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Review Article

Effects of Calcium Supplementation during Pregnancy on Birth Outcomes: A Review Paper

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Abstract

Calcium is a chemical element that is essential for living organisms, including humans. It composes 1.9 % of the body weight making it the most abundant mineral in the body. Other than its structural role 1% of total body calcium supports critical metabolic functions such as nerve transmission, vasocontraction and vasodilation, muscle function, intracellular signaling and hormonal secretion. During pregnancy and lactation women require an increase in their calcium intake to maintain maternal calcium balance, bone density, and to meet the demands of the growing fetus/infant. If a pregnant woman calcium intake is not adequate, she may develop pregnancy related complications such as preeclampsia, preterm delivery and even long-term morbidities, like excessive bone loss. Therefore, the main purpose of this paper is to review effects of Calcium supplementation during pregnancy on Pregnancy and birth outcomes.

Based on the current evidence, in populations where calcium intake is low, calcium supplementation as part of the antenatal care is recommended for the prevention of preeclampsia in pregnant women, particularly among those at higher risk of developing hypertension. The WHO recommends a daily 1.5 - 2 gm of calcium supplementation per day. Especially those women with suboptimal intake (< 500 mg) need calcium supplementation.

A meta-analysis of the role of calcium supplementation during pregnancy in the prevention of gestational hypertensive disorders found a 45% reduction in the development of PIH in women receiving calcium versus placebo. The World Health Organization conducted a calcium supplementation trial (1,500 mg/day or placebo) during pregnancy in women who with suboptimal intake. According to the study, the relative risks of severe gestational hypertension (RR 0.76; 95% CI 0.66 - 0.89) and eclampsia (1.2% calcium vs. 2.8% placebo, P = 0.04) were both significantly lower in women supplemented with calcium. Additionally, a Cochrane review reported that the average risk of preeclampsia was reduced in those receiving calcium supplements (RR 0.45) and that the effect was greatest in women with low baseline calcium intakes (RR 0.36). In regard to infant outcomes, there is still a contradictory finding but most of the literature support there was no effect of calcium supplementation on preterm birth.

Keywords: *Calcium Supplementation; Pregnancy; Birth Outcomes*

Abbreviations

CI: Confidence Interval; DRIs: Dietary Reference Intakes; ENFCS: Ethiopian National Food Consumption Survey; FNB: Food and Nutrition Board; PIH: Pregnancy Induced Hypertension; PTH: Parathyroid Hormone; RDAs: Recommended Dietary Allowances; RR: Relative Risk

Introduction

Calcium is a chemical element that is essential for living organisms, including humans. It composes 1.9% of the body weight making it the most abundant mineral in the body. Just about all (99%) of this is in the skeleton. The rest (0.6%) is in the teeth (0.6%) is in the soft tissue (0.03%) is in the plasma and (0.06%) in the extracellular fluid. Calcium is responsible for the skeleton structure and strength. It is found in some foods, added to others, available as a dietary supplement, and present in some medicines (such as antacids) [1].

Other than its structural role 1% of total body calcium supports critical metabolic functions such as nerve transmission, vasocontraction and vasodilation, muscle function, intracellular signaling and hormonal secretion [2]. Serum calcium is very tightly regulated and does not fluctuate with changes in dietary intakes; the body uses bone tissue as a reservoir for, and source of calcium, to maintain constant concentrations of calcium in blood, muscle, and intercellular fluids [1].

Normal serum calcium is maintained by the kidney, intestinal tract and bone through strongly regulating ion transport, which is facilitated by calcemic hormones especially parathyroid hormone and 1,25-dihydroxyvitamin D3. Irregularities in calcium transport resulted from influx or efflux of extracellular fluid, will result in hypercalcemia or hypocalcemia, respectively. In relation to these abnormalities in serum calcium concentration may have profound effect on neurological, gastrointestinal and renal function. In addition to these, abnormalities in serum calcium is also responsible for range of common disorders. The ionized calcium is biologically significant and it should be measured if possible. To treat hypercalcemia or hypocalcaemia, one should know the underlying disorder, the extent of the serum calcium abnormality, and the severity of symptoms. Luckily, there is a wide-range selection of medications to treat hypercalcemia, especially the bisphosphonates. Treatment of hypocalcaemia relies on the provision of calcium and often vitamin D [2].

