Calcium metabolism in pregnancy and lactation

C P White

Department of Endocrinology and Metabolism, Prince of Wales Hospital, University of New South Wales, Sydney, Australia

Summary: Homeostatic adaptation to maternal calcium metabolism is a prerequisite for optimal delivery of sufficient calcium to the fetus and neonate during pregnancy and lactation, respectively. This article outlines the major adaptations known to occur and the physiological regulators likely to be principally involved. Importantly, different adaptive responses are used in pregnancy and lactation. The rarity of calcium disorders in pregnancy underscores the successful implementation of these adaptations in most women. For those few women with either pre-existing or pregnancy-acquired disorders of calcium metabolism, a knowledge of normal physiology is essential to understand the implications for managing these disorders in pregnant women.

Keywords: calcium metabolism, pregnancy, lactation, hyperparathyroidism, osteoporosis

Maintaining calcium balance in adults is a task often made difficult by stresses imposed from insufficient calcium intake, incomplete gut calcium absorption or enteric losses or renal excretion, potentially compounded by superadded vitamin D insufficiency. These factors account for a net negative calcium balance in the majority of adults, a situation that progressively deteriorates with age.¹

In pregnant women the fetus has a requirement to not only equilibrate its own physiological homeostatic calcium level, but also to ensure sufficient skeletal development in the available gestational window (primarily the third trimester) to permit postpartum survival without compromising malleability. Recent data has also suggested a possible link between the intrauterine nutrient environment, fetal birthweight and the subsequent skeletal development of peak bone mass; a modifiable environmental effect that may be susceptible to a number of genetic influences.² These concerns form the basis for recommendations ensuring adequate dietary calcium intake of 1000–1500 mg and 400–800 IU of vitamin D in pregnant and lactating women as insurance against potentially modifiable nutritional deficits.

As in all other physiological adaptations that occur in pregnant women, a mother must make a number of adaptive changes to promote positive calcium balance in favour of her child. Postpartum the lactating mother must similarly maintain a supply of calcium for the benefit of the neonate at levels that can approach 300–400 mg/day. Paradoxically two different sets of adaptive responses are activated to meet these demands (Table 1).

There are three potential sources whereby maternal adaptation can occur; increasing gut calcium absorption, mobilizing skeletal calcium reserves or restricting renal losses to permit positive fetal and postnatal calcium balance. To understand the adaptive responses available to pregnant and lactating

women it is helpful to briefly review normal calcium metabolism and its major homeostatic regulators (Figure 1) that are the most important factors modified in pregnant and lactating women.

Gut calcium absorption can occur either passively or, particularly in situations of reduced calcium intake, via an actively mediated vitamin D-dependent process. The active transport component is most potently stimulated by the interaction of 1,25-dihydroxyvitamin-D3 (1,25-D3) with its receptor in the gut luminal epithelium. Circulating concentrations of 1,25-D3 in non-pregnant adults are tightly regulated by the activity of the renal 1-hydroxylase located in the renal tubule that is stimulated by parathyroid hormone (PTH) and most potently inhibited by 1,25-D3 itself in a classic endocrine negative feedback loop.

PTH is itself an active regulator of serum calcium homeostasis beyond its effect on 1,25-D3 synthesis, as it stimulates mobilization of calcium from skeletal reserves as well as influencing renal handling of calcium and phosphate to maintain equilibrium of these two components. PTH is under the control of a specific sensor or calcium receptor and negatively correlated with ionized serum calcium.

PTH-related peptide (PTHrP) was first characterized as the peptide that could be produced in an unregulated ectopic fashion by a wide number of tumours causing humoral hypercalcaemia of malignancy. There is no known gland in adults that classically secretes PTHrP in a humoral, targeted and feedback fashion. However, studies have identified a fundamental role for PTHrP in normal skeletal development and maturation acting principally in a paracrine, rather than a classic endocrine function. In keeping with the concept that this peptide is an ancestral analogue of PTH, with which it shares significant amino-terminal sequence homology, is the fact that both PTH and PTHrP can act through the same receptor. Importantly, mid-molecular and C-terminal differences exist between these molecules that may potentially account for some of their differentiated functions in mineral metabolism, skeletal biology and, of greatest relevance to this review, the adaptive responses of

Table 1 Maternal adaptive changes to calcium metabolism in pregnancy and lactation

	Ionized calcium	PTH	1,25(OH) ₂ Vitamin-D ₃	PTHrP
Pregnancy	Normal	Suppressed	Increased	Undetectable
Lactation	Normal	Suppressed	Normal	Measurable

PTH = parathyroid hormone; PTHrP = parathyroid hormone-related peptide

the fetus and lactating and pregnant woman. For instance, PTHrP shows increased expression in lactating breast tissue and is expressed by the placenta and the fetal parathyroid gland.³

