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INVITED REVIEW ARTICLE

Calcium: A Nutrient in Pregnancy

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About the Author

Ashok Kumar studied at the All India Institute of Medical Sciences, New Delhi, and obtained his Ph.D. from Tokyo Women's Medical University, Japan. He has a special interest in maternal health and has published research papers on thyroid hormonal changes during pregnancy, calcium supplementation during pregnancy for preventing hypertensive disorders (included in a Cochrane review, 2010), hepatitis E (reviewed in Obstetrics and Gynecology Survey) and C during pregnancy, latent celiac disease in reproductive performance, dydrogesterone in recurrent pregnancy loss (included in the European Progestin Club guidelines, 2015) and preeclampsia. He participated in the international, multicentre 'CORONIS' trial that aimed to assess cesarean section surgical techniques and maternal morbidity. He has delivered Yuva FOGSI Oration 'Thyroid disorders during pregnancy' at North Zone Yuva FOGSI Conference, 2004 and Golden Jubilee Commemoration Award Lecture of National Academy of Medical Sciences (India) 2013 and won FOGSI–Corion award 2008 for the best scientific work. Dr Kumar has authored the book 'Essentials of Gynaecology' and edited the books: Common Medical Disorders in Obstetrics and Drugs in Obstetrics and Gynecology.

Maternal and newborn health and nutrition status are the significant indicators of the burden of any disease. Calcium is the most abundant mineral in the body and is essential for many diverse mechanisms and reactions such as muscle contraction, bone formation and enzyme and hormone functioning. Calcium in extracellular fluid maintains its physiologic equilibrium is in three forms namely ionic, protein bound and complexed.

Calcium Metabolism During Pregnancy

During the course of pregnancy, a remarkable series of physiologic changes occur, aimed at preserving maternal homeostasis while at the same time providing for fetal growth and development. These changes which have direct implications on calcium metabolism include falling albumin level, expansion of extracellular fluid volume, increase in renal function and placental calcium transfer. Calcium homeostasis is a complex process involving calcium and three calcitropic hormones—parathyroid hormone, calcitonin and 1,25-dihydroxyvitamin D 3 (1, 25(OH)2D). Total serum concentrations fall during pregnancy due to hemodilution. This fall mainly occurs in albumin bound

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fraction of the total calcium and due to fall in serum albumin. Ionized calcium levels do not differ from that in non-pregnant women. However, constant blood levels of calcium are maintained by homeostatic control mechanism. Calcium homeostatic response during pregnancy includes increase in intestinal calcium absorption, increase in urinary excretion of calcium and increase bone turnover. The skeleton of a newborn baby contains approximately 20–30 g of calcium [1]. The bulk of fetal skeletal growth takes place from midpregnancy onward, with maximal calcium accretion occurring during the third trimester.

Absorption

The increase in calcium absorption is directly related to maternal calcium intake. Ritchie et al. [2] reported that women with a daily average calcium intake of 1171 mg during pregnancy absorbed 57% during the second trimester and 72% during the third trimester.

The mechanism of calcium absorption involves binding of calcium to a specific protein (calcium-binding protein) whose synthesis is stimulated by active forms of vitamin D (1,25-dihydroxyvitamin D). Maternal serum 1, 25(OH)2D levels increase twofold during pregnancy, allowing the intestinal absorption of calcium also to double. Serum 25-hydroxy vitamin D (inactive form of vitamin D) levels do not change during pregnancy, but an increase in 1-a-hydroxylase and additional synthesis in the placenta allows for an increase in the conversion of 25-hydroxy vitamin D to 1, 25(OH)2D [3].

Other calcitropic hormones affecting maternal calcium metabolism is parathyroid hormone (PTH). During the first trimester, parathyroid hormone (PTH) levels in women consuming adequate amounts of calcium decrease to low-normal levels and then increase to the higher end of normal in the third trimester, reflecting the increase in calcium transfer from mother to fetus. PTH promotes increased renal synthesis of 1,25-(OH)2D3, which acts in concert with PTH to meet the calcium demands of gestation.

