

ENDOCRINOLOGY IN PREGNANCY

Bone metabolic changes during pregnancy: a period of vulnerability to osteoporosis and fracture

Lucía Sanz-Salvador¹, Miguel Ángel García-Pérez², Juan J Tarín³ and Antonio Cano⁴

¹Fundación para la Investigación Sanitaria y Biomédica (FISABIO), Juan de Garay 21, 46017 Valencia, Spain,

²Department of Genetics, University of Valencia and Research Foundation, INCLIVA, Avenida Blasco Ibáñez 15, 46010 Valencia, Spain, ³Department of Functional Biology and Physical Anthropology, School of Biological Sciences, University of Valencia, Burjasot Campus, Valencia, Spain and ⁴Department of Pediatrics, Obstetrics and Gynecology, Facultad de Medicina, University Hospital Dr Peset, University of Valencia, Avenida Blasco Ibáñez 15, 46010 Valencia, Spain

Correspondence
should be addressed
to A Cano
Email
antonio.cano@uv.es

Abstract

Changes in bone density and bone markers suggest that pregnancy is associated with deterioration of bone mass in the mother. The metabolism of calcium resets to allow for the needs imposed by the building of the fetal skeleton. The fetus contributes to the process through the output of regulators from the placenta. Understanding of the whole process is limited, but some changes are unambiguous. There is an increase in the circulating levels of vitamin D, but its functional impact is unclear. Fetal parathyroid hormone (PTH) and PTH-related peptide (PTHrp) play an indirect role through support of a calcium gradient that creates hypercalcemia in the fetus. Placental GH, which increases up to the end of pregnancy, may exert some anabolic effects, either directly or through the regulation of the IGF1 production. Other key regulators of bone metabolism, such as estrogens or prolactin, are elevated during pregnancy, but their role is uncertain. An increase in the ratio of receptor activator of nuclear factor kappa B ligand (RANKL) to osteoprotegerin (OPG) acts as an additional pro-resorbing factor in bone. The increase in bone resorption may lead to osteoporosis and fragility fracture, which have been diagnosed, although rarely. However, the condition is transitory as long-term studies do not link the number of pregnancies with osteoporosis. Prevention is limited by the lack of identifiable risk factors. When fractures are diagnosed, rest, analgesics, or, when indicated, orthopedic intervention have demonstrated efficacy. Systemic treatment with anti-osteoporotic drugs is effective, but the potential harm to the fetus imposes caution in their use.

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Introduction

Pregnancy defines a challenging period to the mother's bones because the building of the fetal skeleton requires a substantial transfer of calcium. This process is particularly intense during the third trimester, when fetal bones experience substantial growth and calcification. The regulatory mechanisms are still poorly understood, but it seems patent that the drainage of calcium from the mother has to bear some level of deterioration of the

maternal skeleton unless compensatory mechanisms of enough potency are at play. If an adequate balance is not achieved, pregnancy would define a vulnerability period for maternal bones. Osteoporosis or even fragility fractures might be conceived whether the decalcifying process is particularly intense or whether there is an osteopenic background. In fact, isolated cases of osteoporosis or fragility fractures have been described in the literature

(1, 2). However, the process has to be transitory, because pregnancy has not been detected as a risk factor for postmenopausal osteoporosis.

This review aims at describing the present knowledge on bone metabolism during pregnancy. After going through the regulatory mechanisms, the information about the status of bone during pregnancy, as reflected by histological, densitometric, and bone biochemical marker (BBM) data, will be presented. An analysis of the published cases of osteoporosis, together with their clinical presentation and their management, will complete the review. Although related with pregnancy, the specific conditions determined by lactation will not be covered.

Search strategy

We performed a comprehensive literature search using the PubMed database for articles published from 1990 to 20 March 2014. Search terms were ('pregnancy' OR 'placenta') AND ('bone' OR 'osteoporosis' OR 'growth hormone' (GH) OR 'parathyroid hormone' (PTH) OR 'insulin-like growth factor-1' (IGF-1) OR 'parathyroid hormone related peptide' (PTHrp) OR 'bone markers' OR 'receptor activator of nuclear factor kappa-B ligand' (RANKL) OR 'osteoprotegerin' (OPG)).

Language filters for English, French, and Spanish were activated. Papers reporting basic or clinical studies on bone metabolic changes during pregnancy, or clinical cases or series of cases on osteoporosis during pregnancy were considered for inclusion. The process of article selection consisted of the following two steps: i) three authors (L Sanz-Salvador, M Á García-Pérez, and J J Tarín) independently screened the titles or abstracts to yield a list of candidate papers and ii) all potentially relevant papers meeting the predefined inclusion criteria were reviewed to further refine the search. Disagreements between investigators at each of the two steps were resolved by A Cano. The list was completed with a hand-search of reference lists of pertinent original or review articles.

Types of patients

Data from studies on bone metabolic changes during pregnancy were collected from experimental and clinical papers. Case reports or case series on women who were diagnosed of densitometric osteoporosis during pregnancy were considered eligible irrespective of whether a fragility fracture had occurred.

