Hypercalcemia in Pregnancy

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KEYWORDS

• Hypercalcemia • Management • Pregnancy • Primary hyperparathyroidism
• Cinacalcet • Calcitonin • Parathyroidectomy

KEY POINTS

- Primary hyperparathyroidism is the most common cause of hypercalcemia in pregnancy and is the result of a solitary parathyroid adenoma in the majority of cases.
- It is essential to exclude a diagnosis of familial hypocalciuric hypercalcemia, because parathyroidectomy is not indicated.
- Mild primary hyperparathyroidism may be managed conservatively with supportive measures.
- In primary hyperparathyroidism with albumin-adjusted calcium levels of 3.00 mmol/L or more (≥12 mg/dL) in which conservative measures fail, parathyroidectomy in the second trimester is advised.
- Pharmacologic options are limited during pregnancy, with no long-term safety data on any of the treatments available.

INTRODUCTION

Hypercalcemia in a pregnant woman is a rare occurrence that may, however, have serious consequences on both the mother and the fetus. Primary hyperparathyroidism (PHPT) represents the leading cause of hypercalcemia in pregnancy.[1] Other causes of hypercalcemia need to be considered and excluded before confirming a PHPT diagnosis. These include familial hypocalciuric hypercalcemia (FHH), milk–alkali syndrome, parathyroid hormone-related protein (PTHrP)-mediated hypercalcemia of pregnancy, hypercalcemia of malignancy, and abnormal vitamin D metabolism.[2] The physiologic reduction in serum parathyroid hormone (PTH) during pregnancy may render a PHPT diagnosis challenging. Because there are currently no long-term safety data in pregnancy for any of the drugs traditionally used to treat hypercalcemia in nonpregnant patients, medical intervention is limited to adequate hydration and avoidance of drugs that may further increase serum calcium. No randomized controlled trials have been conducted comparing medical management with

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parathyroidectomy (PTX) in pregnancy, and therefore current evidence supporting management strategies is severely limited.

We describe calcium homeostasis during euparathyroid pregnancy and the various causes of hypercalcemia reported in pregnant women. We also provide guidance on the evaluation and optimal management of hypercalcemia during pregnancy.

PHYSIOLOGY OF CALCIUM METABOLISM DURING EUPARATHYROID PREGNANCY

Calcium, Magnesium, and Phosphorus

Unadjusted total serum calcium decreases by nearly 10% during pregnancy, owing to the dilutional effect of intravascular volume expansion on serum albumin.[3] This apparent decrease is artifactual, because albumin-adjusted calcium and ionized calcium both remain stable throughout all trimesters.[3] Serum phosphorus and magnesium both remain stable[4] (**Fig. 1**).

Parathyroid Hormone

PTH is suppressed to low normal or slightly below normal reference range in the first trimester secondary to increases in PTH-rP.[5,6] It then either remains suppressed or increases back to mid normal values toward term.[5,6] In the presence of vitamin D inadequacy or low calcium intake, PTH level may not suppress as expected, representing a state of secondary hyperparathyroidism.[7]

Parathyroid Hormone–Related Protein

PTH-rP is synthesized in the breasts and placenta (**Fig. 2**) and may also be produced in other maternal and fetal tissues (parathyroid, amnion, decidua, myometrium, and umbilical cord[2]). PTH-rP increases as early as the 3rd to 13th weeks of gestation, peaking in the third trimester.[8,9]

Calcitriol

Calcitriol increases in the first trimester and peaks in the third trimester.[7] PTH-rP, along with estrogen, prolactin, and human placental lactogen, seem to be the main factors responsible for renal 1α-hydroxylase upregulation.[2]