Although PTH levels typically do not increase above normal during pregnancy, levels of a prohormone, parathyroid hormone receptor protein (PTHrP) do increase in maternal circulation. PTHrP is recognized by PTH receptors and therefore has PTH-like effects. This prohormone is produced by mammary and fetal tissues to stimulate placental calcium transport to the fetus. PTHrP may also protect the maternal skeleton from bone resorption by increasing both calcium absorption in the small intestine and tubular resorption in the kidney.

Thus, the principal maternal adjustment during pregnancy is increasing parathyroid hormone and PTHrP secretion which maintains the serum ionic calcium level within its characteristically narrow physiologic range in the face of extracellular fluid volume expansion, renal function increase and placental calcium transfer. However, even with these high rates of absorption, maternal and fetal needs may not be met in women with chronically low calcium consumption (<500 mg/day) [3].

Maternal calcitonin levels have been reported to be increased in early pregnancy. A rise in calcitonin may protect the maternal skeleton against PTH-induced resorption, while permitting the latter hormone's gut and kidney effects to continue.

Excretion

Physiological hypercalciuria occurs during pregnancy as a result of increased maternal calcium absorption. Interestingly, urinary calcium is within normal limits during fasting but increases postprandially, indicating that elevated excretion is related to the increase in calcium absorption. Urinary calcium excretion has been shown to increase by as much as 43% between prepregnancy and the third trimester, reflecting the 50% increase in the glomerular filtration rate (GFR) that also occurs during pregnancy. For women with low dietary calcium intake (<500 mg/day), urinary calcium is more tightly regulated. Although urinary calcium excretion increases during pregnancy, the increase in intestinal calcium absorption is not ameliorated, and net maternal calcium retention is positive [3, 4].

Fetus

The cardinal feature of calcium metabolism in the fetus is the active placental transport of large quantities of calcium, whereas PTH and calcitonin do not cross the placenta. Fetal calcium levels suggest that ionized calcium is transferred from the mother to the fetus at a rate of 50 mg/day at 20 weeks of gestation to a maximum of 330 mg/day at 35 weeks of gestation [4]. The resultant fetal hypercalcemia suppresses the fetal parathyroid and stimulates fetal calcitonin release. 25-hydroxyvitamin D appears to cross the placenta freely but the placental permeability of 1,25(OH)2D is questionable. With birth, the placental source of calcium terminates abruptly and the serum calcium level declines, perhaps aggravated by hypoparathyroidism and/or hypercalcitonemia residual from fetal life. After reaching a nadir between 24 and 48 h of age, the neonatal calcium level stabilizes and then rises slightly to adult levels.

Calcium and Maternal Health

Calcium supplementation in pregnancy has the potential to reduce adverse gestational outcomes, in particular by decreasing the risk of developing hypertensive disorders

during pregnancy, which are associated with a significant number of maternal deaths and considerable risk of preterm birth, the leading cause of early neonatal and infant mortality.

Preeclampsia

An inverse relationship between calcium intake and hypertensive disorders of pregnancy was first described in 1980 [5]. This was based on the observation that Mayan Indians in Guatemala, who traditionally soak their corn in lime before cooking, had a high calcium intake and a low incidence of preeclampsia and eclampsia. A very low prevalence of preeclampsia had been reported from Ethiopia where the diet contains high levels of calcium [6].

We have done a study on a cohort of 524 healthy primigravidas in a tertiary care hospital in North India and observed that daily supplementation of 2 grams of elemental calcium in pregnancy was associated with 66.7% risk reduction in developing preeclampsia. This group of women had a low mean baseline calcium intake (313.83 ± 203.25 mg/day) which is lower than the recommended daily dietary intake [7].