During pregnancy and lactation women require an increase in their calcium intake [3-5]. This is not only to maintain maternal calcium balance and bone density, but also to meet the demands of the growing fetus/infant. Calcium do play a role in cardiovascular development of the fetus, if deficient in maternal serum it increases the risk of high blood pressure in the newborn.

If a pregnant woman suffers from a lack of calcium, this building material begins to be extracted from the teeth and bones of the mother during the development of the baby. Therefore, the lack of calcium is dangerous, because a woman can develop a dental disease, up to the loss of teeth, as well as develop early osteoporosis, and the child may stay underdeveloped and suffer from rickets [6]. Calcium deficiency during pregnancy also increases the risk of miscarriage or premature birth, development of hypertension and other diseases, complications [4]. Therefore the main purpose of this paper is to review effects of Calcium supplementation during pregnancy on birth outcomes.

Methodology and Data Source

Comprehensive review of published works on effects of calcium supplementation during pregnancy on birth outcome was conducted. A computerized internet search using Medline/PubMed, Scopus, and Google scholar, and reference lists of previous calcium supplementation during pregnancy studies were searched.

A combination of Medical Subject Headings (MeSH) and key word terms were used to search the database like "calcium "," supplementation", "pregnancy", "birth outcome", "micronutrient", "preeclampsia", 'eclampsia', 'hypertension during pregnancy' were used as a combination of free text and thesaurus terms in different way to search literatures to include in the review.

Pregnancy and nutrient

Under nutrition during the reproductive age group and pregnancy remains a major problem in countries where women usually do not have equitable access to food, education and healthcare [7]. Many women are undernourished at birth, stunted during childhood, become pregnant at adolescence, and are underfed and overworked during pregnancy and lactation, resulting in nutritional deficiencies [5].

The growing fetus and physiological changes resulted during pregnancy increases the metabolic demand of a pregnant woman (King JC, 2000). During pregnancy poor store or intake of micronutrients such as vitamins or minerals can cause complications such as anemia, hypertension, complicated labor and also death [8]. Additionally, the fetus can also be affected causing abnormal organ development immunocompromised, congenital malformation, intrauterine growth retardation, pre-term birth and even stillbirth [5].

Through the documentation of clinical conditions associated with severe deficiencies of particular vitamins or minerals and following animal experiments, the essential nature of micronutrients has been long recognized. Except few micronutrients such as iodine the role of many micronutrient deficiencies in pregnancy is only recently becoming appreciated [8]. Because micronutrients deficiencies frequently co-exist it makes it difficult to understand it, in addition to this deficiency of a single vitamin and mineral affected by stage of life, season, year, ethnic group, economic status, place of residence within a country, and among individuals in the same community. Such variation resulted from diet consumption with differing content and bioavailability of micronutrients and differing losses and requirements of micronutrients (The Lancet, 2013). With regard to biological effects micronutrients can have either positive or negative interactions, such interaction may not be the same for all possible consequences of deficiencies, which further complicates the situation. As a result of these confounding factors it is important to give attention to micronutrient deficiencies in pregnant women in developing countries [5,8].

Pregnancy is a period when the requirements for micronutrient increases more than macronutrients, thus a low nutritional quality of diet can have a major consequence for both mother and fetus. Micronutrient is obviously important for the good outcome of pregnancy if provided adequately during conception and gestation. If not reproductive age women at least for those at high risk of conception an effective intervention is needed to improve their status for specific micronutrients such as calcium, folic acid and possibly zinc, at the time of conception to prevent birth defects. In particular, there is evidence to support the physiologic role played by selected minerals and vitamins [9,10].

