Osteoporosis of pregnancy and lactation

Dr Beth Curtis
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Introduction

Fragility fractures are rare in young women during pregnancy, post partum period or lactation

Pathogenesis poorly understood

Often have pre-existing reductions in BMD, which, with added metabolic and mechanical stresses of pregnancy result in fragility fractures...others have a completely normal skeleton pre-pregnancy

Breastfeeding: obligatory loss of skeletal mineral content

After lactation it recovers – in general parity / lactation neutral/protective. Therefore much uncertainty about treatment approach (evidence base lacking and recovery almost always)
Case Study Mrs B

32 yr old accountant

PMH: one wrist fracture age 12 roller skating, one episode of urticarial, no cause found

First pregnancy aged 29

R Sacroiliac pain for 2 weeks, resolved

In labour, severe back pain lasting one day

10 weeks post partum, severe back pain, could not turn over in bed

Stopped breast feeding, pain settled over 6 weeks
Case Study Mrs B

Second pregnancy aged 32
10 weeks post partum: severe back pain
Stopped breast feeding
Multiple vertebral fractures T10-L4
DXA: osteoporosis
No RFS: normal diet, exercise, sunlight exposure, drank 200ml milk per day, no steroids, normal BMI, normal menarche, non smoked, no alcohol.
No FH
Case Study Mrs B

O/E: wt 74.4kg, height 1.71m, BP 104/96

Normal HS, pulses, chest, abdomen, no splinter haemorrhages or lymphadenopathy, joints normal. Normal sclerae.

Ix: PTH 2.7, vit D 30nmol/l, FBC, U+E, LFT, CRP, Igs, protein, cortisol, TSH, glucose, HbA1c, FSH, LH, oestradiol normal, TTG neg, mast cell tryptase N (?mastocytosis), 9am cortisol

Urine: NAD, urinary cortisol and BJP Normal
DXA T-2.0 femoral neck, -1.8 total hip, -3.2 spine
Results Summary:

<table>
<thead>
<tr>
<th>Region</th>
<th>Area [cm²]</th>
<th>BMC [g]</th>
<th>BMD [g/cm²]</th>
<th>T-score</th>
<th>PR (Peak Reference)</th>
<th>Z-score</th>
<th>AM (Age Matched)</th>
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<tbody>
<tr>
<td>L1</td>
<td>14.31</td>
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<td>70</td>
<td>-2.7</td>
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<td>L2</td>
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<td>L3</td>
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<tr>
<td>L4</td>
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<td>Total</td>
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<td>40.47</td>
<td>0.694</td>
<td>-3.2</td>
<td>66</td>
<td>-3.2</td>
<td>66</td>
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</table>

Total BMD CV 1.0%, ACF = 1.034, BCF = 1.003, TH = 7.944

Fracture Risk: High, WHO Classification: Osteoporosis
Results Summary:

<table>
<thead>
<tr>
<th>Region</th>
<th>Area [cm²]</th>
<th>BMC [g]</th>
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<tr>
<td>1/3</td>
<td>2.83</td>
<td>1.62</td>
<td>0.574</td>
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<td>76</td>
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Total BMD CV 1.0%; ACF = 1.934, BCF = 1.003

Fracture Risk: Increased; WHO Classification: Osteopenia
Case Study Mrs B- management

Vitamin D replacement 3200 units daily for 12 weeks
Vitamin D 400-800 units daily in winter months
Repeat DXA in 6 months
Gentle weight bearing exercise
Support: NOS contacts for OP in pregnancy
Results Summary:

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<tr>
<th>Region</th>
<th>Area [cm²]</th>
<th>BMC [g/cm²]</th>
<th>BMD [g/cm²]</th>
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<th>FR (Peak Reference)</th>
<th>Z-score</th>
<th>AM (Age Matched)</th>
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<tbody>
<tr>
<td>Neck</td>
<td>5.62</td>
<td>3.51</td>
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<td>75</td>
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Total BMD CV 1.06%, ACF = 1.034, BCF = 1.063, TH = 6.039

WHO Classification: Osteopenia

16-year Fracture Risk:
FRAX not reported because
Premenopausal woman
Results Summary:

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<tr>
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<tr>
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<td>13.19</td>
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<tr>
<td>L2</td>
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<td>64</td>
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<tr>
<td>L3</td>
<td>16.34</td>
<td>11.33</td>
<td>0.694</td>
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<td>-3.3</td>
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<td>-3.3</td>
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</table>

Total BMD CV 1.0%, ACF = 1.034, BCF = 1.005, TH = 7.591

Fracture Risk: High, WHO Classification: Osteoporosis
Questions

Why did she fracture?
Any further investigations?
Should she receive any medication?
What are her risks in subsequent pregnancy?
The maternal skeleton in pregnancy

Average fetus has 30g calcium in skeleton at term.

80% fetal calcium deposition happens in the 3rd trimester.

Mother must provide 100-150mg/day of calcium in 3rd trimester, 300-500mg in last 6/52.

