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Vitamin D and Calcium Levels Related to Bone Mineral Density during Pregnancy and Postpartum

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Abstract

Bone Mineral Density (BMD) is crucial for bone strength, with even a modest decrease significantly elevating fracture risk. Calcium imbalance during pregnancy contributes to BMD loss, as maternal stores are mobilized to support fetal skeletal development. Vitamin D deficiency exacerbates this issue, with prevalence rates alarming in various populations. Supplementation with vitamin D and calcium aims to mitigate BMD decline; however, optimal dosing and efficacy remain debated. Studies utilizing innovative diagnostic tools like Radiofrequency Echographic Multi Spectrometry (REMS) and Quantitative Ultrasonometry (QUS) shed light on BMD changes during pregnancy, offering safer alternatives to traditional methods such as Dual-Energy X-Ray Absorptiometry (DEXA), prohibited during pregnancy due to fetal radiation risks. Despite methodological challenges, research reveals significant BMD reductions during pregnancy, particularly in weight-bearing bones. Postpartum, the demand for calcium continues due to breastfeeding, further impacting maternal bone health. While BMD recovery post-weaning is observed, full restoration remains uncertain, with prolonged lactation potentially exacerbating BMD decline. Complicating matters, studies demonstrate varied effects of vitamin D and calcium supplementation on postpartum BMD, necessitating further investigation. Parity's association with reduced BMD adds another layer of complexity, with conflicting evidence on its impact. Pregnancy And Lactation-Associated Osteoporosis (PLO), presents unique challenges, with fragility fractures occurring predominantly during the last trimester or early postpartum. In conclusion, maintaining maternal bone health during pregnancy and postpartum is critical, requiring comprehensive monitoring and support. Further research is needed to elucidate optimal strategies for preserving BMD throughout the reproductive lifespan, reducing fracture risk and enhancing maternal well-being.

Introduction

Bone Mineral Density (BMD) is one of the most important elements in determining bone strength. A 10% reduction in BMD has been demonstrated to double the fracture risk [1]. It is conceivable that their prolongation (e.g. in the form of multiparity, prolonged lactation) may contribute to bone deterioration and consequently increase the risk of fracture. Many factors during pregnancy and lactation cause calcium imbalance in the female body and lead to a decrease in BMD. Loss of BMD During pregnancy is the result of mobilisation and absorption of calcium from the mother's skeleton for fetal bone growth. The resulting maternal osteoporosis leads to sustained low back

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pain which may be correlated with higher number of fractures. To avoid fetal exposure to radiation, most examinations have been conducted before and after pregnancy. The cause of that is very restricted information on maternal BMD changes during pregnancy. The purpose of this review is to gather existing knowledge on vitamin D3 and calcium supplementation, their effects on BMD and the impact of pregnancy on BMD, as well as to identify changes in BMD during pregnancy, primarily using new, safe diagnostic methods.

Vitamin D and Calcium status. Deficiency and supplementation: Bone metabolism and its minerals are strongly influenced by vitamin D. Increasing the supply and/or supplementing it reduces bone turnover and helps increase bone mineral density. However, it should be noted that excessive vitamin D supplementation and/or supply can negatively affect health, as it belongs to the group of fat-soluble vitamins that have the ability to accumulate in the body [2]. As a biomarker of vitamin D status, 25-hydroxycholecalciferol is used due to its longer half-life [3]. In Europe, vitamin D is produced in the skin under the influence of sunlight from April to September, when the sun is more than 50°N above the horizon. People with darker skin pigment absorb UV light, so that sun exposure does not have the same effect on vitamin D production [4]. A paper from 2023 including 6 metanalyses on the Indonesian population comprising 830 women aged 27.6-30.6 years concluded that the incidence of vitamin D insufficiency in this country of nearly 300 million among Indonesian pregnant women was 63% [5]. Work from Singapore published in 2024 found that 97,8% of the study population did not have enough vitamin D levels. It was also shown that the greater the weight, the greater likelihood of vitamin D deficiency [6]. The essence of testing vitamin D, calcium and bone density measurements is the impact of mineral disorders and their negative effects on the mother and child's body. A paper involving as many as 42 meta-analyses published between 2018 and 2023 on the relationship between serum 25-hydroxycholecalciferol levels and outcome of pregnancy found that vitamin D deficiency increases the likelihood of spontaneous miscarriage, preterm labor, especially in multiple pregnancies, Pre-Eclampsia (PE), gestational anemia, postpartum depression, autism spectrum disorders in early childhood [7]. In contrast, a reduced risk of low birth weight and gestational diabetes was correlated with higher vitamin D levels. Kurmangali et al. demonstrated that the development of insulin resistance and bronchial asthma in the first years of life, as well as pre-eclampsia, is prevented by vitamin D supplementation during gestation at least 2,000 IU. Pregnant women should maintain serum levels of 25-hydroxycholecalciferol above 30 mg/mL [7].

