calcium, renal function, phosphorus and magnesium)
Liver function tests
Thyroid-stimulating hormone (TSH) +/- free T_4
25(OH)D
Parathyroid hormone (PTH)
Total testosterone and gonadotropin in younger men
Bone turnover markers
Consider in selected patients
– Serum protein electrophoresis (SPEP), serum immunofixation, serum free light chains
– Tissue transglutaminase antibodies (IgA and IgG)
– Iron and ferritin levels
– Homocysteine
– Prolactin level
– Tryptase
Urine
24-hour urinary calcium
Consider in selected patients
– Protein electrophoresis (UPEP)
– Urinary free cortisol level
– Urinary histamine

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Physiology during pregnancy

- **Calcium in fetus**
  - **average 30g in skeleton by term**
  - **accreted 80% during 3rd trimester(Δ)**

- **Calcium from mother**
  - **must provide 100-150 mg/kg/day during 3rd Δ or 300-500 mg/day during final 6 weeks**
  - **largely met by a doubling in efficiency of intestinal Ca absorption**
    : positive calcium balance by mid-pregnancy in most women

Kovacs CS, Physiol Rev 2014

Physiology during pregnancy

BBMs (resorption)	**BBMs** (formation)	**BMD**	***n***	**Type of study**
↑ Along pregnancy	↓ In first and second trimesters ↑In third trimester	NA	153	Controlled cohort
↑ Along pregnancy	↔ In first and second trimesters ↑ In third trimester	↓ LS ↓ Hip ↔ Radius	10	Cohort
↑ Along pregnancy	↓ In first and second trimester ↑ In third trimester	↓ LS and trochanter ↔ Total hip, femoral neck, and total forearm	15	Controlled cohort
↑ Along pregnancy	↑ In third trimester	↓ LS and pelvis ↑ Arms and legs	16	Cohort
↑ Along pregnancy	NA	NA	22	Controlled cohort
↑ Along pregnancy	↑ Along pregnancy	NA	20	Cohort
NA	NA	↔ LS and hip	5	Cohort
NA	NA	↓ LS, femoral neck, and radial shaft ↑Tibia	6	Controlled cohort
NA	NA	↓ LS, total hip, and trochanter ↔ Femoral neck	60	Cohort
NA	NA	↓ LS, distal, and ultradistal radius	38	Cohort
↑ Third trimester	↑ In third trimester	↔ Distal and ultradistal radius	10	Cohort
NA	NA	↔ Femur	32	Controlled cohort
NA	NA	↓ LS, trochanter, femoral shaft, total hip, and whole body	34	Controlled cohort
NA	NA	↓ LS, total hip, whole body, and ultradistal forearm	92	Controlled cohort

BBMs, bone biochemical markers; BMD, bone mineral density; *n*, number of women; NA, not available; LS, lumbar spine.

Sanz-Salvador L et al., Eur J Endocrinol 2015

Physiology during pregnancy

- **Bone resorption marker: ↑ from early pregnancy**
- **Bone formation markers: ↓ till later pregnancy**
- **Decline BMD during pregnancy?**
  - **No axial BMD during pregnancy d/t radiation exposure**
  - **May be confounded by pregnancy-related changes in body fluid, fat mass, weight, skeletal volumes**
  - **Not necessarily during pregnancies**

Kovacs CS, Endocrinol Metab Clin North Am 2011

Physiology during pregnancy

Summary

- **Increased intestinal calcium absorption normally meets the fetal demand for calcium.**
- **However, a ‘small’ amount of bone loss from the maternal skeleton has been detected in some longitudinal studies.**
- **More ‘marked’ bone loss is likely to occur in response to low dietary calcium intake, while variations in the amount of (or sensitivity to) PTHrP released by the breasts and placenta may in turn modulate the magnitude of bone resorption that occurs during a normal pregnancy.**

