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Appelman-Dijkstra, N.M.; Pilz, S.

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Approach to the Patient

Approach to the Patient: Management of Parathyroid Diseases Across Pregnancy

Natasha M. Appelman-Dijkstra[1] **and Stefan Pilz**[2]

[1]Center for Bone Quality Leiden University Medical Center: Department of Internal Medicine, Division of Endocrinology, Leiden University Medical Center, 2333 ZA Leiden, The Netherlands
[2]Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, 8036 Graz, Austria

Correspondence: Natasha M. Appelman-Dijkstra, MD, PhD, Division Endocrinology and Center for Bone Quality, Department of Internal Medicine, Leiden University Medical Center, Albinusdreef 2, 2333 ZA Leiden, The Netherlands. Email: n.m.appelman-dijkstra@lumc.nl; or Stefan Pilz, MD, PhD, Division of Endocrinology and Diabetology, Department of Internal Medicine, Medical University of Graz, Auenbruggerplatz 15, 8036 Graz, Austria. Email: stefan.pilz@medunigraz.at.

Abstract

Taking care of patients with parathyroid disorders during pregnancy requires consideration of the physiological fundamental changes in bone and mineral metabolism occurring in these women. Diagnostic and therapeutic procedures regarding primary hyperparathyroidism (PHPT) and hypoparathyroidism significantly differ from the nonpregnant population. PHPT should preferably be cured by parathyroidectomy before pregnancy since in women with hypercalcemic PHPT, maternal and fetal pregnancy complications seem to increase according to the degree of hypercalcemia. Parathyroidectomy, if needed during pregnancy, is preferentially performed in the second trimester. Conservative treatment is recommended for milder cases and is mainly restricted to hydration, with only limited evidence regarding drug treatment. Women with hypoparathyroidism can be informed that there are no major concerns regarding disease-associated infertility and that the risk of pregnancy complications is low if the disease is properly managed. Regular active surveillance is recommended, as requirements for calcium and active vitamin D may change during the course of pregnancy in either direction, with an overall trend for rather reduced doses. Any woman suffering from parathyroid disorders during pregnancy requires further surveillance in the postpartum period and during lactation, as there is an increased risk of hypercalcemia after delivery. Newborns of mothers with parathyroid diseases should, depending on disease severity, be carefully monitored for calcium levels in the first days (to weeks) after delivery since intrauterine exposure to hyper- or hypocalcemia may impact their postnatal regulation of calcium metabolism.

Key Words: pregnancy, hypoparathyroidism, familial hypocalciuric hypercalcemia, lactation, primary hyperparathyroidism, vitamin D

Abbreviations: 1,25(OH)2D, 1,25-dihydroxyvitamin D; 25(OH)D, 25-hydroxyvitamin D; 99mTc-MIBI, 99mTc-methoxyisobutylisonitrile; BMD, bone mineral density; CCCR, calcium/creatinine clearance ratio; eGFR, estimated glomerular filtration rate; FHH, familial hypocalciuric hypercalcemia; HypoPT, hypoparathyroidism; PET/CT, positron emission tomography/computed tomography; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; PTHrP, PTH-related peptide; SPECT/CT, single-photon emission computed tomography.

Case Presentations

Case 1

A 33-year-old woman presented with severe nausea and vomiting during the eighth week of her first pregnancy for which she had not had any medical check yet. Her medical history showed nephrolithiasis 12 months before this presentation. Her family history was positive for preeclampsia. She was not taking any medication at the moment. Physical examination showed no abnormalities, and her body mass index was 24.7 kg/m^2. Laboratory results showed a hypercalcemia with an albumin-adjusted serum calcium level of 3.0 mmol/L (ref, 2.15-2.55 mmol/L), a parathyroid hormone (PTH) of 15 pmol/L (ref 1-8 pmol/L), a phosphate of 0.8 mmol/L (ref, 0.9-1.5 pmol/L), and high urinary calcium excretion of 8.5 g/L. At presentation there was an acute kidney injury with a creatinine level of 130 µmol/L (ref, 40-90 µmol/L). After treatment with intravenous hydration, her kidney function normalized and albumin-adjusted serum calcium levels dropped to 2.75 mmol/L and remained there with proper oral hydration. A diagnosis of PHPT was made. Ultrasound of the neck showed a clear parathyroid adenoma just above the right thyroid lobe.