Calcidiol

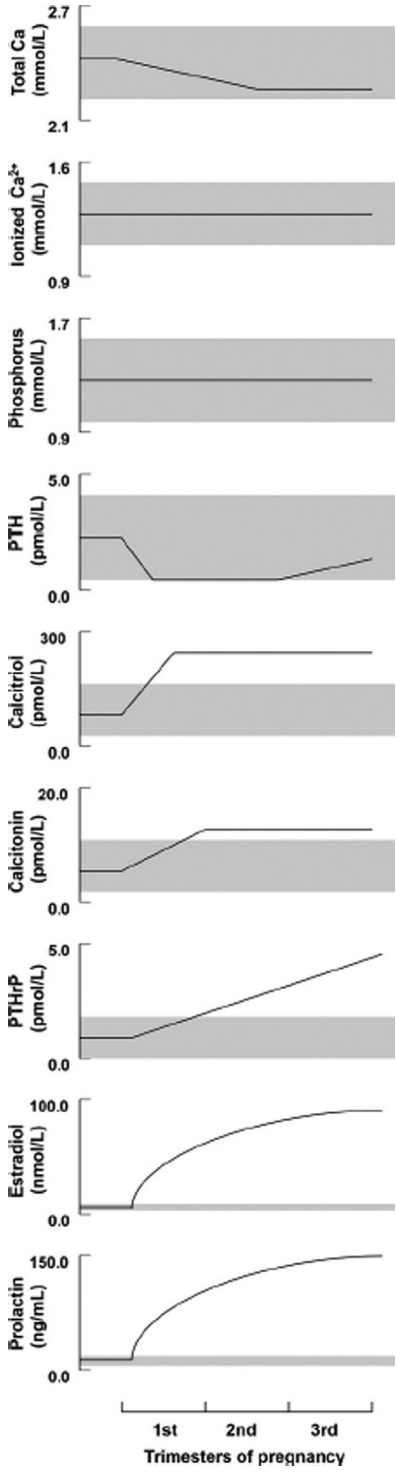
Calcidiol levels remain stable throughout pregnancy, despite the increased conversion into calcitriol and transplacental transfer of 25(OH)D_3 to the fetus.[7]

Calcitonin

The majority of the data suggest an increase in calcitonin during pregnancy[2]; however, some studies have demonstrated stable[10] or even decreased[6] values.

Calcium Balance

The fractional absorption of calcium from the gut doubles as early as 12 weeks of gestation[10] and is maintained to term, creating a positive calcium balance. Increased calcitriol levels may be responsible for part of that adaptive mechanism; however, prolactin, placental lactogen, and growth hormone may all potentiate the capacity of enterocytes to absorb calcium.[2] Combined with the physiologic increase in the glomerular filtration rate, it leads to absorptive hypercalciuria as early as 12 weeks of gestation.[10] Overall, a positive calcium balance is reached by mid pregnancy,[2,11] and as such bone resorption markers seem to be low in the first trimester. Bone resorption afterward increases by the third trimester.[11]


Total Ca (mmol/L)
2.7
2.1
Ionized Ca^{2+} (mmol/L)
1.6
0.9
Phosphorus (mmol/L)
1.7
0.9
PTH (pmol/L)
5.0
0.0
Calcitriol (pmol/L)
300
0.0
Calcitonin (pmol/L)
20.0
0.0
PTHrP (pmol/L)
5.0
0.0
Estradiol (nmol/L)
100.0
0.0
Prolactin (ng/mL)
150.0
0.0
1st
2nd
3rd
Trimesters of pregnancy