In pregnancy, the fetus must maintain a positive transplacental gradient in the face of potential maternal nutrient deficiencies of calcium and/or vitamin D. This remarkable ability of the fetus is underscored by the observations that infants born to vitamin D-deficient mothers are rarely hypocalcaemic (but can become so in the first week postpartum) and that rickettic changes usually only evolve in the first month of life but are rarely present at birth.⁴

A number of putative regulators have been studied or proposed and while much of our understanding has been derived from experimental animal models, it is highly likely that fetal PTHrP may be regulating this transplacental gradient. PTHrP does not cross the placenta and cord levels reflect that produced by the fetus for its own physiological needs. Cord blood levels of PTHrP are higher than the mother's while fetal PTH levels are suppressed and 1,25-D₃ levels are also marginally lower. In this environment, accrual of fetal skeletal calcium is favoured. However, use of the classic amino-terminal responsive 'shared' PTH/PTHrP receptor is not likely to be the mechanism whereby PTHrP exerts its principal action given that the fetal skeleton does not demonstrate a hyperparathyroid phenotype. Rather, putative roles of unique mid-molecular regions of the PTHrP molecule have been suggested by a number of knockout models, but their wider application to human biology is unknown and, to date, a unique mid-molecular PTHrP receptor has not been identified.⁵

The major maternal adaptation is a doubling of gut calcium absorption mediated most efficiently via increasing 1,25-dihydroxyvitamin-D₃ (1,25-D₃) levels in an effort to optimize placental calcium availability (Figure 2). In the face of

Figure 2 Increasing 1,25-D₃ levels in an effort to optimize placental calcium availability

abundant calcium, maternal PTH levels are universally suppressed and, together with an adaptive increase in glomerular filtration rate, renal calcium retention over-ridden to permit excretion and hypercalciuria. Typically, this hypercalciuria demonstrates an 'absorptive' pattern, unaltered in the fasting state but rising postprandially.⁶ The mechanism by which maternal increases in 1,25-D₃ arise is unknown but could include either decreased clearance or increased synthesis. Putative mediators of increased maternal 1,25-D₃ synthesis could include human placental lactogen, prolactin, PTHrP, oestradiol or other as yet unidentified regulators; for example FGF23, a potent inhibitor of 1,25-D₃ in normal adult homeostasis, has not been studied in pregnant women. In this scenario, the vast skeletal reserves of calcium are not required and do not appear to be appreciably affected in pregnant women despite biochemical evidence of increased turnover. Multiparity does not appear to be a major risk factor for osteoporosis in later life and while only limited data exist, the changes between prepregnancy and postpartum bone mineral density (BMD) are marginal.⁷

Postpartum there is a relatively rapid reversal of these adaptive responses. However, lactation will impose an obligate net negative maternal balance in favour of the nursing infant; a reversible process salvaged by weaning. In nursing mothers, ionized calcium is slightly higher, a trend enhanced in mothers nursing twins. A central role for the breast in regulating calcium homeostasis in lactation is further supported by cases of lactational hypercalcaemia that spontaneously resolve with weaning.⁸ In marked contrast to the two-fold increases in maternal gut calcium absorption that occurs in pregnancy, the lactating mother does not maintain this adaptive response. Levels of 1,25-D₃ return within days to the non-pregnant normal adult range. Indeed while recommended dietary increases in maternal calcium intake are made to ostensibly provide the necessary nutritional substrate, it is unlikely that these measures are efficient or sufficient as increased gut calcium absorption does not occur and the balance of any nutritional deficit is sourced from skeletal reserves.⁹ Traditionally, such a primary physiological demand would orchestrate a secondary adaptive increase in PTH to mobilize skeletal reserves, but PTH levels in lactating women are unchanged from when pregnant, remaining suppressed in the face of increased ionized calcium levels. This indicates that an alternative,

Figure 1 Normal calcium metabolism and its major homeostatic regulators

calcium-independent strategy must be responsible. Mammary synthesis of PTHrP production is probably the best candidate (Figure 3). PTHrP levels are higher in the serum of lactating mothers and are positively correlated to prolactin levels and serum calcium. Importantly, PTHrP levels also correlate with the decline in BMD. Losses in BMD can range from 3–8% at two to six months postpartum, are more evident at trabecular than cortical sites and are better correlated with output of breast milk than dietary calcium. However, the highest losses may occur in younger women with greater dietary calcium deficits. A contribution to skeletal losses may also arise from the hypoestrogenization associated with lactational amenorrhoea. Resumption of normal menses does not completely attenuate the losses and to some extent a decline in BMD in lactating women is almost inevitable.¹⁰ These losses appear reversible with weaning. Restoration of baseline BMD can be expected within six to 12 months.¹¹

What is the clinical relevance of these data? Primary disorders of calcium metabolism are uncommon in women of child-bearing age but of those that can occur, there are three likely scenarios that the obstetric physician may need to address: pre-existing primary hyperparathyroidism, hypoparathyroidism and osteoporosis.