Case 2

A 26-year-old woman with hypoparathyroidism (HypoPT) was referred to the outpatient clinic of Endocrinology at the Medical University of Graz, Austria, as she considered becoming pregnant in the next few years. According to previous medical reports, HypoPT was diagnosed 11 years ago and classified as an idiopathic HypoPT without prior neck surgery or evidence of autoimmune or genetic causes (1). She was currently largely free of hypocalcemic symptoms and was treated twice daily with a calcium plus vitamin D supplement (1000 mg calcium and 800 international units [IU] of vitamin D_3) and calcitriol 0.25 µg twice daily. Family history was negative for preeclampsia and her body mass index was 20.8 kg/m^2. She asked whether HypoPT affected her chances

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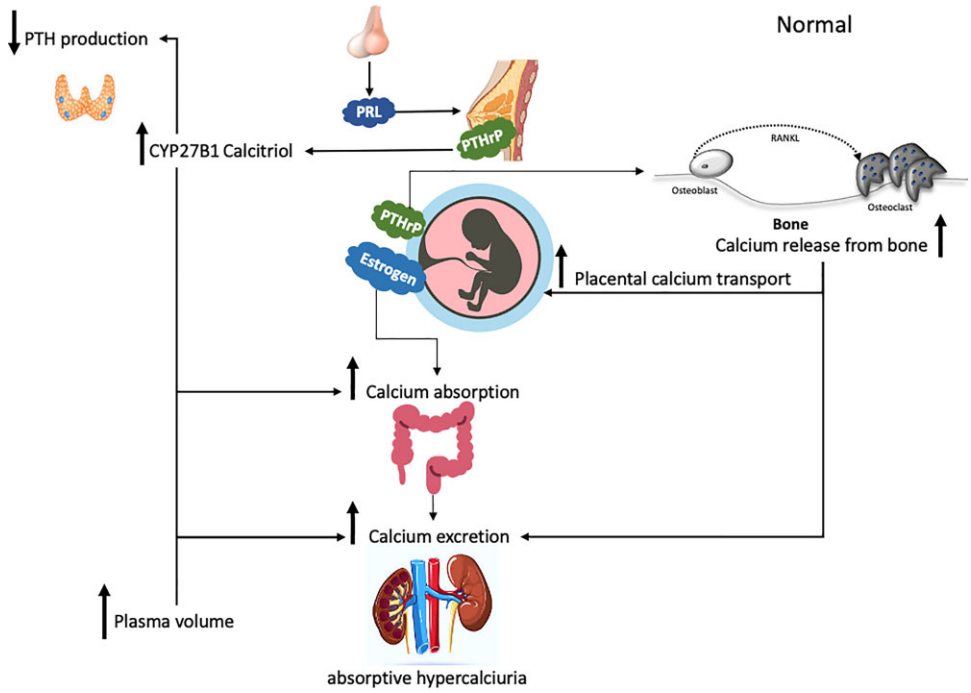

Figure 1. During pregnancy, intestinal calcium absorption is increased by calcitriol and estrogen. Prolactin stimulates PTHrP release, which in turn increases calcium levels by PTH-like effects. During lactation, calcium is mainly derived from bone resorption or osteocytic osteolysis. Abbreviations: PRL, prolactin; PTH, parathyroid hormone; PTHrP, PTH-related peptide; RANKL, receptor activator of nuclear factor kappa-B ligand.

to become pregnant, whether it is safe to become pregnant for her and her child, and whether and how pregnancy and lactation impact on HypoPT in terms of symptoms and treatment requirements. She was informed that as of the year 2019, there is limited evidence on pregnancy outcomes and symptoms in HypoPT in this context. In general, there is no major concern to become pregnant when she is currently well treated, and fertility should not be significantly affected by HypoPT. If she did become pregnant, we strongly recommended regular visits (every 3-4 weeks) including laboratory tests, as the requirements for calcium plus active vitamin D treatment may change during the course of pregnancy and lactation. Overall, it can be assumed that as long she adheres to active surveillance and maintains her laboratory values within the target ranges, such as serum calcium concentration in the lower end of the normal range, she has a high probability of having a pregnancy without major complications and a healthy baby.

Background

Parathyroid disorders during pregnancy are relatively rare and are characterized by disturbances in calcium and mineral metabolism (2-4). In primary hyperparathyroidism (PHPT) elevated or inappropriately high parathyroid hormone (PTH) levels increase serum calcium concentrations, while in hypoparathyroidism (HypoPT), reduced or inadequately low PTH levels lead to hypocalcemia. PHPT is a common endocrine disease with a female predominance and an age-dependent increase in prevalence, whereas HypoPT is a rare condition that is mainly caused by anterior neck surgery (1-4).

Management of parathyroid disorders during pregnancy can be challenging and significantly differs in various ways from nonpregnant patients. Scientific evidence from systematic evaluations regarding this issue is very limited, in particular regarding maternal management and fetal outcomes (2, 5-9). Clinicians taking care of pregnant patients with parathyroid disorders do not only require sufficient knowledge on the pathophysiology of the diseases itself, but also on the physiology of pregnancy which induces the fundamental changes in bone and mineral metabolism in women during pregnancy and lactation which have been summarized in Fig. 1 (5).

