Endocrinología, Diabetes y Nutrición 69 (2022) 530–539

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

CONSENSUS DOCUMENT

Guide of management of alterations in mineral and bone metabolism during gestation and lactation

Antonia García Martín[a,b,*], **María Rosa Alhambra Expósito**[c,d], **María Cortés Berdonces**[e,f], **Esteban Jódar Gimeno**[e,f], **Isabel Huguet**[g], **Pedro Rozas Moreno**[h], **Mariela Varsavsky**[i], **Verónica Ávila Rubio**[a,b], **Araceli Muñoz Garach**[j], **Manuel Muñoz Torres**[a,b,k]

[a] *Servicio de Endocrinología y Nutrición, Hospital Universitario Clínico San Cecilio, Granada, Spain*
[b] *Red Temática de Investigación Cooperativa en Envejecimiento y Fragilidad (RETICEF), Granada, Spain*
[c] *Unidad de Gestión Clínica de Endocrinología y Nutrición, Hospital Universitario Reina Sofía, Córdoba, Spain*
[d] *Instituto Maimónides de Investigación Biomédica de Córdoba (IMIBIC), Córdoba, Spain*
[e] *Departamento de Endocrinología y Nutrición Clínica, Hospital Quirón Salud Madrid y Complejo Hospitalario Ruber Juan Bravo, Quirón Salud, Madrid, Spain*
[f] *Departamento de Formación Médica, Universidad Europea de Madrid, Madrid, Spain*
[g] *Servicio de Endocrinología y Nutrición, Hospital Universitario Infanta Leonor, Madrid, Spain*
[h] *Sección de Endocrinología y Nutrición, Hospital General Universitario, Ciudad Real, Spain*
[i] *Servicio de Endocrinología, Metabolismo y Medicina Nuclear, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina*
[j] *Unidad de Gestión Clínica de Endocrinología y Nutrición, Hospital Universitario Virgen de las Nieves, Granada, Spain*
[k] *Departamento de Medicina, Universidad de Granada, Granada, Spain*

KEYWORDS
Pregnancy;
Lactation;
Osteoporosis;
Fractures;
Hypovitaminosis D;
Primary hyperparathyroidism;
Chronic hypoparathyroidism

Abstract
Objective: To provide practical recommendations for the management of mineral and bone metabolism alterations in pregnancy and lactation. Participants: Members of the Working Group on Osteoporosis and Mineral Metabolism of the Spanish Society of Endocrinology and Nutrition. *Methods:* Recommendations were formulated according to the *Grading of Recommendations, Assessment, Development, and Evaluation* (GRADE) system to describe both the strength of recommendations and the quality of evidence. A systematic search was carried out in Medline of the available evidence for each pathology. Papers in English with publication date until 29 February 2020 were included. A methodologist resolved the differences that arose during the process of reviewing the literature and formulating recommendations. The recommendations were discussed and approved by all members of the Working Group.

* Corresponding author.
E-mail address: garciamartin_t@hotmail.com (A. García Martín).

Conclusions: The document establishes practical recommendations based on evidence about the management of mineral and bone metabolism disorders in pregnancy and lactation.

PALABRAS CLAVE
Embarazo;
Lactancia;
Osteoporosis;
Fracturas;
Hipovitaminosis D;
Hiperparatiroidismo primario;
Hipoparatiroidismo crónico

Guía de manejo de las alteraciones del metabolismo mineral y óseo en la gestación y la lactancia

Resumen
Objetivo: Proporcionar unas recomendaciones prácticas para el manejo de las alteraciones del metabolismo mineral y óseo en la gestación y la lactancia. Participantes: Miembros del Grupo de Metabolismo Mineral de la Sociedad Española de Endocrinología y Nutrición.
Métodos: Las recomendaciones se formularon de acuerdo con el sistema *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) para establecer tanto la fuerza de las recomendaciones como el grado de evidencia. Se realizó una búsqueda sistemática en Medline de la evidencia disponible para cada patología. Se revisaron artículos escritos en inglés con fecha de inclusión hasta 29 de febrero del 2020. Un metodólogo resolvió las diferencias que surgieron durante el proceso de revisión de bibliografía y formulación de recomendaciones. Tras la formulación de las recomendaciones éstas se discutieron en una reunión conjunta del Grupo de Trabajo.
Conclusiones: El documento establece unas recomendaciones prácticas basadas en la evidencia acerca del manejo de las alteraciones del metabolismo mineral y óseo en la gestación y la lactancia.

Introduction

Because mineral and bone metabolism disorders in pregnancy and breastfeeding are rare, it is useful to have specific recommendations for their management. Given this, the Grupo de Trabajo de Metabolismo Mineral [Working Group on Mineral Metabolism] of the Sociedad Española de Endocrinología y Nutrición [Spanish Society of Endocrinology and Nutrition] (SEEN) proposed the drafting of guidelines for the management of mineral and bone metabolism disorders in pregnancy and breastfeeding based on the available scientific evidence on osteoporosis and fragility fractures, hypovitaminosis D, primary hyperparathyroidism and chronic hypoparathyroidism, as well as a review of the indication for specific drugs in pregnancy and breastfeeding. Where evidence was limited or nonexistent, the members of the Working Group made recommendations based on their experience in, and knowledge of, these diseases.

Development of evidence-based recommendations

The recommendations were formulated in accordance with the *Grading of Recommendations, Assessment, Development, and Evaluation* (GRADE) system to establish the strength of the recommendations and the quality of evidence.[1] This system establishes a graphic description of the quality of the available evidence and the strength of the recommendation that is made based on this evidence. Two strengths of recommendation are distinguished: strong recommendations, expressed as ''We recommend'' and the number 1, and weak recommendations, expressed as ''We suggest'' and the number 2. Quality of evidence is expressed with symbols: ⊕___ indicates very low-quality evidence; ⊕⊕__ low-quality evidence; ⊕⊕⊕_ moderate-quality evidence; and ⊕⊕⊕⊕ high-quality evidence. Each recommendation is accompanied by a description of the evidence supporting that recommendation.