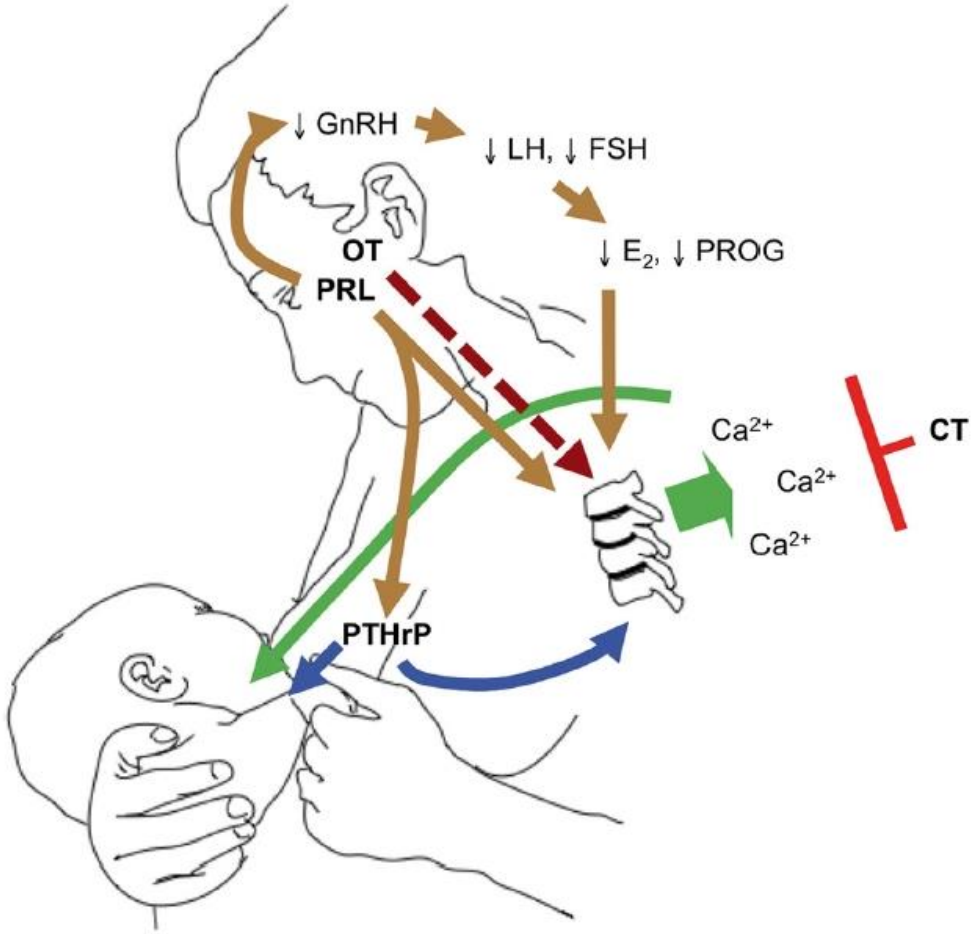
Physiology during lactation

- **Calcium in neonate**
  - **normally accreted 30-40 mg/kg/day**
  - **average daily maternal loss of calcium in milk: 210 mg**
  - **first 6 months = x4 amount during 9 months of pregnancy**

- **Calcium from mother**
  - **intestinal calcium absorption**
    - **: NOT the mechanism for supplying calcium for milk**
    - **: declined to normal, non-pregnant level**
  - **supplied through resorption of maternal skeleton**
    - **: "brain-breast-bone circuit"**

Physiology during lactation

Brain-breast-bone circuit



Kovacs CS, J Mammary Gland Biol Neoplasia 2005

Physiology during lactation

- **Resorption of skeletons during lactation**
  - 5-10% trabecular BMD loss during first 3-6m of lactation
  - 10-15% trabecular BMD loss during lactation in adolescents

- **Typical rate of BMD loss during lactation**
  - approx. 1-3% per month
    vs. rapid loss of 1-2% per 'year' in postmenopausal women
    vs. 0.5-2% loss by GnRH analog for 6 months
    : synergistic effect!

- **Breastfeeding prolonged periods**
  - progressive bone loss?
  - normally dependent on solid food at 6 months of age
    : much reduced amount of milk production after that time

Kovacs CS, Endocr Rev 1997

Physiology during lactation

Summary

- **Bone resorption** occurs during lactation for calcium supply.

- 5–10 % losses in trabecular BMD (greater in adolescents), and reductions in skeletal microarchitecture can be expected.
  - MORE SUBSTANTIAL than modest resorption during pregnancy.

