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Clinical Quiz

Successful surgical treatment of primary hyperparathyroidism during the third trimester of pregnancy

S. Petousis[1], A. Kourtis[1], C.D. Anastasilakis[2], K. Makedou[1], A. Giomisi[3], I. Kalogiannidis[1], C. Margioula-Siarkou[1], E. Xanthopoulou[1], D. Rousso[1]

[1]3rd Department of Obstetrics and Gynaecology, Aristotle University of Thessaloniki, Greece; [2]Department of Pharmacology, 424 Military Hospital, Thessaloniki, Greece; [3]Department of Obstetrics and Gynaecology, 424 Military Hospital, Thessaloniki, Greece

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Case report

A 28-year old pregnant, parity one, was submitted to our department at 26w+1d of gestation because of mild abdominal pain. Her medical history was free and her pregnancy uncomplicated. Detailed gynecological and ultrasound examination was normal. Baseline hematological and biochemical testing was normal with the exception of increased white blood cells (13.6 K/μL). The patient was admitted to the hospital; in the next days mildly but persistently increased serum calcium [(Ca) 10.4 to 11.1 mg/dL, normal range (NR) 8.2-10.2 mg/dL] and alkaline phosphatase [(ALP) 156-183 IU/l, NR 30-120 IU/l] along with decreased serum phosphate [(P), 2.4 mg/dL, NR 2.5-4.5 mg/dL) were observed. Urine calcium was also found to be high-normal (217 mg/24h, NR 100-250 mg/24h) while fractional calcium excretion calculated by the formula: Ca/Cr clearance ratio= (24h urinary Ca x serum Cr)/(serum Ca x 24h urinary Cr) was 0.023 excluding the possibility of FHH. Subsequently, parathyroid hormone (PTH) levels were measured and found increased (177 pg/mL), setting the diagnosis of primary hyperparathyroidism (pHPT). Genetic testing for MEN1 was negative. As the patient was in the third trimester of pregnancy, had only mild symptoms and mildly elevated serum Ca, a conservative approach with hydration and intranasal calcitonin was decided and she was discharged.

Another examination 10 days later, at 28w+2d of gestation, revealed a raise in serum Ca levels (11.4-11.9 mg/dL) and decreased P (2.2 mg/dL) despite the management. Although her symptoms were mild, the elevation in serum Ca up to 12 mg/dL made us reconsider the surgical approach. Neck ultrasound implied the existence of a solitary left inferior parathyroid adenoma while Magnetic Resonance Imaging of the neck confirmed this finding and led us to decide a surgical approach.

Surgery was performed at the 29th gestational week and the abnormal left interior parathyroid was resected. Histological examination confirmed the presence of a parathyroid adenoma. Both serum Ca and PTH decreased to normal soon after surgery (9.1 mg/dL and 30.7 pg/mL 2 days post-surgery, respectively). The patient was discharged on the 29w+4d of gestation. Follow-up on weekly basis, demonstrated normal serum Ca levels throughout pregnancy. The patient had a spontaneous delivery at 37w+3d. Neonate's birth weight was 2830 gr with Apgar score 7 in the 1st and 8 in the 5th minute of life. The newborn presented no tetany or other pathology.

Commentary

pHPT during pregnancy is a rare complication, occurring in 0.5-1.4% of all cases[1]. Mostly caused by a solitary parathyroid adenoma, it has an impact on maternal and neonatal health status. Maternal complications because of PHPT during pregnancy may include nephrolithiasis, hyperemesia or even severe hypercalcemic crisis, potentially threatening even maternal life itself[2]. The danger of complications is further enhanced by the fact that increased Ca demands during pregnancy normally result in decreased maternal serum Ca levels; thus, hypercalcemia, the most prevalent laboratory finding in pHPT, may not be evident and therefore the diagnosis of pHPT during pregnancy may be challenging, presenting severe pitfalls[2].

Because of the serious complications reported in untreated cases, pHPT during pregnancy necessitates an effective management[3]. Lack of evidence-based guidelines often raises the dilemma between a conservative or a surgical approach. According to Schnatz et al[4], medical treatment may be an option

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Corresponding author: Anargyros Kourtis, Konstantinoupoleos 49, PC 54642, Thessaloniki, Greece
E-mail: argic@med.auth.gr

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during the first trimester of pregnancy, especially if symptoms and Ca levels may be controlled by drug administration. However, oral phosphates are class C in a pregnancy state. Furthemore, despite the fact that BSP have also recently been used without detrimental effects on both mother and fetus, their usage is rather indicated as short-term treatment in cases of severe hypercalcemia; therefore, the preferable medication options include only hydration, calcitonin, intravenous magnesium or, the recently mentioned, usage of cinacalset[1]. On the other hand, surgical treatment in the third trimester has been associated with high complication rates[3]; therefore, some propose to continue conservative management until postpartum, in case symptoms and serum Ca levels are well controlled. In our patient the combination of advanced gestational age at diagnosis, mild symptoms and mildly elevated serum Ca levels led to an initial conservative approach, under close follow-up.

