Bone metabolism during pregnancy

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Abstract

During pregnancy, mineral concentrations, of calcium and phosphorus in particular, are maintained at a high level in fetal blood so that the developing skeleton may accrete adequate mineral content. The placenta actively transports minerals for this purpose. Maternal intestinal absorption increases in order to meet the fetal demand for calcium, which is only partly dependent on calcitriol. Mineral regulation is essentially dependent on parathyroid hormone (PTH) and PTH-related protein (PTHrP). The calcium-sensing receptor (CaSR) regulates PTH and PTHrP production. If calcium intake is insufficient, the maternal skeleton will undergo resorption due to PTHrP. After birth, a switch from fetal to neonatal homeostasis occurs through increase in PTH and calcitriol, and developmental adaptation of the kidneys and intestines with bone turnover contributing additional mineral to the circulation. Calcium absorption becomes progressively active and dependent on calcitriol. The postnatal skeleton can transiently present with osteopenia but adequate mineral diet usually allows full restoration. Cases of primary osteoporosis must be identified. Loss of trabecular mineral content occurs during lactation in order to provide calcium to the newborn. This programmed bone loss is dependent on a “brain-breast-bone” circuit. The physiological bone resorption during reproduction does not normally cause fractures or persistent osteoporosis. Women who experience fracture are likely to have other causes of bone loss.

Keywords: Pregnancy; Osteoporosis; Lactation; Newborn; Parathyroid hormone-related protein

Résumé

Pendant la grossesse, les concentrations en minéraux, notamment en calcium et en phosphore, sont maintenues élevées dans le sang fœtal afin d’assurer au squelette en développement un apport en minéraux suffisant. Le placenta effectue ce transport actif. L’absorption intestinale du calcium augmente chez la mère, afin de répondre à la demande du fœtus, ce qui n’est que partiellement dépendant de la 1,25-dihydroxy vitamine D (1,25-OH2D). La régulation du métabolisme minéral dépend essentiellement de la parathormone (PTH) et du PTH-related protein (PTHrP). Le récepteur sensible au calcium (RSCa) régule la production de PTH et PTHrP. En cas d’apport en calcium insuffisant, le squelette maternel fera l’objet de résorption sous l’effet du PTHrP. Après la naissance, une modification de l’hémostasie aura lieu du fœtus au nouveau-né par augmentation de la PTH et 1,25-OH2D, par une adaptation physiologique des reins et des intestins et par augmentation du remodelage osseux, l’ensemble contribuant à assurer un apport de minéraux suffisant à la circulation. L’absorption du calcium devient ensuite progressivement active et dépendante du 1,25-OH2D. Le nouveau-né peut présenter transitoirement une ostéoporose mais une alimentation adéquate permet habituellement une restauration complète du contenu minéral du squelette. Certaines causes primitives d’ostéoporose doivent être identifiées à ce stade. Une perte de contenu minéral se produit pendant l’allaitement au niveau trabéculaire, pour assurer l’apport de calcium nécessaire à l’enfant. Cette perte osseuse programmée dépend d’un circuit « cerveau-sein-os ». La résorption osseuse physiologique qui se produit au cours de la reproduction ne provoque habituellement pas de fractures ou d’ostéoporose persistante. Les femmes présentant des fractures dans ce contexte sont susceptibles d’avoir d’autres causes d’ostéoporose.

Keywords: Pregnancy; Osteoporosis; Lactation; Newborn; Parathyroid hormone-related protein

Mots clés : Grossesse ; Ostéoporose ; Lactation ; Nouveau-né ; Parathyroid hormone-related protein

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1. Introduction

Build-up of bone mass in utero depends upon two kinds of cells: osteoblasts as bone-forming cells, and osteoclasts as resorbing cells. An advantage is naturally given to bone formation, which characterizes the phenomenon of modeling. Bone modeling is maintained throughout development until the end of puberty. It is followed by permanent remodeling during adulthood, with a balance between bone formation and bone resorption. Prenatal modeling, which corresponds to initial skeletal development, may have consequences on ultimate bone mass. While postnatal bone metabolism can largely be explained by the interplay of a limited number of hormones [parathyroid hormone (PTH), 25-hydroxyvitamin D (25-OHD), 1,25-dihydroxyvitamin D (calcitriol), fibroblast growth factor 23 (FGF23), calcitonin and sex steroids (estradiol and testosterone)] acting more or less directly on osteoclasts and osteoblasts, prenatal bone metabolism is regulated differently and these hormones play a less prominent role.

