ROLE OF CALCIUM DURING PREGNANCY

Although the demand for additional calcium during pregnancy is recognized, the dietary reference intake (DRI) for calcium was lowered for pregnant women in 1997 to amounts recommended for nonpregnant women (***Institute of Medicine, 1997)***.

The Institute of Medicine (IOM) committee concluded that any calcium deficit not provided by an increased efficiency in calcium absorption could be supplied by mobilizing maternal bone calcium. Based on data from one cross-sectional study of postpartum women (***Kalkwarf HJ et al, 1996)***, It was assumed that maternal bone loss to support the demands of both pregnancy and lactation are recovered by 1 year postpartum (***Institute of Medicine, 2011)***.

The committee based the recommendation on three areas of evidence: 1) randomized controlled trials of women supplemented with calcium during pregnancy reveal no evidence that additional calcium has any benefit to the mother or fetus, 2) the number of children a woman has does not increase her risk of fracture later in life, and 3) the physiological changes that occur during pregnancy allow for maternal and fetal needs to be met ***(Andrea N Hacker et al, 2012)***.

CALCIUM METABOLISM DURING PREGNANCY

The effect of pregnancy on the maternal skeleton has preoccupied the scientific medical community for decades. Fetal calcium deposition has been shown to peak at 350mg/day in the third trimester ***(Sparks JW, 1984)*** and maternal calcium absorption increases to meet that demand, with greater increases reported among women with low intakes (***Vargas Zapata et al, 2004)***.

Maternal bone turnover also increases ***(Hellmeyer L et al, 2006)***; although women with low calcium intakes may respond differently to the additional demand ***(Ritchie LD et al, 1998)***.

Maternal calcium absorption

Longitudinal studies of calcium metabolism during pregnancy have concluded that maternal calcium absorption increases significantly during the second and third trimesters ***(Cross NA, et al, 1995)***.

This increase in calcium absorption is directly related to maternal calcium intake. It is reported that women with a daily average calcium intake of 1,171 mg during pregnancy absorbed 57% during the second trimester and 72% during the third trimester ***(Ritchie LD et al, 1998)***.

Several studies have reported that calcitriol [1,25(OH)2D] levels increase progressively each trimester, thereby influencing the increase in calcium absorption ***(Cross NA, et al, 1995)***.

A study of Brazilian women consuming low amounts of calcium during pregnancy (438–514 mg calcium/day) reported even higher increases in calcium absorption, i.e., 69% during early pregnancy, increasing to 87% during late pregnancy. 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). Calcium absorption during pregnancy is mediated by changes in maternal calcitropic hormones. During the first trimester, parathyroid hormone (PTH) levels in Caucasian women consuming adequate amounts of calcium decrease to low-normal levels and then increase to the higher end of normal in the third trimester **(*Cooper C et al, 2006)***.

That reflects the increase in calcium transfer from mother to fetus. 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 ***(Kovacs CS, 2005)***.

PTHrP is recognized by PTH receptors and therefore has PTH-like effects. This pro-hormone 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 ***(Kovacs CS et al, 1997)***. PTHrP may also support mineralization of trabecular and cortical bone in the fetus ***(Cooper C et al, 2006)***.

Other calcitropic hormones affecting maternal calcium metabolism are both the active [1,25(OH)2D] and the inactive [25(OH)D] forms of vitamin D. Serum 25(OH)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(OH)D to 1,25(OH)2D. Maternal serum 1,25(OH)2D levels increase twofold during pregnancy, allowing the intestinal absorption of calcium also to double ***(Zeni SN et al, 2003)***.

Both free and protein-bound forms of calcitriol increase during pregnancy ***(Kent GN et al, 1993)***, as do concentrations of vitamin-D- binding protein ***(Bouillon R et al, 1981)***.

Due to the corresponding changes in vitamin-D-binding protein and 1,25(OH)2D, the index of free 1,25(OH)2D does not increase until the third trimester, which may explain the large increase in calcium absorption seen during late pregnancy ***(Ritchie LD et al, 1998)***.

