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Regulation of bone modifications in the mother during pregnancy

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Summary
Pregnancy defines a model where the development of the fetal skeleton occurs in a short lapse of time. This achievement is accomplished under the control of the own fetus, who regulates the process through the signals generated in the so-called feto-placental unit. The maternal organism undergoes an adaptation process in which a drastic readjustment of mechanisms involved in the bone turnover takes place. Among the most obvious changes detected in maternal blood there are the increases in calcitriol, placental growth hormone, insulin-like growth factor -1 (IGF-1), estrogens and prolactin. There are also increases in osteoprotegerin and in the ligand of the receptor activator of nuclear factor kappa (RANKL). The phenomenon leads to transitory states of bone deterioration, which extends up to the end of lactation. The whole process is still insufficiently explored. We present an update of the changes affecting the mother and of those that arise in the placenta.

Key words: *pregnancy, bone, mother, regulators.*

Introduction

The body of the pregnant mother goes through a combination of changes to accommodate itself to the conditions imposed by the presence of the fetus and its needs. The driver of these changes is the feto-placental unit, which acts as a focus of the emission of signals to the mother's organs and systems. In some cases deficiencies in these changes result in pathologies, such as vascular dysfunctions underlying high blood pressure and preeclampsia-related proteinurea, among others.

The bone is not immune to the need for change, due, among other factors, to the fact that the foetal ossification requires the transfer of large quantities of calcium, above all in the third trimester. The final weeks are characterised by an acceleration in the growth and calcification of the foetal skeleton, which takes advantage of most of the on average 30 g of calcium transferred from the mother through the placenta. Curiously, the calcium transfer occurs against the gradient, since the foetus lives in a hypercalcemic environment in comparison with the mother[1].

The transfer of calcium does not occur without having an impact on the mother s bone. There is a debate as to whether it causes a more or less significant period of decalcification, which may even result in there being a window of susceptibility to fracture. There are a significant number of publications, clinical cases or case series which support of this view, containing information about fragility fractures in pregnant or breastfeeding women[2]. The transitory nature of the process can, in any case, be deduced from the lack of evidence associating pregnancy with the risk of osteoporosis in the long term. Therefore, whatever the impact may be, there is a subsequent recuperation of the bone. This phenomenon has been seen in data from densitometric studies, which show a progressive recuperation. It remains to be clarified whether this recuperation is specific to the state of pregnancy or not. In fact, a similar restoration in the deterioration of bone mass has been reported which is found in hypo-estrogenic states concomitant with birth control with systemic gestagens such as medroxyprogesterone acetate[3], but it appears less clear when the hypoestrogenism is associated with endocrine pathology, such as hypogonadotropic hypogonadism[4].

The endocrine regulators which control changes in bone metabolism in the mother during pregnancy are still not sufficiently well-understood. For example, there is an open debate about the possible role of vitamin D, and therefore, as to whether to supplement this vitamin or not. The details regarding the mediators generated in the feto-placental unit are also not well-understood.

Here we present the most important features of this theme which is also very interesting to researchers in perinatology.

Is there deterioration in bone during pregnancy?

This first question arises in the context of the readjustment of the mother's body, which uses many compensatory systems. It cannot be discounted, therefore, that the draining of calcium through the placenta may take place without affecting the maternal skeleton if there are sufficiently powerful compensatory systems in place. An increase in the intestinal absorption of calcium, for example, could be an option if it reaches a sufficient level, as is mentioned in the section regarding vitamin D.

However, although this issue is not beyond dispute, everything appears to suggest that there is a net loss of calcium in the mother. The evaluation strategies have been limited by a refusal to carry out densitometric examinations in pregnant women, in spite of their low radiation dose, and by the continuous changes in blood volume and glomerular filtrate, which reduce the values of the biochemical markers for bone turnover. There are histological studies of bone biopsies, but they are relatively old and not very clear in their interpretation[5]. There are also experimental models, in rodents and primates, which do not always correspond with histological data in humans[6]. In spite of this, the most recent studies have carried out densitometries immediately pre- and post-pregnancy, or have included examinations of peripheral regions, such as the forearm, during pregnancy[7]. Furthermore, although with different technology, systems based on ultrasound have been used by various authors[8].

