

Calcium and bone disorders in pregnancy

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ABSTRACT

Significant transplacental calcium transfer occurs during pregnancy, especially during the last trimester, to meet the demands of the rapidly mineralizing fetal skeleton. Similarly, there is an obligate loss of calcium in the breast milk during lactation. Both these result in considerable stress on the bone mineral homeostasis in the mother. The maternal adaptive mechanisms to conserve calcium are different in pregnancy and lactation. During pregnancy, increased intestinal absorption of calcium from the gut mainly due to higher generation of calcitriol (1,25 dihydroxy vitamin D) helps in maintaining maternal calcium levels. On the other hand, during lactation, the main compensatory mechanism is skeletal resorption due to increased generation of parathormone related peptide (PTHrP) from the breast. Previous studies suggest that in spite of considerable changes in bone mineral metabolism during pregnancy, parity and lactation are not significantly associated with future risk for osteoporosis. However, in India, the situation may not be the same as a significant proportion of pregnancies occur in the early twenties when peak bone mass is not yet achieved. Further, malnutrition, anemia and vitamin D deficiency are commonly encountered in this age group. This may have an impact on future bone health of the mother. It may also probably provide an opportunity for health care providers for prevention. Other metabolic bone diseases like hypoparathyroidism, hyperparathyroidism and pseudohypoparathyroidism are rarely encountered in pregnancy. Their clinical implications and management are also discussed.

Key words: Bone mineral, calcium, lactation, osteoporosis, pregnancy, vitamin D

INTRODUCTION

In the non-pregnant state, calcium homeostasis is maintained mainly by the intricate inter-relationship between parathormone (PTH) and vitamin D.^[1] PTH secreted from the parathyroid glands in response to a fall in serum calcium level mediates skeletal resorption of calcium through its effect on osteoclasts. It also enhances renal tubular reabsorption of calcium by stimulating 1-alpha hydroxylase in the kidneys that promotes conversion of 25 hydroxy vitamin D to 1,25 dihydroxy vitamin D [1,25(OH)₂ D]. This in turn helps in intestinal absorption of calcium. The calcium physiology and maternal adaptations to meet

the rising demand of calcium from the fetus are discussed below.

CALCIUM HOMEOSTASIS DURING PREGNANCY: PHYSIOLOGY

Calcium homeostasis in pregnancy is slightly different from that of non-pregnant state to meet the calcium demands of the mother and fetus.

Calcium

At birth, about 30 g of calcium is present in a term neonate.^[1,2] This amount of calcium is actively transferred across the placenta and most of it occurs during the third trimester when the collagen matrix is rapidly ossified. Total calcium level is decreased during pregnancy due to hemodilution associated low albumin. Albumin-corrected calcium and ionized calcium values remain normal throughout pregnancy.^[2] Theoretically, the calcium demand may be met by increased resorption of maternal skeleton, increased absorption or decreased urinary excretion. Much of the calcium conservation observed during pregnancy

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is due to increased intestinal absorption of calcium. This occurs mainly due to the increased generation of 1,25 (OH)₂D.^[2,3] Compared to non-pregnant state, the 24-hour urinary excretion of calcium during pregnancy is higher but fasting urinary calcium levels are similar. Hence, it is likely to be a reflection of increased absorption of calcium (absorptive hypercalciuria) and to a lesser extent due to higher calcitonin levels seen in pregnancy.^[2]

Other minerals

Serum levels of magnesium and phosphorus are usually within normal limits during pregnancy.^[1,2]

Parathormone

Previously, the assays for PTH were less specific and the levels were found to be high during pregnancy, leading to an erroneous assumption of a state of “hyperparathyroidism” during pregnancy.^[2] However, the modern immunometric assays that are specific for two sites and measure the intact PTH clearly show that the PTH levels are relatively low during the first trimester and remain normal through the rest of pregnancy. This relatively low PTH may be due to the suppressive effect of raised 1,25 (OH)₂D levels.^[2,4,5]

