Primary hyperparathyroidism during pregnancy – current approach

Pierwotna nadczynność przytarczyc w czasie ciąży – aktualne podejście

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- primary hyperparathyroidism
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- parathormone
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ABSTRACT

Primary hyperparathyroidism (PHPT) during pregnancy is a rare, but may cause many maternal and fetal complications. Most cases are mild and very often remain undiagnosed throughout the whole pregnancy period, especially since its symptoms overlap those occurring in normal pregnancy. Additionally, physiological changes in calcium metabolism and PTH secretion may make the diagnosis difficult. Some current data indicate, that in pregnant women with mild PHPT the risk of obstetrical complications do not increase. However, according to others some complications, including miscarriage, intrauterine growth retardation or preeclampsia continue to occur even in subjects with mild hypercalcemia or those previously successfully treated for PHPT. Additionally, the course of PHPT during pregnancy may exacerbate, and rapid severe worsening of hypercalcemia may occur in the postpartum period. Parathyroidectomy, optimally performed during the second trimester, remains the main and the only definite treatment of PHPT, especially, when the serum calcium level exceeds 2,75 mmol/l. In patients with mild, asymptomatic PHPT some experts recommend conservative treatment with postponing surgery to the postpartum period. There are no medical guidelines regarding the treatment of PHPT during pregnancy. Therefore, to achieve optimal care of pregnant women with PHPT, they should be diagnosed, monitored and treated in reference centers by multidisciplinary teams of closely cooperating specialists. Conservative treatment is possible only on condition of close monitoring of the mother and child during pregnancy and after delivery.

SŁOWA KLUCZOWE:

- pierwotna nadczynność przytarczyc
- ciąża
- parathormon
- hiperkalcemia

STRESZCZENIE

Pierwotna nadczynność przytarczyc (PNP) w czasie ciąży występuje rzadko, ale może powodować wiele powikłań u matki i płodu. Większość przypadków jest łagodna i bardzo często pozostaje nierozpoznana przez cały okres ciąży, zwłaszcza że jej objawy pokrywają się z objawami występującymi w fizjologicznej ciąży. Dodatkowo związane z ciążą zmiany metabolizmu wapnia i wydzielania parathormonu mogą utrudniać rozpoznanie. Część aktualnych badań wskazuje, że u ciężarnych z łagodną PNP ryzyko powikłań położniczych nie wzrasta. Jednak według innych niektóre powikłania, w tym poronienie, opóźnienie wzrostu wewnątrzmacicznego czy stan przedrzucawkowy nadal występują, nawet u osób z łagodną hiperkalcemią i wcześniej skutecznie leczonych z powodu PNP. Ponadto w trakcie trwania ciąży może dojść do zaostrzenia przebiegu PNP, a w okresie poporodowym – do gwałtownego nasilenia hiperkalcemii. Głównym postępowaniem (i jedynym zapewniającym trwałe wyleczenie), pozostaje paratyreoidektomia. Optymalnie powinna być ona przeprowadzona w drugim trymestrze ciąży, zwłaszcza wówczas, gdy stężenie wapnia w surowicy przekracza 2,75 mmol/l. U kobiet z łagodną, bezobjawową PNP niektórzy eksperci zalecają leczenie zachowawcze z odroczeniem zabiegu operacyjnego na okres poporodowy. Brak wytycznych dotyczących leczenia PNP w ciąży. Dlatego, aby zapewnić optymalną opiekę ciężarnym z PNP, powinny być one diagnozowane, monitorowane i leczone w ośrodkach referencyjnych przez interdyscyplinarne zespoły ściśle współpracujących ze sobą specjalistów. Postępowanie zachowawcze jest możliwe jedynie pod warunkiem ścisłego monitorowania matki i dziecka, zarówno w trakcie ciąży, jak i po porodzie.