The findings of some studies suggest that there is a deterioration in those factors studied, be it bone mineral density or parameters evaluated by ultrasound, sound velocity transmission, broad band attenuation or rigidity modulus[8]. Therefore, the results are consistent with what is known about rates of calcium transfer: there are slight adjustments during the first half of pregnancy, but bone resorption is accelerated in the third trimester, well above the rate of formation, although this also increases.

Endocrine correlate

As has already been said, the maternal changes have their principal origin in the feto-placental unit, the real driver for all these changes. However, on some occasions the connection between the signals originating in the feto-placenta and the modifications in the regulators of calcium metabolism in the mother are not known. One of the clear cases is that of vitamin D. In other cases there are agents which, on the contrary, clearly originate in the placenta, and which impact on the maternal systems. The placenta growth hormone (PGH) is a good example of this. The most evident changes are described below (summarised in Table 1).

Regulators originating in the mother

Parathyroid hormone and parathyroid hormone-related peptide

Parathyroid hormone (PTH) has received much attention as a consequence of its great pro-resorptive potential. Its action in liberating significant amounts of calcium from the bone would be consistent with observations regarding the transfer of

significant quantities of the cation through the placenta, with the consequent deterioration of bone mass in the mother. The increase in intestinal absorption and the characteristic hypocalcaemia in pregnancy would support this interpretation.

However, in spite of the attractiveness of this hypothesis, the maternal PTH is not currently considered a determining factor. There has been a debate about circulatory changes, with substantial increases reported in tests subsequently considered to have been defective. Better technologies based on the use of antibodies, which are more reliable, suggest that PTH undergoes little change in pregnancy, and that its involvement in the adjustments in bone metabolism is probably of little importance[9].

Because of its theoretical proximity PTH-related peptide (PTHrP) has been proposed as another determining factor. The debate about the methodological difficulties in reliable measurement are also reproduced here. The influence that the isoforms of the molecule, or the heterogeneity of the region recognised by the antibodies, have on this have recently been reviewed[2]. To date, there are still questions to be answered, with isolated data which suggest an increase in the final phases of pregnancy. Its potential is not negligible, as the finding of pathological hypercalcemia as a consequence of an abnormally high production of PTHrP suggests[10].

Vitamin D

Vitamin D is receiving particular attention. Its role in bone metabolism during pregnancy is still largely unknown. Its possible participation, however, is potentially attractive since, in increasing the intestinal absorption of calcium, it appears to be a candidate for supplying the maternal body with a substantial portion of that lost through the placenta.

There is already a notable increase in the levels of calcitriol (1,25 $(OH)_2$ vitamin D) from the first trimester, and especially in the second half of pregnancy. This increase is parallel to the intestinal absorption of calcium. The increase in the enzyme activity of renal 1α-hydroxylase is key to this change, given that the increase in calcitriol is not found in a pregnancy in an anephric woman[11]. Minor roles in the supply of 1α-hydroxylase would be taken by the placenta, decidua, and possibly the fetus' own kidney.

Combined with this there is what appears to be an almost universal phenomenon, a high prevalence of blood levels of 25-OH vitamin D considered as insufficient in pregnant women in all latitudes of the globe[12,13]. In the lowest socioeconomic groups, at least in our country, the situation is especially dramatic[14].

The modulating role which the vitamin D binding protein may have is not clear. As in all hyperestrogenic states, its concentration rises during pregnancy, but it remains to be determined to what extent it regulates the activity of vitamin D in this context. We would therefore be dealing with a crucial element in the system. In favor of this view is a series of studies which supplemented vitamin D and which gave results which support the idea of vitamin D as a key element in the programming of intra-uterine fetal bone growth. We would not now be talking about bone mineral density, but rather a new dimension, which is that of fetal growth[15]. However, the participation of vitamin D has been disputed by experimental models in rodents lacking vitamin D or its receptor, in which, curiously, the increase in intestinal absorption of calcium was similar to the controls[16]. It is not known whether or not these models reproduce the situation in humans.

Changes have been reported in other regulators such as calcitonin, but their impact appears slight.

Regulators produced in the feto-placental unit

PGH

PGH is a clear example of the transfer of modulators from the feto-placental unit to the mother, since it is produced in the syncytiotrophoblast but only circulates in the mother's blood. It is detected from the first trimester and from then the increase does not cease until the end of pregnancy. It plays a direct role in providing nutrients to the placenta, but it is not known what is the exact magnitude of its potential as regulator of insulin-like growth factor type 1 (IGF-1) in the mother. The details of the action of this on the bone has not been specifically investigated in pregnancy. It is also not yet clear which part of its action is endocrine, paracrine or both[17].