A Cochrane review of 13 trials involving 15,730 pregnant women reported that the average risk of preeclampsia was reduced in those receiving calcium supplements compared to placebo [relative risk (RR) 0.45; 95% confidence interval (CI) 0.31–0.65]. The review concluded that pregnant women consuming low amounts of calcium (mean calcium intake <900 mg/day) could reduce their risk of preeclampsia by 31–65% if they consumed an additional 1000 mg of calcium each day. The Cochrane review found good quality evidence that calcium supplementation with high doses (>1 g daily) during pregnancy is a safe and relatively cheap way of reducing the risk of preeclampsia, especially in women from communities with low dietary calcium and those at increased risk of preeclampsia [8].

Imdad et al. analyzed 15 randomized control trials and showed that calcium supplementation (0.5–2 gm/day) during pregnancy reduced risk of preeclampsia by 52% (RR 0.48; 95% CI 0.34–0.67) and that of severe preeclampsia by 25% (RR 0.75; 95% CI 0.57–0.98). There was no effect on incidence of eclampsia (RR 0.73; 95% CI 0.41–1.27). There was a significant reduction for risk of maternal mortality/severe morbidity (RR 0.80; 95% CI 0.65–0.97). A subgroup analysis for incidence of preeclampsia according to dosage (<2 vs. 2 g/day) showed that effect is more pronounced and statistically significant in studies that used a dose of 2 g/day (RR 0.39; 95% CI 0.23–0.67) compared with those that used a dose <2 g/day (RR 0.56; 95 CI 0.30–1.03). This indicates that the most effective dose for calcium supplementation during pregnancy is 2 g/day [9].

Low calcium intakes during pregnancy may stimulate PTH secretion, increasing intracellular calcium and smooth muscle contractibility and/or release renin from the kidney, leading to vasoconstriction and retention of sodium and fluid. These physiological changes can lead to the development of preeclampsia.

WHO recommends an intake of 1.5–2.0 g elemental calcium/day with the total daily dosage divided into three doses (preferably taken at mealtimes) from 20 weeks' gestation until the end of pregnancy. Target group includes all pregnant women, particularly those at higher risk of gestational hypertension and in areas with low calcium intake [10].

In our study, biochemical markers of bone turnover are found to be greater in preeclampsia compared with normal pregnancy [11]. This may be due to the multisystem involvement of the disease that occurs in response to circulating factors released during the development of preeclampsia. Increased levels of proinflammatory cytokines and occurrence of endothelial dysfunction in preeclampsia have been implicated in stimulating osteoclast activity and hence increased bone resorption. The levels of NTx (N-telopeptide of type 1 collagen), marker of bone resorption are increased significantly during pregnancy in women with preeclampsia ($P < 0.02$) [11]. This further necessitates the supplementation of elemental calcium during pregnancies complicated with preeclampsia, for preservation of maternal skeleton.

Preterm Birth

Calcium supplementation has shown effectiveness in reducing the risk of preterm delivery in women with low calcium intakes. A possible mode of action of calcium is that it reduces parathyroid release and intracellular calcium and so reduces smooth muscle contractility. By this mechanism, calcium supplementation reduces uterine smooth muscle contractility and prevents preterm labor and delivery.

A study done on 524 North Indian primigravidas with low mean daily calcium intake showed a significant reduction in risk of preterm births following calcium supplementation in pregnancy. Two gram of elemental calcium was supplemented daily between 12 and 25 weeks of pregnancy, and compared with the placebo group, there was a significantly lower risk of preterm delivery in the calcium group than that in control group (12.7 and 7%, respectively, OR 0.51; 95% CI 0.28–0.93) [7].

A review of 11 randomized trials by Imdad et al. [9] showed 24% reduction (RR 0.76; 95% CI 0.60–0.97) in

preterm births following calcium supplementation (0.5–2 gm/day) in pregnancy. However, the latest Cochrane review reports that there are no clear additional benefits to calcium supplementation in prevention of preterm birth [12]. There were no statistically significant differences between women who received calcium supplementation and those who did not in terms of reducing preterm births less than 37 weeks' gestation or less than 34 weeks' gestation [12].