Data extraction

The extraction of data was performed by L Sanz-Salvador, M Á García-Pérez, and J J Tarín, and discrepancies were resolved by A Cano. Data collected were entered into a spreadsheet (Excel 2000, Microsoft). Information related to the type of paper and results were extracted and constituted the basis for the report. The profile of the retrieved information, where the clinical studies were observational, conditioned a narrative review, which limited the use of the GRADE scoring criteria (3).

Search results

The search yielded 16 473 entries, from which 1658 papers were reviewed (Fig. 1). A total of 146 articles were selected for detailed assessment. Following a full-text review, 34 additional articles were included from manual bibliographic search. Finally, 101 papers were chosen for citation.

Bone metabolism during pregnancy

The main objective of calcium adjustments during pregnancy is to enable the adequate transplacental transfer of ~30 g of calcium required for the successful mineralization of the fetal skeleton. Eighty percent of that amount is transferred during the third trimester, when placental calcium transport averages 110–120 mg/kg per day (4). The fetus enjoys a status of persistent hypercalcaemia, where a calcium placental pump maintains a gradient

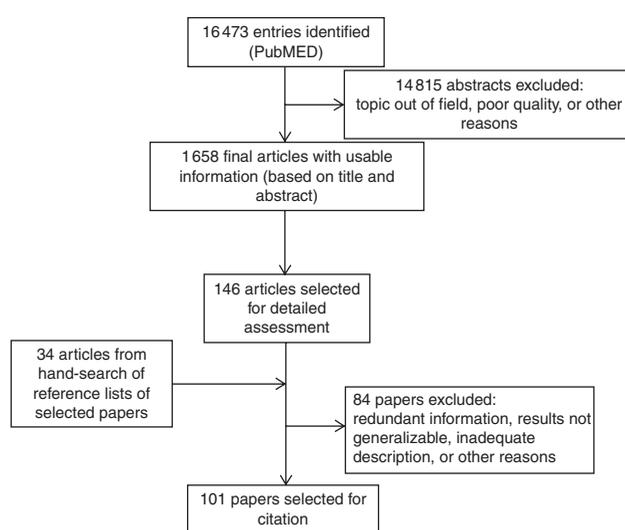


Figure 1
Organization of the literature search.

irrespective of the calcium status in the mother. This means that insufficiencies in the adjusting machinery in the mother will entail decalcification at her skeleton, something that may be a universal phenomenon at the third trimester, when the transfer of calcium increases drastically.

The physiological maternal adaptation in the metabolism of calcium results from the implication of different regulators. Interestingly, the fetus collaborates in most of them, with placenta being an important contributor. Modern analytical techniques and sophisticated animal models have provided some advances in the field, although several obscured areas remain. A clear picture of the specific role of each of the potentially concerned agents is elusive, but some key responsibilities have come into focus (Fig. 2).

Vitamin D

The concentration of 1–25 (OH)₂ vitamin D₃ (calcitriol), the active metabolite of vitamin D, increases during pregnancy. The increase, already detected at the first trimester, continues up to term, when it attains levels that are several fold higher than before pregnancy (5, 6). Maternal kidney, and possibly placenta, decidua, and fetal kidney, provide the necessary 1 α -hydroxylase activity. The contribution of the extra-renal sources, however, seems to be of little significance, as suggested by the inappreciable changes in calcitriol reported in an anephric woman during pregnancy (7).

The changes in vitamin D are concomitant with the improvement in the efficiency of the intestinal absorption of calcium, which doubles its capacity. This intestinal adaptation seems to be important in helping the mother to accommodate the fetal demand for calcium. It may be speculated, therefore, that further increases in the levels of vitamin D might translate into a more efficient calcium transfer at the intestine. The point is of interest, because the prevalence of vitamin D insufficiency, including the population of pregnant women, is elevated (8), even in low-latitude countries, where sun exposure is high (9). In this context, it may be conceived that a potential role exists for vitamin D analogs, as these compounds are designed to increase the effects of vitamin D while minimizing pathological hypercalcemia (10). Moreover, these analogs might escape from the limiting factor represented by the increase in vitamin D-binding protein (DBP (GC)), which, as in other high-estrogen states, increases during pregnancy (11). This hypothesis, however, has not been tested.