Calcium and its health benefit

Calcium is an essential nutrient as all living cells require calcium to remain viable; calcium is also required for a number of specific roles in the body. Hydroxyapatite is a form of calcium that is present in the human skeleton, which is an inorganic crystalline structure made up of calcium and phosphorus ($Ca_{10}(PO_4)6(OH)_2$), that provides rigidity. The rate of calcium deposition in bone is proportional to rate of growth, since it is required for the mineralization of bone making it vital for bone growth. An adequate intake of calcium is the main factor for acquiring bone mass and attaining peak bone mass. In contrary inadequate amounts calcium intake may lead to lower bone mineral density, and this may have consequences on bone health, especially risk of osteoporosis, in later life [11].

In addition to skeletal function, calcium regulates most specialized functions in the body. Calcium has part in muscle contraction, neurotransmitter secretion, digestion and blood coagulation. The structural role of calcium is not limited to skeleton but also in organelles and membranes. If these structural and regulatory role of calcium is disturbed, it can have implications for health and disease. As a result, the set range (i.e. 1.1 - 1.3 mmol/L) of plasma concentrations of calcium ions is maintained by tightly regulating calcium homeostasis. This homeostasis is controlled mainly in the kidneys, bone and the gastrointestinal tract. At these main sites there will be response to the changes in plasma calcium concentrations, such as alteration of gastrointestinal tract absorption of calcium, beside with urinary excretion and calcium resorption from bone. This Control is mediated through the calciotropic hormones; parathyroid hormone (PTH), calcitriol and calcitonin [11].

Calcium is not made in the body; it must be absorbed from the foods we eat. Vitamin D is necessary to successfully absorb calcium from food. If our diet is deficient with calcium to maintain our body function, stored calcium in bones will be removed. Over time, this causes our bones to grow weaker and may lead to osteoporosis - a disorder in which bones become very fragile [12].

Recommended intakes

Intake recommendations for calcium and other nutrients are provided in the Dietary Reference Intakes (DRIs) developed by the Food and Nutrition Board (FNB) at the Institute of Medicine of the National Academies (formerly National Academy of Sciences). The FNB established RDAs for the amounts of calcium required for bone health and to maintain adequate rates of calcium retention in healthy people. They are listed in table 1 in milligrams (mg) per day [13].

Table 1: *Recommended dietary allowances (RDAs) for Calcium.*

Age	Male	Female	Pregnant	Lactating
0 - 6 months*	200 mg	200 mg		
7 - 12 months*	260 mg	260 mg		
1 - 3 years	700 mg	700 mg		
4 - 8 years	1,000 mg	1,000 mg		
9 - 13 years	1,300 mg	1,300 mg		
14 - 18 years	1,300 mg	1,300 mg	1,300 mg	1,300 mg
19 - 50 years	1,000 mg	1,000 mg	1,000 mg	1,000 mg
51 - 70 years	1,000 mg	1,200 mg		
71+ years	1,200 mg	1,200 mg		

**: Adequate Intake (AI)*

Sources of calcium

Food

Milk, yogurt, and cheese are rich natural sources of calcium and are the major food contributors of this nutrient [13]. Nondairy sources include vegetables, such as Chinese cabbage, kale, and broccoli. Spinach provides calcium, but its bioavailability is poor. Most grains do not have high amounts of calcium unless they are fortified; however, they contribute calcium to the diet because they contain small amounts of calcium and people consume them frequently. Foods fortified with calcium include many fruit juices and drinks, tofu, and cereals [13].

Who should consider calcium supplements?