Building up of the fetal skeleton is dominated by a massive transfer of minerals, which is mandatory for adequate skeletal formation during pregnancy and later on during lactation. This transfer necessarily affects the maternal skeleton. These points will be addressed here. Key elements are fully developed in some excellent exhaustive reviews [1–4].

2. Modification of bone and mineral status during pregnancy

Pregnancy results in a huge net transfer of minerals from the mother to the fetus through the placenta, with notable physiological adaptations. During pregnancy, major modifications of the calcium metabolism and bone mineral status of the mother occur, in order to meet the needs of the fetus for optimal growth of its skeleton and its mineralization [2–4].

Calcium mobilization from the maternal skeleton is possible only through significant hormonal adaptation during pregnancy. While the kidney and intestine ensure adequate control of the postnatal balance of minerals, positive transfer from the maternal circulation to the fetus is the task of the placenta. The placenta actively transports minerals by extracting adequate quantities even if concentrations in the maternal circulation are low. The total net accumulation of calcium in a full-term fetus is about 30 g. While maximum transfer of calcium to the fetus occurs during the third trimester (80%), the adjustment of maternal homeostasis starts early during pregnancy.

Mineral concentrations are higher in the fetus than in the maternal circulation. The concentration of ionized calcium increases by 0.3 mmol/L and that of phosphorus by 0.5 mmol/L. Fetal calcemia increases as early as the 15th week of pregnancy, demonstrating that active transfer to the fetus is precocious. Materno-fetal transfer of calcium increases markedly during the third trimester and reaches 300 to 400 mg/day at 38 weeks of pregnancy. Why such elevated levels of calcium and phosphorus are maintained is uncertain. Low fetal calcemia does not compromise the vitality of mouse fetuses but decreases skeletal mineralization. Postnatal adaptation may be improved by high calcemia at birth. High phosphate level probably contributes to apoptosis of hypertrophic chondrocytes in the growth plates.

PTH level is maintained at a low level in the fetal circulation. The fetal parathyroid glands synthesize PTH, which does not cross the placenta. PTH production by the fetus is controlled by the calcium-sensing receptor (CaSR) in response to the high levels of calcium [5]. Fetal calcitriol is also maintained at a low level. Fetal 1α-hydroxylase activity is detectable in fetal kidneys and in the placenta. Calcitriol, unlike 25-OHD, does not cross the placental barrier [2]. Several parameters contribute to lowering 1α-hydroxylase activity: low PTH level, high calcemia and phosphoremia. FGF23 may also play a part, however human fetal FGF23 level appears low compared with the adult level. Overall, the level of activity of FGF23 in the human fetus is still uncertain, because elevated levels of its inactive C-terminal fragment and its coreceptor Klotho have been observed. The main point is that the PTH-like activity in the fetal circulation is due to high concentrations of PTH-related protein (PTHrP) (see below).

Digestive absorption of calcium increases in the mother during pregnancy. Increased calcium absorption results from increased calcitriol, without modifications of PTH or 25-OHD concentrations. However, increased calcitriol concentration alone does not explain increased calcium absorption. Moreover, calcium absorption increases during pregnancy even when 25-OHD is deficient [6,7]. Increased 1α-hydroxylase activity, responsible for increased synthesis of calcitriol during pregnancy, seems mainly due to PTHrP and estradiol.

PTHrP is produced from the beginning of pregnancy and its levels are very high during the second part of pregnancy. Amino-terminal forms of PTHrP (PTHrP 1-86) mimic the effect of PTH on the kidneys and bone through activation of the PTH/PTHrP receptor. Other circulating fragments of PTHrP potentially display other functions [4]. PTHrP level is consistent with increased calcitriol and decreased PTH levels in the mother during pregnancy.