During pregnancy, the plasma volume expansion with subsequently reduced albumin concentrations contributes to a decrease in total calcium concentrations. Ionized (free) and albumin-adjusted calcium remain unchanged in pregnancy and should therefore be used for clinical decision making in this setting (2). Required minerals for the growing fetal skeleton are mainly derived from increased intestinal absorption of calcium and other minerals in the mother (5). This process is stimulated by estrogen and 1,25-dihydroxyvitamin D (1,25(OH)2D), the so-called active vitamin D hormone calcitriol, that is increased by 2- to 3-fold in pregnant women. Of note, 25-hydroxyvitamin D (25(OH)D) is materially unchanged throughout pregnancy but crosses, in contrast to calcitriol, the placenta. Thus, maternal 25(OH)D is critical for fetal vitamin D status, reflected by a strong correlation between maternal and cord blood 25(OH)D concentrations at birth (10). Maternal PTH concentrations are lower in pregnant compared to nonpregnant women, usually at the lower end of the normal range or slightly below, and they do not cross the placenta (5). PTH-related peptide (PTHrP) is significantly increased in pregnancy and is mainly derived from the placenta and the breasts, where it is itself stimulated by prolactin. PTHrP exerts, among others, PTH-like effects, and is thus an important regulator of mineral homeostasis during pregnancy. After delivery and during lactation,

calcitriol normalizes while PTHrP is further increased, whereas data on PTH are inconsistent. While maternal bone mineral density (BMD) remains either stable or is only slightly reduced during pregnancy, there is a significant loss of BMD during lactation, as required minerals for transfer to breast milk are mainly derived from bone resorption or osteocytic osteolysis (5, 11). After weaning, BMD increases again and usually reaches pre-pregnancy values after about 6 to 12 months.

Preconception Advice in Patients With Known Parathyroid Disorders

Proper preconception advice should be given to women suffering from parathyroid disorders in the fertile age when they visit the outpatient clinic. In case of an active pregnancy wish, we would suggest a preconception visit with the endocrinologist, who should be, if possible, joined by a gynecologist and pediatrician. In these preconception visits, the following items should be addressed (see also Table 1).

- What are the complications of the disease? For instance, recurrent pancreatitis or kidney stones are possible complications of PHPT and might be additional risk factors for developing preeclampsia. In HypoPT, renal function might be impaired, causing another risk factor for preeclampsia.
- Are there any other "known" contributors that might increase the preeclampsia risk, such as positive family history or obesity?
- Medication review: For PHPT and treatment of hypercalcemia, the majority of medication needs to be stopped. Bisphosphonates and denosumab should be stopped before conception. Cinacalcet is also not considered to be a suitable drug during pregnancy, although more evidence is gathered about the safety of the drug during pregnancy (2, 12-14). For HypoPT, drugs such as calcium and vitamin D supplements, calcitriol, and alfacalcidol are considered safe during pregnancy. Thiazide diuretics, however, should be discontinued (2, 6, 9). Recombinant PTH has not been adequately evaluated during pregnancy but there are 2 case reports showing favorable outcomes (15, 16).

The United States Preventive Services Task Force concluded, in a position statement published in 2021, that there is a substantial net benefit of daily low-dose aspirin use to reduce the risk for preeclampsia, preterm birth, small for gestational age/intrauterine growth restriction, and perinatal mortality in pregnant persons at high risk for preeclampsia. Therefore, the use of low-dose aspirin (80 mg/d) as preventive medication for preeclampsia after 12 weeks of gestation in persons who are at high risk for preeclampsia is advocated and should be discussed in these preconceptional advice visits. If started, preferably before 16 weeks of pregnancy, it should be continued until delivery. Initiating low-dose aspirin after 28 weeks is not considered useful (17). PHPT is currently not officially considered a risk factor for preeclampsia, but the evidence on pregnancy outcomes in PHPT patients argue for this. Other standard preconception advice such as adequate folic acid intake and so forth, should, of course, also be given.

Table 1. Known risk factors for preeclampsia (17)

Risk level	Factor	Recommendation
High	Previous preeclampsia	Start low-dose aspirin when ≥1 high-risk factors
	Multifetal gestation	
	Chronic hypertension	
	Pregestational type 1 or 2 diabetes	
	Kidney disease	
	Autoimmune diseases	
	Combinations of moderate risk factors	
Moderate	Nulliparity	Start low-dose aspirin when ≥2 moderate risk factors
	Body mass index >30 kg/m²	Consider low-dose aspirin when 1 of these moderate risk factors are present
	Family history of preeclampsia	
	Lower income or social class	
	Age >35 years or older	
	Personal history factors (eg, low birth weight or small for gestational age, previous adverse pregnancy outcome, >10-year pregnancy interval)	
	In vitro conception	

Preeclampsia incidence is classified as high if at least 8% in a population of pregnant individuals having 1 of these risk factors.

Regarding known parathyroid disorders, the general advice for patients with PHPT is to withhold pregnancy until parathyroid surgery is performed and cure of the disease is established by postsurgical evaluation of calcium levels (2). This advice is in line with existing guidelines on PHPT to recommend parathyroid surgery in patients under the age of 50 years (2). In addition, the majority of observational studies indicate an increased risk of adverse pregnancy outcomes for the mother and the child in the case of hypercalcemic PHPT throughout pregnancy, although the data on this topic are not fully consistent (12, 18-20).