Even if one eats a healthy, balanced diet, it may bedifficult to get enough calcium if;

- Follow a vegan diet
- Have lactose intolerance and limit dairy products
- Consume large amounts of protein or sodium, which can cause the body to excrete more calcium
- Have osteoporosis
- Receiving long-term treatment with corticosteroids
- Have certain bowel or digestive diseases that decrease the ability to absorb calcium, such as inflammatory bowel disease or celiac disease [14].

Calcium and pregnancy

Why is calcium so important during pregnancy?

Calcium is important for the growth of fetal bones teeth, heart, nerves and muscles. Because of this, if a pregnant woman does not include enough calcium in her diet the baby will start draining it from her reserve; this will not benefit either the mother or the baby. It is best to recognize that vitamins and minerals do not have limited functions in the body. Calcium is not only correlated with bones and teeth, but also in many body functions such as muscle contraction (including cardiac muscle), secretion of hormones, nerve conduction and blood clotting. This indicates that calcium is mandatory for regular body function.

The amount of calcium recommended for pregnant woman used to be1,200 mg per day, but after findings from research show that the body cannot absorbed more than1,000 mg it is recently lowered to this level [15].

The Journal of Nutrition", published a study on maternal calcium deficiency and its effect on baby in 2010 concluding that maternal calcium deficiency can play a role in cardiovascular development in the fetus and increases the risk of high blood pressure in the newborn. In addition, the study also associated maternal calcium deficiency to a risk of increased body fat percentage elevated triglycerides and insulin resistance in children. Maternal calcium deficiency also affects bone mineral density of the baby. Moreover, Calcium deficiency can cause prolonged labor and delay recovery [16].

Calcium metabolism during pregnancy

Calcium provided from the maternal decidua aids in fertilization of the egg and implantation of the blastocyst; from that point onward the rate of transfer from mother to offspring increases substantially. About 80% of the calcium present in the fetal skeleton at the end of gestation crossed the placenta during the third trimester and is mostly derived from dietary absorption of calcium during pregnancy. Intestinal calcium absorption doubles during pregnancy, driven by 1,25-dihydroxyvitamin D (calcitriol) and other factors, and this appears to be the main adaptation through which women meet the calcium demands of pregnancy [17].

The influence of pregnancy on maternal skeleton has been a center of attention for decades by the scientific medical community. Maternal calcium absorption increases in the third trimester to meet that demand by fetal calcium deposition which peaks to 350 mg/day, grater increase of absorption also reported among women with low intake [18]. As a result, maternal bone turnover increases, though women with low calcium intakes (< 500 mg/day) may respond differently [17,19-21].

As discussed before calcium homeostasis is a complex process involving calcium, other ions, and three calciotropic hormones (parathyroid hormone, calcitonin, and 1,25-dihydroxyvitamin D3). The increase in secretion of parathyroid hormone during pregnancy plays major role in the maintenance of serum calcium concentration in the feature of physiological changes during pregnancy, such as falling albumin level, expanding extracellular fluid volume, increasing renal excretion, and placental calcium transfer. On the other hand, parathyroid hormone secretion by the fetus might be suppressed as a result of active transportation of calcium ions through the placenta causing fetal hypercalcemia relative to its mother, which in turn stimulates calcitonin release by the mother [17,19]. Other than the renal system, the placenta and/or decidua provide a source for 1,25-dihydroxyvitamin D3 to the fetus. Right after birth the neonate's serum calcium level falls for 24 to 48 hours as a result of placental source discontinuation, then after the fall will stabilizes and rises slightly. Hyperparathyroidism during pregnancy should be treated surgically as soon as diagnosed, as it causes complication for both mother and infant. As for maternal hypoparathyroidism it can be treated with high doses of supplemental calcium and vitamin D [17,19,20].