Parathormone related peptide

Parathormone related peptide (PTHrP) is a prohormone that produces multiple N-terminal, mid-molecule and C-terminal peptides which differ in their biological activities and specificities. However, none of these peptides have been systematically measured during pregnancy. The most studied is the large molecule which comprises 1–86 amino acids. The levels start rising usually around the mid-second to third trimester of pregnancy. It has several sources both from the fetus and the mother, including breast, myometrium, decidua, amnion and fetal parathyroids. Which one contributes more to the elevated level seen in pregnancy is unclear. Several roles of PTHrP are postulated from animal studies, including fetal calcium transfer and stimulating 1-alpha hydroxylase activity. Further, the carboxy terminal of PTHrP called “osteostatin” may suppress osteoclastic activity and may have a possible bone protection role in the mother.^[1,4,5]

Calcitonin

Circulating levels of calcitonin are high during pregnancy. The most likely sources are hypertrophied C cells of thyroid and possibly from breast and placenta. Though postulated to affect the maternal bone, human studies have not convincingly shown any significant effect of calcitonin on calcium metabolism during pregnancy.^[1,2]

Vitamin D

Serum 1,25 (OH)₂D level is increased during pregnancy up

to twice the upper limit observed in non-pregnant state.^[1,6] The total 1,25 (OH)₂D level (bound to vitamin D binding protein + free unbound fraction) may be elevated due to the increased binding globulins seen in pregnancy. However, studies have shown that free 1,25 (OH)₂D level is also raised and is likely to be a result of increased production rather than decreased clearance.^[6] Transplacental transfer of vitamin D takes place and the fetal levels are around 20% less than the maternal level as studied from cord blood. This rise in 1,25 (OH)₂D level is largely PTH independent and is mainly due to elevated 1-alpha hydroxylase activity in the maternal kidneys. High PTHrP, estrogen, prolactin and human placental lactogen may also augment the enzyme activity. Placenta and fetal kidneys may also be additional sources.^[1,6,7]

Other hormones

During pregnancy, various other hormones like estrogen, progesterone, growth hormone (human placental lactogen) and insulin-like growth factor 1 (IGF-1) which affect bone mineral homeostasis are increased. However, systematic studies addressing the role of each in the fetomaternal calcium physiology have not been done.^[1,2]

BONE CHANGES DURING PREGNANCY

Bone histomorphometric studies in animals suggest a slight increase or no significant change in bone mineral content during pregnancy. Systematic studies of bone biopsy and histomorphometry in human pregnancy are not available.^[1-3]

Serum markers of bone turnover have been studied in human pregnancy, but as in non-pregnant state, they also have several caveats in interpretation during pregnancy, viz. lack of normal values during pregnancy, correction for hemodilution, increased glomerular filtration rate, diurnal variation and difficulty in obtaining fasted samples. Further, contribution of these markers from the fetus and placenta cannot be excluded. Placental secretion of alkaline phosphatase results in elevation of total alkaline phosphatase and hence cannot be used as a bone marker in pregnancy. Overall, the bone marker studies do not confirm significant resorption during pregnancy. This again points to the main adaptive mechanism of calcium conservation during pregnancy, being increased intestinal absorption.^[1]

Bone mineral density (BMD) studies by Dual Energy X-ray Absorptiometry (DXA) scan or its other versions are contraindicated during pregnancy. Few studies in pregnant women where it was done immediately after delivery or after an abortion at various periods of gestation showed variable results precluding any concrete conclusions.

Further, change in bone volume and body composition during pregnancy may also interfere with bone density estimation by DXA.^[1,3]

Ultrasound estimation of bone density at calcaneus has been done with variable results and whether it truly reflects the changes in the axial skeleton is unclear.^[1]

Overall, the existing studies have insufficient power to clarify whether any significant bone loss occurs during pregnancy. It may be reasonable to decipher that pregnancy does not impair skeletal strength or density. Few epidemiological studies in post-menopausal osteoporosis have not demonstrated a relationship between parity and bone density.^[1,8-11]

CALCIUM HOMEOSTASIS DURING LACTATION

Calcium

During lactation, the mother undergoes a continued stress on calcium demand with production of breast milk. On an average, 300–400 mg of calcium is lost in breast milk daily.^[1] Except in mothers with vitamin D deficiency and low serum calcium levels, the calcium concentration in milk does not change.^[1,12] In contrast to the pregnant state, this demand is met mainly by increased resorption of calcium from the bone and partly by increased reabsorption from the kidneys.^[1-3] Both the effects are mediated by very high levels of PTHrP secreted by the breast and not by PTH. Intestinal absorption of calcium returns to pre-pregnant levels after delivery.