Primary hyperparathyroidism (PHPT) affects approximately 1% of general population in developed countries and is the most common cause of hypercalcemia. Increasing availability of total serum calcium concentration and other tests in developed countries over last few decades caused significant change in clinical presentation of the disease, so that nowadays 80% of cases are asymptomatic. It requires modifications in therapeutic approach. Primary hyperparathyroidism is caused by single parathyroid adenoma in approximately 85%, less commonly by parathyroid gland hyperplasia – in 15%, while parathyroid carcinoma is a very rare condition, that affects less than 1% of patients (8).The incidence of PHPT increases remarkably over the age of 40, while in the group of women in reproductive age it is low (0,05%) (10). About 10% of PHPT is caused by inherited syndromes (MEN1, MEN2A and others), in which it occurs 20-30 years earlier and is often a result of parathyroid hyperplasia. PHPT during pregnancy is a very rare condition, but may cause many serious complications both for the mother and the child. It is often difficult to diagnose, as symptoms of hypercalcemia significantly overlap those occurring in normal pregnancy. Additionally, gestational changes in calcium homeostasis and PTH secretion may obscure the diagnosis.

Physiological changes in calcium-phosphate metabolism during pregnancy

During pregnancy a remarkable series of physiologic changes occur to provide fetal growth and development and preserve maternal homeostasis. Maternal plasma volume increases, serum hemoglobin and albumin decrease and remain low until delivery. As a result, the albumin-bound calcium fraction and total serum calcium fall and may be well below the normal range (1). High estrogen concentrations may also contribute to the decrease of calcium level. However, the physiologically active fraction of ionized calcium remains constant (1). Therefore, to asses the true calcium level in a pregnant woman, the ionized calcium fraction should be measured or the albumin-corrected total calcium should be calculated.

The average fetus requires about 30 g of calcium and 20 g of phosphorus to maintain multiple physiological processes and mineralize its skeleton. Most of the fetal skeletal growth takes place from mid-pregnancy and 80% calcium and phosphate accretion occurs in the third trimester. The major maternal adaptation to meet these demands is more than double increase of calcium and phosphate intestinal absorption, driven by 1,25-dihydroxyvitamin D [1,25(OH)$_2$D, calcitriol] and other factors, probably like in animals – high levels of estrogen, placental lactogen and prolactin (1, 3).

The increase in calcium absorption doubles as early as 12 weeks of gestation and is far ahead the peak fetal demand for calcium, so the woman remains in a positive calcium balance by mid-pregnancy (27). It may promote skeletal mineralization to store calcium for late pregnancy and lactation. However, current research results indicate, that maternal bone density is usually stable throughout pregnancy, despite the increased bone turnover (18).

Enhanced calcium absorption induces rise in renal calcium excretion, that often exceeds the normal range. This "absorptive hypercalciuria" contributes to the increased risk of kidney stones during pregnancy (27).

Total calcitriol concentration raises two to five-fold early in pregnancy and maintains elevated until delivery. The main source of 1,25(OH)$_2$D are maternal kidneys (1). The placenta, trophoblast and maternal decidua also express 1alpha-hydroxylase and may, together with the fetus itself, in some extend contribute to calcitriol increase.

Gestational elevation of 1,25(OH)$_2$D values is not, however, driven by parathormone (PTH), which is normally the main stimulator of 1alpha-hydroxylase. During the first trimester intact PTH concentration decreases to the low-normal values (range: 10-15 ng/l) and might slightly increase to mid-normal range in the second (range: 18-25 ng/l) and third trimester (range: 9-26 ng/l) (2).The studies on animals suggest, that the renal 1alpha-hydroxylase during pregnancy might be stimulated by PTH-related protein (PTHrP), estradiol, prolactin, and placental lactogen (1).

Maternal PTHrP concentrations steadily increase during gestation up to the third trimester (1). PTHrP is produced by many mother's and fetal tissues, mainly the placenta and breast (1, 5). PTHrP N-terminal peptides through the parathyroid hormone 1 receptor (PTH1R) may stimulate renal 1alpha-hydroxylase, increasing calcitrol concentration and indirectly suppressing PTH secretion, while osteostatin – the C-terminal peptide of PTHrP inhibits bone resorption and may participate in prevention of excessive maternal bone loss during pregnancy (1).