PTHrP is essential for fetal metabolism. Animal models have provided some clues. Fetuses of PTHrP knockout mice display hypocalcemia and hyperphosphatemia. PTHrP is synthesized mainly by the placenta. PTHrP production by the fetal parathyroid glands is not clearly documented. The fetal parathyroid glands synthesize PTH after the 10th week of pregnancy. In the absence of parathyroid glands, more marked hypocalcemia is observed than in the absence of PTH or PTHrP alone. This suggests that the fetal parathyroid glands may produce PTHrP and that, even at a low level, PTH exerts an additive effect to that of PTHrP for the control of fetal calcemia.

Fetal calcitriol does not appear necessary for the regulation of fetal calcemia and phosphatemia. Deletion of the vitamin D receptor or 1α-hydroxylase genes does not result in altered calcium or phosphorus level [7]. FGF23 does not seem mandatory because Phex gene abnormality, which results in high FGF23 levels, or FGF23 gene invalidation do not modify fetal calcium or phosphorus concentrations in mice [3].

The fetal kidneys and digestive absorption do not seem to contribute significantly to fetal mineral homeostasis. The placenta...
makes the main contribution to the active transfer of minerals, calcium, phosphorus and magnesium, depending on PTHrP (and to a lesser extent on PTH), independently of 1,25-OH2D and FGF23. If the mother has hypercalcemia, placental transfer of calcium increases, which explains the negative control of fetal PTH and postnatal hypoparathyroidism.

Primary ossification centers start to develop in the axial skeleton and limbs as early as the 8th week of pregnancy. However, bone mineral accretion remains modest until the third trimester, when the net transfer of minerals to the fetus culminates. In addition to its net gain of minerals throughout gestation, fetal bone is also permanently remodeled. Bone remodeling concomitant with bone accretion helps to maintain high fetal calcemia. Bone resorption markers are detectable in fetal urine and bone. Due to low remodeling, fetal mice, which do not express the PTH/PTHrP receptor, develop severe hypocalcemia [2,3,8].

PTHrP also plays a major role in the regulation of endochondral ossification through the control of proliferation and differentiation of hypertrophic chondrocytes in the growth plate. In the absence of PTHrP, chondrocytes undergo premature apoptosis with absence of limb development while mineralization is accelerated. In the absence of PTH, fetal hypocalcemia results in a skeleton that is morphologically normal but under-mineralized. Lack of the PTH/PTHrP receptor results in a combined phenotype with chondrodysplasia and low mineralization [9], described in humans as lethal Blomstrand chondrodysplasia [10]. Fetal endochondral development does not appear to be significantly affected by the lack of vitamin D, calcitriol or FGF23. Regulation of phosphate level in the fetus seems largely independent of FGF23 and calcitriol levels.

3. Maternal bone status related to pregnancy

Analysis of iliac bone biopsies at the beginning and end of pregnancy has demonstrated that pregnancy significantly modifies maternal bone status [11]. Bone mass decreases at the beginning of pregnancy and is restored at the end. A global increase of bone remodeling occurs, with a first phase of resorption followed by subsequent bone formation [12]. Bone resorption markers, CTX and desoxypyridinoline, increase during the first trimester while bone formation markers, such as bone specific alkaline phosphatase (BSAP) remain stable until 22 weeks of gestation, and then further increase until full term. Serial studies evaluating bone mineral density (BMD) are scarce, concern few subjects and include the lactation period, but they report a loss of up to 5% BMD at the hips and spine [1]. In a recent controlled study, BMD modifications were considered small if the lactation period was excluded, at least in women with normal vitamin D and calcium status [13].

Bone resorption and BMD decrease are not explained by an increase of maternal PTH level, as discussed above, but rather by the PTHrP level, which reaches a maximum during the third trimester. In rare cases, excessive PTHrP secretion may occur, resulting in increased resorption and hypercalcemia (pregnancy pseudohyperparathyroidism) due to massive production of PTHrP by the placenta or mammary glands [1,14,15].