A systematic search was conducted in MEDLINE of the available evidence for each disease using the following pregnancy- and breastfeeding-associated keywords: AND osteoporosis, fractures, hypovitaminosis D, primary hyperparathyroidism and chronic hypoparathyroidism.

Papers in English with a publication date up to 29 February 2020 were included. Each subject was reviewed by two people from the Working Group. A methodologist resolved the differences that arose during the process of reviewing the literature and formulating recommendations. After the recommendations were formulated, they were discussed in a joint meeting of the Working Group.

Physiological changes

Physiological changes in bone metabolism during pregnancy

During pregnancy, ionised calcium, phosphorus and magnesium levels are within normal limits. Serum parathyroid

hormone (PTH) levels, on the other hand, drop during the first trimester and return to normal in the third trimester in European and North American women. 1,25 (OH)2D3, or calcitriol, increases to two or three times above normal levels largely due to kidney hydroxylation and to a lesser extent placental hydroxylation. PTH-related protein (PTHrP) levels gradually increase, thus contributing to increased calcitriol and PTH suppression. Intestinal absorption of calcium doubles from the first trimester and calcium excretion in urine increases. Calcium intake during pregnancy should be 1,200–1,500 mg daily, ideally through food. Histomorphometric parameters of bone remodelling increase during pregnancy, while bone mineral content increases or decreases depending on calcium intake. However, these acute and physiological changes in bone metabolism during pregnancy do not cause long-term changes in calcium content or bone strength, and parity has been associated with a neutral or protective effect on bone mineral density (BMD) and fracture risk.[2]

Physiological changes in bone metabolism during breastfeeding

In breastfeeding, ionised calcium levels increase but remain within normal range. Phosphorus levels, on the other hand, increase above normal. PTH levels decrease and may be undetectable in European and North American women. Calcitriol returns to levels within normal limits and PTHrP increases significantly due to its production in breast tissue, regulated through calcium-sensing receptors in the breasts. Intestinal absorption of calcium returns to normal and calcium excretion in urine decreases. The daily calcium deficiency in breastfeeding is approximately 210 mg, which leads to temporary bone demineralisation stimulated by PTHrP associated with a drop in oestradiol levels. Dietary intake of calcium should also be greater during breastfeeding. Histomorphometric parameters of bone remodelling increase during breastfeeding due to increased osteoclastic activity and PTHrP-mediated osteocytic osteolysis. BMD drops between 3% and 10% in relation to calcium loss from breast milk, but reverses six to 12 months after weaning.[2]

Osteoporosis and fragility fractures

General information

Pregnancy- and lactation-associated osteoporosis is a rare abnormality in which fragility fractures occur in women at the end of pregnancy, in the postpartum period or during breastfeeding. It has potentially serious consequences such as chronic pain and disorders of the static equilibrium of the spine due to vertebral fracture. Pregnancy and breastfeeding are states of high calcium demand and increased bone resorption, which are associated with rapid physiological and asymptomatic decreases in BMD, especially in trabecular bone, although these recover in six to 12 months and only very rarely end up causing fractures.[3,4] The condition is diagnosed through the identification of a fragility fracture together with low bone mass measured by densitometry in pregnancy or breastfeeding, and other causes of secondary osteoporosis must be ruled out. Pregnancy- and lactation-associated osteoporosis has an estimated incidence of four to eight cases per million pregnancies.[5] Multiple vertebral fractures represent the most common type of fracture. Most women who experience fractures during pregnancy or in the postpartum period are generally healthy, and therefore their prior bone status is not known as test results are not normally available. Women who end up having fractures might have already had low bone mass or an underlying genetic abnormality, although the exact pathogenesis is unknown.[6] In these cases, it is preferential to rule out secondary causes of osteoporosis such as amenorrhoea, anorexia nervosa, Cushing's syndrome, hyperthyroidism, primary hyperparathyroidism, severe vitamin D deficiency, malabsorption conditions such as coeliac disease, surgery for obesity and inflammatory bowel disease, rheumatoid arthritis, lupus, connective tissue diseases, and kidney disease or liver disease. Drugs that may affect bone mass such as glucocorticoids, heparin and antiepileptic medications must also be taken into account. Finally, other typical risk factors for osteoporosis such as tobacco use, alcohol consumption, family history and physical activity also need to be considered.[7] Other factors such as changes in weight and lordotic posture during pregnancy can contribute to the development of fractures.[3] Densitometry in cases of pregnancy- and lactation-associated osteoporosis shows extremely low BMD values, in general with Z-scores below −3.[8,9] A study using iliac crest biopsy in women who had pregnancy- and lactation-associated osteoporosis detected decreased bone formation.[8] Other studies have yielded evidence of increased bone resorption with an increased receptor activator of nuclear factor-kappa B ligand–to–osteoprotegerin (RANKL/OPG) ratio.[10]

Pregnancy-associated transient osteoporosis of the hip

This is a rare, self-limiting form of focal osteoporosis with decreased BMD in the femoral head and neck and other locations. It manifests in the final trimester of pregnancy or the postpartum period as severe pain in one or both hips; limping; or, more rarely, hip fracture. X-ray reveals a radiolucent image in the femoral head and neck, BMD in the hip appears low and magnetic resonance imaging (MRI), the diagnostic technique of choice, can show oedema in the bone marrow.[11,12] Signs and symptoms as well as radiological findings in cases without fracture resolve two to 12 months after childbirth.[3,12] This abnormality appears not to be related to phosphorous and calcium metabolism and changes therein during pregnancy, but rather to local pregnancy-related factors. Theories have been put forward on causes as diverse as complex regional pain syndrome (Sudeck's atrophy), reflex sympathetic dystrophy, femoral venous stasis due to pressure from the uterus, viral infec-

tions, immobilisation and foetal pressure on the obturator nerve, among others.[3]

Lactation-associated osteoporosis and fragility fractures

The risk of vertebral fracture increases more in women during breastfeeding than during pregnancy; even so, as mentioned, the risk of fracture is low. PTHrP's role in breastfeeding, as well as oestrogen deficiency, are important and are involved in the increased bone remodelling that occurs in this period.[9] In cases of osteoporosis or very low bone mass with a history of fracture, it could be reasonable to advise against breastfeeding due to the risk of a greater drop in bone mass and the development of a fragility fracture.