Human placental lactogen (HPL)

Also called chorionic somatomammotropin, this is produced in the trophoblast from the very first moments of gestation. It is a protein hormone resulting from the expression of the GH gene cluster. This group, located in chromosome 17q, contains two genes which code for GH, one expressed in the hypophysis and the other in the placenta (which codes for PGH) and two other genes related to HPL[18].

The genetic family relationship determines some common actions, essentially in the metabolic field. HPL plays a pro-lipolytic role, mobilising fatty acids with a potential impact on the energy of the mother and fetus, and on insulin resistance. This second action forms part of the pro-diabetogenic complex in pregnancy. The consequence of this is an increase in the glycemic, and protein, offer to the feto-placental unit. So, the HPL participates in the offer of nutrients to the fetus, and hence constitutes a promotor factor for fetal growth (see[19] for review).

The possibility cannot be discounted that, as with PGH, HPL may regulate IGF1 and other elements of the group of insulin-like growth factors, even if in a less direct way than with PGH. The impact that this may have on the process of calcification of fetal bone to a separate magnitude from its growth is uncertain, as is, at present, the dissection of these two functions in relation to the same IGF1.

Table 1. Schema of the changes in the blood of the mother of agents which are potential modulators of bone turnover. The questioning signs indicate that the increase is only suspected (in the case of PTHrP) or that there is no certainty about the direction of the changes (sclerostin)

Modulators of bone turnover	1st half pregnancy	2nd half pregnancy
PTH	↔	↔
PTHrP	↔	↔/↑(¿?)
Vitamin D (calcitriol)	↑	↑↑↑
DBP	↑	↑↑
PGH	↑	↑↑↑
HPL	↑	↑↑↑
Estrogens	↑	↑↑↑
Prolactin	↑	↑↑↑
Osteoprotegerin	↔	↑
RANKL	↔	↑
IGF-1	↑	↑↑
Sclerostin	¿?	¿?

PTH: parathyroid hormone; PTHrP: PTH-related peptide; DBP: vitamin D bonding protein; PGH: placental growth hormone; HPL: human placental lactogen; RANKL: receptor activator of nuclear kappa-B factor ligand; IGF-1: insulin-like growth factor type 1.

PTH and PTHrP

The role played by PTH and PTHrP in feto-placental unit could be considered to be at once both significant and cryptic. Contrary to data from the maternal blood, a series of observations whose only limitation is that they come from experimental models, suggest that the gradient pump which transfers calcium from the mother to the fetus works thanks to the active role of both peptides (reviewed in[2]). It is not known whether there is some kind of permeability between the fetal and maternal microenvironments as far as both hormones are concerned.

Estrogens

The estrogens are another agent produced in the placenta and exported to the maternal blood. Their powerful reductive effect on bone resorption is known, and their blood levels increase in parallel with that of the mass of the placenta, as the period of pregnancy increases. Therefore, their changes do not fit in to a context in which, as appears to occur in pregnancy, resorption in the mother increases in its final phase.

Prolactin

Also produced in the placenta and exported to the mother's blood, prolactin (PRL) may have an influence on metabolic changes in maternal bone. Data from rodents show that PRL acts on the osteoblasts, where the RANKL/OPG increases at the cost of lowering the OPG. This could therefore be a modulator consistent with the changes observed. However, it remains unclear whether or not this is similar in humans[20].

Mixed or of uncertain ascription

There are data showing changes in other regulators, such as the receptor activator of nuclear factor kappa-B ligand (RANKL), osteoprotegerin (OPG) or IGF-1. There is also a series of recent data related to the Wnt pathway. However, there is no certainty as to whether the contribution of the of the mother's body is significant if compared with the feto-placental unit. Given the doubts which exist, they are included in this second block dedicated to factors of mixed or uncertain origin.

OPG exemplifies this imbalance between the two sections (Figure 1). Its maternal blood levels are stable until the final weeks when, paradoxically in relation to the increase in bone resorption, it rises[21]. The rapid decrease postpartum and the findings of high concentrations in the placenta and membranes are interpreted as indicating that it is the placenta which is its main source[22].

The changes in the levels of RANKL follow a similar pattern, but are less consistent due to the well-known methodological difficulties of measuring its blood levels[23,24].