Because maternal 25(OH)D does cross the placenta and because there is a positive association between maternal serum 25(OH)D, cord blood 25(OH)D, and infant 25(OH)D levels at delivery, it is thought that vitamin D plays a role in fetal bone development ***(Kovacs CS et al, 1997)***. However, there is a paucity of research in this area, and it is not clear what effect maternal vitamin D status has on maternal and/or fetal bone outcomes ***(Andrea N Hacker et al, 2012)***.

Maternal calcium 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 ***(Bezerra FF et al, 2004)***.

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 ***(Ritchie LD et al, 1998)***.

For women with low dietary calcium intake (<500 mg/day), urinary calcium is more tightly regulated and urinary excretion is actually significantly higher in the first than in the third trimester. Although urinary calcium excretion increases during pregnancy, the increase in intestinal calcium absorption is not ameliorated, and net maternal calcium retention is positive before fetal needs are calculated ***(O'Brien KO et al, 2006)***.

Maternal bone turnover

Biochemical markers of bone turnover increase gradually during pregnancy, with the highest levels measured in the third trimester. Markers of both bone formation and resorption increase significantly from the first to the third trimester, demonstrating the increase in maternal bone turnover and fetal bone development ***(Bezerra FF et al, 2004)***.

Two resorption markers, carboxy terminal collagen cross-links (CTX) and n-telopetide cross-links (NTX), increase steadily throughout pregnancy, with the largest increase occurring between the second and third trimesters ***(Naylor KE et al., 2003)***.

Markers of bone formation also increase during pregnancy but follow a different pattern of change; for example, procollagen type-1 carboxyterminal propeptide and bone-specific alkaline phosphatase vary little during the first trimester but increase significantly (44%) between the second and third trimesters ***(Zeni SN et al, 2003)***.

The use of biochemical markers to measure bone turnover during pregnancy has its limitations. Due to the large intra-individual variability, interpretation of changes in bone turnover markers during gestation is challenging unless pre-pregnancy levels are available for comparison. Serum markers of bone turnover can be falsely decreased due to the effects of hemodilution. During pregnancy, maternal plasma volume expands an average of 45% to allow for the increased circulatory needs of the maternal organs ***(Davison JM et al., 1989)***.

Because of this increased blood volume, measurement of serum proteins, hormones, and other biochemical markers may be altered and not comparable to

non-pregnant measurements. Additionally, urinary markers may be distorted by an increase in GFR and renal clearance as well as by altered creatinine excretion ***(Kovacs CS, 2005)***.

Data suggest that, in women with low calcium intakes in late pregnancy (<500 mg/day), serum 1,25(OH)2D concentrations rise to boost biochemical markers of bone resorption. Both Californian women with adequate calcium intakes and Brazilian women with low calcium intakes showed increases in 1,25(OH)2D during pregnancy, though to a greater or lesser extent, depending upon intake ***(Ritchie LD et al, 1998)***.

Multiple regression analyses of the combined Californian and Brazilian data showed that serum 1,25(OH)2D in combination with serum 25(OH)D and parity explained 80% of the variability in bone resorption rates during the third trimester; serum 1,25(OH)2D was negatively related to bone resorption, whereas serum 25(OH)D and parity were positively related ***(Andrea N Hacker et al, 2012)***.

Insulin growth factor-1 (IGF-1) has a stimulatory effect on bone turnover during pregnancy; concentrations increase with advancing gestational age. During early pregnancy, serum IGF-1 concentration is positively associated with bone resorption, measured by stable calcium isotope multi-compartmental models, particularly in women with low calcium intakes (approx. 500 mg/day). Various studies have reported increases in IGF-1 of between 34% and 68% during pregnancy. IGF-1 is also a significant predictor of bone resorption during the third trimester. During late pregnancy, IGF-1, 1,25(OH)2D, and calcium intake together explain 88% of the variability in net bone calcium balance ***(O'Brien KO et al, 2006)***.