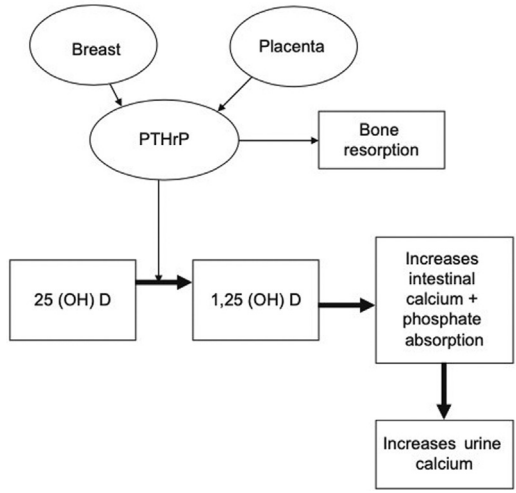


Fig. 2. Role of PTHrP during pregnancy. Schematic illustration demonstrating the role of parathyroid hormone-related protein (PTHrP) during pregnancy. It is produced by the placenta and breast tissue and can result in increase in serum calcium and phosphorus secondary to increased bone resorption and rise in calcitriol. (*From* Khan AA, Clarke B, Rejnmark L, Brandi ML. MANAGEMENT OF ENDOCRINE DISEASE: Hypoparathyroidism in pregnancy: review and evidence-based recommendations for management. Eur J Endocrinol. 2019 Feb 1;180(2):R37-R44.)

CAUSES OF HYPERCALCEMIA IN PREGNANCY

Primary Hyperparathyroidism

PHPT is the most common cause of hypercalcemia in pregnancy, although its exact incidence remains unknown. The incidence of PHPT peaks in female patients 65 to 74 years of age,[12] which makes pregnancy and delivery among women with PHPT an uncommon occurrence. The largest retrospective study to report on prevalence of PHPT in pregnancy examined routine calcium screening of more than 290,000 women aged 20 to 40 years and found PHPT in 0.05% of women of reproductive age, with 0.03% of the cohort conceiving while they had active PHPT.[13] PHPT can present as a solitary adenoma in 85% to 90% of cases, multiglandular hyperplasia in approximately 15% of the cases, or parathyroid carcinoma, which is a very rare occurrence (<1%)[13,14] with only 8 cases reported in pregnancy to date.[15–17] The hereditary causes of PHPT can present as part of syndromes, and include multiple endocrine neoplasia (MEN1, MEN2A, and MEN4) and hyperparathyroidism–jaw tumor syndromes, or occur in isolation as in familial isolated PHPT. Hereditary causes of PHPT tend to occur at a younger age than their sporadic counterparts and are likely to be overexpressed in a population of reproductive aged women. As such, clinical and biochemical screening for associated comorbidities and genetic testing must

Fig. 1. Schematic depiction of longitudinal changes in calcium (Ca), phosphorus, and calciotropic hormone levels during human pregnancy. *Shaded regions* depict the approximate normal ranges. (*From* Kovacs CS. Maternal Mineral and Bone Metabolism During Pregnancy, Lactation, and Post-Weaning Recovery. Physiol Rev. 2016 Apr;96(2):449-547; with permission.)

be considered for patients with PHPT younger than 40 year old (see the Paul Newey's article "Hereditary Primary Hyperparathyroidism").

The physiologic positive calcium balance achieved by midgestation may further exacerbate hypercalcemia and lead to an increased risk of PHPT-related complication (see Signs, Symptoms, and Complications). In contrast, the high transplacental transfer of calcium to the fetus by the end of pregnancy may also confer some protection against increasing serum calcium levels. This finding explains why some cases of hypercalcemic crisis have been described in the immediate postpartum period,[18] when the shunting of excess calcium to the fetus is lost.

Familial Hypocalciuric Hypercalcemia

FHH is a rare autosomal-dominant disorder characterized by life-long, nonprogressive, asymptomatic, mild to moderate hypercalcemia. PTH can either be normal or mildly elevated with relative hypocalciuria.[19] There are 3 identified variants, all leading to abnormal function of the calcium sensing receptor (see Hereditary Primary Hyperparathyroidism). Only 6 cases of FHH in pregnancy have been reported in the literature,[20–22] but the true incidence may be higher because the associated asymptomatic hypercalcemia may go unnoticed if not otherwise detected on routine blood work. Even though the hypercalcemia associated with FHH has traditionally been described to be of mild to moderate severity, in 3 of the reported cases,[20,21] serum calcium reached values or more than 3 mmol/L.