Other minerals/ions

Phosphorus level is marginally elevated above normal during lactation and is likely to be related to the dietary flux and decreased clearance seen during lactation. Magnesium level is not altered in lactation.^[1]

Parathormone related peptide

The level of this hormone increases by more than 1000-fold seen in pregnant state and the main source is the breast. Though it is biologically weak when compared to PTH, the high levels result in bone resorption and increased tubular reabsorption of calcium and also suppress PTH. Studies from hypoparathyroid mothers show that the calcium and active vitamin D requirement may significantly come down during lactational period.^[1,2,4,5]

Parathormone

Due to high levels of PTHrP during pregnancy, PTH remains low during lactation and gradually rises to normal level once weaning is started.^[1,4,5]

Calcitonin

The high serum calcitonin levels seen during pregnancy gradually fall to normal few weeks postpartum. Its role in bone physiology in human pregnancy is unclear.^[1,2]

BONE CHANGES DURING LACTATION

Loss of bone mass during lactation occurs mainly due to elevated PTHrP as well as hypoestrogenic state associated with high prolactin levels. BMD data suggest a 2–3% loss of bone per month during lactation. This is very significant as compared to 1–3% bone loss per year that occurs in menopause.^[1,3] Overall, observations suggest that during lactation, the obligate loss of calcium in the milk and PTHrP effect contribute more to bone resorption than hypoestrogenemia.^[2] Total alkaline phosphatase level drops to pre-pregnant levels immediately after delivery of the placenta but may be slightly elevated due to increased bone turnover.^[1-3]

Cross-sectional and longitudinal studies on bone turnover markers in lactation show an overall predominance of resorption markers. However, bone formation occurs rapidly and the density and turnover markers normalize rapidly within 2–6 months of weaning. Hence, in an otherwise healthy woman, the pregnancy and lactation induced bone changes may not have long-term effect on the skeletal health.^[1,3,8,9,13]

VITAMIN D DEFICIENCY IN PREGNANCY

Maternal vitamin D deficiency is associated with detrimental effects on the fetus/infant as well as complications for the mother during pregnancy.^[12] Fetal and neonatal risks include intrauterine growth retardation, neonatal hypocalcemic seizures, impaired postnatal growth, rickets in infancy and cardiomyopathy.^[12,14,15] Future risk of immune-mediated conditions like atopy, asthma and type 1 diabetes may also have a relation to vitamin D deficiency. Maternal adverse outcomes include possible increased risk of preeclampsia, gestational diabetes and increased rate of cesarean section.^[12,16]

In spite of being a tropical country with abundant sunshine, vitamin D deficiency is quite prevalent in India.^[17-19] A study on 207 mothers from rural and urban North India showed a prevalence of 83.6% and 84.3% of vitamin D deficiency (vitamin D deficiency defined in that study as <22.5 ng/ml), respectively.^[17]

As discussed above, physiological studies mainly from the developed countries show that the impact of the

huge calcium demand on the mother during pregnancy and lactation is reversible and usually does not affect the maternal skeleton significantly. Also, in a vitamin D and calcium replete healthy mother, it is unlikely to have an effect on the future bone health, especially osteoporosis, post-menopause. However, in our Indian setting of poor maternal nutrition and early pregnancy before peak bone mass being achieved coupled with severe vitamin D deficiency, the scenario may be different and further studies are needed to clarify the long-term impact on osteoporosis.^[17,18,20]

After extensive review of literature, the recent Endo Society guidelines recommend that the 600 IU of vitamin D that was the previous recommended daily allowance for a pregnant mother is not sufficient. To meet the demands of the growing fetus and to maintain the vitamin D level above the currently accepted optimum of >30 ng/ml, the mother needs to take at least 1500–2000 units of vitamin D (cholecalciferol) per day.^[19] If she is already on a prenatal multivitamin pill containing 400 IU of vitamin D, an additional 1000 units may be supplemented. Similarly during lactation, if the child is not on any supplementation, the mother needs to be on at least 1500–2000 units of vitamin D to satisfy the needs of the suckling infant and protect her bones with an optimal vitamin D level of >30 ng/ml.^[19]