Efficiency of intestinal calcium absorption doubled from week 12 – positive calcium balance mid pregnancy.
Calcium absorption

Calcitriol (1,25(OH)$_2$ D3) – levels triple early in pregnancy through renal production

Though not the full story – severe vitamin D deficiency or absent vitamin D receptors do not obliterate the pregnancy induced increase in calcium absorption

A small amount of absorption occurs from the maternal skeleton

Inadequate maternal calcium intake would cause secondary hyperparathyroidism and more marked bone loss (proven in studies in rats)
Calcium in Pregnancy

Parathyroid hormone related protein – secreted from placenta and breasts into maternal circulation, stimulates bone turnover, mimics effects of PTH

↑ blood PTHrP

↑ maternal calcium

↑ fetal skeleton formation
Vitamin D in Pregnancy

Vitamin D levels increase during pregnancy, vitamin D binding proteins also increase. The placenta expresses the 1-alpha-hydroxylase enzyme for activation of vitamin D (as does the skin, kidney, immune cells).

• The role of vitamin D in pregnancy is still not clear.
• Vitamin D deficiency correlates with preeclampsia, gestational diabetes mellitus, and bacterial vaginosis, and an increased risk for C-section delivery.
BMJ Open  Effect of vitamin D replacement on maternal and neonatal outcomes: a randomised controlled trial in pregnant women with hypovitaminosis D. A protocol

M Chakhtoura,1 A Nassar,2 A Arabi,1 C Cooper,3 N Harvey,3 Z Mahfoud,4 M Nabulsi,5 G El-Hajj Fuleihan1

ABSTRACT

Introduction: The vitamin D recommended doses during pregnancy differ between societies. The WHO guidelines do not recommend routine prenatal supplementation, but they underscore the fact that women with the lowest levels may benefit most. The effects of routine supplementation during pregnancy on maternal and neonatal clinical outcomes have not been investigated in the Middle East, where hypovitaminosis D is prevalent. Our hypothesis is that in Middle Eastern pregnant women, a vitamin D dose of 3000 IU/day is required to reach a desirable maternal 25-hydroxyvitamin D [25(OH)D] level, and to positively impact infant bone mineral content (BMC).

Chakhtoura et al, BMJ Open 2016
The brain breast bone circuit

High levels of **prolactin**
Low **oestadiol** stimulates osteoclast function
Breasts produce **PTHrP**, stimulates resorption of bone
**Calcitonin** (acts against PTH) is also expressed by lactating tissue – negative feedback to prevent prolactin synthesis and PTHrP synthesis
**Oxytocin** acts to regulate bone turnover
Rate of **calcium absorption from the gut** normalises post partum
The brain breast bone circuit

So.... Increased PTHrP and low estradiol have **synergistic effects** to increase skeletal resorption

Bone resorption markers go up in lactation

There is **5-10% loss of trabecular BMD in first 3-6 months** (1-3% per month.... In post-menopausal women a loss of 1-2% per yr is considered rapid), much greater than in pregnancy when 3-5% lost

The loss has been shown to be even greater in **adolescent** women

Also in women nursing twins...this is pre-programmed and is independent of diet.

Therefore there are **temporary reductions** in skeletal strength
The skeleton after lactation

After weaning, the maternal skeleton undergoes remodelling and remineralisation – obliterates the deficit from lactation within 6 months of weaning.

Osteoclasts apoptose, osteoblasts are active.

Vertebrae recover more quickly than longer bones, though longer bones increase in diameter.

Intestinal calcium absorption shown to increase in this period.
The skeleton after lactation – long term effects

Trabecular bone is resorbed more than cortical bone, but it is completely restored in the spine, less so in long bones but they increase their diameter....

Several studies have shown that parity and lactation do not increase the risk of low BMD and osteoporosis in the long term.

Some large scale studies have shown a protective effect of lactation.

There is not even a negative effect of pregnancy or lactation on BMD in adolescents.
Vertebral fractures during pregnancy / lactation

75% go undetected...most women who fracture are otherwise healthy...and we do not generally have pre pregnancy DXA

Pregnancy – wt gain at least 12kg, lordotic posture

Predisposing factors are often present:
- mild osteogenesis imperfecta, hypercalciuria, Cushing’s syndrome, RA,
- premature ovarian failure, vitamin D deficiency, dairy intolerance, anorexia, low body wt, petite frame, longstanding oligoamenorrhoea, steroid use, certain anti-convulsants, heparin use, depo-Provera, chemotherapy, alcohol and smoking, lack of physical activity
Transient osteoporosis of the hip

A focal disorder, hips commonly affected
A separate entity....
Present in 3rd trimester with hip pain, limp or hip fractures
Radiographs show osteopenia
Low hip BMD, normal Lumbar spine BMD
MRI shows oedema of femoral head and marrow
Resolves within 2-12 months
Can recur in subsequent pregnancy
Causes: pelvic nerve compression, vascular insufficiency, fibrinolytic system changes in pregnancy
Long term outlook

Fractures typically occur in a first pregnancy
They typically do not recur
Parity does not increase risk of fractures
....this suggests that the predisposing factor is often present before pregnancy and has been corrected later

It may be appropriate to discourage breastfeeding in women who are known to be predisposed to skeletal fragility... But there is not enough evidence to say it is contraindicated
**Table 2**  Suggested initial investigations