Treatment

Spontaneous recovery of bone mass occurs after pregnancy and the end of breastfeeding in around six to 12 months. As such, during pregnancy and in this one-year period, starting osteoporosis treatment is not recommended, apart from calcium and vitamin D supplementation in most cases. Insufficient bone mass recovery has been seen in women with vertebral fractures during pregnancy and breastfeeding. This may suggest that BMD loss occurred prior to pregnancy or was particularly severe during pregnancy. In these cases, treatment could be planned according to the degree of bone mass recovery.[3,8] The following have been used in women who experienced fractures after pregnancy: nasal calcitonin (no longer indicated for this purpose), bisphosphonates, strontium ranelate (also not indicated in Spain) and teriparatide. Due to a lack of controls, there is lingering uncertainty as to whether the same bone mass recovery would have occurred spontaneously a year after pregnancy or the end of breastfeeding.[13–15] However, an analysis of 30 studies reporting outcomes of treatment with calcium and vitamin D, bisphosphonates or teriparatide suggested that both bisphosphonates and teriparatide had a favourable effect on BMD that surpassed spontaneous recovery.[16] Vertebroplasty and kyphoplasty have been used to treat painful vertebral fractures in the postpartum period, but their efficacy is unclear.[1,11] In cases of transient osteoporosis of the hip, positive outcomes in terms of recovery time have been seen with the use of bisphosphonates, calcitonin or teriparatide, but in pregnancy-associated cases, conservative treatment, weight-bearing restrictions, physiotherapy, analgesics and thromboprophylaxis are pursued to prevent maternal complications during pregnancy.[12] Surgical treatment of a femoral fracture in a pregnant woman should be multidisciplinary in order to maintain foetal well-being during surgery. Antithrombotic prophylaxis should be administered in the postoperative period and physical rehabilitation should be started early with an emphasis on hip abduction.[17]

Recommendations

- We recommend treatment with calcium and vitamin D in women with osteoporosis during pregnancy and breastfeeding (1⊕OOO).
- We recommend not routinely starting osteoporosis treatment during pregnancy (1⊕OOO).
- In cases of pregnancy-associated osteoporosis, we suggest suitably balancing the risks and benefits of breastfeeding for the mother and the newborn, taking into account the potential effects on the bones of the mother (2⊕OOO).
- We suggest re-evaluating bone mass a year after pregnancy or six to 12 months after the end of breastfeeding and proposing treatment depending on the degree of bone mass recovery (2⊕OOO).
- In cases of multiple vertebral fractures, whether during pregnancy or breastfeeding, we suggest, after ruling out secondary causes, considering a cycle of anabolic therapy (teriparatide for up to two years) or treatment with a bisphosphonate for two to three years and then re-evaluating after that time (2⊕OOO).
- We suggest pursuing conservative treatment of transient pregnancy-associated osteoporosis of the hip (2⊕OOO).

Hypovitaminosis D

Effects of hypovitaminosis D

The relationship between maternal serum vitamin D levels and vitamin D supplementation on the one hand, and pregnancy outcomes on the other, has been extensively analysed from different points of view. Prior to pregnancy, vitamin D deficiency is associated with a lower likelihood of success of becoming pregnant in women who undergo treatment with assisted reproductive technology.[18] Hypovitaminosis D, for its part, is a common condition during pregnancy. According to estimates, up to 28% of the Spanish population has vitamin D deficiency (<20 ng/ml) and around 30%–35% has vitamin D insufficiency (<30 ng/ml).[19,20] These results are consistent with those reported in other countries.[21]

Many observational studies have analysed the relationship between 25-hydroxyvitamin D (25(OH)D) levels in pregnancy and maternal and foetal health. It should be borne in mind that the different studies conducted have been disparate, especially with respect to population included, time of evaluation, results analysed and matters related to 25(OH)D determination itself (method of determination, baseline values and levels considered indicative of deficiency and insufficiency). Taking these limitations into account, in recent years, several meta-analyses have been published whose main results have confirmed low vitamin D levels to be associated with worse outcomes during pregnancy.

Regarding the health of pregnant women, values below 20 ng/ml increase the risk of suffering from pre-eclampsia by 33%–54%, with a specificity for diagnosis of 90% with values

below 10.6 ng/ml.[22] Women with gestational diabetes mellitus (GDM), for their part, have lower serum 25(OH)D levels compared to women with normal glucose tolerance, such that vitamin D deficiency increases the risk of having GDM by 18% (OR = 1.18; 95% CI: 1.01–1.35; $p < 0.001$).[23] In addition, there appears to be an inverse, dose-dependent relationship between 25(OH)D levels and risk of preterm birth (PTB). Levels below 30 ng/ml, determined before 32–34 weeks of gestation, have been associated with an 83% increased risk of PTB.[24]

Regarding newborn health, in a recently published meta-analysis that included 54 studies, children of mothers with severe vitamin D deficiency (<12 ng/ml) exhibited worse anthropometric outcomes with lower birth weights [mean difference (MD) −87.82 g; 95% CI: −119.73, −55.91 g] and head circumferences (MD − 0.19 cm; 95% CI: −0.32, −0.06 cm), as well as a 59% increased risk of being small-for-gestational-age (SGA) children. Levels below 20 ng/ml were also associated with a higher risk of being SGA. However, values ≥30 ng/ml were not related to being SGA or to birth weight.[21]