Both placental and mammalian PTHrP are synthesized in reaction to prolactin receptor activation (5). Several case reports indicate, that hypersecretion of PTHrP by breast and placenta can cause hypercalcemia with undetectable PTH levels, called pseudohyperparathyroidism of pregnancy. It can be a result of mammalian tissue hypersensitivity to prolactin and so be successfully treated with dopamine agonists (5).

Fetal ionized and total calcium as well as inorganic phosphate concentrations are higher than the maternal ones. Calcium and phosphorus are actively transported across the placenta (4, 6). The fetus sets a fixed calcium level independent of the maternal calcium value (6).The physiological relevance of this condition is not fully understood – it is not necessary for the fetus survival, but is required for the mineralization of the fetal skeleton and seems to reduce the occurrence of neonatal hypocalcemia (6).

The fetus depends on the maternal supply for 25-hydroxyvitamin D, but calcitriol, PTH, PTHrP and calcitonin cannot cross the placental barrier (4, 6).

The fetal kidneys and placenta possess the 1α-hydroxylase enzyme, however fetal calcitriol levels are usually lower than maternal concentrations. This is probably the effect of fetal renal 1α-hydroxylase suppression by low PTH and high serum calcium and phosphorus levels as well as increased activity of the 24-hydroxylase catabolic enzyme (6).

The parathyroid glands originate from the interaction of the endoderm of the third and fourth pharyngeal pouch and neural crest mesenchyme. They differentiate at the 5th-6th gestational week and are probably capable of synthesizing PTH since the 10th week. The fetal blood levels of PTH have been typically found to be low in late gestation at a time when its blood calcium is high. Therefore, it seems that other factors must be involved in regulating fetal calcium levels.

PTHrP is produced by multiple fetal tissues, but placenta is the dominant source. When expressed in equivalent units (pM), human cord blood PTHrP levels are up to 15-fold higher than PTH levels (6). Placental mineral transfer depends mainly on PTHrP, however PTH work together with PTHrP to maintain fetal serum calcium and phosphorus

at high levels for optimal bone mineralization. They are both also necessary to regulate endochondral bone development in utero. Calcitriol, calcitonin and FGF23 are not required for maintaining serum calcium and phosphorus concentrations or endochondral bone development (6).

Multiple clinical observations proved, that changes in maternal calcium concentrations affect fetal parathyroid gland development and function (30, 31). Maternal hypercalcemia likely increases the flow of calcium across the placenta and may lead to a higher than normal fetal blood calcium levels, that in turn cause suppression of the fetal parathyroid glands, that can last for months after birth or even be permanent. On the other hand, prolonged and severe maternal hypocalcemia induces fetal parathyroid gland hyperplasia and secondary hyperparathyroidism, causing a severe skeleton demineralization and fractures in utero or during birth (27). As the hyperplastic parathyroid gland function remains autonomous for a time, hypercalcemia and skeletal demineralization can develop in the neonate before the parathyroid function subsides to normal.

Prevalence of primary hyperparathyroidism in pregnancy

Primary hyperparathyroidism (PHPT) is a common endocrine disorder. In the earlier studies its incidence in general population was calculated to be 0,15-0,4%, while according to more recent data PHPT is affecting approximately 1% of the population in the developed countries (8). The overall increase in incidence may be the result of more frequent plasma calcium measurements. The predominant clinical phenotype over the past 40 years in USA, Canada, and Europe has been asymptomatic disease (9).

The true incidence of PHPT in pregnant women is unknown. Only about 1% of PHPT was diagnosed during pregnancy (12, 13). However, serum calcium is not routinely measured during gestation, and PHPT in pregnancy, as in the general population, is often asymptomatic and remains undiagnosed (13, 19). In addition, some nonspecific symptoms of PHPT (i.e., fatigue, malaise, nausea, vomiting) overlap with normal pregnancy symptoms, and pregnancy – induced physiological changes in calcium-phosphorus metabolism (i.e., total calcium decrease, PTH suppression) may hamper the diagnosis of mild PHPT (13). Therefore, many experts assume PHPT during gestation is underdiagnosed (7, 18).