Determining maternal calcium status

Determining a woman's calcium status during pregnancy is challenging. Serum calcium and serum albumin fall due to expanded plasma volume; however, ionized calcium remains normal ***(Kovacs CS et al, 1997)***.

Regardless, even in the non-pregnant state, serum calcium is considered to be independent of dietary calcium intake and thus not a reliable measure of calcium status ***(Darwish AM et al., 2009)***.

Calcium balance studies are typically used to determine if calcium intake is adequate to meet requirements, but this technique has limitations. Calcium retention is measured by providing a controlled constant calcium diet and collecting all excrement (urine and feces). While balance studies may elucidate an individual's calcium metabolism, they only provide information regarding current calcium status, not long-term rates of calcium retention ***(Weaver CM et al., 2005)***.

In women with adequate calcium intakes, calcium balance is positive early in pregnancy and becomes either neutral or negative in the third trimester. The measurement of fractional calcium absorption, using stable calcium isotopes, demonstrates both the increase in intestinal calcium absorption and the hypercalciuria that occur during pregnancy ***(Ritchie LD et al, 1998)***.

O'Brien et al. have reported that, when corrected for estimates of fetal bone calcium deposition, net calcium balance decreases significantly between early and late pregnancy. Net bone calcium balance is positively associated with dietary calcium intake during early pregnancy, late pregnancy, and early lactation ***(O'Brien KO et al, 2006)***.

Additionally, the amount of calcium transferred to the fetus during pregnancy cannot be truly measured, only extrapolated with calcium kinetic studies using calcium balance data. The net calcium balance during the third trimester of pregnancy in adolescents has been reported as 126 mg +/- 152, ***(O'Brien KO et al, 2006)***, which does not account for estimated fetal calcium accretion of 250–350 mg/day ***(Sparks JW, 1984)***.

The increased rate of fetal bone accretion during the third trimester places women with low (<500 mg/day) calcium intakes at risk of having a negative calcium balance ***(Andrea N Hacker et al, 2012)***.

CALCIUM AND MATERNAL HEALTH

There are biological limits to a pregnant woman's capacity to increase calcium absorption, and if she does not consume adequate amounts of dietary calcium, she may be at increased risk for gestational complications, such as preeclampsia, and preterm delivery or long-term morbidities, such as excessive bone loss ***(Andrea N Hacker et al, 2012)***.

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) ***(Belizan JM et al 1980)***, defined as systolic blood pressure of >140mmHg and/or diastolic blood pressure of >90 mmHg that has occurred on at least two occasions at least 4 hours to 1 week apart ***(Villar J et al, 2006)***. PIH has been estimated to complicate 5% of all pregnancies and 11% of first pregnancies ***(Villar J et al, 2004)***, often resulting in preterm birth ***(Ananth CV et al, 2010)***.

Preeclampsia is a condition in which hypertension occurs during the latter half of gestation and is associated with an increase in urinary protein. Low calcium intakes during pregnancy may 1) stimulate PTH secretion, increasing intracellular calcium and smooth muscle contractibility, and/or 2) release renin from the kidney, leading to vasoconstriction and retention of sodium and fluid. These physiological changes can lead to the development of PIH and preeclampsia ***(Andrea N Hacker et al, 2012)***.

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 ***(Imdad A et al., 2011)***.

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 and that the effect was greatest in women with low baseline calcium intakes ***(Kumar A et al, 2009)***. The review concluded that pregnant women consuming low amounts of calcium could reduce their risk of preeclampsia by 31% to 65% if they consumed an additional 1,000 mg of calcium each day ***(Hofmeyr GJ et al., 2006)***. This review also reported that the risk of developing PIH could be reduced with calcium supplementation, especially in women with low baseline dietary calcium intakes ***(Hofmeyr GJ et al, 2010)***.

Preterm delivery

Calcium supplementation has shown effectiveness in reducing the risk of preterm delivery in women with low calcium intakes. Among pregnant women who regularly consumed less than 600 mg of calcium per day and were supplemented with additional calcium (1,500 mg/day), decreases in the risk of preterm delivery, in maternal morbidity, and in the neonatal mortality index were observed ***(Villar J et al, 2006)***.