Women with known HypoPT should be informed that the current literature does not report on major fertility problems due to HypoPT itself and that the most likely outcome of their pregnancy is that they will have a healthy baby and a low risk of pregnancy complications when adhering to the recommended management (21-25). This involves frequent visits, with laboratory assessments, since the supplementation or treatment requirements may change during pregnancy. This preconceptional counseling of women with HypoPT is of particular importance, as it is much more likely that a woman with known HypoPT has a pregnancy wish than that a new diagnosis of HypoPT is established during pregnancy. For women with HypoPT who are currently not adequately treated, we recommend deferment of conception until they achieve their treatment goals regarding their symptoms and laboratory values (2).

Parathyroid Disorders During Pregnancy and Postpartum

PHPT

Diagnosing PHPT

Detecting hypercalcemia might be challenging during pregnancy, as hypercalcemic symptoms such as polyuria, fatigue, or nausea mimic those in "normal" pregnancy. Given that there is usually no universal screening for calcium levels in pregnancy, many mild cases of hypercalcemia probably remain undiagnosed. Severe and longstanding hypercalcemia in pregnancy may rather be detected, as it can cause several clinically obvious adverse effects, such as nephrolithiasis, pancreatitis, and preeclampsia in the mother and multiple problems, including polyhydramnios and premature death, in the child (12, 18, 19, 26).

When detecting hypercalcemia in a pregnant woman, physiological changes in calcium homeostasis during pregnancy, as described above, have to be considered. As in the nonpregnant population, the evaluation of established hypercalcemia should start with the measurement of PTH to distinguish parathyroid related disorders from other causes (see Table 2). While an elevated or inappropriately high PTH level is indicative for PHPT or familial hypocalciuric hypercalcemia (FHH), hypercalcemia with a reduced PTH level may be caused by a variety of different diseases that may pose a diagnostic challenge. These include nonpregnancy-related conditions such as malignancies, granulomatous diseases (like tuberculosis or sarcoidosis), vitamin D intoxication, or milk-alkali syndrome, although the latter may possibly be luxated by pregnancy-induced pyrosis. Another option is that hypercalcemia is specifically triggered by pregnancy, as is the case with pseudohyperparathyroidism due to elevated PTHrP levels from enlarged breasts or the placenta, pathogenic mutations of CYP24A1, an enzyme responsible for vitamin D catabolism, or other pregnancy-related adaptations (27-29).

Regarding the differentiation of PHPT and FHH, changes in urinary calcium excretion during pregnancy have to be considered. Increased intestinal calcium absorption leads to higher 24-hour urinary calcium excretion, while fasting urinary calcium excretion is usually normal, a condition that is referred to as absorptive hypercalciuria (5). In the nonpregnant population, the measurement of calcium/creatinine clearance ratio (CCCR) can be useful in distinguishing between PHPT (>0.02) and FHH (<0.01) (2). However, it is known that almost 20% of FHH patients might present with a CCCR of more than 0.01, and individuals with PHPT and simultaneous vitamin D deficiency might show lower than expected urinary calcium excretion (2). Genetic testing, when available, should be considered for confirming the clinical suspicion of FHH. More than 130 calcium-sensing receptor (*CaSR*) mutations have been reported so far in relation to FHH1, a fact that explains the phenotypical variations in relation to the observed differences in serum calcium and PTH levels. During pregnancy, the distinction between FHH and PHPT is even more challenging, as the CCCR is not a reliable diagnostic tool in this setting so that laboratory values before pregnancy, evaluation of family members, and genetic testing play an even more important role (30).

Treatment and monitoring of PHPT during pregnancy

Treatment of the hypercalcemia is dependent on the underlying cause and might involve invasive or conservative measures, but all decisions need good counseling, since they concern not only the mother, but also the fetus and partner. As physicians, we need to be aware that the treatment does not stop with the delivery of a healthy baby and that the postpartum period might actually be the period with the highest risk for the mother, due to the risk of sudden rises or drops in calcium levels and due to excessive mental stress caused by possible events during pregnancy or delivery.

For surveillance, clinical visits with determination of relevant laboratory values, at least serum calcium and creatinine/estimated glomerular filtration rate (eGFR), should be performed every 4 weeks and even more frequent (eg, all 1-2 weeks) after changes in the medical treatment of PHPT (2).