The prevalence of PHPT in pregnancy may be extrapolated from that in women of reproductive age. PHPT is 3-5 times more prevalent in females than males. The incidence of PHPT sharply increase over the age of 40, so the disease mainly affects elderly women. Only 5-10% of women with PHPT are diagnosed in their childbearing years (18). According to other authors the incidence in females of childbearing age is around 6-8/100 000 per year (11, 15). In a study performed on Israeli women, based on serum calcium and PTH testing, the prevalence of PHPT in a group of females aged 20-40 was 0,05%, while pregnant women with PHPT represented 0,03% of all women of reproductive age (10).

Between 1970 and 2017, the mean age of women at childbirth in developed countries increased by 2-5 years (16). The growing tendency to late motherhood is further intensified by the development of assisted reproductive technology (ART). Therefore, an increase in the number of PHPT cases in pregnant women can be expected in the future.

Clinical manifestations and complications of PHPT in pregnant women

The spectrum of PHPT manifestations is very large. There is approximately 200 case reports and small series, that indicate multiple serious maternal and fetal complications in pregnant women with PHPT. In older publications, unfavorable outcomes were reported to occur in up to 67% of mothers and 80% of fetuses (12, 18). These data are definitely overestimated, as the studies concerned mainly patients with moderate to severe disease, while most cases of PHPT in pregnancy are not reported and are typically mild (10, 12, 18, 19). According to recent large cohort studies based on total serum calcium screening, mild PHPT is often asymptomatic and generally not associated with an increased risk of obstetrical complications (10, 19).

There are many non-specific manifestations of PHPT (including fatigue, malaise, nausea, vomiting, dizziness, emotional lability, lethargy or agitation, depression, headaches, constipation, polydipsia, polyuria, bone and muscle aches and pains), which overlap with normal pregnancy symptoms (13, 26, 29). Additionally, pregnancy predisposes to bone loss as well as to the occurrence of renal colic (caused by urinary calculi or physiological hydronephrosis), that can be also misleading (17).

Untreated hypercalcemia during pregnancy may lead to maternal complications, typical also for non-pregnant patients with PHPT, like nephrolithiasis (reported in 25-36% of cases), nephrocalcinosis, pyelonephritis, bone mass loss, skeletal lesions, fractures, hypertension (13-25%), cardiac arrhythmias, acute pancreatitis, renal insufficiency, confusion, muscle weakness, hypercalcemic crisis and even death (18, 24, 25, 29). Moreover, PHPT increases the incidence of pregnancy-related unfavorable outcomes – hyperemesis gravidarum (in 21-37% of cases) and preeclampsia (25%) (31). There are also case reports of PHPT patients with otherwise unexplained polyhydramnios, that is thought to be the result of fetal hypercalcemia – induced polyuria (25, 26, 30). Additionally, Stahl et al. reported Wernicke encephalopathy caused by PHPT – induced hyperemesis gravidarum in a malnourished patient (22).

Nephrolithiasis is one of the most common maternal complications in females with PHPT during pregnancy (18, 26). Pregnant women may be more prone to it, as the formation and growth of kidney stones is favored by physiological gestational hypercalciuria (27).

Pregnancy predisposes also to a potentially life-threatening condition – pancreatitis. In pregnant PHPT patients the frequency of this complication is higher (7-13%) than in non-pregnant PHPT individuals (1-2%). Pancreatitis is assumed to be more common in primiparas and to occur mainly in the first and third trimester (18, 20).

The postpartum period increases the risk of hypercalcemic crisis, as a consequence of cessation of placental calcium transfer and surging PTHrP production in the breast following delivery (26, 27) – approximately one-third of reported cases occurred postpartum (29).