Mineral transfer during lactation corresponds to a maternal loss of 200 mg/day of calcium, which is delivered in the maternal milk. Calcium absorption decreases, as does calcitriol level. Mineral transfer to the baby becomes detrimental to the maternal skeleton. In osteoblasts, nuclear factor kappa-B ligand (RANKL), the main indicator of osteoclastic activation, increases while osteoprotegerin secretion decreases. A specific endocrine circuit is then described as a “brain-breast-bone” circuit [16,17]. PTHrP is still abundantly produced by the maternal glands, its secretion being stimulated by sucking. The CaSR also contributes to PTHrP secretion [1,18,19]. Elevated prolactin level, which contributes to decreased estradiol secretion by the gonads, together with serotonin seem to be additional factors in the secretion and/or effect of PTHrP on bone resorption during lactation [20–23]. Oxytocin also has an effect on bone and may promote maternal bone remodeling during lactation [20–22]. PTH remains downregulated. In rodents, bone loss may reach 20% decrease in trabecular BMD during lactation. In women, skeletal resorption accounts for a 5 to 10% decrease in trabecular BMD and a less marked decrease in cortical bone and total body bone mass. Biological markers of resorption (CTX, desoxypyridinoline) are elevated.

The increased resorption is mainly due to two processes. Osteocytic osteolysis is an uncommon mechanism which has been well documented in rodents, with specific resorption occurring in the pericellular matrix of differentiated osteocytes embedded in bone, under the effect of PTHrP [24]. Less differentiated osteoblasts also promote bone resorption through RANKL secretion. Osteocytic osteolysis and osteoblast-driven resorption appear to contribute equally to bone loss during lactation.

In women, unlike in rodents, bone remodeling is not significantly influenced by the level of calcium intake. Bone loss may probably be increased during lactation in women with twins and when lactation is prolonged. Nevertheless, when infants aged over 6 months are given a diversified diet, the quantity of milk provided by the mother usually decreases. The overall loss of 5 to 10% of bone mass during lactation may transiently increase the fracture risk in the most severe cases.

Bone mass recovers after lactation, when osteocytes restore the pericellular lacunae through new osteoblastic activity, and in parallel the number of osteoblasts increases. Bone resorption markers decrease while bone formation markers increase, which suggests that bone remodeling is decoupled in favor of bone formation. In rodents, vertebral bone structure is restored while the trabeculae of long bones do not completely recover. Long bones still show changes. Diaphyseal diameter is increased, which compensates for the decrease of thickness during pregnancy [25].

Taken together, pregnancy and lactation result in significant bone changes in women, with transient remodeling and possibly osteoporosis. Full recovery is the rule. Increased risk of fracture is rare during pregnancy and lactation. In such cases, additional factors, primary or acquired, such as major calcium deficiency, which may increase the fracture risk, must be sought.
4. Fetal development and mineralization

During fetal growth, plasma concentrations of calcium and phosphorous are maintained higher than in the mother and than in postnatal life. The PTH level is downregulated. Calcium and phosphorous delivery stops abruptly after birth and ionized calcium level decreases dramatically, while PTH secretion becomes strongly stimulated and its level increases markedly. Major adaptations occur in the newborn skeleton during early postnatal life. Increased PTH contributes to stimulation of osteoclasia in order to maintain the calcium homeostasis. This must logically be followed by a period of bone formation to ensure the overall growth of the skeleton. In fact, the BMD of long bones usually decreases by 30% during the first months of life, with a rapid increase of marrow cross-section that grows more rapidly than global diameter, a process sometimes called “physiological infantile osteoporosis”. Bone solidity is however preserved. The mechanisms involved in postnatal bone modifications are not fully understood, but the decrease in mobility may play a part [4]. During fetal growth, bone is regularly stimulated by the movements of the fetus against the uterine wall. After birth, the infant’s movements are made without external resistance, which may lower bone stimulation during this period.

Premature babies demonstrate a phase of rapid growth with high mineral requirements, which can carry the risk of osteomalacia. Premature babies, weighing less than 1500 g at birth, are at risk of significant mineral deficiency, mainly of phosphorus. Elevated alkaline phosphatase levels, and in particular phosphatemia below <1.5 mmol/L strongly suggests potential premature osteomalacia. However, this is restricted to premature infants with very low birth weight. This phenomenon is far less frequent in moderate prematurity without hypotrophy. Premature babies must be given diets with adequate calcium and phosphorus. However, the need for increased vitamin D administration is less obvious. Infants display remarkable bone plasticity, which allows considerable postnatal catch-up growth.