The previously mentioned Cochrane review reported that women who were chronically low consumers of calcium but who took 1,000 mg of calcium supplement per day also reduced their risk of preterm birth by 24% ***(Hofmeyr GJ et al., 2006)***.

Short-term maternal bone changes

Changes in maternal bone mineral content (BMC) and bone mineral

density (BMD) resulting from gestation have been studied using three different imaging techniques: dual x-ray absorptiometry (DXA), quantitative ultrasound, and peripheral quantitative computed tomography (pQCT). pQCT is the only technique available for measuring changes in trabecular bone, the type of bone most likely to be mobilized in the adult skeleton during pregnancy ***(Dambacher MA et al, 1998)***.

The majority of studies of gestational bone changes have used DXA to assess BMD at preconception and again early in the postpartum period ***(Prentice A et al., 2008)***.

Postpartum bone measurements may be confounded by the bone loss that occurs in early lactation ***(Jarjou LM et al, 2010)***. One study found reductions in maternal bone, with the biggest changes occurring at the lumbar spine and the trochanteric region of the hip (3–4.5% loss) ***(Ritchie LD et al, 1998)***.

These skeletal sites are rich in trabecular bone but inaccessible during pregnancy due to the confounding effect of the developing fetal skeleton lying over the maternal spine and hip areas. Additionally, DXA scans expose the mother and fetus to radiation, which is an unnecessary risk. Quantitative ultrasound is able to measure bone without the use of ionizing radiation, allowing it to be used during pregnancy, primarily at the calcaneus and phalanges. Evidence has shown that the speed of sound, an indication of the density and structure of the trabecular bone, decreases significantly at the phalanges and the calcaneus between the first and third trimesters. ***(Della Martina M et al, 2010)***.

A limitation of quantitative ultrasound is its greater variability in measurement than either DXA or pQCT; since pregnancy is a time period in which changes in fluid status and body size occur, the variability in the quantitative ultrasound measurements may increase ***(Andrea N Hacker et al,***

2012).

To date, Wisser J et al, are the only investigators to use pQCT to measure gestational changes in trabecular and cortical bone. The measurement was performed at only one site, the non-dominant distal radius. Cortical bone volume and density did not change between the first and third trimesters of pregnancy, but a significant decrease was seen in trabecular bone density ***(Wisser J et al, 2005)***.

Trabecular bone density is more sensitive to bone turnover, particularly that resulting from hormonal changes in women, such as what occurs during gestation ***(Andrea N Hacker et al, 2012)***.

Calcium supplementation 1,000 mg/day during gestation has resulted in a reduction in bone turnover markers in late pregnancy, ***(Janakiraman V et al. 2003),*** a reduction in risk of preterm delivery, and reduced maternal morbidity and infant mortality ***(Villar J et al, 2006)***.

As previously mentioned, the results of maternal calcium supplementation on infant morbidity have been mixed ***(Abalos E et al, 2010)***. The greatest impact of calcium supplementation is observed in women who consume <500mg calcium per day; calcium supplementation is positively associated with infant BMC and BMD ***(Koo WW et al, 1999)***.

Long-term bone changes: parity and fracture risk

It has been reported that parity influences bone loss during gestation, with greater losses reported in primiparous women than in multiparous women

(Sowers MF et al, 2000).

Hydroxyproline, a marker of bone resorption, is excreted 58% more in primiparous compared with multiparous women ***(Donangelo C et al, 1996)***. This could potentially be an adaptive mechanism in women with previous pregnancies, providing protection against excessive bone loss. Parity does not appear to increase later fracture risk in women, with studies showing either a negative ***(Paton LM et al, 2003)*** or a neutral ***(Lenora J et al, 2009)*** relationship between parity and risk of fracture.