PHPT during pregnancy is associated with many serious fetal complications as spontaneous abortion (in 15% of pregnancies), intrauterine fetal demise (7%), neonatal death (11-16%) and neonatal hypocalcemia with or without tetany (22-50%) (18, 31). Adverse outcomes include also premature birth, intrauterine growth restriction, low birth weight, and neonatal nephrocalcinosis (18, 25, 26, 27).

Neonatal hypocalcemia may be sometimes the only sign of maternal hyperparathyroidism. It usually develops

between the second and 14th day of life, and is transient, but may be prolonged to 3-5 months after birth, and in some cases even permanent (12). Its occurrence and severity is related to the level of maternal hypercalcemia before delivery (27, 29). Hypercalcemic crisis has been reported to provoke neonatal tetany in as much as one-half of cases and perinatal death in one-quarter of cases (18).

The maternal calcium levels are crucial for pregnancy outcomes. Norman et al. analyzed 32 women who had PHPT while pregnant with a mean total calcium concentration of 2,80 mmol/l and found, that untreated PHPT is associated with 3,5-fold higher risk of miscarriage rates when compared to general population (48% vs. 12-15%) (12). Pregnant women with a calcium level over 2,85 mmol/l and prior pregnancy loss were at a particularly high risk. In a recent retrospective case series, from 2000 to 2017, with the mean total calcium levels 2,8 mmol/l, Cassir et al. reported 6 of 19 women (32%) with a history of early pregnancy loss (26). In the work of Norman et al. pregnancy loss often occurred in the second trimester and, when not recognized, was associated with multiple miscarriages. In accordance to these data, the results of a prospective pilot study published in 2018 suggested increased prevalence of undiagnosed PHPT in women with recurrent miscarriage (14). The maternofetal outcomes were substantially better in subjects with mild PHPT. In the study of Hirsh et al., based on community data, in which 89,2% of patients with PHPT had total serum calcium levels <2,74 mmol/l (58% treated surgically), abortion occurred in 12 of 124 pregnancies (9,7%), and other complications – in 19 (15,3%) and did not statistically differ from healthy controls (19). None of the women had a hypercalcemic crisis or acute pancreatitis during pregnancy. These data are in concordance with the results of Danish register-based retrospective cohort study of women aged 16-44 years, which indicated that the diagnosis of PHPT does not seem to be associated with an increased risk of abortions or to affect birth weight, length and Apgar score (10).

Several case series have proved elective surgery dramatically reduce the rate of adverse events. In a retrospective analysis of 109 pregnant females with PHPT from 1930 to 1990, those treated medically (N = 70) had a 53% incidence of neonatal complications and 16% incidence of neonatal deaths, compared to those who underwent parathyroidectomy (N = 39), with complication and mortality rates of 12,5% and 2,5%, respectively (21). Norman et al. analyzed 77 pregnancies in 32 women with PHPT, and found that about 20% of them who received surgical treatment during the second trimester had good outcomes associated with the pregnancy, while 48% of the remaining pregnancies were lost (12). Cassir et al. reported 23 pregnancies of 19 women with PHPT of whom 89% were treated surgically – the maternal or obstetric complications were observed in 14% of pregnancies, but the fetal or neonatal problems – in as much as 45% (26). However, all neonates were liveborn, there were no major fetal anomalies, or neonatal hypoparathyroidism. Interestingly, the authors reported, that some of the adverse outcomes (pyelonephritis, anemia, decreasing growth velocity) were also present in women with normal calcium levels because of PHPT treatment preceding conception, although whether these outcomes were incidental or associated with PHPT remained unclear (26). Similarly, Hultin et al. showed that the risk of preeclampsia persist significantly increased (odds ratio 6,89) even several years after curative parathyroidectomy (28).

Diagnosis of primary hyperparathyroidism in pregnancy

Diagnosis of PHPT is classically based upon the detection of elevated serum calcium accompanied by inadequately high PTH levels. Pregnancy-induced physiological changes leading to total serum calcium decrease and suppression of PTH may hinder the diagnosis of mild PHPT. For this reason, ionized serum calcium concentration or calculated albumin-corrected calcium level should be used during this time (27). In the absence of other causes of hypercalcemia, an increased ionized or albumin-corrected calcium level with detectable PTH during pregnancy, indicates maternal PHPT (27).

