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# Bone metabolism during pregnancy

## *Métabolisme osseux pendant la grossesse*

Jean Pierre Salles [a,b,*]

[a] *Unité d'endocrinologie, maladies osseuses, génétique et gynécologie, hôpital des Enfants, CHU de Toulouse, TSA 70034, 31059 Toulouse cedex 09, France*
[b] *Inserm UMR 1043 (Centre de physiopathologie de Toulouse-Purpan, CPTP), université de Toulouse-Paul-Sabatier, 31059 Toulouse, France*

**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 osteoposis 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-$OH_2$D). 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'homéostasie aura lieu du fœtus au nouveau-né par augmentation de la PTH et 1,25-$OH_2$D, 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-$OH_2$D. 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.


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

* Correspondence. Unité d'endocrinologie, maladies osseuses, génétique et gynécologie, hôpital des Enfants, CHU de Toulouse, TSA 70034, 31059 Toulouse cedex 09, France.
*E-mail address:* salles.jp@chu-toulouse.fr

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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 1 α-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