Primary hyperparathyroidism can be due to either a discrete parathyroid adenoma or hyperplasia of all four parathyroid glands, the latter more common in familial syndromes of the disorder. These disorders are rare in young premenopausal women of child-bearing age and historical reports are likely biased toward presenting the more severe cases. As outlined above, the normal adaptive response is to favour a fetal gradient of calcium; a pre-existing or evolving maternal predisposition to hypercalcaemia will over-ride this adaptation and predisposes to fetal parathyroid suppression and neonatal hypocalcaemia.¹² An increased risk of stillbirth and neonatal hypocalcaemia has been described. However, the recommendation to proceed to surgery early in the second trimester is possibly biased by these reports. The concern of significant maternal hypercalcaemia is clearly a risk given the uncoupling that can occur between PTH secretion and 1,25-D₃ synthesis in pregnancy. While mild asymptomatic cases have been watched closely through pregnancy, a management decision needs to be made by the second trimester, and both neonate and mother need to be closely monitored through the course of the pregnancy and neonatal period. Importantly, the rare inherited

disorder of familial hypocalciuric hypercalcaemia (FHH) that can be diagnostically confused with primary hyperparathyroidism needs to be recognized for two reasons; surgery is never effective at resolving the disorder and is not indicated, and the autosomal dominant pattern of inheritance means that there is a 50% chance that the neonate is unaffected and therefore at risk of neonatal hypocalcaemia from parathyroid gland suppression having developed in a mildly hypercalcaemic environment.¹³

Hypoparathyroidism is more uncommon, but is a management issue in patients who have previously required a total thyroidectomy for hyperfunctioning or malignant thyroid disease and in whom iatrogenic hypoparathyroidism has occurred. Idiopathic and autoimmune cases of hypoparathyroidism constitute the remainder of the cases likely to be encountered. Thus, the majority of these women will have already been previously symptomatic of hypocalcaemia and tetany when not pregnant and will already be on treatment with multiple dosing per day of calcium and 1,25-D₃ to maintain a eucalcaemic state. Variability in absorption and/or compliance can lead to fluctuations in serum calcium levels even when not pregnant and an acceptable therapeutic target in non-pregnant women is to maintain serum calcium in a low normal or marginally subnormal but asymptomatic range to minimize the risk of long-term hypercalciuria and nephrocalcinosis.

The maternal adaptive response, characterized by a spontaneous increase in 1,25-D₃ synthesis, increases gut calcium absorption and suppresses PTH secretion. The pregnant hypoparathyroid woman who is already treated with calcium and 1,25-D₃ is at risk of both hypocalcaemia if under-treated with 1,25-D₃ and hypercalcaemia if treatment with 1,25-D₃ is additive to her endogenous capacity to increase renal or placental 1,25-D synthesis when pregnant. Pregnant women with this disorder can rapidly oscillate between hypocalcaemia and hypercalcaemia.

While the fetal gradient attempts to maintain a relative abundance of calcium for fetal development and function, neonatal hypocalcaemia has been reported as well as an increased risk of stillbirth, spontaneous abortion and neonatal death associated with low birthweight. Fetal hyperparathyroidism characterized by skeletal demineralization, osteitis fibrosa cystica and subperiosteal resorption, bowing deformity and fractures can occur.¹⁴ Therefore, while there is an imperative to limit the degree to which treated hypoparathyroid women can become hypercalcaemic in the third trimester by reducing the amount of exogenous 1,25-D₃ that they require, it is also imperative to ensure that maternal and fetal hypocalcaemia are avoided. Clearly close observation of the mother and the neonate are required throughout, with the greatest risk of adverse oscillations occurring in the third trimester when maternal adaptation and endogenous 1,25-D₃ synthesis is highest. There is also a reduced need for 1,25-D₃ replacement in these women when breastfeeding because of a restored capacity while lactating to produce endogenous 1,25-D₃; possibly by inducing PTHrP secretion by the lactating mammary tissue.

