Complications and Management of Primary Hyperparathyroidism During Pregnancy

Gebelik Sırasında Görülen Primer Hiperparatiroidizmin Komplikasyonları ve Tedavisi

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Abstract

Calcium metabolism undergoes physiologic alterations in normal pregnancy, which can potentially lead to confusion and difficulty in the diagnosis of primary hyperparathyroidism occurring during gestation. This does not mitigate the fact that primary hyperparathyroidism can lead to increased morbidity for the mother and fetus, including the life-threatening complication of acute pancreatitis. A high level of suspicion should be maintained if hypercalcemia is detected, and management should be carefully individualized to minimize maternal and fetal complications. Surgery in the second trimester appears to be a safe and viable form of definitive therapy. A team effort from clinicians of different disciplines is the best approach. In this review, we summarize the occurrence, manifestations, and possible treatment options of primary hyperparathyroidism and resultant hypercalcemia during pregnancy by presenting a brief illustrative clinical case and searching the relevant medical literature from 1966 to the present. *Turk Jem 2008; 12: 75-9*

Key words: Primary hyperparathyroidism, pregnancy, hypercalcemia, pancreatitis

Özet

Normal gebelik sırasında kalsiyum metabolizması fizyolojik değişiklikler göstermektedir. Bu değişiklikler gebelikte oluşan primer hiperparatiroidizm tanısını zorlaştırmaktadır. Gebelikte görülen primer hiperparatiroidizm, hayati tehlike içeren akut pankreatit komplikasyonu dahil, hem anne hem de fetus için morbidite artışına neden olmaktadır. Gebelik sırasında hiperkalsemi belirlendiği takdirde çok dikkatli olunmalıdır ve tedavi her hastaya özel olarak maternal ve fetal komplikasyonları azaltmaya yönelik olarak planlanmalıdır. İkinci trimester sırasında cerrahi güvenli ve etkili tedavi yaklaşımıdır. Farklı disiplinlerden hekimlerin oluşturduğu bir ekip ile hastaya yaklaşım belirlenmelidir. Bu derlemede, temsili bir vaka kısaca sunularak ve 1966'dan bu yana ilgili tıp literatürü taranarak, gebelik sırasında primer hiperparatiroidizm ve bağlı olarak görülen hiperkalseminin sıklığı, belirtileri, ve muhtemel tedavi seçenekleri özetlenmiştir. *Turk Jem 2008; 12: 75-9*

Anahtar kelimeler: Primer hiperparatirodizm, gebelik, hiperkalsemi, pankreatit

Illustrative Clinical Case

A 22-year old gravida 2, para 1 presented to the emergency room at 20 weeks gestation with abdominal and flank pain, nausea, vomiting and diffuse abdominal tenderness. Review of her medical history revealed that she had been diagnosed with primary hyperparathyroidism (PHP) during her previous pregnancy but had refused to follow medical advice about recommended treatment. Following delivery, she had not returned for office visits until seeking care during the current pregnancy. Laboratory studies revealed a lipase of 220 units/L (normal range 6-51) and calcium 12.1 mg/dL (normal range 8.5-10.5). She had leucocytosis but normal liver and kidney function tests. An abdominal ultrasound showed an edematous enlarged pancreas with no evidence of gall stones or biliary duct dilatation. Computed tomography (CT) scan of the abdomen was not done because of her pregnant state. A diagnosis of pancreatitis was made and the patient was treated with bowel rest, intravenous fluids, and parenteral nutritional support. The serum calcium level ranged from 10.9 to 12.2 mg/dL, with the ionized calcium ranging from 1.66 to1.76 mmol/L (normal range 1.16-1.32). The intact parathyroid hormone (PTH) level was found to be 105 pg/mL (normal range 30-71). With the

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diagnosis of PHP, the patient underwent neck exploration and two enlarged parathyroid glands were removed. Pathologic analysis confirmed the presence of adenomatous change in one of the two glands.The intraoperative PTH level decreased to 10 pg/mL, and her calcium fell to 9.5 mg/dL following surgery. The patient did well postoperatively, and no untoward effects on the fetus were observed. The lipase level gradually came down to 69 units/L one week after surgery and she made a satisfactory clinical recovery. There was no recurrence of hypercalcemia after discharge from the hospital. The patient delivered a healthy infant by caesarian section after 37 weeks of pregnancy. Calcium level was 8.4 mg/dL after delivery, with an albumin level of 3.1 g/L.