Other factors may contribute to lowering the postnatal bone mass. Babies born small for gestational age (SGA) have lowered bone mineral content and reduced level of osteocalcin, which reflects low bone formation [26]. Analysis of cohorts of SGA babies shows a tendency to osteoporosis [27–29]. Initial in utero programming of bone may therefore affect the development of the future skeleton. Poor control of maternal diabetes, especially during the first trimester, alcohol and tobacco intake as well as glucosteroid administration during pregnancy all contribute to SGA. Glucosteroid administration can be responsible for transient osteoporosis in newborns. Carboxy-terminal propeptide of type I procollagen (PICP) level is decreased at birth after sustained maternal glucosteroid administration [30]. However, glucosteroid administration, which is clearly of benefit to decrease morbidity of newborns, is not called into question. In any event, glucosteroid-induced osteoporosis is probably highly temporary, given the potential of adaptation of newborn bone [31]. Bisphosphonates administered before pregnancy have not been shown to have a negative impact on the bone mass of newborns [32].

Maternal calcium supplementation may increase fetal bone mineral content only in women whose calcium status is inadequate. Recent data suggest that supplementation has no real effect in mothers with normal calcium intake during pregnancy, given the increased rate of calcium absorption naturally occurring during gestation. Calcium supplementation may be justified only in particular circumstances, such as multiple pregnancies or calcium deficiency in adolescents [1,4].

A comment may be made regarding fetal hyperparathyroidism. PTH, and more particularly PTHrP, contribute to maintaining high fetal calcemia, partly affecting fetal bone resorption. Fetal secretion of PTH and PTHrP is dependent on the CaSR. In the fetus, inactivating mutations of the CaSR result in hyperparathyroidism with major bone remodeling which persists during postnatal growth and can be controlled by...
administration of bisphosphonates and calcimimetics [33] (Fig. 1). In past studies, CaSR polymorphisms have been related to bone status in adults but this is not firmly established [34].

Finally, major fetal defects of mineralization are encountered in inherited disorders, first of all osteogenesis imperfecta, whose genetic etiology is variable [35], or perinatal/infantile hypophosphatasia [36]. It is important to differentiate between these two diseases because the postnatal treatment differs. Specific recombinant enzyme therapy is now proposed for hypophosphatasia [37,38].

All the above factors must be taken into account when analyzing the bone status, osteoporosis or osteomalacia of newborns. Evaluation of bone status in the newborn is challenging. It is important to distinguish between bone deficiency (osteoporosis) and low mineralization (osteomalacia). Double X-ray absorptiophotometry (DEXA) is difficult to perform in the newborn and presents potential biases, especially with regard to height, and reliable normative reference data are lacking. Laboratory methods, such as measurement of bone markers have limited utility at individual level. Biological markers display a high variability in postnatal life, with high levels of PICP and carboxy-terminal telopeptide of type I collagen (ICTP) in cord blood, suggestive of high remodeling, and further decrease in the first months of life for ICTP in particular [39,40]. So, it is difficult to establish a clear evaluation of the bone status of newborns. All parameters, including the conditions of the pregnancy, prematurity and hypotrophy, maternal drugs and disorders must be taken into account. Beyond this, genetic and epigenetic factors with potential influence on the bone of newborns must be considered. Newborn bone demonstrates a high capacity to catch up after SGA or prematurity. Premature babies develop normally if adequate diet is provided with sufficient calories and mineral intake.

5. Conclusion

Bone and mineral metabolism undergoes significant changes during pregnancy. The placenta actively transfers minerals from maternal blood to the developing fetal bone. Animal and clinical data have defined the involvement of PTHrP and hormones in a brain-breast-bone circuit during lactation. The CaSR plays a role in the secretion of PTHR and PTH. Minerals are also transferred from the maternal skeleton to fetal bone, particularly during lactation. Postnatal adaptation may also lead to transient demineralization in order to control calcium homeostasis. These phenomena are usually moderate and temporary without increased risk of fracture for the mother. However, additional pathological factors may increase the risk of maternal fracture. Knowledge of the physiological factors involved during pregnancy is necessary in order to evaluate the bone status of the mother or the infant before making a decision with regard to treatment if there is significant bone deficiency.

Disclosure of interest

The author declares that he has no competing interest.

References