Surgical treatment

Decisions regarding conservative treatment vs parathyroid surgery in pregnancy are challenging and strongly depend on the individual case and expertise. In order to provide a rough guidance, we suggest performing parathyroidectomy, preferentially in the second trimester, if the albumin-adjusted calcium levels consistently are increased above 2.85 mmol/L and/or an ionized serum calcium is above 1.45 mmol/L in pregnant women with PHPT (2). This recommendation is based on observational data showing a dose-response relationship between serum calcium levels and adverse pregnancy outcomes, with a significant increase in risk at the suggested cutoffs for parathyroid surgery (2, 18). Importantly, a systematic review including 382 pregnant women with PHPT showed a significantly lower infant complication rate for

Table 2. Differential diagnosis of hypercalcemia during pregnancy

Condition	PTH	Phosphate	Urinary calcium excretion
Primary hyperparathyroidism	Increased	Low or normal	High
Malignancy	Low	Normal	High
Granulomatous disease	Low	Normal or increased	High
Familial hypocalciuric hypercalcemia (FHH)	Normal or slightly elevated	Normal	Normal/low
Pseudohyperparathyroidism	Low	Low or normal	High
Milk-alkali syndrome	Low	Normal	High
CYP24A1 mutations	Low	Mostly normal	High

Abbreviation: PTH, parathyroid hormone.

surgery compared with conventional therapy (9.1% vs 38.9%) when surgery was performed within the second trimester (31). Although the recommendation for parathyroid surgery in pregnancy is only based on observational data with a risk of confounding and bias, the current literature and practice strongly favor surgery over conservative treatment in this setting (19, 26, 31-35).

After establishing the biochemical diagnosis of PHPT, the next step should be imaging if surgery is considered. If surgery during pregnancy is not indicated, imaging can be postponed until after delivery. Avoiding radiation exposure in pregnancy is important and therefore, neck ultrasonography should, of course, be the first imaging method. To improve the probability of correct preoperative localization of parathyroid adenoma(s) and to therefore improve the surgical success, it seems reasonable to perform 2 different imaging methods (36). In the case of pregnant women with PHPT, considerations require taking into account the potential benefits of an additional imaging method vs the potential harms, availability, and costs, etc. A 4D-dynamic contrast-enhanced magnetic resonance imaging (MRI) scan lacks ionizing radiation, but this technique might not be universally available. In addition, 99mTc-methoxyisobutylisonitrile (99mTc-MIBI) scans, sestamibi single-photon emission computed tomography (SPECT/CT), 18F-fluorocholine PET/CT or methionine PET/CT could also be considered after careful consideration of potential risks and benefits (2). Of note, the fetal radiation exposure by a 99mTc-MIBI scan is below the threshold associated with fetal harm (37). 18F-Fluorocholine PET/CT may have a lower maternal radiation dose than 99mTc-MIBI SPECT/CT, but the fetal radiation exposure by this imaging method is unclear and may be of concern. The generally high radiation of 4D-computed tomography argues against this method in pregnancy. Therefore, we personally consider it reasonable to perform an ultrasonography of the neck in combination with either 99mTc-MIBI scan or 4D-dynamic contrast-enhanced MRI as a suggested preoperative imaging approach in pregnant women with an indication for parathyroid surgery (2, 13). Other approaches or ultrasonography alone in case of a clear ultrasonographic imaging result, may of course be acceptable choices for selected cases and special centers (2, 34, 38). It has to be stressed that any imaging method with radiation exposure should only be performed if considered to have a favorable benefit to risk ratio for the individual pregnant woman and her child.

The ideal surgical approach for sporadic PHPT in pregnancy is minimally invasive parathyroidectomy, at best performed with intraoperative PTH measurements, if available (2). Bilateral neck exploration may be performed for other specific forms of PHPT, such as hereditary forms (2).

Conservative treatment

Conservative treatment to decrease calcium levels in pregnant women with PHPT is primarily based on oral and/or intravenous rehydration and avoidance of overwhelming nutritional calcium intake. However, if not successful to control hypercalcemia and surgery is not an option, it might be considered to start with cinacalcet in women with severe hypercalcemia (eg, in women with an albumin-adjusted serum calcium above 3.0 mmol/L we would seriously consider this). Benefits should, of course, outweigh the risks, as it is advocated by both the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA). The FDA classifies cinacalcet as a category C drug, meaning that the drug has been taken by only a limited number of pregnant women and women of childbearing age, but without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. In animal studies, it has been shown that cinacalcet crosses the placenta, but no embryonal/fetal toxicities were seen, with the exception of decreased fetal body weights at doses associated with maternal toxicities. In the literature, only a few case reports and case series have been published about pregnant women on cinacalcet and the outcome was generally favorable (8, 12-14, 39). If initiated, it should be taken into account that the calcium-sensing receptor is located in the placenta, so cinacalcet may potentially alter the placental function and inhibit transplacental calcium transport. Thus, the drug could potentially suppress fetal PTH secretion. Acute neonatal hypocalcemia was reported in some of the gestational cinacalcet cases, but it was transient and no other adverse events were reported. Other drugs to treat hypercalcemia appear to be less suitable: calcitonin does not cross the placenta but has only transient effects to lower calcium that diminish within a few days due to tachyphylaxis (2). Bisphosphonates and denosumab should also not be used during pregnancy due to safety concerns, but they could be considered in case of severe hypercalcemia (eg, albumin-adjusted serum calcium above 3.5 mmol/L) that cannot be adequately controlled by other treatment approaches (2).