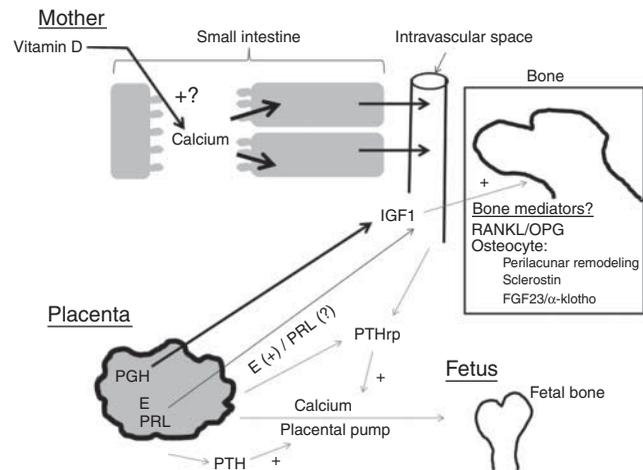


Figure 2

Main changes in the mother and the fetoplacental unit that favor adequate transfer of calcium to the fetal skeleton. The calcium transferred to the fetus is provided by the mother. Three main domains, mother, placenta, and fetus, are described in the figure. The changes in the maternal domain include an increased intestinal absorption of calcium, where the role of vitamin D is still obscure. Further calcium supply is favored by maternal parathyroid hormone related-peptide (PTHrP) and by local changes within maternal bone, where receptor activator of nuclear factor kappa B ligand/osteoprotegerin (RANKL/OPG) and osteocytes may participate. The calcium drainage is partly counterbalanced by an increased anabolic process, where IGF1, stimulated by placental growth hormone (PGH), may be involved. Other potential agents are prolactin (PRL) and estrogens (E). Despite the reactive bone formation process, the bone balance seems negative for the mother. The placental calcium gradient is sustained by the placental pump, where fetal PTH and PTHrP are determinant (see text for further details).

DBP deserves attention in pregnancy because, together with its role as the major binding protein for 25(OH) vitamin D and calcitriol, it may act as an actin scavenger, bind fatty acids, and modulate immune and inflammatory responses (12). Moreover, DBP may be found not only in serum, but also in other biological fluids. The detection in cervicovaginal fluid (13), for example, has been taken to propose DBP as an indicator of up-regulated cell death and tissue remodeling accompanying labor (14).

The role of vitamin D in the modulation of the increased intestinal transport of calcium should still be clarified. Experiments with pregnant vitamin D-deficient rats and vitamin D receptor-null mice have shown that the increase in calcium absorption was similar to controls (15).

Interestingly, recent experimental data in mice indicate that maternal hypervitaminosis D may actually reduce fetal bone mass and mineral acquisition (16).

PTH and PTHrp

The increased intestinal absorption of calcium has prompted the hypothesis of a possible contribution of PTH. The characteristic hypocalcemia of pregnant women has further contributed to the concept that hyperparathyroidism is an important mechanism fueling the fetal skeleton with calcium sequestered from the mother. However, it is now known that hypocalcemia derives from the physiological hypoalbuminemia of pregnancy, which coexists with unaltered levels of free calcium, the real reset regulator of PTH levels (17). Moreover, there is no change in phosphate levels, and more reliable immunoassays, either immunoradiometry with the use of a double-antibody technique or electrochemiluminescence, confirm that the circulating PTH level slightly decreases during pregnancy and normalizes at the end of this state (18). Murine models further exclude the participation of the hormone in the increase in calcitriol level during pregnancy or the recovery of bone mass after lactation (19).

The PTHrp constitutes another potentially important agent, given its significant role in calcium loss from maternal bone during lactation (17). Owing to the difficulties in the performance of the assays used to measure PTHrp in pregnancy, there has been debate on whether the circulating levels of PTHrp increase (20, 21) or remain unchanged (22). The complications with the accurate measurement of PTHrp start by the expression of three different isoforms by the human gene (23). Each of these isoforms may be subjected to distinct post-translational processes and further breakdown and metabolic clearance. The use of specific antibodies against different epitopes in the molecule has confirmed the heterogeneity. Ovine studies have shown that it is the midregion PTHrp, and not the amino-terminal region, that is functionally active during pregnancy (24). The consideration of this regional selectivity, together with the use of two-site IRMAs, has improved the accuracy of the measurements. Leaving aside the data obtained in animal models, which may not faithfully reflect the picture in the human, the general concept derived from most clinical studies is that PTHrp increases during late pregnancy, the sources being both maternal and fetal, as breast, decidua, placenta, amnion, umbilical cord, and fetal parathyroid glands have been involved (17). The details about the role of PTHrp

during the end of pregnancy are not totally clear, but pathological hypercalcemia follows when abnormally increased due to disease (25).

The changes in fetal PTH and PTHrp also play an indirect role in the regulation of maternal skeleton. Both PTH and PTHrp participate in maintaining the calcium placental pump, which acts as an active mechanism draining calcium from the mother. The role for the calcium-sensing receptor (CaSR) in setting the balance between PTH and PTHrp within the fetus has been demonstrated in murine models (26). Genetic models in mice, where a crucial role for PTHrp (27) and the concurrent collaboration of PTH (28) have been shown, confirm the fetal responsibility in orchestrating these adjustments.

IGF1 and PGH

Pregnancy also involves changes in the circulating levels of IGF1. The oscillations are small during the first and second trimesters, but then the peptide increases during the third trimester and decreases *post partum* (18, 22, 29). These changes seem to be influenced by active participation of PGH, which gradually replaces the control in the synthesis of IGF1 during the second half of pregnancy (30).