Introduction

Primary hyperparathyroidism (PHP) is uncommon during gestation, occurring in less than 1% of all pregnancies. It is associated with significant risk of fetal and maternal morbidity and mortality. The diagnosis can be difficult to make because of changes in calcium homeostasis that affect calcium and parathyroid hormone (PTH) metabolism, which may mask concurrent PHP. The features of PHP during pregnancy can range from subtle alterations in calcium dynamics to overt clinical manifestations like persistent nausea and vomiting, dyspepsia, nephrolithiasis, and bone loss. The diagnosis can be overlooked or delayed and is usually only suspected when recalcitrant hypocalcemia or even tetany and convulsions are noted in the neonate or infant. Maternal pancreatitis has also been reported as a rare, but dangerous, complication of hypercalcemia. There is no general consensus regarding the optimal management of PHP complicating pregnancy, and both medical and surgical options have been advocated. Therefore, we summarized our findings from a review of the relevant literature (Medline search, 1966-2008) concerning the occurrence, impact, and management of PHP manifesting during pregnancy.

Calcium-PTH Metabolism in Pregnancy

There is an interesting alteration of the calcium-PTH dynamics during pregnancy (Table 1). Early reports described a "physiologic hyperparathyroidism" of pregnancy with an increase in serum immunoreactive PTH levels beginning in the second trimester (1). However, the recent development of more accurate and specific immunoradiometric (IRMA) methods have discredited this notion by showing a reduction, rather than an elevation, of intact PTH levels (2). In fact, one study found mean serum PTH levels in nonpregnant women to be 72% higher than in pregnant women (3). These changes in PTH during pregnancy may be a response to altered calcium metabolism. Intravascular fluid expansion and hypoalbuminemia makes less protein available to bind calcium, thus lowering total but not ionized calcium. In addition, an increase in urinary excretion of calcium occurs due to increased glomerular filtration rate, and maternal calcium in the blood is actively transported across the placenta to fulfill the needs of the growing fetus (4). The latter imposes an increased calcium requirement that is partly fulfilled by mobilization of calcium from the maternal skeleton. Together, these effects have a tendency to lower maternal calcium levels (5). However, they are more than offset by a large increase in intestinal calcium absorption that occurs during pregnancy (6,7). Hormonal changes during pregnancy may also be responsible for an increase in the production or activity of the enzyme 1-α-hydroxylase in the kidney (8), which in turn may account for the observed differences between pregnant and nonpregnant women, including the elevation of 1,25-dihydroxyvitamin D (2), the slight increase in serum calcium levels (9), and the reduction in PTH levels (3).

Table 1. Changes in calcium regulation and PTH levels during pregnancy

1. Active transport of calcium across the placenta to the fetus
2. Hypercalciuria due to elevated glomerular filtration rate
3. Increased calcium mobilization from the maternal skeleton
4. Enhanced 1,25-dihydroxyvitamin D activity due to increased estrogen, human placental lactogen, and parathyroid-related protein (PTHrP)
5. Increased intestinal calcium absorption
6. Mild increase in serum calcium levels
7. Tendency to have reduced serum PTH levels
Information is based on references 1-9.

Presentation and Complications

Although the occurrence of PHP during pregnancy has been described in the medical literature (10,11), its true incidence is not known. Parathyroid adenoma is the most common underlying cause of hyperparathyroidism during pregnancy. Changes in calcium and phosphate metabolism occurring in pregnancy have been proposed to influence the biochemical expression of PHP (4,12). Complications associated with PHP in pregnancy have been reported to occur in up to 67% of mothers and 80% of fetuses (13). Table 2 lists some of these complications. According to a report by Schnatz et al, constitutional symptoms include muscle weakness (70%), arthralgias and myalgias (54%), and hyperemesis, while other less common symptoms include mental status changes, nephrolithiasis (3%), peptic ulcer disease (12%), bone disease (2%) and pancreatitis (1%) (13). Since the manifestations are variable in nature, the diagnosis may be overlooked or delayed. Several of the symptoms and clinical

Table 2. Potential complications of primary hyperparathyroidism in pregnancy and the postpartum state

Maternal*
1. Severe nausea and vomiting (hyperemesis)
2. Muscle weakness, arthralgias, and myalgias
3. Peptic ulcer disease
4. Pancreatitis
5. Mental status changes
6. Nephrolithiasis
7. Bone disease
8. Hypercalcemic crisis
9. Seizures
1. Cardiac arrythmias
Fetal and Neonatal**
1. Hypocalcemia
2. Seizures
3. Tetany
4. Spontaneous abortions
5. Intrauterine fetal demise and still-birth
6. Intrauterine growth retardation
7. Low birth weight
8. Preterm delivery
* Information is based on references 4, 5, 9-15.
** Information is based on references 16-21.