<table>
<thead>
<tr>
<th>Category</th>
<th>Investigations</th>
</tr>
</thead>
</table>
| Anthropometric | Height by stadiometer  
                | Weight                                                             
                | Body mass index  
                | Comparison to best recalled or prior documented height                   |
| Radiological   | Areal bone mineral density by DXA (preferred use of Z-scores)  
                | Plain radiographs of thoracic and lumbar spine to assess for compression fractures  
                | Radiographs of both hips (when presenting with hip pain or fracture)  
                | MRI of affected hips (when presenting with hip pain or fracture)         |
| Dietary assessment for nutritional deficiencies | Calcium intake  
                | Vitamin D intake  
                | Other nutritional deficiencies |
| Hematological  | Complete blood count  
                | ESR  
                | Serum protein electrophoresis / myeloma screen |
| Biochemical    | Electrolytes  
                | eGFR  
                | Ionized calcium or albumin-corrected serum calcium  
                | Serum phosphate  
                | Alkaline phosphatase  
                | 25-Hydroxyvitamin D  
                | TTG |
| Hormonal       | PTH  
                | PTHrP  
                | TSH  
                | LH, FSH, estradiol (off hormonal contraceptives)  
                | Prolactin |
| Urine          | 24-h urine calcium (in non-pregnant, non-lactating women, low values support dietary calcium deficiency whereas high values suggest a renal calcium leak) |
Investigations

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Potential secondary investigations in severe cases</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiological</strong></td>
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</tr>
<tr>
<td>Skeletal survey for evidence of sclerosing bone disorders</td>
<td></td>
</tr>
<tr>
<td>Radionuclide bone scan for evidence of myeloma or other pathology</td>
<td></td>
</tr>
<tr>
<td><strong>Biochemical</strong></td>
<td></td>
</tr>
<tr>
<td>Bone formation markers—<em>e.g.</em>, bone-specific alkaline phosphatase, PINP, or osteocalcin</td>
<td></td>
</tr>
<tr>
<td>Bone resorption markers—<em>e.g.</em>, CTX, NTX, or deoxypyridinoline/creatinine</td>
<td></td>
</tr>
<tr>
<td>Ferritin or serum iron measurements</td>
<td></td>
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<tr>
<td><strong>Hormonal</strong></td>
<td></td>
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<tr>
<td>Calcitriol</td>
<td></td>
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<tr>
<td>24-h urine free cortisol</td>
<td></td>
</tr>
<tr>
<td>Late-night salivary cortisol</td>
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</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
</tr>
<tr>
<td>Bone biopsy at hip fracture site</td>
<td></td>
</tr>
<tr>
<td>Tetracycline-labelled, transiliac bone biopsy</td>
<td></td>
</tr>
<tr>
<td>Genetics referral when family history of early or severe fragility present</td>
<td></td>
</tr>
<tr>
<td>Gastroenterology referral for small bowel biopsy</td>
<td></td>
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</tbody>
</table>
Non-pharmacological treatment

Optimise calcium intake
1200mg from all sources

Vitamin D – keep >50nmol/L
Some weight bearing and resistance exercise
Avoid heavy lifting
Supportive corsets
Reassurance
Pharmacologic / surgical treatment

BMD normally increases during the 6-12 months after weaning...by 10-20%

Therefore appropriate to delay pharmacological treatment for 12-18 months until the extent of recovery established

Treatment on a case by case basis: safety concerns about long term treatment with calcitonin (cancer risk), bisphosphonates (concerns re. fetal bone development), strontium, teriparatide, denosumab (crosses placenta)

If treatment is needed (BMD not improving significantly on its own), generally bisphosphonate or denosumab for 4-5 yrs is used

Vertebroplasty and kyphoplasty occasionally used – overall efficacy uncertain
Revisitation of case....

**Why did she fracture?** Not clear... vit D deficiency? Inherited disorder?

**Any further investigations?** Bone turnover markers? Skeletal survey (sclerosing bone disorders)? Look further for nutritional deficiencies... gastro and dietician referral? Genetics referral?

**Should she receive any medication?** Not yet...perhaps if next DXA at 12 months shows subsequent improvement

**What are her risks in subsequent pregnancy?** Probably minimal but she developed fractures after her second pregnancy...

Any other suggestions?
Conclusions

Fragility fractures in association with pregnancy or breastfeeding are rare

Often bone fragility precedes pregnancy

Normal metabolic and structural changes of pregnancy can compromise skeletal strength

Following lactation bone mass increases

Nutritional deficiencies must be corrected

Further study is needed to determine when drug / surgical therapy is indicated
Pregnancy and osteoporosis

Pregnancy and Osteoporosis
Consumer Leaflet
References

http://www.niams.nih.gov/health_info/Bone/Bone_Health/Pregnancy/default.asp

www.uptodate.com

https://www.nos.org.uk/health-professionals/~/document.doc?id=405

Kovacs CS and Ralston SH; Presentation and management of osteoporosis presenting in association with pregnancy or lactation. Osteoporosis Int (2015) 26: 2223-2241
Osteoporosis of pregnancy and lactation

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