The Study of Osteoporotic Fractures, a prospective cohort study in 9,704 women over the age of 65, assessed parity and incidence of fracture ***(Hillier TA et al, 2003)***. Nulliparous women had a 44% increase in the risk of hip fracture compared with parous women, when adjusted for BMD and body mass index. When stratifying the women into five groups by parity, the probability of hip fracture decreased as parity increased. Among parous women, the risk of hip fracture decreased by 9% with each additional birth. Women with children may be more physically active, leading to increased weight bearing and potentially higher BMD, although the Study of Osteoporotic Fractures adjusted for BMD and still reported a negative relationship between parity and fracture risk ***(Hillier TA et al, 2003)***.

Research has shown that physical activity does reduce the risk of future fracture ***(Englund U et al, 2011)***, but it is not known if the relationship between physical activity and fracture risk is also associated with parity. It has been hypothesized that the weight gain associated with pregnancy may place an increased load on the maternal hip (femoral neck), increasing bone strength and bone area and decreasing future fracture risk ***(Olausson H et al, 2008)***.

RELATIONSHIP BETWEEN CALCIUM INTAKE DURING PREGNANCY AND INFANT HEALTH

To date, it is unclear what effect maternal calcium intake has on the bone

mineralization of the developing fetus. Observational studies have found a positive relationship between maternal dietary calcium intake and fetal or child bone outcomes ***(Ganpule A et al, 2006)***. Yet, results from calcium supplementation trials during pregnancy have reported inconsistent results ***(Jarjou LM et al, 2010)***.

Calcium transfer from mother to fetus

By the time of parturition, a fetus has formed 98% of its skeleton, accumulating approximately 30 g of calcium. Calcium is actively transported across the placenta, with the transfer from mother to fetus beginning by week 12 of gestation and peaking at week 36 ***(Forbes GB. 1976)***.

Placental calcium transport is dependent upon transport proteins located in the syncytiotrophoblast, which forms a barrier between the mother and fetus ***(Martin R et al, 2007)***. Ninety-nine percent of the flow of calcium is maternal-to-fetal, and this active, one-way process is under way by the third trimester, when the majority of calcium is transferred, with the fetus accumulating 250–350 mg/day ***(Prentice A., 2003).***

Infant growth

The effect of maternal calcium intake on infant growth remains unclear. Calcium intake during pregnancy may have a positive effect, but the research has

provided conflicting results ***(Abalos E et al, 2010)***.

A positive relationship between maternal calcium intake and infant length or mid-upper arm circumference has been shown, but the results have not been reproduced in other studies ***(Abdel-Aleem H et al, 2009)***. The literature also reports inconsistent findings of positive relationships between maternal calcium intake and newborn weight and infant total body calcium ***(Chan GM et al, 2006)***.

Bone outcomes in offspring

Observational studies that have assessed maternal diet have found a positive relationship between maternal dietary calcium intake and bone outcomes of off- spring ***(Ganpule A et al, 2006)***.

Measurement of fetal femur length by ultrasound has been used as a method to assess fetal bone development. In 2003, Chang et al. assessed dairy intake in 350 pregnant African-American adolescents and measured fetal femur length at 20 and 34 weeks of gestation. Servings of dairy, but not calcium intake, were assessed in the women. Dairy intake had a significant positive effect on fetal femur growth, and fetal femur length was significantly lower in the lowest dairy intake group (<2 servings/day) compared with the highest dairy intake group (>3 servings/day) ***(Chang SC et al., 2003)***.

Two studies report that low-calcium-consuming (approx. 500 mg/day) women assigned to calcium supplements (300, 600, or 2,000 mg/day) during pregnancy had infants with higher bone density; the greatest benefit was seen in women consuming the lowest amount of calcium at baseline ***(Koo WW et al, 1999)***.

However, calcium supplementation (1,500 mg/day) in pregnant Gambian women (week 20 of gestation to delivery) who chronically consumed approx. 350 mg of calcium per day had no effect on infant bone density measured using single photon absorptiometry (2, 13, and 52 weeks post delivery).79 In the later part of the study, DXA showed a trend of slightly lower BMC in infants born to the calcium-supplemented mothers (total calcium intake approx. 1,850 mg/day) ***(Jarjou LM et al, 2006)***.