PGH, which should be distinguished from placental lactogen (HPL), is the product of the expression of the *GHV (GH2)* gene, as opposed to pituitary GH, which is the product of the *GHN (GH1)* gene (31). PGH is secreted in the syncytiotrophoblast from the 6th week of pregnancy and gradually replaces pituitary GH during pregnancy (30, 32). PGH is found only in maternal blood and is supposed to influence the availability of nutrients to the placenta. A prospective clinical study found a significant association between PGH and fetal growth during normal pregnancy (29). This modulation may be direct, by autocrine or paracrine mechanisms, or indirect, by regulation of IGF1 (33).

Other regulators

RANKL and OPG ► The system represented by RANKL (TNFSF11) and OPG (TNFRSF11B), its decoy receptor, has gained interest. Both proteins, which belong to the tumor necrosis factor (TNF) superfamily, are produced in bone by osteoblasts, the bone forming cells, although less significant production by other cells has been confirmed as well (34). Besides other actions in organs and systems (35), both proteins exert a powerful regulatory effect on bone metabolism (36). RANKL binds to membrane RANK

receptors and sets in motion a series of post-receptor events leading to activation, migration, and final differentiation of mature osteoclasts, the bone resorbing cells (34). Binding of OPG to RANKL prevents the interaction of RANKL for RANK and limits osteoclastogenesis (37).

Later studies have investigated the changes in RANKL and OPG during pregnancy. OPG has received particular attention; its levels are stable during pregnancy and only rise at term, when they double in parallel with an apparently paradoxical increase in bone resorption (38, 39). The rapid *post partum* fall in OPG suggests a placental origin, which has been corroborated by the finding of a high concentration of OPG in placental membranes (40). The circulating levels of RANKL have been investigated in studies that have reported parallel changes to those of OPG (41, 42). However, these data require a cautious interpretation because of the methodological problems with current assays for measurement of serum RANKL. Most commercial kits measure free RANKL, which is $\sim 1/1000$ of the total serum RANKL. This feature explains that some investigators have reported undetectable levels of RANKL in up to 50% of individuals (43). Moreover, the antibodies may measure different RANKL types of the soluble molecular species of the cytokine (44), a conceivable difficulty given the research profile of the available assays. These limitations are also attained, and may be augmented, when the ratio RANKL/OPG is used instead of RANKL.

Sclerostin and fibroblast growth factor 23 ► The participation of osteoblasts and osteocytes as active regulators of bone homeostasis has been shown in studies conducted in animal models and in the human. The case of osteocytes is of particular interest because, contrary to past concepts, they have manifested as multifunctional cells with crucial regulatory roles in several mechanisms affecting bone homeostasis (45). Among their abilities, osteocytes may remove and replace their perilacunar matrix, a concept baptized as ‘perilacunar remodeling’, which has been shown to be regulated by hormonal changes in mice. Lactation, for example, is associated with increases in osteocyte lacunar area (46). The potential participation of this mechanism in the maternal and fetal bone changes during pregnancy is still obscure.

Sclerostin is an osteocyte-derived protein with a significant capacity for inhibiting the Wnt signaling pathway, a powerful promoter of bone formation. In fact, recent studies have shown that the inhibition of sclerostin with specific MABs has a noteworthy effect in terms of increase in the bone mass in osteopenic women (47).

Fibroblast growth factor 23 (FGF23), mainly expressed in osteoblasts and osteocytes, is another powerful modulator of bone metabolism because of its regulatory potential of phosphate and 1,25-dihydroxyvitamin D3 (48).

There is still sparse information on the possible implication of the Wnt pathway in the development of the fetal skeleton. A recent Scandinavian study (49) has found that the circulating levels of sclerostin were lower in the mother at the 30–32 weeks of pregnancy than in the umbilical cord at delivery. Interestingly, cord sclerostin, but not maternal sclerostin, was significantly associated with dual-energy X-ray absorptiometry (DXA)-measured total body bone mineral content (BMC) in the newborn. The levels of FGF23 and of α -klotho, the FGF23 obligatory co-receptor, were measured in the same study. While the levels of FGF23 were similar in the maternal and the fetal compartment, those of α -klotho were higher in the umbilical cord plasma. However, neither FGF23 nor α -klotho was associated with fetal BMC (49).

The positive correlation between cord sclerostin and fetal BMC raises many unresolved questions. Sclerostin counteracts the anabolic effects of the Wnt pathway, which should translate into less effective bone formation potential. The possibility that sclerostin might be reactive in the context of a high bone anabolic milieu, as found in the fetus during the third trimester, may be an explanation. Studies in adults exhibiting high bone mass phenotype are consistent with this hypothesis (50). The progressive elucidation of the complex interplay between regulators of bone metabolism in the fetus will help to understand these findings.

Estrogens and prolactin ► Pregnancy also involves changes in other agents with powerful effects on bone metabolism, such as estrogens and prolactin (PRL), which in both cases are produced in the placenta. Their specific potential in modulating maternal bone metabolism is still unresolved.

