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Primary hyperparathyroidism in pregnancy

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Although primary hyperparathyroidism (PHPT) is the third most common endocrinopathy, comprising about 0.1–0.4% of the population, it is described relatively infrequently in pregnant women, posing a challenge for the treatment team, and is significantly different from current standards of practice. And it is important to remember that serum calcium concentration monitoring in pregnant women is not part of the panel of routinely performed tests. In addition, the results of calcium testing should be interpreted in the context of the occurrence of gestational hypoalbuminaemia ("corrected calcium"). For these reasons, the overall disease picture is ambiguous, in terms of diagnosis, maternal management, and the impact of the disorder on the foetus. The attending physician should be knowledgeable about the pathophysiology of the disease and the resulting possible disorders, as well as complications.

Foetal development is associated with an increase in calcium absorption from the mother's intestines, as well as reabsorption from her bones [1]. This process is triggered by oestrogen, prolactin, and vitamin D3, the concentration of which increases 2–3-fold in pregnant women.

The parathyroid hormone (PTH) concentration in pregnancy usually remains at the lower normal limit, or just below it, but it can also be elevated, as was the case in the 2 patients described [2, 3].

During pregnancy, on the other hand, there is an excessive increase in parathyroid hormone-related peptide (PTHrP), which is stimulated by oestrogen through the secretion of the mammary gland as well as the placenta itself, which is an impermeable barrier to PTH. PTHrP is the main regulator of calcium levels in pregnant women (an increase of which in about 30% is the only symptom of PHPT). Maternal calcium enters the foetus by active transport, which implies a decrease in foetal parathormone secretion but does not affect PTHrP secretion [1, 2, 4].

The above-described patients are examples of the course of PHPT in pregnant women, where the first symptom of the disease may be acute pancreatitis (AP) [5] or symptoms that are absolutely uncharacteristic (nausea, vomiting, fatigue) [6]. It should be taken into consideration that both in pregnant and non-pregnant women the symptoms of PHPT are similar, and the disease can only be indicated by an increase in serum calcium concentration. It should also be remembered that about 80% of pregnant women may not show any other symptoms of PHPT (except for an increase in serum calcium concentration) [7, 8].

In both women in this article, the affected parathyroid glands were visualised by performing a neck ultrasound, which is the examination of choice in pregnancy, especially in the hands of an experienced ultrasonographer. It is advisable in uncertain cases (especially when parathyroid ectopia is suspected) to perform magnetic resonance imaging (MRI) of the mediastinum (as was done in the patient treated for recurrent pancreatitis). On the other hand, imaging studies using isotopic markers [scintigraphy, computed tomography (CT)] are not recommended [4].

The management of pregnant women diagnosed with PHPT should be individualised. The timing of the diagnosis of PHPT in relation to pregnancy (before or during, and in which trimester) determines the treatment. This is because it is important to keep in mind the possible complications associated with hyperparathyroidism both on the part of the mother and the foetus. One of the most serious, although rare, complications associated with the mother is acute pancreatitis, which can occur during pregnancy, in addition to kidney stones, eclampsia, and in extreme cases miscarriage or premature labour. Exceptionally, foetal

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necrosis may occur within the uterus. In the newborn, on the other hand, hypocalcaemia with symptoms of tetany and finally symptoms of pulmonary hypertension are observed. According to the Fifth International Workshop, pregnant women with moderate severity of PHPT should receive conservative treatment: oral and/or intravenous hydration, loop diuretics, or possibly cinacalcet, which penetrates the placenta for a short period of time [7, 9]. Both described patients underwent similar management, except that the first patient also required suppression of recurrent AP symptoms.

Due to the lack of studies on the use of Cinacalcet in pregnant women, it is allowed only if the benefit to the mother outweighs the potential risk to the foetus [Australian Therapeutic Goods Administration (AU TGA) pregnancy category B3; American Food and Drug Agency (FDA) pregnancy category C]. Other serum calcium-restricting drugs, besides the one mentioned above, are of limited use or not recommended [10, 11].

Indications for parathyroidectomy (PTX) strictly include symptoms associated with PHPT (such as AP, pathological fractures, kidney stones). It is also understood that an absolute indication for PTX is a corrected calcium concentration ≥ 2.85 mmol/L (11.4 mg/dL) [7, 10, 11]. However, as the analysis of the disease course of the 2 patients shows, the serum calcium concentration absolutely cannot be considered the only indication for surgery, without assessing the general condition and without performing other laboratory tests [PTH, protein concentration, creatinine glomerular filtration rate (GFR), phosphates, calcium concentration in daily urine collection].