Parathyroid Hormone–Related Protein Mediated Hypercalcemia

Because PTH-rP release by the breasts and placenta seems to be relatively autonomous and independent of serum calcium levels,[2] excess physiologic secretion has been described as a cause of hypercalcemia. Five case reports described the breasts as a source of excessive PTH-rP,[23–25] one of which presented with massive mammary hyperplasia and had to undergo bilateral mastectomy. In the other cases, hypercalcemia resolved with weaning of breastfeeding, but PTH-rP levels remained elevated for many months postpartum.[26] Placental source of excess PTH-rP was also described in a woman who developed hypercalcemic crisis in the third trimester of pregnancy, followed by profound hypocalcemia with undetectable PTH-rP levels hours after emergency cesarean section.[27] In PTH-rP–mediated hypercalcemia cases, it is not possible to ascertain the specific source of the PTH-rP excess until after delivery.

Abnormal 1.25-Dihydroxyvitamin Metabolism

The catabolism of calcitriol to its inactive metabolite $1,24,25(OH)_3D$ is mediated by vitamin D-24-hydroxylase, encoded by Cyp24a1, which also regulates the conversion of 25(OH)D to $24,25(OH)_2D$.[2] Homozygous and compound heterozygous loss of function mutation of Cyp24a1 have been described in patients presenting with hypercalcemia, hypercalciuria and low to low-normal PTH levels.[28] Although it may lead to mild hypercalcemia in nonpregnant adults, the physiologic increase in production combined with the pathologic decrease in catabolism of calcitriol has been reported to lead to severe hypercalcemia that may be complicated by nephrolithiasis and pancreatitis in pregnancy.[29–31]

Milk–Alkali Syndrome

Milk–alkali syndrome is defined by the triad of hypercalcemia, metabolic alkalosis, and renal impairment, in association with excessive ingestion of calcium and absorbable alkali. At least a dozen cases of milk–alkali syndrome have been described in pregnant patients.[32–34] Some of these women presented with severe life-threatening

hypercalcemia complicated by pancreatitis and eclampsia; it must, therefore not be overlooked as a possible cause of severe hypercalcemia.

Hypercalcemia of Malignancy

Hypercalcemia associated with malignancy has rarely been described in pregnant patients. Pancreatic neuroendocrine tumors,[35,36] metastatic breast cancers,[37,38] ovarian cancer,[39,40] renal cell carcinoma,[41] uterine leiomyoma,[42] and multiple myeloma presenting with hypercalcemia during pregnancy have been described.[43,44] Most of the reported cases seemed to be related to tumoral PTH-rP production and all patients presented with severe hypercalcemia.

Miscellaneous Causes

Other causes of hypercalcemia include granulomatous disease, extrarenal calcitriol production, hyperthyroidism, adrenal insufficiency, pheochromocytoma, immobilization, as well as hypervitaminosis A and D.

CLINICAL PRESENTATION AND MATERNAL–FETAL COMPLICATIONS OF HYPERCALCEMIA

Hypercalcemia in pregnancy is often asymptomatic. In a series of 17 PHPT cases in pregnancy, nearly one-half of them were diagnosed incidentally.[45] When present, symptoms may be nonspecific and easily misdiagnosed as physiologic changes of pregnancy. Symptoms may include malaise, fatigue, constipation, nausea, and vomiting.[46] Hypercalcemia can also present as hyperemesis gravidarum.[47] Polyuria, polydipsia, bone pain, renal colic, and abdominal pain have also been described.[48] Hypercalcemia may be associated with neurocognitive symptoms such as depression, emotional lability, headache, and agitation.[47]

Nephrolithiasis has been described as the most frequent complication of PHPT.[49] PHPT in pregnancy has been consistently reported to be associated with hypertension and preeclampsia[50] with an estimated 25% incidence of preeclampsia.[51] A registry-based study demonstrated a significant association between the presence of a parathyroid adenoma and subsequent preeclampsia, with the risk of preeclampsia remaining increased for up to 5 years after successful intervention.[50] Untreated hypercalcemia in pregnancy may result in end-organ damage, including acute pancreatitis, renal impairment, cardiac arrythmia, peptic ulcer disease, altered mental status, and confusion.[52]