Finally, consistent with the pleiotropic effects of vitamin D, low 25(OH)D levels during pregnancy have also been linked to less classic adverse effects. In this sense, children of mothers with vitamin D insufficiency had lower scores on tests of mental development (MD −1.12 points; 95% CI: −1.82, −0.42 points) and language development (MD −0.35 points; 95% CI: −1.00, 0.31 points).[20] In an Australian group of women with asthma, levels below 30 ng/ml were associated with an increased risk of respiratory diseases in their children in the first year of life.[25]

In summary, low serum 25(OH)D levels in pregnant women are linked to multiple maternal and foetal complications, but the usefulness of supplements in relation to these complications is a matter of debate. Multiple randomised studies that include pregnant patients who received vitamin D supplementation have been published, but most have had insufficient numbers of patients, have suffered from low methodological quality and have been highly disparate with regard to the dose of vitamin D used, the time during pregnancy when supplementation was given, plasma 25(OH)D levels and the effects evaluated.[26,27]

Effects of vitamin D supplementation

A meta-analysis recently conducted by Cochrane found that the use of vitamin D supplements during pregnancy probably reduces the risk of pre-eclampsia (RR: 0.48; 95% CI: 0.30–0.79). However, the meta-analysis could only feature four high-quality studies including a total of just 499 women. Vitamin D supplements might also reduce the risk of GDM (RR 0.51; 95% CI: 0.27–0.97), but again, only four high-quality studies with just 446 women could be evaluated. The same meta-analysis found that vitamin D supplements could reduce foetal risk of low birth weight (<2,500 g) with a RR of 0.55 (95% CI: 0.35–0.87), yet it evaluated just five high-quality studies with 697 women.[25,26] Another study that included 1,134 women showed a decreased risk of severe postpartum haemorrhage (RR 0.68; 95% CI: 0.51–0.91) in women who received vitamin D supplementation.[26]

Regarding the long-term effects of vitamin D supplementation, a meta-analysis by Roth et al. found a reduction in the risk of asthma and wheezing in children up to three years of age (RR 0.81; 95% CI: 0.67–0.98), although it was performed with just two studies with a total of 1,387 women.[18,28] Joint vitamin D and calcium supplementation might be linked to a reduced risk of pre-eclampsia (RR: 0.5; 95% CI: 0.32–0.78), similar to what happens when vitamin D is administered in isolation, but it is also related to an increased risk of preterm birth (RR: 1.52; 95% CI: 1.01–2.28).[26,27]

The optimal dose of vitamin D during pregnancy remains undefined and varies across associations, but it should be sufficient to keep serum 25(OH)D levels over 20 ng/dl.[29] Most studies in pregnant women have used vitamin D3 (cholecalciferol) as a supplement, with doses ranging from 200 IU/day to 7,500 IU, with a mean of 2,000 IU/day.[30,31] No data are available on the use of calcifediol in pregnant women, although vitamin D supplements appear to be safe for use during pregnancy.[32] In women on treatment prior to pregnancy for reasons such as surgery for obesity, maintaining calcifediol could be an option, although no studies have been conducted to investigate this.

Recommendations

- We recommend keeping 25(OH)D levels over 20 ng/dl during pregnancy (1⊕OOO).
- We suggest that 25(OH)D supplementation be done with vitamin D3 (cholecalciferol) (2⊕OOO).
- We suggest administering a vitamin D3 dose of 1,500–2,000 IU daily in cases of deficiency (2⊕OOO).

Primary hyperparathyroidism

General information

Primary hyperparathyroidism (PHP) in pregnancy or breastfeeding is rare. It has an estimated incidence of eight per 100,000 population in women of reproductive age[33] and of 0.05%–1.4% during pregnancy.[34]

Few studies have focused on the repercussions of PHP for fertility and complications during pregnancy and breastfeeding. A major population study of 1,057 women of reproductive age with PHP found no differences in terms of number of pregnancies, miscarriages, live births, Apgar scores or newborn length or weight, even in the last year before diagnosis, compared to healthy controls.[35] In a study by Rigg J et al., pregnancy duration was shorter in the PHP group than in the control group; this was linked to more Caesarean births to bring an early end to the pregnancy and thus enable diagnostic evaluation of the mother.[33] No differences in obstetric complications were found from different studies.[34,35]

Data on the incidence of miscarriages in patients with PHP are conflicting,[34,35] although some studies have found

miscarriages to be more common in women with a history of prior miscarriage and higher calcium levels. On this point, if the patient has had repeat miscarriages, surgery prior to pregnancy can be considered.[36]

Regarding symptoms, PHP during pregnancy and breastfeeding is usually asymptomatic and mild, especially during pregnancy.[34,37] Some rare, serious complications have been reported: hypercalcaemia, especially in women with hyperemesis; renal colic[38]; acute pancreatitis; cardiovascular events; and gastric or duodenal ulcers.[39]

Clinically, it is extremely important to make a differential diagnosis with familial hypocalciuric hypercalcaemia (FHH). Increased calcium absorption during pregnancy causes physiological hypercalciuria, which can affect clinical-chemistry differentiation of FHH and mild PHP; delaying diagnosis to the postpartum period is an option if possible.[40] It is essential to avoid unnecessary examinations of the neck and associated risks. There are more than 100 mutations in the calcium-sensing receptor (CaSR) gene. There are rare cases of parathyroid carcinomas in which CDC73 mutations must be suspected.[41] It must also be taken into account that PHP can occur as part of multiple endocrine neoplasia type 1 (MEN1), multiple endocrine neoplasia type 2A (MEN2A), familial PHP associated with a mandibular tumour or familial PHP. In this case, what matters most for diagnosis is the patient's family history.[40]