Estrogens are known down-regulators of bone resorption (51), and therefore, should act to contain the accelerated loss of bone mass. There is no indication suggesting an alternative role for estrogens during pregnancy. The case of PRL is more complicated. Data from experimental studies have shown that there are PRL receptors in human osteoblasts and that their activation leads to reduced proliferation and mineralization potential of these cells (52). Moreover, studies on rats have shown that PRL directly stimulates osteoblasts to increase the ratio of RANKL to OPG (53). The limiting action of OPG on the

pro-resorptive potential of RANKL would translate into increased loss of bone mass.

The status of the skeleton in pregnancy

The overall effect of pregnancy on the skeleton has been investigated by methods that include histology, imaging techniques, and BBMs. Before describing the findings observed with each approach, it is important to stress that, whichever the derangement of bone metabolism during pregnancy, it seems that there is no carryover effect. This is so even considering that the deterioration of bone density accelerates during lactation, when maternal bone is the main source of the considerable amounts of calcium provided with breast milk (17). However, the rapid loss in bone mineral density (BMD) during lactation, which may attain 5–10% in 2–6 months, restores along the 6–12 months after weaning through still unclear mechanisms (54). This fast recovery is reflected in epidemiological studies, which do not find an association between the number of pregnancies or the duration of lactation and the future diagnoses of either osteoporosis (55, 56) or fragility fracture (57).

Histology

Histological analysis provides direct data on the status of bone from biopsies obtained during pregnancy. Given the invasiveness of the procedure, there is limited information in the human, and unfortunately, none that is recent. In an apparent paradox with the increased transfer of calcium to the fetal compartment during the second half of pregnancy, one study detected a reduction in bone resorption and promotion of bone formation and mineralization in the maternal compartment during that period (58).

Studies on rodents, however, have detected an increase in bone resorption at the end of pregnancy (59). There has been more interest, due to the closer similarity to the human, regarding the examination of biopsies from cynomolgus monkeys. Consistent with the previous study in humans, the rate of bone turnover was not increased during the third trimester of pregnancy in one study (60).

Imaging techniques

A few studies have tried to directly measure the impact of pregnancy on BMD. Some investigators have found decreases of ~3–5% in the lumbar spine BMD, when comparing pre-pregnancy values with those in the very early puerperium (61, 62, 63). However, methodology has

changed in other reports, which have measured BMD at longer intervals after delivery. This is a very important issue, because the substantial loss in BMD associated with lactation, or the BMD recovery occurring after weaning, may have affected the validity of the results. Despite this consideration, some studies in which BMD measurements were performed within the period of 8 weeks *post partum* (22, 64, 65), or in an undefined early puerperal period (66), still report changes of similar magnitude. The pattern, however, was not uniform, and heterogeneity has been described, particularly in areas with a higher percentage of cortical bone, such as the femur or the radius. This heterogeneity has been observed independent of the interval used for the *post partum* measurement. In this regard, reduction of BMD in areas of cortical bone predominance has been reported (22, 62, 64, 65) but other studies have found no significant change (5, 63, 67). The low number of subjects included in the initial studies, the use of old-fashion densitometric technology, and the lack of parallel controls in some of the reports may have influenced the differences.

More recent findings from controlled studies have reinforced the notion that pregnancy involves deterioration of BMD. A study detected a decrease of 1–4% in the whole body, spine, and total hip when BMC and BMD were measured before pregnancy and soon after delivery (68).

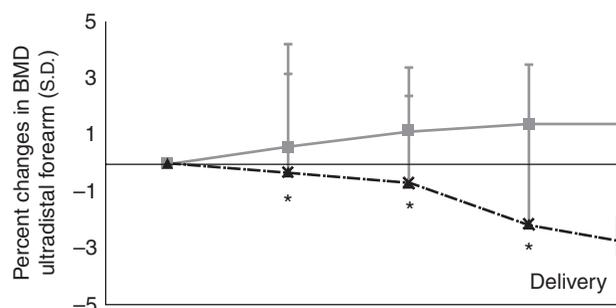


Figure 3

Percent change (mean \pm s.d.) from pre-pregnancy levels in BMD at the distal forearm during pregnancy. Ninety-two pregnant women (filled triangles) were prospectively followed and compared with 75 non-pregnant age-matched controls (filled squares). A significant and persistent reduction in BMD was detected during gestation at the three visits, which correspond to the 10th, 22nd, and the 34th weeks of pregnancy. * $P < 0.05$ (Reproduced with permission from Møller UK, Streyms S, Mosekilde L & Rejnmark L. Changes in bone mineral density and body composition during pregnancy and *postpartum*. A controlled cohort study. *Osteoporosis International* 2012 **23** 1213–1223).

Another prospective controlled study confirmed BMD decreases in the ultradistal forearm (69) (Fig. 3). Age-matched non-pregnant and non-lactating women were used as controls in both studies.

Table 1 summarizes the results obtained from clinical studies, all of them being observational. Most of the findings confirm that pregnancy defines a state of increased resorption, which at the final stages, usually the third trimester, adds increased bone formation. BMD deteriorates, particularly in areas of trabecular bone predominance, such as lumbar spine or the trochanter. The response of cortical bone is less unanimous, although a reduction in BMD is frequently reported.