- **Temporary loss** of bone mass and strength during lactation being **fully restored or compensated** for in the long-term
  - recovers BMD fall within 6-12 months
  - parity & lactation do not normally increase the long-term risk of fracture
  - possibility that recovery may be incomplete in some women

Low trauma fracture +/- low BMD

- **Weight-bearing exercise**
- **Nutrition**
- **Calcium and vitamin D**
  - 1000 mg of calcium & 600 IU of vitamin D for preMP (IOF)
- **Lifestyle modification**

Medications

- **COCs**
  - **in estrogen deficient women**
  - **insufficient in anorexia nervosa or more complex condition**
  - **unclear effects on fracture risk**

- **SERM**
  - **should NOT be used in menstruating women**
    : block estrogen action on bone & lead to further bone loss

- **Bisphosphonate**
  - **alendronate & risedronate: approved by FDA for GIO in preMP**
  - **rare data on fracture data and long-term risks**
  - **category: C**

Medications

- **Denosumab**
  - **for postmenopausal osteoporosis**
  - **shorter half-life vs. bisphosphonate, lack of skeletal accumulation**
  - **NO defined efficacy and safety in preMP**
  - **category X (fetal harm in animal studies)**

- **Teriparatide**
  - **prevent bone loss or Increase BMD in,**
    - **: premenopausal women on GnRH agonist for EMS**
    - **: premenopausal women taking glucocorticoids**
    - **: premenopausal women with idiopathic osteoporosis**
    - **: in those with anorexia nervosa**
    - **: pregnancy-associated osteoporosis**
  - **sample size? fracture risk? long-term effect?**

Fractures

- **Uncommon & uncertain frequency**
  - may be under-reported
  - > 75% of vertebral compression fractures/deformities develop silently

- **Vertebral fractures during pregnancy**
  - mostly healthy: few available baseline data & generally normal blood test
  - increased weight-bearing load & lordotic posture: contributing factors
  - common coincident conditions or factors
  - usually do not recur, no increased risk of fractures with parity

- **Breastfeeding or not**
  - may be reasonable & appropriate to discourage when predisposed to skeletal fragility or high risk of fractures
  - but NOT contraindicated!

Management for fracture

- **Limited evidence for pregnancy-associated osteoporosis**
  - **no RCTs or large case series**
  - **clinical judgement to balance benefit & risks**

- **<u>Spontaneous recovery</u> of bone mass/strength typically occur!**
  - **even in women who have fractured**

- **Pharmacological and surgical treatment**
  - **multiple vertebral fractures**
  - **persistent disabling pain**
  - **failure to achieve a satisfactory spontaneous BMD increase after weaning**

Management for fracture

Suggested strategy: for all women

Optimize calcium and vitamin D intake
Early mobilization; avoid bedrest
Encourage weight-bearing physical activity
Consider avoiding lactation (with pregnancy fractures) or
weaning baby (with lactation fractures)
Avoid lifting heavy objects
Avoid high risk activities that include sudden loads or risk of falls
Supportive corset (temporary) for vertebral fracture pain
Assess spontaneous recovery of vertebral BMD at 12–18 months and reassess

Management for fracture

Suggested strategy: for severe cases

Analgesia
- Paracetamol/acetaminophen
- NSAID
- Opioids
- Anti-neuropathic drugs

Bone-specific therapy
- Estrogen replacement for oligomenorrheic women
- Bisphosphonate (e.g., alendronate, risedronate, zoledronic acid)
- Denosumab
- Teriparatide
- Parenteral calcitonin—short-term use for vertebral fracture pain relief, if at all

Surgical treatment
- Kyphoplasty
- Vertebroplasty
- Spinal fusion

Management for fracture

Pharmacological therapy

- **Lack of controls in all reports**
  - **BMD increase exceeds magnitude of expected spontaneous recover?**

- **Indicated for postmenopausal women**
  - **safety concerns about long-term effect**
  - **no clearly defined endpoint for treatment**

- **Concern for bisphosphonates**
  - **cross placenta & theoretically could interfere with fetal bone development**
  - **no obvious problems in most cases in recent review of 78 cases**

  cf. denosumab/cation strontium also cross placenta

Conclusions

- **It is important to understand the definition of ‘osteoporosis’ in young women**
  - not solely based on BMD, without fracture

- **In general, osteoporosis medication is not indicated in young women even with fracture**
  - non-pharmacological management has higher priority
  - use of medication with caution in specific conditions


Thank you for your attention!
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