Interpreting the effect of maternal calcium intake during pregnancy on infant bone density measured during the postpartum period is challenging. Infant bone density measured soon after birth (2 weeks postpartum) may be reflective of the fetal environment, while measurements made in later infancy (13 weeks postpartum) may be reflective of infant nutritional intake. However, the current calcium dietary reference intake (DRI) (1,000 mg/day) has not been tested during pregnancy to see how it may affect infant BMC and BMD as measured by both DXA and pQCT. Additionally, the fetus may respond differently to calcium-rich foods versus calcium supplement pills ***(Andrea N Hacker et al, 2012)***.

Fetal bone metabolism appears to be influenced by maternal metabolism; however, there may also be independent regulation by the fetus. Serum maternal and cord blood markers of bone turnover are highly correlated and the amounts of osteocalcin, bone-specific alkaline phosphatase, and CTX found in cord blood are higher than what is found in maternal serum ***(Yamaga A et al, 1999).***

Leptin and IGF-1 may also impact fetal growth and bone mass, with fetal cord blood levels having a positive relationship with infant bone mass ***(Javaid MK et al, 2005)***. Both leptin and IGF-1 are produced by the fetus and influence fetal osteoblast differentiation, but it is not known to what extent maternal

lifestyle influences these factors ***(Andrea N Hacker et al, 2012)***.

Developmental origins of osteoporosis

The environment of the fetus during development may play an important role in the risk of future growth delay and health impairment ***(Cooper C et al, 2009)***. Maternal dietary intake, especially calcium and vitamin D status, may influence future bone development ***(Javaid MK et al, 2006)***.

The literature reports a positive correlation between women consuming higher intakes of calcium (median daily calcium intake of 1,287 mg) during pregnancy and a child's whole body bone area, BMC, and areal bone at 9 years of age, demonstrating the potential effect of maternal nutrition on bone development later in life ***(Cole ZA et al, 2009)***.

Although a link between maternal calcium intake and vitamin D status and offspring bone mass at 9 years of age has been reported, it is also important to consider the influence that the child's lifestyle85–87 plays in bone development ***(Specker B et al, 2003)***.

Studies measuring BMD in female monozygotic and dizygotic twins have reported that genetic factors determine between 77% and 80% of the variance ***(Hunter DJ et al, 2001)***. Current genetic markers are able to explain only a small proportion of the variation in individual bone mass or fracture risk ***Ralston SH. (1998)***. Several genes may affect bone density, but each only contributes a modest effect ***(Albagha OM et al, 2001)***.

Fetal programming refers to a critical period during gestation when a system is plastic and sensitive to the environment. Environmental stressors during

intrauterine growth may increase the sensitivity of the growth plate to growth hormone (GH), resulting in reduced peak skeletal size ***(Cooper C et al, 2009)***.

GH stimulates chondrocytes in the growth plate to secrete IGF-1, leading to bone growth. A single-nucleotide polymorphism has been found on the GH gene, GH1-A5157G, and is associated with lower basal GH levels ***(Dennison EM et al, 2004),*** which are negatively associated with BMD ***(Fall C et al, 1998)***.

The GH/IGF-1 axis may also be involved in the relationship between weight at 1 year of age and adult bone area at the spine and hip ***(Lips MA et al, 2007)***. An association has also been observed between reduced maternal height, weight, smoking status during pregnancy, and reduced whole body BMC of children at 9 years of age ***(Javaid MK et al, 2006)***.

DIETARY REFERENCE INTAKES FOR CALCIUM INTAKE DURING PREGNANCY

Amid controversy, the updated DRIs for calcium (1,000 mg/day) and vitamin D (600 IU/day) were released in November 2010. Calcium recommendations were changed from Adequate Intakes (AIs) to Recommended Dietary Allowances (RDAs), reflecting the additional research that has been conducted since the previous report in 1997. However, neither the amount of the RDA nor the Tolerable Upper Level (UL) of calcium changed for pregnant

women. The IOM reported that the evidence supported a role for calcium and vitamin D in bone health but not in other health conditions (***Institute of Medicine, 2011)***.