For diagnosis, scintigraphy should be performed only in very select cases; it is recommended that ultrasound be maintained as the diagnostic test of choice. Therapeutic management is conservative in most cases. If surgery were necessary, considering the criteria for definitive treatment in non-pregnant patients, it is safe in expert hands, with the same complications as outside of pregnancy, and is preferably performed in the second trimester. It is the only curative treatment in symptomatic women.[34] Cinacalcet can be used as a medical treatment.[41] It has been classified as a category C drug, meaning that studies in animal models have demonstrated an adverse effect on the foetus and suitable, well-controlled studies have not been conducted in humans; however, the potential benefits could justify the use of the drug in pregnant women with symptomatic hypercalcaemia.[41] In the few available studies, it was administered throughout pregnancy or for just a few weeks at doses ranging from 15 mg/day to 240 mg/day. However, the drug was poorly tolerated due to nausea, and maternal serum calcium levels did not normalise during pregnancy in any of the cases. Bisphosphonates should be restricted to cases in which the patient's life is at risk.[35] In the event of vitamin D deficiency, supplementation can be provided, and calcium supplements can be suspended. In neonates, the risk of hypocalcaemia due to suppression of the foetal parathyroid glands must be considered.[36]

Recommendations

- We suggest considering surgery in patients who have had repeat miscarriages prior to their pregnancy (2⊕OOO).
- We recommend making a suitable differential diagnosis to avoid unnecessary treatments and examinations (1⊕⊕OO).
- We recommend medical follow-up in most cases with ultrasound as the diagnostic technique of choice (1⊕⊕⊕O).
- We suggest considering surgery, if essential, in the second trimester or, as a last resort in case of symptomatic hypercalcaemia, cinacalcet or calcitonin (2⊕OOO).
- We recommend restricting bisphosphonates to cases in which the patient's life is at risk (1⊕⊕⊕O).

Chronic hypoparathyroidism

General information

Hypoparathyroidism is an uncommon condition that may have significant implications in pregnancy. Physiological changes in pregnancy may markedly affect the management of hypoparathyroidism and require frequent monitoring to prevent hypocalcaemia or hypercalcaemia. These changes can affect foetal skeletal and parathyroid development and increase foetal and maternal morbidity.

The management of hypoparathyroidism in pregnancy has not been systematically studied, with data coming from case series. The physiological changes mentioned may decrease requirements for calcium and calcitriol supplementation during pregnancy and breastfeeding. However, cases of increased requirements have been reported; therefore, there is no single pattern and adjustments should be made on an individual basis.[42,43] This requires close monitoring with the goal of keeping blood calcium levels at the lower limit of normal.[42] Due to PTHrP fluctuations, theories have been put forward on two times that are particularly susceptible to changes in blood calcium levels: the immediate postpartum period and the end of breastfeeding.[44]

Normally, the placenta protects the foetus from hypocalcaemia, and foetal hypocalcaemia only occurs when the mother has severely decreased calcium levels. Foetal hypocalcaemia stimulates the foetal parathyroid glands,[45] which demineralise the foetal skeleton and in extreme cases may even cause preterm births and miscarriages. This means that it is essential to perform immediate follow-up of the newborn.[43]

Regarding treatment with calcitriol, there is no evidence to suggest that vitamin D is teratogenic, despite evidence of supravalvular aortic stenosis in rabbit foetuses subjected to toxic oral doses of vitamin D. Its use in pregnancy is restricted to scenarios in which the benefits outweigh the risks. In breastfeeding women, close monitoring of serum calcium levels in mothers and infants is recommended.

Recommendations

- We recommend closely monitoring plasma calcium levels, checking them every three to four weeks during pregnancy

and, after making an adjustment, reviewing them after one to two weeks (1⊕OOO).
- We suggest keeping calcium levels at the lower limit of normal (2⊕OOO).
- We recommend considering women with hypoparathyroidism and pregnancy to have high-risk pregnancies, as well as having paediatrics conduct an immediate neonatal assessment (1⊕OOO).
- We recommend suspending treatment with thiazides (1⊕⊕⊕O).
- There are no data on the use of PTH analogues in pregnant women with hypoparathyroidism; therefore, we recommend suspending treatment with PTH analogues (1⊕OOO).
- We recommend close monitoring of blood calcium levels in the perinatal period and at the start of breastfeeding (at least weekly) (1⊕OOO).
- We recommend close monitoring at the end of breastfeeding (1⊕OOO).

Drugs in pregnancy and breastfeeding

Calcium supplements

At present, there is no data to support advising universal calcium supplementation during pregnancy. A calcium intake of 1,000 mg/day is suggested, the same as for women of reproductive age who are not pregnant.[46] Recent evidence suggests that women with low calcium intake (less than 600 mg/day) are at higher risk of developing hypertensive disorders of pregnancy. At present, the World Health Organization (WHO) recommends supplementation with 1.5–2.0 g/day of calcium during pregnancy in women at high risk of osteoporosis or fractures due to fragility and/or women with low dietary calcium intake.[47] The quality of the evidence is low for other outcomes, and the results should be interpreted with caution.

Vitamin D supplements

Maternal vitamin D deficiency has been linked to neonatal rickets,[48] as well as multiple adverse outcomes of pregnancy, including gestational diabetes and pre-eclampsia.[49]

Recommendations on vitamin D administration to pregnant women vary by institution. The intake recommended by the WHO is 200 IU/day, while the Institute of Medicine of the United States recommends 600 IU/day.[50] A recent systematic review of the Cochrane database found that administration of vitamin D supplements to pregnant women at higher-than-recommended doses could reduce the risk of gestational diabetes. Effects on other outcomes could be limited or nonexistent.[27] Administration of vitamin D supplements seems to be safe, with very low numbers of adverse events.

In general, preventing and treating vitamin D deficiency during pregnancy is important in order to optimise maternal and foetal bone health and support foetal growth, but the evidence to improve other pregnancy outcomes is limited.[49] More rigorous, high-quality randomised trials that are more extensive are needed to evaluate the different regimens for administration of vitamin D supplements during pregnancy.