Maternal calcium excretion

During pregnancy maternal calcium absorption increases resulting physiological hypercalciuria. Interestingly, hypercalciuria is observed postprandially, but during fasting the urinary calcium is within the normal limits With the 50% increase in the glomerular filtration rate (GFR) during pregnancy urinary calcium excretion has been shown to increase by as much as 43% between pre-pregnancy and the third trimester [20]. Though urinary excretion is considerably higher in the first trimester than in the third, for women with low dietary calcium intake (< 500 mg/day). Even if the urinary calcium excretion increases during pregnancy the intestinal calcium absorption is not perfected [19,22,23].

Determining maternal calcium status

Determining a woman's calcium status during pregnancy is challenging. The expanded plasma volume causes fall in Serum calcium and albumin level; but, ionized calcium remains normal. However, serum calcium is not a reliable measure of calcium status, because even

in the non-pregnant state, serum calcium is considered to be independent of dietary calcium intake. With technique that has limitations calcium balance studies are normally used to determine if calcium intake has met requirements [24]. By controlling in-put and out-put (diet and excretion) of calcium it is possible to measure the calcium retention. But this measurement of retention only determines current status of calcium retention not long term rates. In women with adequate calcium intakes, calcium balance is positive early in pregnancy and becomes either neutral or negative in the third trimester [25].

Calcium and maternal health

Increase in absorption of calcium during pregnancy is with its own biological limits, if a pregnant woman calcium intake is not adequate, she may develop pregnancy related complications such as preeclampsia, preterm delivery and even long-term morbidities, like excessive bone loss.

Preeclampsia and pregnancy-induced hypertension

In the 1980s, it was reported that there is an inverse relationship between calcium intake and pregnancy-induced hypertension (PIH) [26] defined as systolic blood pressure of > 140 mmHg and/or diastolic blood pressure of > 90 mmHg that has occurred on at least two occasions at least 4 hours to 1 week apart PIH has been estimated to complicate 5% of all pregnancies and 11% of first pregnancies [27] often resulting in preterm birth. Preeclampsia is a condition in which hypertension (as defined above) occurs after 20 weeks of gestation and is usually associated with urinary protein level increment. The proposed association between development of PIH and preeclampsia with low calcium intake is that it will stimulate PTH secretion which results increase in intracellular calcium and smooth muscle contractibility, and/or release renin from the kidney, leading to vasoconstriction and retention of sodium and fluid [28].

Calcium supplementation during pregnancy

Available evidence

The World Health Organization conducted a calcium supplementation trial in women who habitually consumed < 600 mg calcium per day providing 1,500 mg/day or placebo [26]. The supplementation began at 20 weeks for women (n = 8,325) and were monitored until delivery. The primary maternal outcome being the incidence of preeclampsia and/or eclampsia, eclampsia (a seizure in a woman with preeclampsia in the absence of a known or subsequently diagnosed convulsive disorder). Eventually the incidence of preeclampsia between the control group and the calcium group was not significantly different, being 4.5% and 4.1% respectively. On the other hand, the relative risks of severe preeclampsia and eclampsia were significantly lower in women supplemented with calcium; severe preeclampsia (RR 0.76; 95% CI 0.66 - 0.89) and eclampsia (1.2% calcium vs. 2.8% placebo, P = 0.04).

A Cochrane review reported that those women who were receiving calcium supplements have reduced average risk of preeclampsia (RR 0.45) and also greatest effect in women with women with low baseline calcium intakes (RR 0.36). Thus it is concluded that the risk of preeclampsia could be reduced by 31% to 65% for pregnant women who are consuming low amounts of calcium if they consumed an additional 1,000 mg of calcium each day. This review also reported that the risk of developing PIH could be reduced with calcium supplementation (RR 0.65; 95% CI 0.53 - 0.81), especially in women with low baseline dietary calcium intakes (RR 0.44; 95% CI 0.28 - 0.70) [26,29-31]. A meta-analysis on the role of calcium supplementation during pregnancy found a 45% reduction in the development of PIH in women receiving calcium supplementation during pregnancy versus placebo (relative risk [RR] 0.55; 95% confidence interval [CI] 0.36 - 0.85) [31].