Women with Vitamin D levels <20ng/ml had 4-fold increased risk of severe preeclampsia [8]. According to the World Health Organization (WHO), preeclampsia affects 2-8% of pregnancies, posing a major challenge for obstetricians, being a major cause of morbidity as well as perinatal mortality [9,10]. Hypovitaminosis D is linked to neonatal consequences of rickets and asthma [11,12]. Vitamin D supplementation could appear to be the solution. In the Singapore study already cited, women with periconceptional multivitamin supplementation had a mean vitamin D level 2.10ng/ml higher than women without supplementation [6]. During pregnancy, the need for calcium supply increases. Calcium absorption from the intestine is increased. In the duodenum, active transport, dependent on 1,25-dihydroxylcholecalciferol, predominates. It is further subject to active transport to the foetus via the placenta. Calcium absorption from the maternal bones becomes prevalent in late gestation if calcium consumption is poor [13]. This can lead to lower BMD, the risk of delayed bone maturation in the newborn, and reduced BMD or hardness of the offspring's teeth in later life [14]. The WHO has advised calcium supplementation of 1,500-2,000 mg daily since 2011 [15]. A study involving 18,064 women (27 studies) showed that, especially in women with calcium-poor diets, high-dose Ca supplementation (≥ 1 g/day) reduces the risk of preeclampsia as well as premature labour [16]. On the other hand, there are two randomized trials of low-dose calcium supplementation during pregnancy, involving 11,000 non-pregnant women in each study. These 2 studies indicated that high-dose calcium supplementation did not provide a significant advantage in terms of preeclampsia risk, relative to low-dose supplementation [17]. As far as the importance of calcium in pregnancy is concerned, only pre-eclampsia appears, however other important health effects should not be overlooked. One paper indicated that vitamin D supplementation along with calcium leads to significant weight loss, primarily as a result of reduced fat mass in the body's central areas [18]. Maternal Ca deficit during gestation may affect gene expression and thereby contribute to altered metabolic phenotype, causing insulin resistance in the offspring [19]. The data do not converge and require further investigation into the effects of vitamin D3 and calcium concentrations on BMD.

Radiofrequency Echographic Multi Spectrometry (REMS): The utilize of double vitality X-ray absorptiometry (DXA) is disallowed in pregnancy, not at all like ultrasound, which is commonly utilized in the conclusion of pregnant women. Radiofrequency Echographic Multispectrometry (REMS) is considered as an advanced tool for diagnostic evaluation of bone health (Figure 1). A study from Siena, Italy, showed that REMS has an even higher capacity to diagnose osteoporosis compared to DXA [20]. This and other works [21] have led researchers to use the REMS technique to examine BMD in pregnant women as a safe alternative to DXA. Researchers from Parma, Italy, studied 78 pregnant women at 39.1 ± 1.5 weeks using REMS. They found that femoral BMD decreased by up to 8.1% compared to the control group. BMD of the femoral neck showed a positive association with BMI before pregnancy and a negative association with the mother's age. In a further note, femoral neck BMD was reported to be lower in Caucasians compared to non-Caucasians [22]. Another study from Italy in 2024 examined 65 female patients using REMS. **T**he study found that there is a considerable decrease in bone mineral density in the femoral neck from early to late in pregnancy [23]. Other work using REMS also indicates a decrease in BMD during pregnancy [24,25]. REMS is a new technology which usage has just begun in obstetrics. Definitely more studies on its use are needed, as the primary results are very promising.