Birth Weight

Abalos et al. [13] randomized 510 healthy, primiparous pregnant Argentinean women at less than 20 weeks gestation and administered either placebo ($n = 230$) or calcium supplements (1500 mg calcium/day in three divided doses; $n = 231$), no significant differences were found in birth weight and anthropometric measurements at delivery in the two groups. Imdad et al. in their review showed a reduction of 15% in low birth weight (RR 0.85; 95% CI 0.72–1.01) following calcium supplementation. However, the results were statistically nonsignificant [9].

Postpartum Hemorrhage

Postpartum hemorrhage (PPH) is a leading cause of maternal morbidity and mortality worldwide and is caused most commonly by uterine atonicity following delivery. The first-line agent used in the prevention and treatment of PPH is oxytocin, which acts by binding with the oxytocin receptor found on myometrial cells to cause uterine contraction. It does this by increasing levels of calcium within the myometrial cell, which promotes contraction. Following prolonged exposure to oxytocin, there is desensitization of the myometrium resulting in a significant reduction in contractility upon delivery of further oxytocin.

Calcium is an important messenger required within the uterine muscle cell to result in muscle contraction following administration of oxytocin. A physiological level of calcium is known to provide optimal contractility to normal myometrium. Characterization of low, normal or high calcium levels in a setting of prolonged exogenous oxytocin administration may provide guidance for the use of exogenous calcium as a uterotonic adjunct. In a study done on 36 women, Talati et al. [14] concluded that in oxytocin-naive myometrium, normocalcemia provides superior oxytocin-induced contractility compared with hypocalcemic conditions.

Short-Term Bone Changes

Changes in skeletal calcium content have been assessed through the use of sequential bone density studies during pregnancy. Due to concerns about fetal radiation exposure, few such studies have been done. Such studies are confounded by the changes in body composition and weight during normal pregnancy, which can lead to artifactual changes in the bone density reading obtained. Three recent studies have used dual-energy X-ray absorptiometry (DXA) before conception and after delivery to assess bone mineral density. In two of the studies, maternal lumbar spine bone density had dropped 4.5 and 3.5%, respectively, when preconception readings were compared with readings obtained within 4 and 6 weeks postpartum. The third study found no change in lumbar spine bone density measurements obtained before conception and within 1–2 weeks after delivery [2, 15, 16]. The BMD values at the anteroposterior lumbar spine (L2–L4) and femoral neck by using DXA in multiparous North Indian women aged 20–60 years showed decline with advancement in age indicating that pregnancy probably aggravates to the bone loss in the women with faulty dietary pattern and quality.

Osteoporosis and Pregnancy

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. In India, a significant proportion of pregnancies occur in the early twenties when peak bone mass is not yet achieved [17, 18]. Further, protein energy malnutrition calcium and vitamin D deficiency are commonly encountered in this age group [18]. Poor prepregnancy bone mineral density, low calcium and vitamin D intake during pregnancy and poor socioeconomic status puts these women on increased risk of low bone mass and later developing osteoporosis.

Calcium and Infant Health

Interpreting the effect of maternal calcium intake during pregnancy on infant bone density measured during the postpartum period is challenging. In a clinical trial conducted by Koo et al., 256 women were randomized before 22 weeks gestation to 2 g/day of elemental calcium or placebo until delivery. Dual-energy X-ray absorptiometry measurements of the whole body and lumbar spine of the neonates were performed within the first week of life. The total body bone mineral content was significantly greater in infants born to calcium-supplemented mothers (64.1 ± 3.2 g) than that in the placebo group (55.7 ± 2.7 g). Maternal calcium supplementation averaging 1300 mg/day from midpregnancy to term can

enhance fetal bone mineralization in women with low calcium intake [19].

Dietary Intake of Calcium

Average daily dietary intakes of the 255 study subjects from North India were as follows: energy 1563 ± 267 kcal; protein 48.7 ± 8.7 g; fat 31.3 ± 9.3 g; and calcium 543.7 ± 161.3 mg. Diets were typically cereal based with a very low intake of protective foods such as milk and milk products, flesh foods, fish, fruits and vegetables. Animal sources of protein were consumed irregularly [18].