Average calcium intake

It has been frequently reported that women of childbearing age do not consume the RDA of calcium (1,000 mg/ day) ***(Jarjou LM et al, 2010)*** and that calcium intake in the United States varies between ethnic groups. USA dietary surveys 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 **(*Thomas M et al, 2006)***.

Others report that multiethnic women aged 19–50 years consume only 50–70% of the RDA of calcium ***(Forshee RA et al, 2006)***. It is estimated that up to 75% of African-Americans are lactose intolerant, which may explain the low dairy and dietary calcium intake ***(Jackson KA et al, 2001).*** Dairy foods provide over 75% of the calcium consumed in the American diet, yet among African-Americans, this proportion is only 25% ***(Fulgoni V III et al, 2007)***.

Some studies have suggested that calcium intake increases during pregnancy, with many reporting intakes of 1,154–1,671 mg/ day ***(Cole ZA et al, 2009)***. Ritchie et al. reported prepregnancy calcium intakes of 1,054 +/- 262 mg/day, which increased significantly to 1,350 +/- 319 mg/day during the third trimester ***(Ritchie LD et al, 1998)***.

Women who chronically consume low amounts of calcium (<500 mg/day) may be at risk for increased bone turnover during pregnancy. Dietary calcium

intake has a negative correlation with bone resorption markers ***(Zeni SN et al, 2003)***.

High calcium intake is associated with improved calcium balance, perhaps providing a protective effect against bone loss during pregnancy ***(O'Brien KO et al, 2003)***. It has been reported that, as dietary calcium intake increased in women with previously low intakes, production of 1-a-hydroxlyase was upregulated to increase activation of 1,25(OH)2D, resulting in increased calcium absorption ***(Zeni SN et al, 2003)***.

This increase in calcium absorption decreased markers of bone resorption. Women with higher dietary calcium intake (mean 1,015 mg/day) had lower NTX levels, suggesting that bone resorption during late pregnancy can be attenuated by increased calcium intake ***(Avendano-Badillo D et al, 2009)***.

Increase demands during gestation

Adolescence is a critical period for peak bone mass development; therefore, it has been thought that pregnancy during adolescence will place an adverse burden on the developing maternal and fetal skeletons ***(Andrea N Hacker et al, 2012)***.

Bezerra et al. found that adolescents have elevated bone resorption during pregnancy, but less than what is typically observed in adult pregnant women. Additionally, the rate of bone formation does not increase in pregnant adolescents as it does in pregnant adults. These differences in rates of bone resorption and formation, as measured by bone markers, indicate that bone turnover and calcium metabolism is different in pregnant females who have a developing skeleton ***(Bezerra FF et al, 2004)***.

Additionally, calcium absorption, measured during the third trimester in pregnant adolescents, averaged 53%, ***(O'Brien KO et al, 2003)*** not notably different than absorption rates in pregnant adults ***(Ritchie LD et al, 1998)***. However, most adolescent females have not reached peak bone mass and are therefore at risk of not meeting their peak rate of bone accretion ***(O'Brien KO et al, 2003).***

Sowers et al. measured bone mass at the os calcis in both adolescents and adults who were pregnant. Ultrasound measurements were made at 16 weeks of gestation and at 6 weeks postpartum. Bone mass was lost in all women, but adolescents had a significantly greater loss than the adult pregnant women. Since it was not reported if the women were nursing or formula feeding, the effect of lactation on bone loss was not considered ***(Sowers MF et al, 2000)***.

Short time intervals between pregnancies may constitute another increased demand on the maternal skeleton. Thus far, no significant effect of birth interval or length of lactation on risk of fracture has been observed, nor has an increased risk of fracture been reported in women who became pregnant while lactating ***(Matsushita H et al, 2002)***.