Bisphosphonates

Most of the literature on the use of bisphosphonates in humans has not reported serious adverse events in the foetus or the mother. However, some published studies have shown a decrease in gestational age, low neonatal weight, transient hypocalcaemia in newborns and very rare cases of miscarriages and congenital anomalies.[51]

Data from the Centre de référence sur les agents tératogènes [French Reference Centre for Teratogenic Agents], which included women who received bisphosphonates in the six weeks before or during pregnancy and had systemic diseases (n = 23) or bone diseases (n = 13) were published in 2018.[52] There were no differences in rates of congenital malformations, but rates of neonatal complications were higher for cases than for controls. The complications included: cardiac arrhythmias, maternal–foetal infection, acute foetal distress, polycythaemia and thrombocytopenia. In women with systemic diseases, the rate of live births was lower compared to healthy controls (80% versus 100%). Taken together, the current recommendations propose as a safety measure that treatment with bisphosphonates should not be started if a woman is planning to get pregnant in the next 12 months.[7]

Denosumab

The effects of denosumab on maternal and foetal development in humans are unclear, and it has been suggested that conception be avoided for at least six months after the last injection of the drug.[53]

In *cynomolgus* monkeys exposed to denosumab in utero, different congenital defects have been reported, including: dental dysplasia, shortening of the bones, reduction of cortical thickness and decreased ultimate strength in the diaphysis of the femur. Other bone characteristics resembling an osteoporotic phenotype were partially reversible.[54]

Teriparatide

No studies have been conducted on the effects on the foetus of treatment with teriparatide in pregnant women. There are reported cases of women with severe osteoporosis during pregnancy treated after birth who forewent breastfeeding with favourable outcomes.[55]

Recommendations

- We recommend administering calcium and vitamin D supplements to pregnant women who do not achieve the established requirements (1⊕⊕OO).

- We recommend not using bisphosphonates, denosumab or teriparatide during pregnancy because their safety has not been determined (1⊕⊕OO).

Conclusions

Adaptive changes in calcium and bone metabolism in pregnancy and breastfeeding are silent and not usually associated with long-term adverse effects. Osteoporosis and fragility fractures are rare, and medical treatment is contraindicated apart from calcium and vitamin D supplements. Vitamin D supplementation during pregnancy and breastfeeding above the recommended doses has demonstrated no obvious additional benefits. With regards to PHP, it is usually mild and can be kept under observation except in serious cases in which surgery is preferable during the second trimester. In hypoparathyroidism, frequent monitoring of calcium levels is required to adjust treatment and maintain normal calcium levels. Finally, calcium and vitamin D supplements are safe in pregnancy and breastfeeding, while osteoporosis drugs are contraindicated.

Conflicts of interest

None of the authors has any conflicts of interest relevant to this undertaking. No funding was received for the drafting of this statement.

References

1. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. Grading quality of evidence and strength of recommendations. BMJ. 2004;328:1490, http://dx.doi.org/10.1136/bmj.328.7454.1490.
2. Kovacs CS, Kronenberg HM. Pregnancy and lactation. In: Bilezikian JP, editor. Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism. Ninth Edition 2019. p. 147–54, http://dx.doi.org/10.1002/9781119266594.ch20.
3. Kovacs CS. Osteoporosis presenting in pregnancy, puerperium, and lactation. Curr Opin Endocrinol Diabetes Obes. 2014;21:468–75, http://dx.doi.org/10.1097/MED.0000000000000102.
4. Kolthoff N, Eiken P, Kristensen B, Nielsen SP. Bone mineral changes during pregnancy and lactation: a longitudinal cohort study. Clin Sci. 1998;94:405–12, http://dx.doi.org/10.1042/cs0940405.
5. Gehlen M, Lazarescu AD, Hinz C, Schwarz-Eywill M, Pfeifer M, Balasingam S, et al. Long-term outcome of patients with pregnancy and lactation-associated osteoporosis (PLO) with a particular focus on quality of life. Clin Rheumatol. 2019;38:3575–83, http://dx.doi.org/10.1007/s10067-019-04758-0.
6. Butscheidt S, Delsmann A, Rolvien T, Barvencik F, Al-Bughaili M, Mundlos S, et al. Mutational analysis uncovers monogenic bone disorders in women with pregnancy-associated osteoporosis: three novel mutations in LRP5, COL1A1, and COL1A2. Osteoporos Int. 2018;29:1643–51, http://dx.doi.org/10.1007/s00198-018-4499-4.
7. Langdahl BL. Osteoporosis in premenopausal women. Curr Opin Rheumatol. 2017;29:410–5, http://dx.doi.org/10.1097/BOR.0000000000000400.
8. Cohen A, Kamanda-Kosseh M, Dempster DW, Zhou H, Müller R, Goff E, et al. Women with pregnancy and lactation–associated osteoporosis (PLO) have low bone remodeling rates at the tissue level. J Bone Miner Res. 2019;34:1552–61, http://dx.doi.org/10.1002/jbmr.3750.
9. Laroche M, Talibart M, Cormier C, Roux C, Guggenbuhl P, Degboe Y. Pregnancy-related fractures: a retrospective study of a French cohort of 52 patients and review of the literature. Osteoporos Int. 2017;28:3135–42, http://dx.doi.org/10.1007/s00198-017-4165-2.
10. Sanz-Salvador L, García-Pérez MÁ, Tarín JJ, Cano A. Bone metabolic changes during pregnancy: a period of vulnerability to osteoporosis and fracture. Eur J Endocrinol. 2015;172:R53–65, http://dx.doi.org/10.1530/EJE-14-0424.
11. Kasahara K, Kita N, Kawasaki T, Morisaki S, Yomo H, Murakami T. Bilateral femoral neck fractures resulting from pregnancy-associated osteoporosis showed bone marrow edema on magnetic resonance imaging. J Obstet Gynaecol Res. 2017;43:1067–70, http://dx.doi.org/10.1111/jog.13313.
12. Thanatsis N, Kollia G, Gkliatis J, Decavalas G, Adonakis G. Bilateral transient osteoporosis of the hip in pregnancy. J Obstet Gynaecol. 2018;38:415–6, http://dx.doi.org/10.1080/01443615.2017.1352571.
13. Li L, Zhang J, Gao P, Lv F, Song Y, Chang X, et al. Clinical characteristics and bisphosphonates treatment of rare pregnancy- and lactation-associated osteoporosis. Clin Rheumatol. 2018;37:3141–50, http://dx.doi.org/10.1007/s10067-018-4185-0.
14. Hardcastle SA, Yahya F, Bhalla AK. Pregnancy-associated osteoporosis: a UK case series and literature review. Osteoporos Int. 2019;30:939–48, http://dx.doi.org/10.1007/s00198-019-04842-w.
15. Choe EY, Song JE, Park KH, Seok H, Lee EJ, Lim S-K, et al. Effect of teriparatide on pregnancy and lactation-associated osteoporosis with multiple vertebral fractures. J Bone Miner Metab. 2012;30:596–601, http://dx.doi.org/10.1007/s00774-011-0334-0.
16. Hong N, Rhee Y. Comparison of efficacy of pharmacologic treatments in pregnancy- and lactation-associated osteoporosis. Clin Rev Bone Miner Metab. 2019;17:86–93.
17. Harold JA, Isaacson E, Palatnik A. Femoral fracture in pregnancy: a case series and review of clinical management. Int J Womens Health. 2019;11:267–71, http://dx.doi.org/10.2147/IJWH.S198345.
18. Pilz S, Zittermann A, Obeid R, Hahn A, Pludowski P, Trummer C, et al. The role of vitamin D in fertility and during pregnancy and lactation: a review of clinical data. Int J Environ Res Public Health. 2018;15:2241, http://dx.doi.org/10.3390/ijerph15102241.
19. Rodríguez-Dehli AC, Riaño Galán I, Fernández-Somoano A, Navarrete Muñoz EM, Espada M, Vioque J, et al. Prevalence of vitamin d deficiency and insuffiency and associated factors in pregnant women of northern Spain. Nutr Hosp. 2015;31:1633–40, http://dx.doi.org/10.3305/nh.2015.31.4.8448.
20. Rodriguez A, Santa Marina L, Jimenez AM, Espluges A, Ballester F, Espada M, et al. Vitamin D status in pregnancy and determinants in a Southern European Cohort Study. Paediatr Perinat Epidemiol. 2016;30:217–28, http://dx.doi.org/10.1111/ppe.12281.
21. Tous M, Villalobos M, Iglesias L, Fernández-Barrés S, Arija V. Vitamin D status during pregnancy and offspring outcomes: a systematic review and meta-analysis of observational studies. Eur J Clin Nutr. 2020;74:36–53, http://dx.doi.org/10.1038/s41430-018-0373-x.