Data obtained by ultrasound techniques further support a negative balance in the skeleton (70, 71), particularly during the third trimester (72, 73).

Bone biochemical markers

Changes in BBMs present the first and the second trimesters of pregnancy as periods of increased bone resorption (18, 22, 63, 66, 74, 75). The situation may

slightly change in late pregnancy, as some investigators have described stabilization in the slope in weeks just before delivery (22). Also in concurrence with histological studies, markers of bone formation remain stable or decrease up to the third trimester, when significant increases have been detected (18, 22, 66). This response is consistent with the increase in bone formation detected in biopsies and with the elevation in the circulating levels of PGH and IGF1 during that period. However, the reliability of BBMs is limited by some physiological changes in the mother, including hemodilution, which influences markers measured in serum, and the increase in glomerular filtration rate or renal clearance, which influences those measured in urine. The variability in these effects between women and between the stages of pregnancy has limited the options of correction for those confounding variables.

Osteoporosis during pregnancy

The transitory deterioration of maternal bone during pregnancy leads to increased bone fragility. Osteoporosis

Table 1 Changes in BBMs and BMD along pregnancy. Data about the number of women included in the study as well as about the type of study are also presented.

BBMs (resorption)	BBMs (formation)	BMD	n	Type of study	References
↑ Along pregnancy	↓ In first and second trimesters ↑ In third trimester	NA	153	Controlled cohort	(69)
↑ Along pregnancy	↔ In first and second trimesters ↑ In third trimester	↓ LS ↓ Hip ↔ Radius	10	Cohort	(22)
↑ Along pregnancy	↓ In first and second trimester ↑ In third trimester	↓ LS and trochanter ↔ Total hip, femoral neck, and total forearm	15	Controlled cohort	(63)
↑ Along pregnancy	↑ In third trimester	↓ LS and pelvis ↑ Arms and legs	16	Cohort	(66)
↑ Along pregnancy	NA	NA	22	Controlled cohort	(74)
↑ Along pregnancy	↑ Along pregnancy	NA	20	Cohort	(75)
NA	NA	↔ LS and hip	5	Cohort	(61)
NA	NA	↓ LS, femoral neck, and radial shaft ↑ Tibia	6	Controlled cohort	(64)
NA	NA	↓ LS, total hip, and trochanter ↔ Femoral neck	60	Cohort	(65)
NA	NA	↓ LS, distal, and ultradistal radius	38	Cohort	(62)
↑ Third trimester	↑ In third trimester	↔ Distal and ultradistal radius	10	Cohort	(5)
NA	NA	↔ Femur	32	Controlled cohort	(67)
NA	NA	↓ LS, trochanter, femoral shaft, total hip, and whole body	34	Controlled cohort	(68)
NA	NA	↓ LS, total hip, whole body, and ultradistal forearm	92	Controlled cohort	(69)

BBMs, bone biochemical markers; BMD, bone mineral density; n, number of women; NA, not available; LS, lumbar spine.

may indeed occur if concomitant conditions, such as baseline osteopenia, or other predisposing circumstances, are present. Prevalence is unknown because the main diagnostic methods involve radiation, which is usually avoided in pregnant women. Consequently, diagnoses are made at a later stage, often when a final severe outcome, consisting of a clinical fracture, occurs. Fragility fractures affecting both the spine and the hip, although rare, have been described in the literature (1, 2).

Clinical presentation

The main clinical symptom is severe and persistent back pain, which usually occurs at the end of pregnancy or early puerperium. The high prevalence of back pain in women during advanced pregnancy explains the poor attention received, and the consequent low number of diagnoses. When suspected, imaging techniques should help in clarifying the diagnosis. Cortical bone may be affected as well. The hip is then the preferred territory, as it occurs in the form of the disease so prevalent in older women. Hip fracture may then present as an additional complication (76). The low prevalence of this form was confirmed by a prospective study in France, which detected three hip fractures in 4 900 pregnancies (77). Table 2 summarizes the presenting symptom and predisposing factors in a selection of reports from the literature.

Consistent with the transitory condition of the process, bone density tends to recover in most, but not all, cases after delivery (78) (Fig. 4), an observation that may explain the low rate of recurrence in subsequent pregnancies (2, 79, 80). The interest in detecting women at risk has been hindered by the sparse number of published cases, which has limited the options for detecting risk factors. The rationale of using established clinical risk factors for fragility fracture, such as thin complexion, or others included in the risk assessment scales (81), may be an option, but it has not been tested. A possible genetic background has been suggested after some reports of familial aggregation (79, 82, 83).