OSTEOPOROSIS IN PREGNANCY

Osteoporosis is difficult to diagnose during pregnancy as DXA scan, the gold standard for diagnosing the condition, cannot be done during pregnancy.^[1] Occasionally, a pregnant woman may present with severe low back ache and may be diagnosed to have a vertebral fracture or osteoporosis. Pre-existing low bone mass or conditions which may affect bone health like low calcium intake and vitamin D deficiency cannot be ruled out in many such instances unless prior information is available.^[8,9] In a series of 35 women with osteoporosis in pregnancy, majority had a maternal history of fracture, possibly implicating a genetic basis.^[10] However, pregnancy itself is a state of relatively high bone turnover and may thus cause further deterioration in bone density in an already predisposed individual. Another point in favor of the role of pregnancy in this condition is that most of the cases recover within few months of delivery.^[1,9-11] Clinical manifestation usually includes severe back pain especially in the lumbar area and may be associated with collapse of the vertebrae. Usually, it presents in the last trimester or puerperal period of the first pregnancy. Management is conservative and most of the patients recover clinically and radiologically in 3–6 months postpartum. It usually does not recur in the

subsequent pregnancies. Though case reports of the usage of potent anti-osteoporotic agents like bisphosphonates, PTH analogues, and calcitonin have been reported, the reversible nature of the condition does not justify their routine use. They may be reserved for the most severe cases if at all.^[9-11,21]

Transient osteoporosis of hip (TOH): This is a distinct condition seen in pregnancy, in contrast to that discussed above. It is also called algodystrophy of the hip.^[1,10,22] The exact incidence of the condition is not known. The pathophysiology is more related to local factors and the various hypotheses include venous stasis due to gravid uterus, bone marrow edema/hypertrophy, reflex sympathetic dystrophy, compression of obturator nerve by the fetus, ischemia, trauma and viral infections. Clinical diagnosis is suspected when the patient presents with low back ache, unilateral or bilateral hip pain, limp or rarely with a hip fracture usually in the third trimester.^[1,10,23] Vitamin D deficiency with or without calcipenia may also need to be considered in the differential diagnosis. Magnetic resonance imaging (MRI) shows reduced bone density, increased water content especially in the femoral head and even joint effusion occasionally. Radionuclide imaging in postpartum situation may be helpful. In TOH, the femoral head takes up the agent; but in osteonecrosis of the femoral head, there is no uptake.^[24] This condition also usually recovers in 3–6 months both clinically and radiologically. However, recurrence of up to 40% has been reported in subsequent pregnancies. Bisphosphonates are contraindicated in pregnancy. However, use of intravenous pamidronate/zoledronic acid or oral alendronate in the postpartum period in women who did not show good recovery have been reported.^[21,25] Rarely, in severe cases, especially with fracture, surgical intervention including total hip arthroplasty may be required.^[22] From the obstetric point of view, in patients with bilateral involvement, cesarean section may be indicated.

Infrequently, women may present in the early part of lactation with fragility fracture.^[1,8,9] Like in pregnancy, a pre-existing low bone mass state cannot be ruled out. However, pathophysiologically, lactation is associated with more bone depletion mainly due to high levels of PTHrP as discussed above. Cessation of lactation helps in recovery along with adequate calcium and vitamin D supplementation as per the recent guidelines.^[19] Specific bone active agents like bisphosphonates may be used in the most severe cases.^[21]

HYPERPARATHYROIDISM IN PREGNANCY

Hypercalcemia is rarely encountered in pregnancy.^[11] The commonest cause of hypercalcemia in pregnancy is

hyperparathyroidism.^[26,27] It is associated with significant morbidity to the fetus and mother in more than two-thirds of the cases. Adverse fetal outcomes include increased rate of abortions, severe intrauterine growth retardation and still birth. Since the fetal parathyroids are suppressed during pregnancy in hyperparathyroidism, once the cord is clamped after delivery, the calcium level drops precipitously in the neonate and the suppressed parathyroids may not be able to respond well. This leads to severe hypocalcemic tetany and seizures requiring prolonged neonatal care. Conversely, mild to moderately severe hyperparathyroidism that is not diagnosed in the mother during pregnancy is detected only when neonatal hypocalcemia is evaluated.^[2,3,26-28] Total calcium estimation may pose some diagnostic difficulties during pregnancy as it is low in normal pregnancy. Any value of ionized calcium or albumin-corrected calcium higher than normal in pregnancy may need to be evaluated further. In the setting of high prevalence of vitamin D deficiency, even high normal calcium may carry significance. As discussed above, PTH levels are low to mid-normal in pregnancy and higher than normal values in the background of high calcium may point to the diagnosis of primary hyperparathyroidism.