22. Akbari S, Khodadadi B, Ahmadi SAY, Abbaszadeh S, Shahsavar F. Association of vitamin D level and vitamin D deficiency with risk of preeclampsia: a systematic review and updated meta-analysis. Taiwan J Obstet Gynecol. 2018;57:241–7, http://dx.doi.org/10.1016/j.tjog.2018.02.013.
23. Amraei M, Mohamadpour S, Sayehmiri K, Mousavi SF, Shirzadpour E, Moayeri A. Effects of vitamin D deficiency on incidence risk of gestational diabetes mellitus: a systematic review and meta-analysis. Front Endocrinol (Lausanne). 2018;9:7, http://dx.doi.org/10.3389/fendo.2018.00007.
24. Amegah AK, Klevor MK, Wagner CL. Maternal vitamin D insufficiency and risk of adverse pregnancy and birth outcomes: a systematic review and meta-analysis of longitudinal studies. PLoS One. 2017;12:e0173605, http://dx.doi.org/10.1371/journal.pone.0173605.
25. Jensen ME, Murphy VE, Gibson PG, Mattes J, Camargo CA Jr. Vitamin D status in pregnant women with asthma and its association with adverse respiratory outcomes during infancy. J Matern Fetal Neonatal Med. 2019;32:1820–5, http://dx.doi.org/10.1080/14767058.2017.1419176.
26. Palacios C, Kostiuk LK, Peña-Rosas JP. Vitamin D supplementation for women during pregnancy. Cochrane Database Syst Rev. 2019;7(7):CD008873, http://dx.doi.org/10.1002/14651858.CD008873.pub4.
27. Palacios C, Trak-Fellermeier MA, Martinez RX, Lopez-Perez L, Lips P, Salisi JA, et al. Regimens of vitamin D supplementation for women during pregnancy. Cochrane Database Syst Rev. 2019;10(10):CD013446, http://dx.doi.org/10.1002/14651858.CD013446.
28. Roth DE, Leung M, Mesfin E, Qamar H, Watterworth J, Papp E. Vitamin D supplementation during pregnancy: state of the evidence from a systematic review of randomised trials. BMJ. 2017;359:j5237, http://dx.doi.org/10.1136/bmj.j5237.
29. IOM (Institute of Medicine). 2011 Dietary reference intakes for calcium and vitamin D. Washington, DC: The National Academies Press; 2011. p. 260–2.
30. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. J Clin Endocrinol Metab. 2012;97:1153–8, http://dx.doi.org/10.1210/jc.2011-2601.
31. Varsavsky M, Rozas Moreno P, Becerra Fernández A, Luque Fernández I, Quesada Gómez JM, Ávila Rubio V, et al. Recommended vitamin D levels in the general population. Endocrinol Diabetes Nutr. 2017;64 Supl. 1:7–14, http://dx.doi.org/10.1016/j.endinu.2016.11.002.
32. Bi WG, Nuyt AM, Weiler H, Leduc L, Santamaria C, Wei SQ. Association between vitamin D supplementation during pregnancy and offspring growth, morbidity, and mortality: a systematic review and meta-analysis. JAMA Pediatr. 2018;172:635–45, http://dx.doi.org/10.1001/jamapediatrics.2018.0302.
33. Rigg J, Gilberston E, Barret HL, Britten FL, Lust K. Primary hyperparathyroidism in pregnancy: maternofetal outcomes at a quaternary referral obstetric hospital, 2000 through 2015. J Clin Endocrinol Metab. 2019;104:721–9, http://dx.doi.org/10.1210/jc.2018-01104.
34. Leere JS, Vestergaad P. Calcium metabolic disorders in pregnancy, primary hyperparathyroidism, pregnancy-induced osteoporosis, and vitamin D deficiency in pregnancy. Endocrinol Metab Clin D Am. 2019;48:643–55, http://dx.doi.org/10.1016/j.ecl.2019.05.007.
35. Norman J, Politz D, Politz L. Hyperparathyroidism during pregnancy and the effect of risin calcium on pregnancy los: a call for earlier intervention. Clin Endocrinol (Oxf). 2009;71:104–9, http://dx.doi.org/10.1111/j.1365-2265.2008.03495.x.
36. Diaz-Soto G, Linglart A, Sénat MV, Kamenicky P, Chanson P. Primary hyperparathyroidism in pregnancy. Endocrine. 2013;44:591–7, http://dx.doi.org/10.1007/s12020-013-9980-4.
37. Leere JS, Karmishort J, Robaczy M, Vestergaard P. Contemporary medical manegement of primary hyperparathyroidism: a systematic review. Front Endocrinol (Lausanne). 2017;8:1–11, http://dx.doi.org/10.3389/fendo.2017.00079.