Low bone mass and skeletal fractures have been estimated to occur in less than 10% of pregnant women with PHPT.[53,54] Polyhydramnios has been reported in undiagnosed hypercalcemia of pregnancy and is believed to be related to associated fetal polyuria.[55]

Fetal complications may include neonatal hypocalcemia as a result of fetal parathyroid suppression secondary to maternal hypercalcemia, which can result in seizures and tetany.[56,57] Other reported adverse fetal outcomes include intrauterine growth restriction, preterm labor, stillbirth, and fetal death.[58]

Clinical Presentation and Associated Complications of Familial Hypocalciuric Hypercalcemia

FHH during pregnancy does not seem to pose a risk for the mother, despite the further increases in serum calcium, as noted in published case reports.[20,21] The impact of FHH on the fetus depends on the inherited genotype. Heterozygous transmission is expected to lead to asymptomatic hypercalcemia without adverse outcomes.[20,59] In

a fetus not harboring the mutation, maternal hypercalcemia may lead to transient or permanent hypoparathyroidism with subsequent neonatal hypocalcemia.[21,22] Homozygous or compound heterozygous transmission, with the second mutation being inherited from the father, may be associated with severe neonatal hyperparathyroidism.[60]

ASSESSMENT

History and Physical Examination

A detailed history and physical examination should be obtained (**Table 1**), and a familial history is of paramount importance. A positive family history of asymptomatic

Table 1
Evaluation of hypercalcemic disorders in pregnancy

History	Hypercalcemia symptoms: polyuria/polydipsia, nausea, vomiting, constipation, abdominal/flank pain, weakness, confusion/lethargy, depression Preeclampsia symptoms: headache, visual disturbance, epigastric pain/upper abdominal pain, altered mental status, dyspnea Kidney stones, height loss, fragility fractures Previous cancer or irradiation Hypertension, stroke or cardiovascular disease Granulomatous disease, adrenal insufficiency Family history of hypercalcemia and/or clinical entities associated with inherited forms of PHPT (see the Paul Newey's article "Hereditary Primary Hyperparathyroidism") Medications: hydrochlorothiazide, lithium, vitamin D supplement, calcium carbonate and other calcium containing antacids
Physical examination	Blood pressure, pulse, height, weight Heart, lung, breasts, and abdomen examination Neck examination: palpable nodules, surgical incision scar Assessment of fetal well-being
Biochemical	Baseline: ionized calcium and/or calcium corrected for albumin[a], iPTH, PO_4, Mg, ALP, vitamin 25(OH)D, creatinine, eGFR, 24-h urine collection for calcium and creatinine, CBC, TSH, CCCR PTH-independent hypercalcemia (suppressed iPTH): PTHrP, vitamin $1.25(OH)_2D_3$, serum immunoelectrophoresis, morning cortisol and ACTH PTH-dependent hypercalcemia (nonsuppressed or elevated iPTH): DNA analysis of *CaSR, GNa11*, and *AP2S1 genes* if FHH is suspected (see text) Preeclampsia panel when clinically indicated
Imaging	Kidney ultrasound examination to exclude renal lithiasis and/or nephrocalcinosis Neck ultrasound as preoperative imaging for PHPT

Abbreviations: ACTH, adrenocorticotropic hormone; ALP, alkaline phosphatase; CaSR, calcium sensing receptor; CBC, complete blood count; eGFR, estimated glomerular filtration ratel; iPTH, intact parathyroid hormone; Mg, Magnesium; PO_4, phosphorus; PTHrP, parathyroid hormone-related protein; TSH, thyroid stimulating hormone.

[a] Corrected calcium = measured total calcium (mmol/L) + (40 − serum albumin [g/dL]) × 0.02, Corrected calcium = measured total calcium (mg/dL) + 0.8 × (4 – serum albumin [g/dL]).