findings in hyperparathyroidism may also be present with preeclampsia, thus causing difficulty in distinguishing one from the other (14). PHP in twin pregnancy has also been reported (15,16). Severe PHP resulting in hypercalcemic crises, seizures, and cardiac arrythmias are a risk to the expectant mother (17,18). Rapid bone loss can lead to fractures in predisposed women (19), and elevated urinary calcium can serve as a precipitant for kidney stones during gestation (20). PHP should be considered in the differential diagnosis in any woman with a history of renal calculi, osteoporosis, peptic ulcer, or persistent nausea and vomiting during pregnancy (21). It is important to keep in mind that imaging studies involving radiation exposure or nuclear tracers (like for CT or sestamibi scans) cannot be used for the evaluation of PHP or its complications in pregnant women.

Although rare, pancreatitis has been identified as a complication of PHP (22), and is described in the illustrative clinical case above. If left untreated, the combination of PHP and pancreatitis can increase maternal and fetal mortality (23). The risk factors for acute pancreatitis as a complication of PHP during pregnancy appear to be the same as in nonpregnant patients. Although the absolute calcium level is an important predictor, it may attenuate during the pregnant state and individual predisposing factors may be important in the manifestation of pancreatic inflammation (24).

The most serious fetal complications of maternal PHP are hypocalcemia, seizures, and tetany. Maternal hypercalcemia leads to fetal hypercalcemia, which suppresses fetal parathyroid development. Once the maternal source of calcium is removed after delivery, the fetus is unable to mobilize an endogenous storage of calcium because of the longstanding parathyroid suppression, leading to fetal hypocalcaemia. The observation of hypocalcemic tetany of the neonatal infant caused by transient hypoparathyroidism is often a clue that reveals asymptomatic maternal PHP (25,26). Indeed, a high level of suspicion should be maintained for underlying PHP in even mild degrees of maternal hypercalcemia. Many maternal PHP cases are identified retrospectively, after the occurrence of unsuspected neonatal convulsions (27-29). The risk of spontaneous abortions and still births, intrauterine growth retardation, low birth weight, and preterm delivery is also increased (30).

Treatment Options

The approach to managing PHP during pregnancy is two-fold: first, treatment of the acute phase, and second, definitive therapy for the long-term. The first step is to lower serum calcium with vigorous intravenous hydration. Oral phosphate administration has also been reported to be effective in some cases (31), while calcitonin and loop diuretics have been used with limited success. Once the patient's condition is stable, consideration should be given to definitive therapy. This is especially applicable in severe disease characterized by progressive symptoms and inadequately controlled hypercalcemia after stabilization has been achieved with adequate hydration. However, the timing of surgery has been a matter of debate. Dorey et al reported the first successful case of surgical intervention for PHP attempted in the third trimester (32). Surgery in the third trimester is still advocated if the condition is diagnosed late in pregnancy, since it is effective in preventing the risk of neonatal hypocalcemia (33,34); indeed, operative intervention should not be deferred unless delivery is imminent, regardless of gestational age. In severe PHP, the risk of fetal complications is much higher if the hyperparathyroidism is left untreated compared to if the mother undergoes the operation during the pregnancy. Importantly, the general consensus is that maternal parathyroidectomy should be performed preferably after the first trimester (once organogenesis has been completed), since morbidity is low and risk to the fetus is slight. The second trimester is believed to be the optimal period for neck exploration (35,36). Surgery performed during this time in the hands of a surgeon familiar with this operation carries few maternal risks and offers the best chance for fetal and neonatal health and survival (37,38). After surgery, normal calcium homeostasis is restored to the fetus and the risk of hypocalcemia in the neonatal period is virtually eliminated. However, surgical complications include the risks involved with anesthesia and induction of premature labor. The well-known propensity to postoperative hypocalcemia and "hungry bones syndrome" after parathyroidectomy can theoretically be exacerbated due to the pregnant state and should be vigilantly guarded against (39). Although an appealing option, to our knowledge there are no reports evaluating the use of minimally invasive parathyroid surgery for the treatment of PHP in pregnant women.

The risks in patients with mild, asymptomatic PHP during pregnancy are much less clear (40). Careful medical (nonsurgical) management appears to have a place in PHP where serum calcium and PTH levels may be measured periodically during gestation while optimizing hydration through liberal fluid intake. The serum calcium level in such patients can remain stable with medical management alone, and such a scenario is compatible with normal fetal development and an uncomplicated pregnancy in select cases (41).