Persistency of symptoms and mainly calcium levels above 11 mg/dL are considered indications for surgical treatment, regardless of the trimester of pregnancy. Truong et al[3] favor this approach, underlying the need to weigh the benefits and risks of the surgical procedure. Successful surgical management of pHPT eliminates the risk of pHPT deterioration postpartum and the risk of neonatal tetany. Surgery during the third trimester has been reported to increase the risk for preterm labor[3] along with other severe complications[4], although the occurrence of these complications could be due to the longstanding hypercalcemic status of both the mother and the fetus[1,3]. However, in our case, persistency of symptoms and gradual increase of Ca levels despite conservative treatment, raising thoughts of a parathyroid carcinoma (1-2% of pHPT) led us to decide surgery.

Although the second trimester of pregnancy is considered the safest period for operations, several cases of uncomplicated surgical treatment of pregnant women in the third trimester have also been reported[4,5]. Despite previous studies reporting postoperative complications rate as high as 58% in third trimester procedures[1], progress in imaging and especially surgical techniques has significantly improved safety for procedures performed after the 24 weeks of gestation[1,5]. Indeed, in our patient a successful parathyroidectomy was performed at the 29th week without any complications from the mother or the fetus. However, it seems that the optimal time to perform papathyroidectomy in case of diagnosed pHPT is preferably the second trimester of pregnancy, with studies indicating significantly improved rates of neonatal and maternal morbidity in cases of surgical treatment in the second trimester comparing with conservative approach[4]. Surgical treatment during the third trimester may be perfomed only in case potential risk of complications is outweighed by the benefit of a definite treatment that surgery may offer, especially in cases conservative approach fails as in our case.

Osteoporosis and nephrolithiasis represent the most common complications of pHPT nowadays, setting the indication for surgery[1,5]. Our patient did not report any incident of colic and had no sign of stone in ultrasound examination. Given that radiographs are contraindicated in pregnancy, we did not proceed with further radiological tests. The same reason along with the lack of bone pain deterred us from measuring bone mineral density (BMD) using a DXA equipment, although DXA is not considered particularly harmful in this setting. It seems that the radiation dose after a DXA is low for the mother and even less for the fetus; thus, the risk from radiation is minimal although not zero.

In conclusion, in cases of pHPT during pregnancy, surgery should be avoided in the first trimester and conservative management should be preferred instead. Despite the superiority of surgical treatment in the second trimester of pregnancy[4], optimal treatment in the third trimester remains an issue. In any case, treatment approach should be individualized, estimating both mother and fetus situation. In our case, the decision to proceed to surgery resulted in the correction of maternal clinical condition and laboratory findings and in the birth of a healthy fetus. Probably, further research on this issue may help physicians overcome fears about a potential non-conservative treatment in late pregnancies as well.

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Questions

1. How should a physician deal with a pregnant woman with primary hyperparathyroidism and serum calcium levels at 12 mg/dL?
A. Do nothing but monitoring, the disorder is harmless
B. Immediately operate to remove the hyperfunctioning parathyroid tissue regardless of the week of pregnancy
C. Administer bisphosphonates and monitor
D Prefer conservative management with hydration and calcitonin if in the first trimester and operate in the second trimester if the disease persists or worsens

Critique

Primary hyperparathyroidism during pregnancy is associated with increased risk for both maternal and fetal-neonatal complications and mortality. Bisphosphonates are contraindicated in pregnancy due to their presumable unfavorable effect on fetal skeleton. Surgical management is considered safe only in the second and perhaps the third trimester of pregnancy.
The correct answer is D.

2. Which is true about primary hyperparathyroidism occurrence during pregnancy?
A. Its frequency is estimated to be over 5% of all pregnancies
B. Conservative management remains the gold standard
C. It is associated with severe complications for both the mother and the fetus
D. Intense clinical symptoms always give a high diagnostic suspicion for the disorder

Critique

pHPT during pregnancy is a rare complication, occurring in 0.5-1.4% of all cases and has an impact on maternal and neonatal health status, with maternal complications and mortality to reach up to 67% and 25% respectively. Occurrence of pHPT during pregnancy may only be implied by non-specific symptoms such as fatigue or muscle weakness.
The correct answer is C.

3. In which trimester of pregnancy surgical treatment seems to be the optimal treatment?
A. First trimester
B. Second trimester
C. Third trimester
D. Surgical treatment is for all trimesters the gold standard method

Critique

In cases of pHPT during pregnancy, surgery should be avoided in the first trimester and conservative management should be preferred instead. Despite the superiority of surgical treatment in the second trimester of pregnancy, optimal treatment in the third trimester remains an issue.
The correct answer is B.

4. Which of the below may be considered as an indication for surgical treatment?
A. Calcium levels over 12 mg/dL
B. Peristancy of hypercalcemia despite administration of drugs
C. Occurrence of nephrolithiasis during pregnancy
D. All the above

Critique

Persistency of symptoms and mainly calcium levels above 11 mg/dL are considered indications for surgical treatment, regardless of the trimester of pregnancy.
The correct answer is D.