Women who chronically consume low amounts of calcium (<500 mg/day) may be at risk for increased bone turnover during pregnancy. If diet does not provide enough calcium, then body steals it from the bones. Dietary calcium intake has a negative correlation with bone resorption markers. High calcium intake is associated with improved calcium balance, perhaps providing a protective effect against bone loss during pregnancy.

Zeni et al. [20] reported that as dietary calcium intake increased in women with previously low intakes, production of 1-a-hydroxylase was upregulated to increase activation of 1,25(OH)2D, resulting in increased calcium absorption. This increase in calcium absorption decreased markers of bone resorption. This suggests that an increase in 1,25(OH) 2D may allow the maternal skeleton to store calcium in advance of peak fetal demands later in pregnancy.

National dietary surveys of American Diet Association have reported that the median calcium intake of women of reproductive age is 467 mg/day for African-American women and 642 mg/day for Caucasian women [21].

A study conducted in North India on pregnant women reported a low calcium intake of less than 300 mg/day in nearly half of the study population. However, no relationship was reported between the daily intake of calcium and the occurrence of hypocalcaemia, attributing the same to faulty dietary habits and vitamin D deficiency [22].

The part of the dietary calcium coming from plant sources is known to have low bioavailability. Also, the inhibitors of calcium absorption such as phytates and oxalates are abundant in the vegetarian diet and retard the absorption of dietary calcium. Oxalates form insoluble salts with dietary calcium, which are eventually excreted in the feces [23].

Moreover, absorption of calcium could be hampered by vitamin D deficiency as it is the major factor influencing absorption of calcium from the gut. A study on 418 North Indian pregnant women reported deficiency of vitamin D (<32 ng/ml) in 95.4% population with severe deficiency of vitamin D (<10 ng/ml) in 34.4% of the population. Women with severe deficiency of vitamin D had low mean serum calcium levels of 7.13 ± 1.41 mg/dl due to poor calcium absorption [24]. Thus, in a population with widespread prevalence of vitamin D deficiency with low dietary calcium intake, the problem is likely to worsen during pregnancy because of the active transplacental transport of calcium to the developing fetus.

Therefore, it is recommended that women with low calcium intakes should either increase their intake of food sources of calcium, such as milk or cheese, or, add a supplement that provides around 600–1000 mg of calcium per day. Women with lactose intolerance need careful assessment of their calcium intake because they tend to drink little milk and to have relatively low calcium intakes [25]. Women should also get adequate sunlight exposure and increase their intake of vitamin D supplements.

We have also reported that various demographic factors like socioeconomic status and educational status affect calcium intake. With improved educational level and per capita income, they have better living conditions and better nutritional intake [26] and better bone mineral density [18].

Hypercalcemia in Pregnancy

Hypercalcemia is rarely encountered in pregnancy. The commonest cause of hypercalcemia in pregnancy is hyperparathyroidism. 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. 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 [17].

Hypercalciuria is present when urinary excretion of calcium exceeds 250 mg/day in women, which frequently occurs during pregnancy as a consequence of increased intestinal absorption and increased GFR. Hypercalcemia and hypercalciuria can cause renal insufficiency (GFR < 60 mL/min 114), vascular and soft tissue calcification and nephrolithiasis. As a result of the hypercalciuria that occurs naturally during pregnancy, pregnant women are at an increased risk for developing kidney stones [3].

Conclusion

Significant maternal physiological changes occur to maintain calcium hemostasis during pregnancy. The mineral demands of the growing fetus are largely met by increased intestinal calcium absorption. The daily calcium intake of

pregnant women has been reported to be low. Calcium supplementation during pregnancy for women with deficient dietary calcium intake offers modest benefit in terms of preventing preeclampsia and preterm births and improving maternal and infant bone health.

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