38. Starup- Linde J, Waldhaver E, Rodighed L, Mosekilde L, Vestergaard P. Renal stones and calficications in patients with primary hyperparthyroidism associations with biochemical variable. Eur J Endocrinol. 2012;166:1093–100, http://dx.doi.org/10.1530/EJE-12-0032.
39. Han ES, Fritton K, Bacon P, Slodzinski M, Argani C. Preterm parturent with polyhidramnios and pancreatitis primary presentation of hyperparthyroidism. Case Rep Obstet Gynecol. 2018:2091082, http://dx.doi.org/10.1155/2018/2091082.
40. Gehlert J, Morton A. Hypercalcemia during pregnancy: review of maternal and fetal complications, investigations, and management. Obstetric Med. 2019;12:175–9, http://dx.doi.org/10.1177/1753495X18799569.
41. Rubin MR, Silveberg SJ. Use of cinacalcet and 99mc Tc-sestamibi imaging during pregnancy. J Endocr Soc. 2017;1:1156–9, http://dx.doi.org/10.1210/js.2017-00308.
42. Khan A, Clarke B, Rejnmark L, Brandi ML. Hypoparathyroidism in pregnancy: review and evidence-based recommendations for management. Eur J Endocrinol. 2019;180:R37–44, http://dx.doi.org/10.1530/EJE-18-0541.
43. Hartogsohn AR, Khan A, Kjærsulf LU, Sikjaer T, Hussain S, Rejnmark L. Changes in treatment needs of hypoparathyroidism during pregnancy and lactation: a case series. Clin Endocrinol (Oxf). 2020;93:261–8, http://dx.doi.org/10.1111/cen.14212.
44. Durst R, Meirovitz A, Gross D, Kolker O, Muszkat M. Post-partum hypocalcemia: idiopatic hypoparathyroidism manifested early in lactation. J Endocrinol Invest. 2002;25:561–3, http://dx.doi.org/10.1007/BF03345501.
45. Landing BH, Kamoshita S. Congenital hyperparathyroidism secondary to maternal hypoparathyroidism. J Pediatr. 1970;77:842–7, http://dx.doi.org/10.1016/s0022-3476(70)80245-1.
46. Institute of Medicine. Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Washington, DC, USA: The National Academies Press; 2006. p. 1344.
47. WHO. Guideline: Calcium Supplementation in Pregnant Women. Geneva, Switzerland: World Health Organization; 2013.
48. Kontic-Vucinic O, Sulovic N, Radunovic N. Micronutrients in women's reproductive health: II. Minerals and trace elements. Int J Fertil Womens Med. 2006;51:116–24.
49. Aghajafari F, Nagulesapillai T, Ronksley PE, Tough SC, O'Beirne M, Rabi DM. Association between maternal serum 25-hydroxyvitamin D level and pregnancy and neonatal outcomes: systematic review and meta-analysis of observational studies. BMJ. 2013;346:f1169, http://dx.doi.org/10.1136/bmj.f1169.
50. Mousa A, Naqash A, Lim S. Macronutrient and micronutrient intake during pregnancy: an overview of recent evidence. Nutrients. 2019;11:443, http://dx.doi.org/10.3390/nu11020443.
51. Pepe J, Body JJ, Hadji P, McCloskey E, Meier C, Obermayer-Pietsch B, et al. Osteoporosis in premenopausal women: a clinical narrative review by the ECTS and the IOF. J Clin Endocrinol Metab. 2020;105:dgaa306, http://dx.doi.org/10.1210/clinem/dgaa306.
52. Sokal A, Elefant E, Leturcq T, Beghin D, Mariette X, Seror R. Pregnancy and newborn utcomes after exposure to bisphosphonates: a casecontrol study. Osteoporos Int. 2019;30:221–9, http://dx.doi.org/10.1007/s00198-018-4672-9.
53. Ijuin A, Yoshikata H, Asano R, Tsuburai T, Kikuchi R, Sakakibara H. Teriparatide and denosumab treatment for pregnancy and lactation-associated osteoporosis with multiple vertebral frac-

tures: a case study. Taiwan J Obstet Gynecol. 2017;56:863–6, http://dx.doi.org/10.1016/j.tjog.2017.10.028.
54. Boyce RW, Varela A, Chouinard L, Bussiere JL, Chellman GJ, Ominsky MS, et al. Infant cynomolgus monkeys exposed to denosumab in utero exhibit an osteoclast-poor osteopetrotic like skeletal phenotype at birth and in the early postnatal period. Bone. 2014;64:314–25, http://dx.doi.org/10.1016/j.bone.2014.04.002.
55. Cerit ET, Cerit M. A case of pregnancy and lactation associated osteoporosis in the third pregnancy; robust response to teriparatide despite delayed administration. Bone Rep. 2020;13:100706, http://dx.doi.org/10.1016/j.bonr.2020.100706.