Calcium level is not, however, routinely measured in pregnant women, so it remains often undiagnosed (12, 13, 19). Unfortunately, a significant percentage of PHPT cases go undiagnosed although repeated blood tests may show elevated serum calcium levels months and years before gestation (12, 19). Therefore, PHPT should be suspected in pregnant women with classic PHPT complications such as pancreatitis, bone fracture, nephrolithiasis, and peptic ulcer (7, 8). It seems also reasonable to measure calcium levels in all pregnant women with persistent significant nausea, vomiting, abdominal pain, atypical presentation of hypertension and isolated polyhydramnios (18, 26, 29). According to some authors, it is justified also in females with otherwise unexplained recurrent miscarriage (12, 14).

The differential diagnosis should include other possible causes of hypercalcemia, including familial hypocalciuric hypercalcemia (FHH). FHH is a rare autosomal dominant condition, in which surgery is unnecessary. Moreover, FHH, when diagnosed, requires genetic testing of the father, subsequent genetic counseling, and very careful neonatal surveillance (18). Unfortunately, physiological increase of glomerular filtration and calcium excretion during pregnancy makes FHH particularly difficult to rule out. Genetic testing can definitively confirm the diagnosis of FHH, but this procedure is often hardly available, lengthy and expensive, therefore not practical to use in a situation of time pressure to proceed to surgery (7).

Taking into account the young age of pregnant women, particular attention should be paid to rule out hereditary syndromes such as MEN-1, MEN-2, MEN-4, jaw tumor syndrome, and familial parathyroid hyperplasia. The diagnosis of congenital syndromes may influence the patient treatment due to concomitant pathologies. It is also important for determining the indications for parathyroidectomy and the planned scope of parathyroid resection. Moreover, this is relevant for the patient's offspring. Genetic testing seems to be reasonable especially in women under 40 years old and when multiple parathyroid enlargement is found (18, 29).

When the patient is qualified for surgery, accurate parathyroid tumor localization enables minimally invasive parathyroidectomy (MIP) to be carried out instead of bilateral neck exploration. It allows to shorten the time of surgery and anesthesia as well as to employ local anesthetic technique, which is particularly desirable in pregnant women. This does not apply to hereditary syndromes, in which multiple gland pathology occurs and therefore total or subtotal parathyroidectomy is indicated. ^{99m}Tc-MIBI scintigraphy and CT imaging should be avoided during pregnancy to prevent fetal radiation exposure. Therefore, ultrasound imagining, with 69% sensitivity and 94% specificity, is the method of choice. It is, however, highly operator-dependent and, if possible, should be performed by specialized ultrasonographist.

The accuracy of the diagnosis may be increased by an ultrasound-guided fine-needle aspiration biopsy of the suspected lesion with the measurement of PTH concentration in the needle washouts. This method was shown to have excellent specificity (95-100%) and sensitivity (91-100%) in identifying parathyroid tissue and was successfully employed in few cases of pregnant women with PHPT (32, 33).

When ultrasound fails to localize parathyroid lesion, MRI of the neck may be safely used, however it lacks sensitivity in smaller adenomas. In the absence of parathyroid lesion location, bilateral neck exploration should be considered after careful weighing out its risks and benefits. In rare cases, like unsuccessful bilateral neck exploration and failure of pharmacological hypercalcemia control, ^{99m}Tc-MIBI scintigraphy or 4D CT may be considered (40). There are very few case reports reporting the use of 4D CT and ^{99m}Tc-MIBI scintigraphy to localize parathyroid lesions in pregnant women (34, 35, 40). The effective radiation dose of 4D CT is relatively low (10,4 mSv), however iodinated contrast media used during CT imaging can cross the placenta, entering the fetal circulation and amniotic fluid (40). The ^{99m}Tc-MIBI dose reduction by 50% to 10 mCi leads to fetal exposure of <5 mGy, that is relatively safe according to the American College of Obstetricians and Gynecologists guidelines, and allows to achieve acceptable maternal imagining (34, 36). Mothers hydratation and frequent urination is recommended to reduce fetal exposure resulting from proximity to radionuclides excreted into maternal bladder (36). However, the long-time risk to the fetus of x-ray exposure and radioisotope administration is largely unquantified, thus radiation exposure should be avoided, if possible.