Osteoporosis, defined as a minimal trauma fracture occurring spontaneously or after a fall from standing height or less can occur in pregnancy. Most often vertebral in origin it is a rare presentation in pregnancy and postpartum restoration of bone mass does not usually see the return of BMD to comparative levels expected of young premenopausal women. The consensus is that this probably reflects a pre-existing idiopathic osteoporotic process due to inadequate peak bone mineral accrual in

Figure 3 Mammary synthesis of PTHrP production

developing years rather than any specific pregnancy-related disorder. There are well-recognized and identifiable secondary causes of osteoporosis such as treatment with heparin, anticonvulsants (via perturbation of vitamin D metabolism promoting osteomalacia) or corticosteroids. There is no symptomatic deterioration with subsequent pregnancies and progeny often shares a low peak bone mass phenotype suggesting a genetic predisposition to the disorder rather than a specific pregnancy-related event.¹⁵ Therefore there is no absolute contraindication to becoming pregnant in women with pre-existing idiopathic osteoporosis though issues in some women with more severe genetic forms of the disease, such as osteogenesis imperfecta, will require some form of genetic counselling and obstetric assessment regarding optimal delivery.

Lactation is more likely to present a significant skeletal demand given the maternal response. While rare, vertebral crush fractures can occur in the one to six months postpartum and histomorphometry confirms increased bone resorption. BMD deficits improve with weaning. Fortunately, there are few, if any, long-term consequences and there are no epidemiological data to link lactation with postmenopausal fracture incidence.¹⁵ It is therefore likely that this reversible decline in BMD confers only a short-term disadvantage to premenopausal women with known pre-existing osteoporosis. This does not present an absolute contraindication to breast feeding in these few women, who may nonetheless sensibly limit its duration.

REFERENCES

- 1 Heaney RP. Bone health. *Am J Clin Nutr* 2007;**85**:300S–3S
- 2 Cooper C, Javaid K, Westlake S, Harvey N, Dennison E. Developmental origins of osteoporotic fracture: the role of maternal vitamin D deficiency. *J Nutr* 2005;**135**:2728S–34S
- 3 Abbas SK, Pickard DW, Illingworth D, *et al.* Measurement of parathyroid hormone-related protein in extracts of fetal parathyroid and placental membranes. *J Endocrinol* 1990;**124**:319–25
- 4 Pereira GR, Zucker AH. Nutritional deficiencies in the neonate. *Clin Perinatol* 1986;**13**:175–89
- 5 Kovacs CS, Lanske B, Hunzelman JL, Guo J, Karaplis AC, Kronenberg HM. Parathyroid hormone-related peptide (PTHrP) regulates fetal-placental calcium transport through a receptor distinct from the PTH/PTHrP receptor. *Proc Natl Acad Sci USA* 1996;**93**:15233–8
- 6 Gertner JM, Coustan DR, Kliger AS, Mallette LE, Ravin N, Broadus AE. Pregnancy as a state of physiologic absorptive hypercalciuria. *Am J Med* 1986;**81**:451–6
- 7 Sowers M, Crutchfield M, Jannausch M, Updike S, Corton G. A prospective evaluation of bone mineral change in pregnancy. *Obstet Gynecol* 1991;**77**:841–5
- 8 Van Heerden JA, Gharib H, Jackson IT. Pseudohyperparathyroidism secondary to gigantic mammary hypertrophy. *Arch Surg* 1988;**123**:80–2
- 9 Kalkwarf HJ, Specker BL, Heubi JE, Vieira NE, Yergey AL. Intestinal calcium absorption of women during lactation and after weaning. *Am J Clin Nutr* 1996;**63**:526–31
- 10 Kent GN, Price RI, Gutteridge DH, *et al.* Human lactation: forearm trabecular bone loss, increased bone turnover, and renal conservation of calcium and inorganic phosphate with recovery of bone mass following weaning. *J Bone Miner Res* 1990;**5**:361–9
- 11 Affinito P, Tommaselli GA, diCarlo C, Guida F, Nappi C. Changes in bone mineral density and calcium metabolism in breastfeeding women: a one year follow-up study. *J Clin Endocrinol Metab* 1996;**81**:2314–18
- 12 Lowe DK, Orwoll ES, McClung MR, Cawthorn ML, Peterson CG. Hyperparathyroidism and pregnancy. *Am J Surg* 1983;**145**:611–14
- 13 Thomas BR, Bennett JD. Symptomatic hypocalcemia and hypoparathyroidism in two infants of mothers with hyperparathyroidism and familial benign hypercalcemia. *J Perinatol* 1995;**15**:23–6
- 14 Loughhead JL, Mughal Z, Mimouni F, Tsang RC, Oestreich AE. Spectrum and natural history of congenital hyperparathyroidism secondary to maternal hypocalcaemia. *Am J Perinatol* 1990;**7**:350–5
- 15 Melton LJ III, Bryant SC, Wahner HW, *et al.* Influence of breastfeeding and other reproductive factors on bone mass in later life. *Osteoporosis Int* 1993;**3**:76–83

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