Preterm delivery

Calcium supplementation (1,500 mg/day) for pregnant women who regularly consumed less than 600 mg per day shown effectiveness in reducing risk of preterm delivery, in maternal morbidity, and in the neonatal mortality. Additionally, the previously mentioned

Cochrane review reported that pregnant women who were chronically low consumers of calcium were supplemented with 1,000 mg of calcium per day has a 24% reduced risk of preterm delivery [29,30].

Analysis suggested that there were fewer preterm births among pregnant women who received between 1.5g and 2g of elemental calcium per day than among those women with a lower calcium intake. However, calcium supplementation has no effect in regard to infant outcomes with preterm birth. Additionally, regarding too low birth weight, admission to a neonatal intensive care unit, stillbirth and neonatal death before hospital discharge, calcium supplementation did not show significant effect [32].

Other two Cochrane systematic reviews investigated calcium supplementation on maternal and infant outcomes. The conclusion was that the intervention considerably reduced the risk of developing pre-eclampsia and high blood pressure. Surprisingly the findings show that women who received calcium supplements had a significantly higher risk of developing HELLP (hemolysis, elevated liver enzymes, and low platelet count) syndrome associated with severe pre-eclampsia. Calcium supplementation had no effects on the risk of developing eclampsia or maternal death or maternal admission to the intensive care unit [30].

Recommendation for calcium supplementation during pregnancy

In populations where calcium intake is low, calcium supplementation as part of the antenatal care is recommended for the prevention of preeclampsia in pregnant women, particularly among those at higher risk of developing hypertension [5,30]. A suggested scheme for supplementation in pregnant women is presented in table 2.

Table 2: *Suggested scheme for calcium supplementation in pregnant women [4,5].*

Dosage	1.5 - 2.0g elemental calcium/days[a]
Frequency	Daily, with the total daily dosage divided into three doses (preferably taken at mealtimes)
Duration	From 20 weeks' gestation until the end of pregnancy
Target group	All pregnant women, particularly those at higher risk of gestational hypertension[b]
Settings	Areas with low calcium intake

[a]: 1g of elemental calcium equals 2.5g of calcium carbonate or 4g of calcium citrate.

[b]: Women are regarded as being at high risk of developing gestational hypertension and pre-eclampsia if they have one or more of the following risk factors: obesity, previous pre-eclampsia, diabetes, chronic hypertension, renal disease, autoimmune disease, nulliparity, advanced maternal age, adolescent pregnancy and conditions leading to hyperplacentation and large placentas (e.g. twin pregnancy). This is not an exhaustive list but can be adapted/complemented based on the local epidemiology of pre-eclampsia.

Remarks: Assessment of the risk of developing gestational hypertensive disorders is to be conducted by a clinician. The clinical management of women with pre-eclampsia or eclampsia requires consideration of other evidence in formed interventions [4,5].

Implementation of this recommendation requires close monitoring of women's total daily calcium intake (diet, supplements and antacids). The overall intake of calcium is not consistent everywhere and there has to be locally established upper tolerable limit which the overall intake should not go beyond. If there is no locally established upper tolerable limit, 3 g/day the upper limit of calcium intake can be used.

The mechanisms through which calcium reduces the risk of gestational hypertension need further elucidation. Available evidence supports the theory that calcium supplementation may reduce the risk of developing pre-eclampsia by filling a dietary gap in calcium intake. In populations where consumption of calcium on average meets the recommended dietary calcium intake, either through calcium-rich

foods or fortified staple foods, calcium supplementation is not encouraged as it may not improve the outcomes related to pre-eclampsia and hypertensive disorders of pregnancy but might increase the risk of adverse effects [4,5].