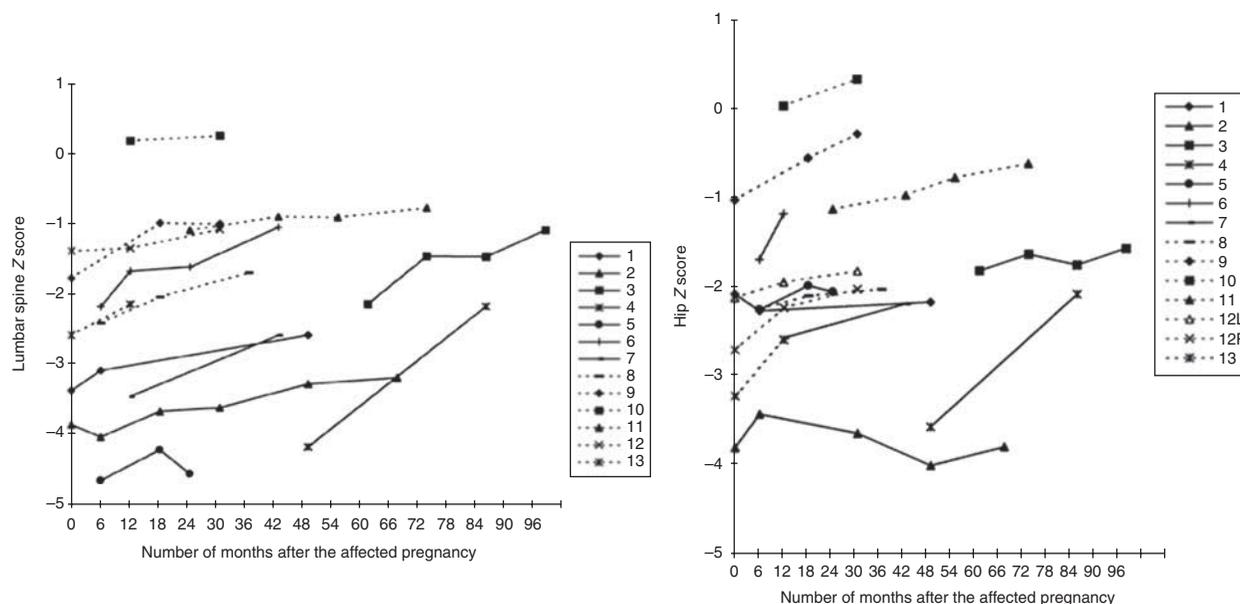
The concrete case of hip fracture may have a mixed origin, because transitory processes have been described in the absence of systemic osteoporosis, or in non-pregnant women or men at midlife (84). The term transitory regional osteoporosis has been proposed to denominate these cases, whose pathophysiological mechanisms remain elusive.

Diagnosis

The value of early diagnosis is mainly limited to the decrease in the clinical impact of fragility fractures, as the low frequency of the picture limits the options for a consensus on risk profiles in pregnant women.

Table 2 Common presentation and predisposing features of osteoporosis in pregnancy, as reported in the representative selection of the literature.

Characteristics of the cases	Presenting symptoms	Predisposing factors	Reference
24 women with pregnancy-associated osteoporosis	Pain at the back in late pregnancy or <i>post partum</i> ($n=18$) Pain at the hip ($n=5$) or the ankle ($n=1$)	Previous decalcifying disorders ($n=4$) Osteopenia	(2)
35 women with pregnancy-associated osteoporosis	Pain during late pregnancy	Drug therapy or previous decalcifying disorders ($n=6$) Osteopenia with possible genetic background	(79)
11 women with pregnancy-associated osteoporosis presenting with fracture at a median 1 month <i>post partum</i>	Painful non-traumatic fracture at the spine ($n=10$) or hip and both wrists ($n=1$) Fractures were multiple in nine cases (median: 3, range: 2–5)	At least one predisposing factor in nine women: Pre-partum densitometric osteoporosis: 3 Pre-partum fracture: 7 Affected first-degree relative: 4 Smoking history: 4 BMI < 20 kg/m ² : 5 Vitamin D insufficiency	(95)
Two pregnant women with hip osteoporosis	Pain at the hip	Osteopenia with a possible genetic background	(82)
One pregnant woman with osteoporosis and several vertebral fractures	Acute back pain	Baseline osteoporosis with a genetic background (<i>LRP5</i> mutation)	(83)
One pregnant woman with osteoporosis and several vertebral fractures	Acute back pain in the early puerperium	Severe osteoporosis	(97)

**Figure 4**

Long-term evolution of lumbar spine and total hip bone mineral density (BMD) in 13 women diagnosed with pregnancy-associated osteoporosis. Women were selected because they had developed symptoms suggesting pregnancy-associated osteoporosis during the last trimester of pregnancy or in the early *post partum* period. There were eight women with back pain and vertebral collapse (continuous line) and five women with hip pain (dotted line). All had obvious vertebral fractures on radiographs (patients 1–8) or hip or groin pain with

magnetic resonance findings consistent with transient osteoporosis of the hip. BMD was measured by DXA with three different equipments and followed by a variable time, from 1 to 8 years. The BMD data are expressed as a Z-score in relation to an age-matched mean. A trend toward BMD improvement with time was detected in some women (from reference Phillips AJ, Ostlere SJ & Smith R. Pregnancy-associated osteoporosis: does the skeleton recover? *Osteoporosis International* 2000 **11** 449–454, with permission).