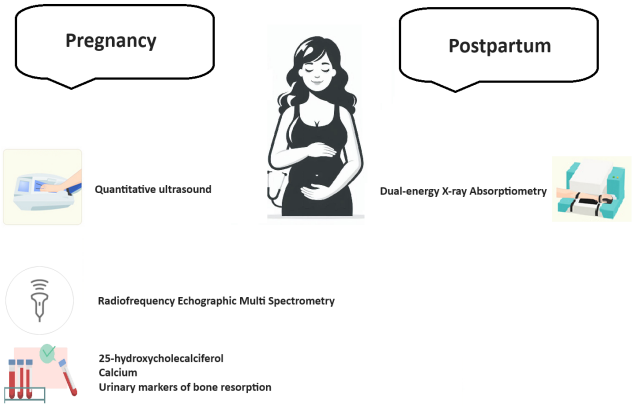

Figure 1: Departmen

X-ray, QUS and other methods of measurements: Quantitative Ultrasonometry (QUS) is an affordable, radiation-free way to evaluate bone mineral density and the quality of bone, which may be applied during pregnancy (Figure 1). Hellmeyer et al. conducted QUS of the phalanges in 60 women without disease during gestation. They found a substantial decrease in the speed of sound (AdSOS) in the first, second and third trimesters. Moreover, they observed that AdSOS was substantially lower in the second and third trimesters in comparison to the first trimester. This reduction had a major impact on the t-score and Z-score of the QUS in this trial, and thus shows potential clinical significance [26]. Study published in 2021, as well as other papers, also showed a significant decrease in QUS parameters in pregnant women [27,28]. Dual energy X-ray Absorptiometry scan (DXA) is forbidden in pregnancy due to potential risk for fetus. Therefore, there are not many studies using this method during pregnancy. The largest DXA study during pregnancy on a group of 153 women was conducted by U. K. Møller et al., measuring BMD in women planning pregnancy and then during each trimester of gestation and at 15, 129 and 280 days postpartum. In comparison with the control group, BMD declined markedly during gestation by 3.2 ± 0.5% in the total hip, 1.8 ± 0.5% in the lumbar spine, 2.4 ± 0.3% in the whole body and 4.2 ± 0.7% in the ultra-distal forearm. After delivery, BMD declined under the influence of breastfeeding [29]. One study analyzed the correlation of 25-hydroxycholecalciferol and BMD in patients with Gestational Diabetes Mellitus (GDM). Elevated blood glucose levels are connected with reduced 25-hydroxycholecalciferol expression, which reduces BMD and leads to impaired bone metabolism [30]. N-telopeptides (NTX), Pyridinoline (PYD) or Deoxypyridinoline (DPYD) as markers of bone resorption in urine during lactation seems interesting (Figure 1). Erin M Kyle et al. found that these 3 urinary markers decreased from early postpartum to 12 months postpartum [31]. Urine markers may be a more affordable and available measurement of BMD and better illustrate present bone status in comparison with DXA, which only offers a static picture of BMD [32].

Mineral status during pregnancy: The aim of this work was to present available data concerning the correlation between blood vitamin D levels and BMD. The main role of vitamin D is to preserve normal calcium and phosphorus concentrations, as phosphorus and calcium are both necessary for bones. Adequate proof of the impact of vitamin D and calcium supplementation on mother's bone mass is still lacking in the literature.

In 2019 assessed BMD values among 93 women aged 18-40 years at 30 days postpartum using DEXA technology. They found that low levels of 25-hydroxycholecalciferol were directly proportionately associated with low BMD, as well as with reporting postpartum back pain [33]. Paper published by William W K To et al. present data on 450 pregnancies with gestational hypertension using QUS. The patients with hypertension had a slightly higher mean BMD loss compared to patients with blood pressure in reference values, probably due to the small number of women with gestational hypertension 4.8% (n = 22) [34]. Dahlman et al. examined the relationship between blood vitamin D concentrations and BMD in 60 women using DXA at 12 weeks' gestation and 6-12 months postpartum. They found no statistically relevant connection between 25-hydroxycholecalciferol concentrations and BMD measurements [35]. Also, a study by Wei Wei et al. using DXA on a group of 301 pregnancies who had BMD measurements at 12-20 week of pregnancy and then at 0-14 week postpartum, discovered that vitamin D supplementation had no significant effect on BMD changes [36]. On the other hand, a study on 160 pregnant Japanese women indicated that 25-hydroxycholecalciferol blood concentrations and BMI in the first trimester of pregnancy were associated with bone mass in breastfeeding women from the time of delivery to 1 year postpartum [37].