Public health implications

From the previous discussion it is recognized calcium has vital role in maintenance of maternal health and development of fetus. This is supported with evidence that maternal calcium intake can affect fetal bone development with long term effect of skeletal growth. Hence it is necessary to educate women of reproductive age to meet their calcium requirements which their own needs and those of their infants. This requirement can be met if they regularly consume adequate amounts of calcium (1,000 mg/day). It's also suggested that calcium supplementation mainly benefits women who chronically consume < 500 mg calcium/day, which explains the importance of taking adequate calcium before pregnancy. Furthermore, in populations where calcium intake is low, calcium supplementation as part of the antenatal care is recommended for the prevention of preeclampsia in pregnant women, particularly among those at higher risk of developing hypertension and other complications that could affect the mother and child survival [33-37].

Conclusion

In order to meet both maternal and fetal requirement of calcium women should start pregnancy with adequate intake at least 1,000 mg, hence they may not need additional calcium. But those women with suboptimal intake (< 500 mg) may need calcium supplementation. It is proven to reduce the risk of PIH and the risk of pre-term birth even though it is still controversial. Calcium supplementation during pregnancy in the prevention of gestational hypertensive disorders found to be effective based on the finding of different trails. Therefore, calcium supplementation as part of the antenatal care is recommended for the prevention of preeclampsia in pregnant women, particularly among those at higher risk of developing hypertension.

Author's Contribution

BG and HA conceived the idea, literature search, drafted the manuscript. Both authors read and approved the manuscript.

Competing Interest

None declared.

Bibliography

1. National Academy Press. Committee to Review Dietary Reference Intakes for Vitamin D and Calcium, Food and Nutrition Board, Institute of Medicine. "Dietary Reference Intakes for Calcium and Vitamin D". Washington, DC (2010).

2. Bushinsk Y., *et al*. "Calcium". *The Lancet* 352.9124 (2014): 306-311.

3. Sparks JW. "Human intrauterine growth and nutrient accretion". *Seminars in Perinatology* 8.2 (1984): 74-93.

4. WHO. "Guideline: Calcium supplementation in pregnant women". Geneva, World Health Organization (2013).

5. WHO. "Guideline: Calcium supplementation in pregnant women". Geneva, World Health Organization (2017).

6. Sowers MF., *et al*. "Changes in bone density with lactation". *Journal of the American Medical Association* 269.24 (1993): 3130-3135.

7. The LINKAGES project: Academy for Educational Development (AED). Maternal nutrition: issues and interventions. A computer-based slide presentation for advancing maternal nutrition.

8. Ramakrishnan U., *et al*. "Micronutrients and pregnancy outcome: a review of the literature". *Nutrition Research* 19.1 (1999): 103-159.

9. Sauerwald TU., *et al*. "Polyunsaturated fatty acid supply with human milk". *Lipids* 36.9 (2001): 991-996.

10. Rahman MM and Nasrin SO. "Mothers nutritional status in an impoverished nation: evidence from rural Bangladesh". *Internet Journal of Nutrition and Wellness* 7.1 (2009).

11. McGuire and Beeman KA. "Nutritional Sciences, from Fundamentals to Food". Australia: Thomson Wardworth (2007).

12. O'Brien KO., *et al*. "Calcium absorption is significantly higher in adolescents during pregnancy than in the early postpartum period". *American Journal of Clinical Nutrition* 78.6 (2003): 1188-1193.

13. U.S. Department of Agriculture, Agricultural Research Service. USDA National Nutrient Database for Standard Reference, Release 24. Nutrient Data Laboratory Home Page (2011).

14. Confused About Calcium Supplements?.

15. Why is calcium important during pregnancy?.

16. Parul C and Christine P. "Maternal Micronutrient Deficiency, Fetal Development, and the Risk of Chronic Disease". *The Journal of Nutrition* 140.3 (2010): 437-445.

17. Cross NA., *et al*. "Calcium homeostasis and bone metabolism during pregnancy, lactation and post weaning: a longitudinal study". *American Journal of Clinical Nutrition* 61.3 (1995): 514-523.