The blood levels of IGF-1 increase as pregnancy progresses, but vary as a function of a number of variables, such as the mother's weight[25]. Given the rich variety of functions of this growth factor, and the frequent contrast between its blood and tissue levels, there is no clear understanding of the relationship between these changes and those which the maternal skeleton undergoes.

Existing information regarding the role of the Wnt pathway, a system with a high osteo-anabolic capacity, in pregnancy is very scarce and inconclusive. In light of the data shown in the studies which have evaluated the impact on the bone of the regulation of sclerostin, a Wnt pathway inhibitor protein, its effect on the modifications in bone metabolism in the mother has been investigated. Sclerostin is produced in the osteoblasts and, given the difference in osteocytic mass bet-

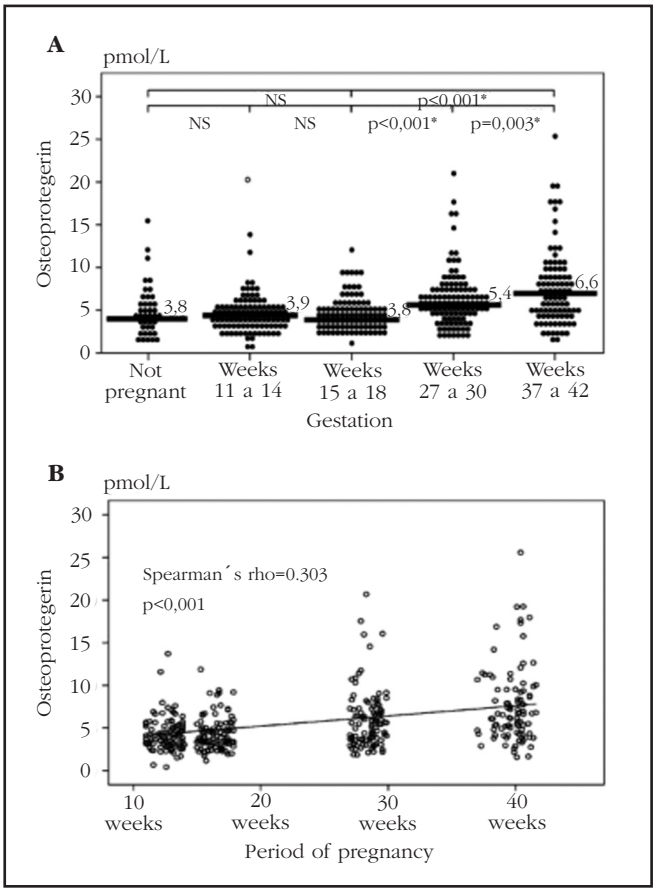
ween the mother and the fetus, it should be the maternal section which is the territory in which any significant changes in sclerostin occurs. It has been found, however, that blood levels are higher in the umbilical cord than in the maternal blood. Interestingly, a direct relationship has been found between the blood levels of sclerostin in the umbilical cord and the density and mineral content of the fetal bone[26]. The inhibitory effect of sclerostin on Wnt makes this this finding paradoxical, and its interpretation is still unclear. There is no reliable information regarding the progression of blood levels of sclerostin in the mother as pregnancy progresses. Given the scarcity of information and the difficulties in its interpretation it seems evident that this field needs to be investigated in more detail.

At a global level, this is a matter which has a great impact on later life, and fortunately there are various clinical studies which go beyond purely growth or bone health[27] and which include the impact on the risk of developing metabolic syndrome, respiratory disease, behavioural or other disorders (see[28] for the detailed review).

Conclusion

The impact of pregnancy on the maternal skeleton is still very poorly-understood, probably because there has not been any perception of there being a significant impact on maternal health. On the other hand, it is not known whether the changes which occur, be they in the mother, the feto-placental unit or both, may have implications beyond bone mineral density, and even affect fetal growth. As such, there are researchers who are investigating the possible role of vitamin D in this context[15,29]. It is conceivable that improvements seen in experimental models and in diagnostic technology may help progress to be made in this field.

Figure 1. Levels of osteoprotegerin in the mother's blood according to weeks of pregnancy. The increase clearly occurs in the second half of pregnancy, since, as seen in panel A, there is no difference between blood levels in a woman who is not pregnant and those in a woman who has been pregnant for up to 18 weeks. Panel B shows that there is an increase as the pregnancy progresses, but the slope of the line of best fit is considerably lower than that of the known curves for the increase in estrogens or prolactin (data not shown). Taken from citation 21, with the permission of Elsevier)



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