Postpartum care in women with PHPT and their offspring

All babies from mothers who suffered from hypercalcemia during pregnancy are at risk of hypocalcemia after birth since intrauterine hypercalcemia may suppress PTH levels in the babies. After an abrupt stop of calcium transfer via the placenta after birth, this may lead to hypocalcemia that may in severe cases manifest as hypocalcemic seizures. Therefore, it has been suggested to measure serum calcium every 2 days starting on day 2, and continuation of this depending on disease severity until 1 to 2 weeks after birth (2). In the event of hypocalcemia that is usually detected around day 2 or 3, active vitamin D treatment (eg, calcitriol or alfacalcidol) is recommended (2). Native vitamin D supplementation should be initiated according to national recommendations, usually 400 IU per day.

Women who have been successfully surgically treated for PHPT during pregnancy with normalization of serum calcium levels in the weeks thereafter, do not require specific care in addition to other mothers and nonpregnant women who have just been cured from PHPT. Those who still suffer from active PHPT at birth require active surveillance in the postpartum period, as there are changes in calcium metabolism during postpartum and lactation that may have clinical consequences. Therefore, we consider it reasonable to measure maternal calcium levels and eGFR approximately every 4 to 8 weeks starting within the first week after delivery (2). Parathyroid surgery should be performed a few weeks after delivery when the mother has fully recovered. With respect to medical treatment, cinacalcet is excreted in the milk of lactating rats with a high milk to plasma ratio. Therefore, a careful consideration of the risks and benefits should be made to decide on whether to discontinue or stop cinacalcet treatment in lactating women who require this treatment (2). Main recommendations for PHPT during pregnancy and lactation are summarized in Table 3.

Table 3. Main recommendations for primary hyperparathyroidism in pregnancy and lactation

Recommendations for the mother during pregnancy
- If the albumin-adjusted serum calcium increases above 2.85 mmol/L and/or the ionized serum calcium concentration above 1.45 mmol/L parathyroid surgery, preferably in the second trimester, is recommended
- Conservative treatment is primarily based on oral and/or intravenous rehydration although cinacalcet might be used as an escape
- There is a higher risk of preeclampsia and women should be screened for risk factors and treated accordingly
- Surveillance with measurements of calcium and creatinine/estimated glomerular filtration rate) should be performed every 4 weeks throughout the pregnancy
Recommendations for the mother after delivery
- Parathyroid surgery should be performed a few weeks after delivery when the mother has fully recovered
- If surgery is not performed surveillance of at least serum calcium and creatinine/estimated glomerular filtration rate) should be monitored every 4 to 8 weeks especially in lactating women
Recommendations for the offspring
- Native vitamin D supplementation according to national recommendations
- Measure serum calcium every 2 days starting on day 2, and continuing this depending on disease severity until 1 or 2 weeks after delivery

HypoPT

Diagnosing HypoPT during pregnancy

Hypoparathyroidism is only rarely diagnosed during pregnancy as it is, in most cases, already known before pregnancy. In pregnant women without a known diagnosis of HypoPT, hypocalcemic symptoms such as paresthesia (eg, tingling in the fingertips), muscle aches, or even cramps should lead to laboratory evaluations with calcium measurements. If hypocalcemia is detected, PTH and 25(OH)D should be determined to evaluate the diagnosis of hypoparathyroidism as a condition with hypocalcemia in combination with reduced or inappropriately low PTH concentrations. Given that anterior neck surgery is a main cause of hypoparathyroidism (75% of the cases), knowledge on such a previous surgery or just a respective surgical scar can be a useful hint for the diagnostic evaluation (1).

Treatment and monitoring of HypoPT during pregnancy

Active vitamin D treatment and calcium supplements are the main treatment modalities during pregnancy and the goal is to aim for an albumin-adjusted and/or ionized calcium level in the lower end of the normal range (2, 6, 9). Native vitamin D supplements to achieve 25(OH)D concentrations in the normal range are also recommended, and magnesium supplements should also be used in case of a respective deficiency. In case of severe (life-threatening) acute hypocalcemia with tetany and/or cardiac arrhythmias we suggest, as an emergency treatment, the intravenous infusion of 1 to 2 g of calcium gluconate over 10 minutes.

It is critical to avoid hypercalcemia and hypocalcemia in the mother during pregnancy. Maternal hypercalcemia leads to hypercalcemia of the fetus and may suppress PTH levels and thus cause HypoPT with risk of symptomatic hypocalcemia in the newborn after birth. Conversely, maternal hypocalcemia may not lead to fetal hypocalcemia until maternal serum calcium is severely reduced because calcium is transferred by the placenta to the fetus at the expense of the maternal skeleton (6). Severe and longstanding maternal hypocalcemia can, however, cause fetal hypocalcemia during pregnancy. This in turn, may lead to fetal hyperparathyroidism and demineralization of the fetal skeleton and increased risk of intrauterine fractures, low birth weight and fetal death (6, 9). While earlier case reports and case series suggested a relatively high risk of pregnancy complications for women with HypoPT, recent larger national registry studies documented a relatively low risk of adverse pregnancy outcomes (21, 22, 24). The largest registry study from Sweden included 97 women with HypoPT and reported on an increased risk of induction of labor (odds ratio 1.87; 95% CI, 1.13-2.94) and lower birth weight (−188 g; 95% CI, −312.2 to −63.8) when compared with age-matched controls, but there was no increased risk for other relevant outcomes, such as small for gestational age, malformations, or perinatal death (21).