Furthermore, the calcium supplementation in pregnancies with insufficient calcium intakes could disturb metabolic adjustment and could not favor the health of maternal bone [38]. A systematic review conducted in Finland analysed the titles and abstracts of 3,555 records, including seven randomised controlled trials did not confirm a beneficial effect of calcium supplementation on maternal BMD after childbirth or during lactation, or on offspring BMD, even with low dietary calcium intake. The effect of calcium supplementation on maternal and offspring bone health was considered unclear due to ambiguous study results [14]. Contradictory to these studies is the Chinese DXA study, which concluded that Ca and/or milk supplementation during gestation is linked with higher BMD [39]. The Shanghai work suggested that Ca levels should be included in the routine examination of pregnant women, but correlations between Vitamin D and BMD were not statistically significant [28]. Shao et al. in a trial of 130 women demonstrated that BMD decrease, measured by QUS of the heel bone between the start and end of pregnancy, was not associated with vitamin D status. Levels of calcium, phosphorus and alkaline phosphatase were significantly negatively correlated with BMD during gestation [28]. Another less invasive method of testing is the measurement of the bone resorption marker, C-Terminal Telopeptide of Type I Collagen (CTX) in the urine. In one study on approximately 400 women, CTX and 25-hydroxycholecalciferol were measured in early and late pregnancy. Cholecalciferol reduces the increase in CTX in maternal urine, but continues to increase during pregnancy [40]. Most of the work published to date has shown a relationship between vitamin D3 concentration and calcium on maternal bone mass. However, their effect on BMD is still not fully understood.

Postpartum mineral status: Postpartum period and lactation can affect woman's bone status due to the increased demand for calcium due to developing fetus and the transfer of calcium to breast milk during lactation. It should be noted that the newborn skeleton has a calcium (Ca) content of 20 to 30 g. Mother's bone minerals could be mobilised for the development of the baby's bones, although there is limited proof of pregnancy-derived mineral mobilization [41]. During lactation, the mother supplies the baby with 200-400 mg of calcium per day (up to 1000 mg if she is nursing twins) and 120 mg of Ca from milk during the next 6 months (extra Ca derives from foods) [13]. This increased Ca requirement is met through a 5-10% loss of mineral skeletal content over 6 months of lactation. The amount of calcium transferred to the baby from the mother's milk is greater than during the entire period of pregnancy [42]. Another postpartum study assessed BMD using DXA at 4-6 weeks, 6 months and 12 months. Postnatal BMD reduced by 1.4% in the total body and 3.1% of the double femur [31]. Brembeck et al. found that at 1,5year postpartum, both cortical volumetric BMD (vBMD) and trabecular thickness were lower in women with long lactation [43]. Most studies suggest that BMD in the first half of the year approaches full recovery after postweaning, however, some studies did not show a full return to baseline BMD [44-49]. Women who breastfed for a full year had a greater decrease in BMD than those who stopped breastfeeding earlier [31]. They also studied whether physical activity or aerobics affects changes in BMD across the first postpartum

year. Studies have not indicated an effect of physical activity on BMD [31]. Both vitamin D and calcium are essential elements in the prophylaxis and cure of osteoporosis. More difficult and inconclusive seems to be the work on vitamin D3 and its effect on BMD. A meta-analysis from New Zealand including 23 papers and 4082 participants indicated that there were 6 results of meaningful benefit, 2 of significant harm and the rest were non-essential [50]. Clearly, new and better planned studies are required to examine the impacts of Vsitamin D3 and Ca on BMD. On the other hand, diseases affecting calcium absorption or supply (lactose intolerance, coeliac disease) may contribute to maternal skeletal depletion in the last trimester [13]. Kovacs et al. described a woman taking 229 mg of calcium per day who experienced multiple vertebral compression fractures during gestation [51]. He suggested that the calcium supply was insufficient for her own pre-pregnancy needs. Pregnancy in her case led to significant resorption of calcium from the subject's bones. The majority of published work has indicated that postpartum BMD decreases but it is not clear whether it spontaneously returns to its original level or whether adequate calcium and vitamin D3 supplementation is needed.