Some areas of controversy still remain regarding the criteria and timing for surgical treatment of PHP in pregnancy. Kelly (42) reviewed 109 reported cases of women with PHP associated with pregnancy from 1930 to 1990, including 39 who were treated surgically before delivery. Although fetal mortality rates for medically treated women during this time period improved, fetal morbidity remained higher than in women who underwent surgical treatment. This study concluded that management should be based on the patient's symptoms and severity of disease; maternal hyperparathyroidism characterized by progressive symptoms should be treated surgically, preferably during the second trimester, while symptom-free patients and those with mild hypercalcemia diagnosed in the third trimester may be managed medically, postponing surgery until after delivery. In another review, Carrella and Gossain (43) attempted to provide general recommendations for the management of PHP during pregnancy, favoring parathyroidectomy during the second trimester. They were of the opinion that a woman who is initially diagnosed with PHP well into the third trimester may be treated medically, barring worsening of hypercalcemia or onset of other complications. For women who have known PHP or are diagnosed at a pre-natal assessment (whether symptomatic or not) and are contemplating becoming pregnant, they should have an elective parathyroidectomy and the calcium-parathyroid status should be normalized prior to conception.

Asymptomatic Primary Hyperparathyroidism in Pregnancy

Up to 80% of pregnant women with PHP are asymptomatic (13), thus potentially eluding diagnosis. The treatment approach to such patients is also much less clear than for symptomatic patients. The recommendation from a consensus panel is that young nonpregnant patients should be treated surgically (44). Although the same recommendation should apply if the condition is discovered in pregnancy, the asymptomatic nature of the

disease and the presumed milder impact on maternal-fetal health may warrant medical management and deferment of surgery until after delivery. Whether a patient is treated medically or surgically in these situations, the pregnancy should be considered high-risk. At parturition, sudden worsening of maternal hypercalcemia can result from dehydration and loss of the protective placental calcium transport. Regardless of the degree of maternal hypercalcemia, it is advisable to carefully monitor the mother for hyperparathyroid crisis postpartum, and to monitor the neonate for signs of hypocalcemia or impending tetany.

To summarize, it is only recently that evidence-based management of PHP in pregnancy has begun to emerge (13). Several factors should raise the suspicion early in pregnancy, including the following: a history of recurrent spontaneous abortions, stillbirths, unexplained neonatal deaths; neonatal hypocalcemia or tetany; and the existence of relevant clinical signs or symptoms in both the mother and fetus. Controversy still exists regarding the appropriate management of PHP in pregnancy, especially late in gestation and in those with mild disease. The second trimester appears to be the best time for surgery, and debate continues regarding the safety of surgery in the third trimester. The PHP includes a total serum calcium concentration greater than 10.1 mg/dL during the second trimester or greater than 8.8 mg/dL during the third trimester (13), hyperemesis that continues well beyond the first trimester, nephrolithiasis, and pancreatitis.

Conclusions

The simultaneous occurrence of PHP and pregnancy is rare, but it can lead to a range of adverse sequelae if unrecognized and left untreated. PHP can precede conception or first begin to manifest during gestation. Due to volume expansion, hemodilution, and altered calcium-PTH relationships during pregnancy, concomitant PHP may not be properly diagnosed in a timely fashion. Complications range from gastrointestinal complaints, osteopenia, fractures, hypercalciuria, and kidney stones, to life-threatening pancreatic inflammation and cardiac rhythm disturbances. Morbidity is not limited to the mother since neonatal hypocalcemia can be persistent and severe enough to cause tetany and seizures in the infant.

The occurrence of both PHP and pancreatitis together is rare, but it is associated with potentially significant maternal and fetal complications. In pregnant women presenting with acute pancreatitis, PHP should be included in the differential diagnosis. The early detection and timely treatment of maternal PHP is critical to avoid complications in both mother and child. Although management should be individualized, recent experience favors neck exploration and parathyroidectomy during pregnancy as the definitive treatment of choice where surgical expertise is available and the impact of continued hypercalcemia on maternal-fetal health is deemed significant. Select patients (such as those who are asymptomatic) can also choose to be followed medically and have the surgery delayed until after delivery.

In conclusion, a multidisciplinary approach involving the obstetrician, endocrinologist, endocrine surgeon, and neonatologist is encouraged to assure optimal outcomes in pregnant women with PHP. For practicing clinicians, our illustrative clinical case report and literature review highlights the fact that PHP can be an important, and treatable, co-morbidity in pregnant women that requires prompt recognition and therapy.

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