When having a positive pregnancy test, the current standard treatment for HypoPT with calcium and active vitamin D supplements must not be stopped or immediately modified but continued at its current dosage. As dosing requirements for calcium supplements and active vitamin D may considerably vary in pregnancy and lactation, we recommend an immediate visit at an endocrinologist for clinical and laboratory evaluation, including measurements of serum calcium, phosphate, eGFR, 25(OH)D, magnesium, and preferentially also urinary calcium excretion (2, 6). Patients and their physicians should be aware that during pregnancy dose adjustments are frequently required and hardly predictable. Pregnancy-associated increases in endogenous calcitriol, estrogen, and PTHrP may theoretically lower treatment requirements for women with HypoPT. In some, but not all, reports on this topic there is a trend for a reduced requirement for calcium and active vitamin D supplements, but roughly half of the patients do not have to change their doses to achieve their treatment goals, and a few patients may have even increased requirements during pregnancy (22, 23, 25). Interestingly, there is some evidence that hypoparathyroidism-related clinical manifestations such as paresthesia, cramps, and tetany, may improve during pregnancy, but the data on this topic are inconsistent (22, 23). Due to the uncertainties regarding potential changes in dose requirements during pregnancy, careful biochemical monitoring should be done all 3 to 4 weeks throughout pregnancy and if changes in the treatment are made, an additional follow-up visit should be performed after 1 to 2 weeks (2). More frequent visits, eg, every week, are suggested within 1 month before giving birth, as there are reports on more dramatic changes in calcium metabolism during this time, with a particular high risk of hypercalcemia (2, 25).

Postpartum care in women with HypoPT and their offspring

In the peripartum period and, in particular, immediately after delivery and during lactation, the requirements for active vitamin D and calcium supplements significantly decrease and may increase the risk of maternal hypercalcemia, as reported in some case series (22, 23, 25). Thus, frequent biochemical monitoring, weekly within the first month after birth and then every 4 weeks during lactation should be performed. In addition, it should also be noted that abrupt cessation of

Table 4. Main recommendations for hypoparathyroidism in pregnancy and lactation

Recommendations for the mother during pregnancy
- Active vitamin D treatment and calcium supplements are the main treatment modalities
- Native vitamin D supplements should be used to achieve 25-hydroxyvitamin D concentrations in the normal range, and magnesium supplements should be used in case of magnesium deficiency
- Surveillance (including laboratory measurements of at least serum calcium, phosphate, magnesium and creatinine/estimated glomerular filtration) every 3 to 4 weeks and every week within 1 month before giving birth
Recommendations for the mother after delivery
- Surveillance (including laboratory measurements of at least serum calcium, phosphate, magnesium, and creatinine/estimated glomerular filtration rate) weekly within the first month after delivery and then every 4 weeks during lactation
- Be aware of increased hypercalcemia risk during the peripartum period
Recommendations for the offspring
- Native vitamin D supplementation according to national recommendations
- Measure serum calcium every 2 days for the first week of life

breastfeeding can be associated with maternal hypocalcemia so that additional laboratory measurements immediately after stopping breastfeeding seem to be reasonable (2).

Newborns of mothers with HypoPT may have been exposed to intrauterine hypo- and/or hypercalcemia that may impact their postnatal calcium metabolism so that it appears reasonable to measure serum calcium levels every second day for the first week of life (2). This should be regarded as a rough guidance that may be modified according to the degree of disease control during pregnancy. Usual native vitamin D supplementation in the newborns is, of course, recommended. Main recommendations for HypoPT during pregnancy and lactation are summarized in Table 4.