Is parity associated with reduced BMD?: Pregnancy is one of the risk factors for the risk of developing osteoporosis. In one paper from Nantong, China, which studied 924 postmenopausal women aged 45-65 years, we can read that ≥ 6 pregnancies were related to reduced lumbar spine BMD, but not femoral neck BMD [52]**.** A number of other papers also show an association between number of pregnancies and BMD [53-55]. In contrast, Bolzetta et al. investigated whether breastfeeding duration and number of pregnancies are risk factors for vertebral fractures. He indicated that women with vertebral fractures breastfed longer and gave birth more times than other women**.** Breastfeeding for over 1.5 years was related to a two-fold risk of vertebral fractures [56]**.** Parity is also related to the risk of hip fracture [57]. Work examining the sensitivity of the WHO FRAX tool also indicated that pregnancy is a major predictor of fractures, independent of age, BMD and fracture history [58].

These studies have their limitations. It is challenging to isolate the impact of parity from the lactation.

Pregnancy and lactation-associated osteoporosis (PLO): Another issue is osteoporosis associated with pregnancy and lactation (PLO), which is a type of premenopausal osteoporosis. It develops fragility fractures, mostly in the third trimester of pregnancy and in breastfeeding women [51]. The disease usually affects women of slim physique, primiparous women and usually manifests itself in the third trimester or early postpartum. Due to the rare nature of the disease, many patients are left undiagnosed. Patients themselves do not have the typical clinical risk factors for postmenopausal osteoporosis, and patients do not show symptoms of the disease, making a diagnosis of PLO challenging. If symptoms do appear, the most common symptom is bone marrow swelling and vertebral fractures that cause acute low back pain [59,60]. Previously it was thought that the prevalence of PLO was estimated to be 4 to 8 for every million patients [61]. According to a retrospective cohort study based on real-world data, the incidence of PLO is estimated at 460 per million deliveries. The development of PLO was related with high maternal age and ovulation disorder. Vertebral fracture was the most frequent PLO fracture [62]. A 6-year follow-up study indicated that almost 25% of patients with PLO will suffer a subsequent fracture, and this fracture risk is associated with the fracture number at the time of the diagnosis [63]. The works published so far have indicated that PLO and PMOP are a particular problem and it is a much more common phenomenon than previously thought.

2. Impact of maternal BMD on offspring's BMD and teeth: An interesting question is the effect of Ca and Vitamin D supplementation in pregnancy on offspring's bone health and dental firmness. Publications in this regard are conclusive. A randomised, placebo-controlled, double-blind study included 125 women who took 1,500 mg of calcium daily, and showed no differences in infant birth weight, breast milk calcium concentration, growth or bone mineral status in the first year of life [64]. Another randomized controlled trial indicated similar results to the work above. BMD of the offspring at 5 years of age is neither related to maternal calcium intake nor to maternal bone resorption during pregnancy [65]. Similarly, in the case of vitamin D, no relationship between pregnancy status and bone mineralisation has been demonstrated [66]. This was also confirmed by another 26-year follow-up [67]. On the other hand, a study from Denmark involving 623 women reached a different conclusion. This study suggests that children of mothers who received Vitamin D at a dose of 2800 IU had a 60% reduced risk of fractures compared to those children of those mothers who received 400 IU/day [68]. In contrast, another study found that maternal 25-hydroxycholecalciferol before 16 weeks' gestation was positively related to bone mineral content and BMD in boys, but not in girls [69]. In conclusion, a systematic review and meta-analysis of randomised controlled trials, including 23 studies involving 5390 participants, showed that there is a lack of evidence for its effect on long-term growth in children [70]. A follow-up study of a randomised controlled trial conducted in Argentina showed that at around 12 years of age, children whose mothers obtained calcium supplementation during pregnancy demonstrated a considerable decrease in tooth decay [71]. To further investigate the effect of vitamin D and calcium supplementation during pregnancy on the BMD of the offspring, additional long-term and larger randomised trials are needed.

Conclusion

It's important for healthcare providers to monitor and support women's bone health during the postpartum period to minimize the risk of osteoporosis and other bone-related complications later in life. Overall, available data suggest that bone turnover increases during pregnancy, especially during the third trimester. There are real but small declines in BMD throughout the skeleton that require a sufficiently large cohort to be detected with confidence. Increased bone resorption occurs during the third trimester of pregnancy and is likely to result in some bone loss, with most women experiencing a moderate decline in BMD until delivery. Increased bone resorption and loss are more likely in women who do not absorb enough calcium to meet the combined needs of themselves and their offspring. Inadequate dietary calcium intake probably contributes to the increased risk of osteoporosis associated with pregnancy.

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