Measurement of BMD with DXA will show either osteopenia or evident osteoporosis, which may be accompanied by vertebral deformities or vertebral collapse. Conventional radiography will confirm the fracture in most cases (85, 86). Both techniques may be used because the low irradiation does not affect fetal safety and even less at the advanced stage of gestation in which the problem arises (87). However, the low incidence of this pathology does not support the generalized use of DXA for screening unless there are clear risk factors, which have not been described. Consequently, it is only the good clinical judgment as a consequence of abnormally increased pain at either the back or the joint, which should raise the suspect of a fracture.

The irradiation dose absolutely limits the use of computed tomography, but interest is arising on the use of alternative technologies, such as magnetic resonance (MR), which can be safely used during pregnancy. MR may

be particularly efficacious in detecting vertebral fractures, which may be missed by conventional radiography (88). Moreover, MR may help in the diagnosis of the regional forms, because the accompanying bone marrow edema may be detected by this technology. Located at the epiphysis and extending into the subcondral bone, edema is often accompanied by joint effusion (89).

Treatment

Once diagnosed, the limited knowledge on the pathophysiology, combined with the absence of randomized controlled trials, strongly limits the availability of solid treatment protocols. Symptomatic treatment, including rest, load reduction, and analgesics, is of help.

Despite the frequent bone recovery in the long term, there is interest in the additional benefit that may provide pharmacological compounds with activity on bone metabolism.

Bisphosphonates emerge as an attractive option, because of their proven efficacy in osteoporosis and other bone diseases. The difficulty derives from two features of these compounds. One consists of the long-time retention in the skeleton, which raises concerns in that even pre-pregnancy administration may involve fetal exposure. The other feature stems from findings in animal studies, which have detected passage of these drugs through the placenta and their deposits in fetal bone (90). Worries about short- and long-term fetal safety have consequently arisen. The short experience in humans, however, has not confirmed any fetal anomalies. Two studies have investigated teratogen information services from different world regions to search for pregnancies in which women were taking bisphosphonates shortly before pregnancy or during the first weeks of pregnancy. One study detected 24 pregnancies in which women took alendronate (91), and the other study found 21 women exposed to different types of bisphosphonates (92). No major anomalies were found in the neonates or after comparison with a control group. These data were corroborated in a systematic search, which detected 51 cases of exposure to different types of bisphosphonates before or during pregnancy up to September 2008. In none of the cases were, skeletal abnormalities or other congenital malformations detected in the neonates (93). More extended exposure, also without apparent impact on the newborn, was found in one isolated case in which the woman was treated daily with alendronate during the whole pregnancy because she was unaware of being pregnant until the beginning of labor (94). The magnitude of the bone response, with the caution imposed by the low numbers, seems to be sizeable and substantially improves the physiological recovery observed after weaning. Increases of up to 23% in spinal BMD after 2 years of treatment were compared favorably with the 11% observed in untreated women (95). Despite being so and the lack of adverse fetal effects in the few cases of inadvertent use, the actual consensus is that this treatment should be avoided during pregnancy (92).

Calcitonin may be an alternative because the molecule does not pass through the placenta. Nonetheless, the use of calcitonin has been sparse and there is a lack of detailed information about protocol or long-term results (96).

The recent use of teriparatide has been followed by a remarkable increase in BMD at both the spine and the hip in a few cases with vertebral fractures diagnosed at *post partum* or within the lactation period (97, 98, 99).

Orthopedic interventions may have a role as well. Some initial experience with vertebroplasty has shown success in vertebral fractures (100, 101). Hip fractures,

in turn, require the surgical approach option that better suit the particular characteristics of the fracture.

Conclusion

The comprehension of bone metabolism during pregnancy has advanced in the latter years, although many questions still remain. The most recent clinical studies have suggested that the second half of pregnancy may involve bone loss, but the process does not increase susceptibility to osteoporosis in the long term. However, the transitory reduction in bone mass may pose some women at risk, possibly as a result of previous osteopenia or other risk factors. Fragility fractures have been described, but this occurs infrequently. It is possible that there is under-diagnosis as a result of the overlapping symptomatology with the frequent aches affecting normal pregnancies. Once the condition is detected, symptomatic and orthopedic treatment may be of help, but caution should be taken with the use of anti-osteoporotic drugs that, in the case of the bisphosphonates, should be restricted until *post partum*.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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Author contribution statement

L Sanz-Salvador participated in the design of the study and in the review of the literature, was involved in the analysis of the data, revised the article critically, and approved the version to be published. M Á García-Pérez participated in the design of the study and in the review of the literature, was involved in the analysis of the data, revised the article critically, and approved the version to be published. J J Tarín participated in the design of the study and in the review of the literature, was involved in the analysis of the data, revised the article critically, and approved the version to be published. A Cano participated in the design of the study and in the review of the literature, was involved in the analysis of the data, wrote the manuscript, and decided its main contents.

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