Areas of Uncertainty

We have to acknowledge that the evidence on management of parathyroid disorders is very limited and largely based on case reports and case series that are prone to different sorts of bias and confounding. Nevertheless, there is growing evidence also from systematic evaluations that help to guide our management decision in this setting (21, 31). Several important areas of uncertainties remain, such as systematic investigations on the dose-response curve for hypercalcemia and adverse pregnancy outcomes in women with PHPT. Data on this topic are inconsistent, probably due to detection and publication bias in case reports on women with adverse clinical outcomes, and thus, large, well-executed registry studies are required. Regarding hypercalcemia in pregnancy, we require further safety data on the possible drugs, in particular on cinacalcet, bisphosphonates, and denosumab. Several case reports on use of cinacalcet in this setting are encouraging, but more safety data on bisphosphonates are also required, as they are officially contraindicated in pregnancy, but the associated risk of adverse clinical outcomes appears to be relatively low in existing reports (40-42). For HypoPT, we still need a better understanding on the mechanisms that explain the wide diversity in required treatment doses during pregnancy and lactation. This may likely be related to differences in hormonal changes in this setting with regard to, for example, PTHrP, but may also be related to dietary patterns of the patients or other unknown reasons. Pregnancy- and lactation-specific reference ranges for calcium-regulating hormones and related parameters, such as urinary calcium excretion, should also be established. Moreover, the diagnostic and predictive value of urinary calcium excretion in pregnancy and lactation requires further evaluation. In addition, we need more safety data on recombinant human PTH (rhPTH) treatment during pregnancy and lactation, as such treatments can currently not be recommended due to the lack of sufficient safety data. Finally, it should be clarified whether universal screening for calcium levels may improve the outcome of pregnant women. We would suggest measuring serum calcium at least once during otherwise indicated pregnancy visits, but this is only an expert opinion requiring further evidence-based data. In this context, we have to acknowledge that our recommendations for the management of parathyroid disorders in pregnancy in this publication should be viewed as an attempt to provide useful guidance for clinicians but should only be viewed and interpreted in the light of the limited available evidence on this topic.

Back to the Cases

Case 1

A diagnosis of PHPT based on a single adenoma was made. Considering the pregnancy term and a calcium level <2.85 mmol/L after conservative treatment, it was deemed safe to postpone surgery into the second trimester. Surgery was deemed necessary due to the presence of the nephrolithiasis and the calcium upon presentation. Considering the presence of 2 moderate risk factors and the underlying PHPT low-dose aspirin as preeclampsia prophylaxis was started. The patient and her partner were counseled by the obstetrician and pediatrician about the consequences for the pregnancy and the child after birth. In young women with PHPT, we have to consider the possibility of genetic testing for familial forms of PHPT, such as multiple endocrine neoplasia type 1 (MEN1), as the presence of such forms may alter patient management. Genetic testing is usually advised in PHPT patients younger than 30 years of age and/or multiglandular disease or specific features for a syndromatic form. We considered and discussed this, but we refrained from genetic testing in our patient as these features were lacking.

The patient was discharged and seen weekly at the endocrinology department with a calcium check and blood pressure measurement. She did not experience nausea and no longer needed supplemental fluids as long as she kept her fluid intake above 3 L. After 17 weeks of pregnancy, calcium levels slowly started to rise, and the patient was operated successfully with a minimally invasive procedure and a clear adenoma was resected. Intraoperative PTH measurements showed a 50% drop within 10 minutes, going up to 75% after 15 minutes. Postoperative calcium levels remained within the normal range and the patient could be discharged after 24 hours. During the further course of her pregnancy, calcium levels remained normal and a healthy baby girl was born at 39 + 1 weeks with a good start and birthweight around the 50th percentile. No abnormalities in calcium were observed in the child.

Case 2

Two years after counseling her regarding pregnancy with HypoPT, the patient reported that she had meanwhile started a treatment with rhPTH(1-84) more than a year prior because she had significant hypocalcemic symptoms despite high dose calcium and calcitriol treatment. A few months later she became pregnant and is now in the third trimester (gestational week 33) with a so-far uncomplicated pregnancy. The rhPTH(1-84) at a dose of 25 µg subcutaneous once daily is currently her only treatment for HypoPT as she takes no additional calcium supplements or active vitamin D, and native vitamin D only occasionally. The rhPTH(1-84) was not stopped during pregnancy by the treating physicians due to concerns of worsening control of HypoPT. At the current visit, her albumin-adjusted serum calcium was 2.2 mmol/L, and her phosphorus and magnesium levels were within the normal range, with no significant hypocalcemic symptoms. The patient consulted us because she worried whether rhPTH(1-84) may have cause any harm to her baby. She was informed that rhPTH(1-84) is not approved in pregnancy due to missing safety data and no experience with this treatment so far. There are only 2 cases published of women who were treated with continuous subcutaneous rhPTH(1-34) infusions during pregnancy and lactation that reported no safety concerns for this drug (15, 16). Due to the lack of sufficient safety data, we generally argue against treatment of rhPTH(1-84) in pregnancy and during lactation. Considering her special situation with the advanced and so-far uncomplicated pregnancy, we decided to refrain from stopping rhPTH(1-84) at the moment and continued with the current treatment plus an additional calcium supplement with 500 mg once daily to ensure an adequate oral calcium intake and regular vitamin D3 intake of about 1000 IU daily. We recommended weekly visits with laboratory assessments 1 month before and after delivery and a respective serum calcium measurement of her baby on day 2, 4, and 6 after birth. The patient did not adhere to this active surveillance at our outpatient clinic, but she delivered a healthy male baby at gestational week 38 + 4 (Apgar 9/10/10; weight: 3365 g, length: 49 cm) at an external hospital. No further complications of the mother and infant were reported according to external medical records. The patient gave written informed consent to publish her case report.

Disclosures

The authors report no conflicts of interest.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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