It is not known how a pregnancy with multiple fetuses affects maternal bone health. Multiple births are occurring more frequently as fertility treatments become more common ***(Boivin J et al, 2007)***. However, there is a paucity of research focused on how this additional stress affects maternal calcium metabolism and/or bone turnover ***(Andrea N Hacker et al, 2012)***.

Women are also having children later in life. The birth rate for women in their forties has more than doubled since 1981 and has increased more than 70%

since 1990. The number of births to women aged 50–54 years increased 18% in 2006 ***(Martin JA et al, 2009)***.

Women with their last birth in the age interval 30–33 years have the smallest risk of hip fracture, and women with their last birth at 38 years of age have an increased risk of hip fracture ***(Petersen HC et al, 2002).*** This increased risk of hip fracture in women whose last birth is at an older age (38 years) may be attributable to decreased estrogen levels in women near the end of their reproductive life stage. Low estrogen levels increase RANKL (receptor activator of nuclear kappa B ligand), which stimulates osteoclast recruitment and activation, resulting in greater bone resorption than formation ***(Lacey DL et al, 1998)***.

Decreased bone formation due to decreased estrogen levels and increased demand for fetal needs may be why women who give birth after age 38 are at an increased risk for hip fracture ***(Andrea N Hacker et al, 2012)***.

Calcium toxicity

The UL for any essential nutrient represents the safe upper boundary that individuals may consume on a regular basis without significant comorbidity; however, it should not be an amount that people strive to consume. Excess calcium from dietary intake alone is difficult to achieve. Typically, overconsumption of calcium is linked to an excess intake of dietary supplements. The IOM report states that “the potential indicators for the adverse outcomes of

excessive calcium intake are not characterized by a robust data set that clearly provides a basis for a dose-response relationship. The measures available are confounded by a range of variables including other dietary factors and pre-existing disease conditions," illustrating the difficulty in setting a UL. Excess calcium intake may cause hypercalcemia and/or hypercalciuria. Hypercalcemia occurs when serum calcium levels are 10.5 mg/dL or greater. It can be caused by excessive intakes of calcium or vitamin D but more commonly is caused by primary hyperparathyroid- ism or a malignancy. Hypercalciuria is present when urinary excretion of calcium exceeds 250mg/day in women, which frequently occurs during pregnancy as a consequence of increased intestinal absorption and increased GFR (***Institute of Medicine, 2011)***.

Hypercalcemia and hypercalciuria can cause renal insufficiency (GFR < 60 mL/min114), 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. ***(Smith CL et al, 2001)***. Yet, because there is minimal data showing an increased risk of nephrolithiasis during pregnancy, the UL for pregnant women aged 19–50 years is 2,500 mg/day, similar to that for non-pregnant, non-lactating women ***(Andrea N Hacker et al, 2012)***.

PUBLIC HEALTH IMPLICATIONS

It is firmly established that calcium plays an essential role in both the development and maintenance of bone health. Given that osteoporosis is actually a condition of childhood that presents in older age, the importance of calcium intake throughout the lifespan cannot be overlooked. With evidence suggesting that maternal calcium intake can affect the bone development of the fetus and potentially program future skeletal growth, it is essential that women of child-

bearing age are educated on the importance of meeting their calcium requirements. Women of child-bearing age will meet their own needs and those of their infants if they regularly consume adequate amounts of calcium (1,000 mg/day). Additional calcium supplementation during pregnancy appears to have the greatest impact in women who chronically consume <500 mg calcium/day, demonstrating the importance of adequate calcium intake before pregnancy begins. In conclusion women who begin pregnancy with adequate intakes of at least 1,000mg calcium/day may not need additional calcium, but women with suboptimal intakes (<500 mg) may need additional amounts to meet both maternal and fetal bone requirements. The relationship between infant BMD, BMC, IGF-1 levels, and cord blood leptin levels suggests that fetal metabolism influences fetal bone development ***(Andrea N Hacker et al, 2012)***.

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