18. Ritchie LD., *et al*. "A longitudinal study of calcium homeostasis during human pregnancy and lactation and after resumption of menses". *American Journal of Clinical Nutrition* 67.4 (2001): 693-701.

19. Heaney RP and Skillman TG. "Calcium metabolism in normal human pregnancy". *Journal of Clinical Endocrinology and Metabolism* 33.4 (1971): 661-670.

20. Kovacs CS and Kronenberg HM. "Maternal-fetal calcium and bone metabolism during pregnancy, puerperium, and lactation". *Endocrine Reviews* 18.6 (1997): 832-872.

21. Vargas Zapata CL., *et al*. "Calcium homeostasis during pregnancy and lactation in Brazilian women with low calcium intakes: a longitudinal study". *American Journal of Clinical Nutrition* 80.2 (2004): 417-422.

22. Kent GN., *et al*. "Effect of pregnancy and lactation on maternal bone mass and calcium metabolism". *Osteoporosis International* 3.1 (1993): 44-47.

23. Darwish AM., *et al*. "Prevalence and predictors of deficient dietary calcium intake during the third trimester of pregnancy: the experience of a developing country". *Journal of Obstetrics and Gynaecology Research* 35.1 (2009): 106-112.

24. Weaver CM and Heaney RP. "Calcium in Human Health". Totowa, NJ: Human Press Inc (2005).

25. Belizan JM and Villar J. "The relationship between calcium intake and edema-, proteinuria-, and hypertension-getosis: an hypothesis". *American Journal of Clinical Nutrition* 33.10 (1980): 2202-2210.

26. Villar J., *et al*. "World Health Organization randomized trial of calcium supplementation among low calcium intake pregnant women". *American Journal of Obstetrics and Gynecology* 194.3 (2006): 639-649.

27. Ananth CV and Basso O. "Impact of pregnancy-induced hypertension on stillbirth and neonatal mortality". *Epidemiology* 21.1 (2010): 118-123.

28. Imdad A., *et al*. "Role of calcium supplementation during pregnancy in reducing risk of developing gestational hypertensive disorders: a meta-analysis of studies from developing countries". *BMC Public Health* 11.3 (2011): S18.

29. Kumar A., *et al*. "Calcium supplementation for the prevention of pre-eclampsia". *International Journal of Gynecology and Obstetrics* 104.1 (2009): 32-36.

30. Hofmeyr GJ., *et al*. "Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems". *Cochrane Database of Systematic Reviews* 6 (2010): CD001059.

31. Hofmeyr GJ., *et al*. "Dietary calcium supplementation for prevention of pre-eclampsia and related problems: a systematic review and commentary". *BJOG: An International Journal of Obstetrics and Gynaecology* 114.8 (2007): 933-943.

32. Buppasiri P., *et al*. "Calcium supplementation (other than for preventing or treating hypertension) for improving pregnancy and infant outcomes". *Cochrane Database of Systematic Reviews* 10 (2011): CD007079.

33. Asheber G., *et al*. "Disease Burden Due to Preeclampsia/eclampsia and The Ethiopian Health System's Response". *International Journal of Gynecology and Obstetrics* 115.1 (2011): 112-116.

34. Biniyam T., *et al*. "Making A Case For Calcium Supplementation For The Prevention Of Pregnancy Hypertension In Ethiopia". *European Journal of Nutrition and Food Safety* 5.5 (2015): 1187-1188.

35. Hofmeyr GJ., *et al*. "Calcium supplementation to prevent pre-eclampsia - a systematic review". *South African Medical Journal* 93.3 (2003): 224-228.

36. Nordin B. "Calcium in health and nutrition". *Food Nutrition Agriculture* 20 (1997): 13-23.

37. Trumbo P., *et al*. "Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids". *Journal of the American Dietetic Association* 102.11 (2002): 1621-1630.

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