Treatment

There are no clinical guidelines regarding management of PHPT in pregnant women. Parathyroidectomy remains the main and the only definitive treatment of PHPT (37). According to the current guidelines it is recommended for every patient with PHPT under the age of 50. However, in the most frequent mild forms of PHPT the risk of maternal and fetal complications is generally low, so a more conservative approach and postponing the operation until postpartum in this group seems to be reasonable (10, 18, 19). On the other hand, despite successful outcomes of conservatively treated mild asymptomatic PHPT subjects, some PHPT – related complications still occur (12, 23, 27, 28). Pharmacological treatment is not an alternative to parathyroidectomy. During pregnancy multiple drugs, challenging. Medical therapy should be, therefore, reserved to patients, who meet the surgical criteria, but refuse parathyroidectomy, have an increased surgical risk or failed surgery. The management should be personalized, taking into account gestational age, the severity of hypercalcemia, and the risk-benefit balance of available therapeutic options.

Conservative management (with postponing the surgery to postpartum period) is generally preferred in patients with mild forms of PHPT (asymptomatic, with adjusted calcium levels consistently below 2,75 mmol/l) (10,18, 19, 29). Intensive hydration with or without the use of loop diuretics to induce forced diuresis is usually recommended. Furosemide is, however, a category C medication, and should be used with caution, as it carries the risk of placental hypoperfusion, as well as maternal and fetal electrolyte abnormalities. Several data indicate, that low dietary calcium and low vitamin D status might stimulate parathyroid

tumor growth and PTH secretion and have a pathogenic role in development of more severe phenotypes of PHPT (37). Therefore, calcium intake should not be restricted and vitamin D deficiency should be corrected, if present, to attain a serum 25(OH)D level above 20 ng/ml (according to some experts even above 30 ng/ml) (37). Vitamin D repletion may lower the risk of postoperative hypocalcemia and hungry bone syndrome in mothers, as well as hypocalcemia in neonates (18, 37). However, it should be done with caution, because rapid excessive supplementation may lead to hypercalcemia.

Despite of mild course of PHPT, close maternal and fetal monitoring are crucial, as the risk of clinical aggravation and hypercalcemic crisis remains significant. It is especially important in the postpartum period, when, as discussed earlier, the mothers are prone to develop hypercalcemic crisis.

Parathyroidectomy is recommended when the serum calcium levels are above 2,75 mmol/l, particularly in patients with previous pregnancy loss (12). In pregnant women with moderate and severe hyperparathyroidism it leads to even four-fold decrease in perinatal complications (21). Surgery should be performed preferably during the second trimester, as it allows organogenesis to be complete in the fetus and to avoid the poorer surgical outcomes and risk of preterm birth associated with surgery during the third-trimester (27, 31). However, several cases of successful surgery in the first and the third trimester have been reported (23, 31, 33). In 2005 Schnatz et al. reviewed 16 pregnant women with PHPT treated surgically after 27 weeks of gestation. According to the authors, only 5,9% of fetuses and no mothers had clinically significant complications associated with surgery. However, postoperative hypocalcemia occurred in 62,5% of operated women and serious complications resulting from delayed diagnosis or postponed surgery (including preeclampsia, renal failure, premature membrane rupture and neonatal hypocalcemia) have been reported in up to 23,5% of fetuses and 25,0% of mothers (31). Surgery risk includes postoperative bleeding, infection, and permanent hypoparathyroidism (mainly after bilateral neck exploration in patients with multiple gland disease), which may deteriorate pregnancy outcomes. Nonobstetric surgery and general anesthesia have been shown to increase the risk of prematurity, intrauterine growth retardation and spontaneous abortion, however, according to recent studies it is not as high as previously reported (39). Minimally invasive approaches are preferred as they allow to limit local injury, reduce time of general anesthesia, or even apply regional cervical block anesthesia (39, 41). The choice of operative technique depends on the type of parathyroid pathology (minimally invasive surgery is possible only in single parathyroid adenoma, but not in multiple adenomas or multigland parathyroid hyperplasia), and the success in determining localization of the parathyroid lesion.