Adapted from Khan AA, Kenshole A, Ezzat S, Goguen J, Gomez-Hernandez K, Hegele RA, Houlden R, Joy T, Keely E, Killinger D, Lacroix A, Laredo S, Prebtani APH, Shrayyef MZ, Tran C, Van Uum S, Reardon R, Papageorgiou A, Tays W, Edmonds M. Tools for Enhancement and Quality Improvement of Peer Assessment and Clinical Care in Endocrinology and Metabolism. J Clin Densitom. 2019 Jan-Mar;22(1):125-149.

hypercalcemia, a personal or familial history of failed neck exploration, and a history of hypercalcemia present in childhood or young adulthood are all in favor of FHH.[19]

Laboratory Investigations

Albumin-adjusted serum calcium or ionized calcium should be obtained when evaluating calcium disorders in pregnant women. PHPT is diagnosed in the presence of hypercalcemia along with a nonsuppressed PTH level.[14] The use of lithium and hydrochlorothiazide may lead to elevated serum calcium and PTH levels and should be discontinued for 3 months before confirming a diagnosis of PHPT. Coexisting vitamin D inadequacy may lead to elevated PTH level and should be corrected, aiming for 25(OH)D values between 50 and 125 nmol/L.[1,61]

FHH must be excluded as surgery is not indicated. Calculating the calcium to creatinine clearance ratio (CCCR) is helpful in making the distinction between FHH and PHPT, because it is less than 0.01 in 80% of nonpregnant FHH cases.[19] Approximately 20% of nonpregnant individuals with FHH have a CCCR between 0.01 and 0.02 and can overlap with the values encountered in patients with PHPT. In pregnancy, the absorptive hypercalciuria may further increase the CCCR. A low CCCR is, therefore, of great value in excluding PHPT, but an elevated value may be misleading in the exclusion of FHH. DNA analysis of the *CaSR, GNa11*, and *AP2S1* genes may be warranted to exclude the possibility of FHH, but results may unfortunately not be available in a timely manner, in which case screening of first-degree relatives may prove useful.

Hypercalcemia with an appropriately suppressed PTH level should lead to consideration of PTH-independent causes of hypercalcemia (**Table 2**).

Imaging for Primary Hyperparathyroidism

Preoperative imaging options for PHPT in pregnancy are limited and ultrasound examination remains the safest and first-line imaging technique in pregnancy, with a sensitivity and specificity of 69% and 94%, respectively, at identifying parathyroid adenoma.[62] The sensitivity is lower for multiglandular disease, reported to be 15% to 35%,[63] and ultrasound examination will fail to identify ectopic hyperfunctioning parathyroid tissue.

A recent American College of Obstetricians and Gynecologists committee opinion has stated that fetal exposure of less than 5 mGy is considered safe during pregnancy.[64] A computed tomography scan of the neck is believed to be an examination with very low-dose fetal radiation (0.001–0.01 mGy). 99mTc-MIBI has been shown to cross the placenta in animals[65] and is listed as category C in pregnancy. Very limited data on its use in pregnancy are available, although a prospective registry of more than 100 women exposed to 99mTc scintigraphy, at a dose of less than 5 mGy, during the first trimester did not report increased birth defects or other adverse outcomes.[66]

MANAGEMENT

General Measures, Calcium, and Vitamin D

Adequate hydration should be maintained in all pregnant women with hypercalcemia to avoid further increases in the serum calcium level. Intravenous volume repletion with correction of electrolyte anomalies may be required in severe cases. Furosemide has been used to increase urinary calcium excretion; however, its benefit has been questioned in the nonpregnant population because a recent review failed to report a consistent effect in acutely lowering serum calcium.[67] Furosemide is a category C drug in pregnancy, and although its use does not seem to present a detectable

Table 2
Suggestive clinical features and biochemical profile in hypercalcemic disorders of pregnancy