Classical presentation of primary hyperparathyroidism like bone pains, fracture or renal stones occurs less commonly in pregnancy and many cases are picked up only during routine evaluation with calcium profile or rarely when they present with hypercalcemic crisis. Symptoms of hypercalcemia like nausea, vomiting, malaise and drowsiness may be attributed to those of hyperemesis gravidarum seen in pregnancy, unless very severe and investigated further. Since significant calcium transfer to fetus occurs during pregnancy, severe hypercalcemia may not occur. However, in the postpartum period, the patient may present with severe hypercalcemia which is further aggravated by the high PTHrP during lactation.^[1,26-28]

Surgical management of the parathyroid adenoma during second trimester is recommended by many authors due to the associated significant adverse fetal outcome. This may not be always feasible in many settings and medical management is necessary. In mild cases, hydration alone may ameliorate high calcium levels. In cases with more severe hypercalcemia, calcitonin may be tried as it does not cross the placenta.^[1,2] Bisphosphonates are very effective in reducing calcium levels and are the agents of choice in non-pregnant setting. However, they are contraindicated in pregnancy. Oral phosphates or phosphate enema are modestly effective in reducing calcium levels. But side effects like diarrhea and hypokalemia need to be monitored. Use of cinacalcet, which is a calcium sensing receptor agonist, to suppress the parathyroids has been reported,

but concerns regarding adverse effects on the fetus are not clear.^[29] Surgical removal of the parathyroid tumor in second trimester seems to be the most definitive treatment in severe cases. Women who have been conservatively managed during pregnancy also need to undergo surgical treatment in the postpartum period.

HYPOPARATHYROIDISM IN PREGNANCY

It is not uncommon to encounter hypoparathyroidism as a pre-existing condition during pregnancy.^[1,2,30,31] Diagnosing hypoparathyroidism for the first time in pregnancy may pose some problems as calcium levels are usually low during normal pregnancy. However, ionized calcium whose levels remain normal during pregnancy may help in confirming the diagnosis. The principle of management of hypoparathyroidism during pregnancy is to maintain near normal calcium in the mother to prevent fetal hyperparathyroidism which has serious consequences including fetal death.^[1] In a patient on treatment for hypoparathyroidism, the requirement of calcitriol and calcium may come down during the latter half of pregnancy and more so during lactation due to the effects of PTHrP.^[32] Hence, close monitoring of calcium levels to titrate the dosage is mandatory to prevent adverse fetal consequences. Inadvertent excessive use of calcitriol may result in hypercalcemia.^[33]

PSEUDOHYPOPARATHYROIDISM IN PREGNANCY

Pseudohypoparathyroidism (PHP) is characterized by resistance to the action of PTH and is very rarely encountered in pregnancy. Hence, the management is less well documented.^[34] Reports on requirements of calcitriol and calcium are variable. In some cases, calcitriol requirement reduced presumably due to increased generation from non-PTH/PTHrP dependent sources like placenta. The management goal here again is to prevent maternal hypocalcemia which may cause fetal hyperparathyroidism. During lactation, since the placental source of 1,25 (OH)₂D is lost and PHP is associated with resistance to renal action of PTHrP, the dosage of calcium and calcitriol usually reverts to pre-pregnant levels.^[1,34]

CONCLUSIONS

Maternal adaptations differ between pregnancy and lactation to meet the mineral demands of the growing fetus. Increased intestinal absorption of calcium during pregnancy and skeletal resorption of calcium during lactation form the main maternal adaptive mechanisms

to meet the raised requirement. In an otherwise healthy pregnant woman, the mild bone resorption which occurs during pregnancy and lactation is rapidly reversed after weaning, resulting in nearly no significant effect on the bones. However, it is likely that maternal malnutrition and vitamin D deficiency, as in our Indian scenario, may lead to more severe skeletal depletion during this reproductive period and may probably have long-term effects on bone health, including an increased risk of skeletal fragility. Further elucidation of the mechanisms of bone loss and restoration during pregnancy and lactation may help evolve newer avenues of management of metabolic bone diseases and osteoporosis. Currently, in our population, we need to focus our emphasis on maternal nutrition, especially adequate vitamin D and calcium intake, which may pave way in the long run for prevention of future bone health related conditions like osteoporosis.

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