Intraoperative PTH monitoring may provide a useful adjunct to the surgeon, particularly in patients treated with minimally invasive surgery in whom the localization of the enlarged parathyroid gland is based on ultrasound examination only or in those with negative localization studies. This method has been successfully applied during parathyroidectomy in several cases of pregnant women with PHPT (7, 13, 38).

When the patient is of high surgical risk, refuses surgery, or previously preformed operation was unsuccessful, and intense oral and intravenous hydration is unable to maintain calcium levels below 2,75 mmol/l, medical treatment should be considered.

Calcitonin, a hormone secreted by thyroid C-cells, which directly inhibits osteoclast function and increases renal

calcium excretion does not cross the placental barrier and is relatively save, thus labeled pregnancy category B medication. However, its effectiveness is poor and tachyphylaxis to this treatment rapidly develops, limiting its use (13, 18).

Bisphosphonates, the most potent antiresorptive drugs, widely used in non-pregnant hypercalcemic patients, are category C drugs and are contraindicated during pregnancy. They cross the placenta and, in animal studies, have been shown to interfere with endochondral bone development, causing fetal bone malformations (18). There are several reports showing the safety of short-term use of bisphosphonates during gestation (27), but little is known of their long-term impact on the fetal skeleton. Therefore, the use of bisphosphonates in pregnancy should be limited to life-threating hypercalcemia, in which their benefits overweight their risks (18).

Cinacalcet is also considered category C medication. It increases the sensitivity of the calcium-sensing receptor (CaSR) on the surface of parathyroid cells, thus reduces PTH synthesis and secretion, and lowers calcium levels. Animal studies showed cinacalcet crosses the placenta and, therefore, may suppress fetal parathyroid glands inducing neonatal hypocalcemia, as well as exert its effects on multiple other tissues, which express CaSR, including kidneys, bone marrow, osteoblasts, osteoclasts, thyroid C-cells, gastrointestinal tract, breast and some area of the brain. Moreover, through the CaSR in the placenta cinacalcet may inhibit active placental calcium transport. Clinical reports of cinacalcet use during pregnancy to reduce hypercalcemia are scarce. There were no significant adverse effects reported, however, poor tolerance and incomplete effectiveness of cinacalcet limited its use (40). Long-term safety data are lacking.

In life-threating cases, management of severe hypercalcemia may require hemodialysis.

Conclusions

Calcium levels should be measured in pregnant females not only with typical complications of hyperparathyroidism, but also with hyperemesis gravidarum, hypertension, pre-eclampsia and polyhydramnios as well as in women with otherwise unexplained recurrent miscarriage. Taking into account pregnancy-related physiological changes in calcium-phosphate metabolism, increased ionized calcium or albumin-corrected calcium levels without adequate inhibition of PTH concentrations, suggests maternal PHPT. In patients with moderate or severe PHPT, surgery, optimally performed in the second trimester, remains preferable and the only curative therapeutic option. Conservative approach is acceptable in mild asymptomatic hypercalcemia (<2,75 mmol/l) provided close monitoring of the mother and the fetus during pregnancy and postpartum. To achieve optimal care of pregnant women with PHPT close cooperation of specialists in a multidisciplinary team is crucial. It should include endocrinologist, obstetrician, surgeon, anesthesiologist and eventually other consultants, depending on the complications that occur.

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