The optimal time for surgery seems to be the second trimester of pregnancy (about 2/3 of all PTXs are performed then) due to the very low complication rate (4.5%). In the first trimester, the percentage is about 25% and mainly concerns disorders of organogenesis. In the third trimester, complications occur in about 21% of those operated on and are mainly related to the possibility of preterm labour. It should be remembered that the lack of surgical treatment can result in a significant increase in complications (close to 53%) from both mother and foetus [10, 11].

PTX in the 2 described patients was performed at 32 weeks' gestation — in the first due to concerns about another recurrence of AP, and with consistently high serum calcium and parathormone levels (despite conservative treatment with cinacalcet as well). In addition, the patient developed ascites and peripheral oedema of the lower extremities, which was associated with low protein levels. In contrast, in the second patient, the immediate cause of surgery for persistent hypercalcaemia was low foetal weight. It is noteworthy that only 6 weeks after PTX, the foetal weight reached the expected value.

In assessing the indications and the PTX method, it should be pointed out that the author believes that this type of surgery in pregnant patients should be performed in obstetrics and gynaecology centres (highest referral units), where the pregnant woman is provided with medical surveillance against the possible emergence of preterm labour as well as management of preterm delivered neonates. The indications for surgery alone should be determined on a case-by-case basis by an experienced team consisting of a gynaecologist (if possible, a perinatologist), an internist, an endocrinologist, and a surgeon to perform the eventual operation (a surgeon with extensive experience in thyroid and parathyroid surgery).

Conflict of interest

The author declares no conflict of interests.

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References

1. Leere J, Vestergaard P. Calcium Metabolic Disorders in Pregnancy. Endocrinol Metab Clin N Am. 2019; 48(3): 643–655, doi: 10.1016/j.ecl.2019.05.007.
2. Ali DS, Dandurand K, Khan AA. Primary Hyperparathyroidism in Pregnancy: Literature Review of the Diagnosis and Management. J Clin Med. 2021; 10(13), doi: 10.3390/jcm10132956, indexed in Pubmed: 34209340.
3. Diaz-Soto G, Linglart A, Sénat MV, et al. Primary hyperparathyroidism in pregnancy. Endocrine. 2013; 44(3): 591–597, doi: 10.1007/s12020-013-9980-4, indexed in Pubmed: 23670708.
4. Appelman-Dijkstra NM, Pilz S. Approach to the Patient: Management of Parathyroid Diseases Across Pregnancy. J Clin Endocrinol Metab. 2023; 108(6): 1505–1513, doi: 10.1210/clinem/dgac734, indexed in Pubmed: 36546344.
5. Zamłyński M, Olejek A, Buła G, et al. Treatment of parathormone dependent hypercalcemia in third trimester of pregnancy. Endokrynol Pol. 2024; 75(3): 336–337, doi: 10.5603/ep.99387, indexed in Pubmed: 38887118.
6. Klimek M, Fecko M, Zieliński T, et al. Acute pancreatitis associated with primary hyperparathyroidism during pregnancy. Endokrynol Pol. 2024; 75(3): 334–335, doi: 10.5603/ep.99376, indexed in Pubmed: 38708913.
7. Bilezikian JP, Khan AA, Silverberg SJ, et al. International Workshop on Primary Hyperparathyroidism. Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop. J Bone Miner Res. 2022; 37(11): 2293–2314, doi: 10.1002/jbmr.4677, indexed in Pubmed: 36245251.
8. Strebeck RJ, Schneider AM, Whitcombe DD, et al. Hyperparathyroidism in Pregnancy: A Review of the Literature. Obstet Gynecol Surv. 2022; 77(1): 35–44, doi: 10.1097/OGX.0000000000000977, indexed in Pubmed: 34994393.
9. Trahan MJ, Antinora C, Czuzoj-Shulman N, et al. Obstetrical and neonatal outcomes among pregnancies complicated by hyperparathyroidism. J Matern Fetal Neonatal Med. 2023; 36(1): 2170748, doi: 10.1080/14767058.2023.2170748, indexed in Pubmed: 36775282.
10. Sharma SG, Levine SN, Yatavelli RK, et al. Parathyroidectomy in First Trimester of Pregnancy. J Endocr Soc. 2020; 4(3): bvaa015, doi: 10.1210/jendso/bvaa015, indexed in Pubmed: 32133431.
11. Zhong H, Liao Q, Liu J, et al. Society of Parathyroid and Metabolic Bone Diseases, Chinese Research Hospital Association; Chinese Society of Perinatal Medicine; Chinese Society of Osteoporosis and Bone Mineral Research. Expert consensus on multidisciplinary approach to the diagnosis and treatment of primary hyperparathyroidism in pregnancy in China. Endocrine. 2023; 82(2): 282–295, doi: 10.1007/s12020-023-03392-w, indexed in Pubmed: 37221429.