	Clinical Entities	Suggestive Features	Suggestive Biochemical Profile
PTH-dependent hypercalcemia	PHPT	Previous fracture, height loss or nephrolithiasis/ nephrocalcinosis Personal or familial history of syndromic features of inherited diseases	Nonsuppressed PTH level Hypophosphatemia CCCR >0.02
	FHH	Hypercalcemia dating back to childhood Family history of asymptomatic hypercalcemia Personal/familial history of failed neck exploration	Nonsuppressed PTH level CCCR <0.01 DNA analysis of proband or first-degree relative positive for *CaSR, GNA11* or *AP2S1* mutations
PTH-independent hypercalcemia	PTH-rP mediated hypercalcemia of pregnancy	Excessive breast enlargement	Suppressed PTH Elevated PTHrP
	Malignancy-associated hypercalcemia	Previous cancer or radiation Bone pain Constitutional symptoms	Severe hypercalcemia Suppressed PTH May have elevated PTHrP
	Milk–alkali syndrome	Excessive calcium supplements or calcium containing antacids	Suppressed PTH Renal failure Metabolic alkalosis
	1.25OHD impaired catabolism	Previous fracture, height loss or lithiasis Positive family history of hypercalcemic disorder	Elevated 1.25 $(OH)_2D_3$

Abbreviations: PTHrP, parathyroid hormone-related protein.

teratogenic risk, there are concerns related to risk of decreased uteroplacental circulation.[68] It is, therefore, felt that furosemide should be reserved for patients with or at risk of developing congestive heart failure while receiving intravenous hydration.

Calcium supplements should be stopped. Thiazide diuretics and lithium should be avoided if the clinical situation permits, because they can exacerbate the hypercalcemia.

The prevalence of vitamin D inadequacy is higher among patients with PHPT than in the general population and vitamin D supplementation in nonpregnant patients with PHPT has been associated with a mild decrease in PTH levels without increases in serum calcium or urinary calcium levels.[69] It is, therefore, recommended to correct vitamin D inadequacy with supplemental cholecalciferol while closely monitoring serum and urinary calcium excretion, aiming for vitamin D levels of 50 to 125 mmol/L.[70]

Pharmacologic Interventions

Calcitonin decreases calcium levels by directly suppressing bone resorption and promoting urinary calcium excretion. It does not cross the placenta and is a category B

medication in pregnancy.[71] It has been used safely during pregnancy at doses 4 to 8 IU/kg given subcutaneously every 12 hours and has been helpful in acutely decreasing calcium levels. However, its continuous use leads to tachyphylaxis that may rapidly blunt its efficacy.

Bisphosphonates cross the placenta and animal studies have suggested that they may be teratogenic at high doses,[72] and therefore are considered category C in pregnancy. Although their use was not reported to cause any serious short term adverse effects on the fetus aside from transient neonatal hypocalcemia and a tendency to low birth weight when used either before or during pregnancy and lactation,[73] long-term data are lacking. As such, their use in pregnancy should be limited to life-threatening situations.

Cinacalcet, a calcimimetic agent, increases the sensitivity of the calcium sensing receptor to activation by extracellular calcium, in turn leading to decreased synthesis and secretion of PTH. It is also classified as category C, but its use has been reported in several cases of PHPT during pregnancy,[74,75] at a dose ranging from 30 mg to 360 mg/d, and animal studies do not suggest adverse fetal outcomes even though it crosses the placenta.[76] Neonatal hypocalcemia has been described with cinacalcet use,; however, it is not known if it was related to maternal hypercalcemia itself.[74]

Denosumab is a category D drug in pregnancy, because its transplacental passage has been shown to increase fetal mortality and cause an osteoporotic-like disorder in animals studies[77] and, therefore, must be avoided in pregnant patients.

Oral phosphate supplementation have been used to decrease calcium levels in PHPT pregnant patients,[78] but owing to limited efficacy[49] and concern for intravascular and extravascular calcifications,[79] its use is not recommended.

Surgical Management of Primary Hyperparathyroidism

Patients with mild hypercalcemia who are relatively asymptomatic can be followed conservatively during pregnancy. However, PTX remains the only curative option for PHPT and should be considered in the presence of severe hypercalcemia (corrected calcium of $\geq$3.0 mmol/L) or in patients with significant symptoms of hypercalcemia. If PTX needs to be performed, it should ideally be carried out in the second trimester of pregnancy, although there are now several reports of successful surgical interventions in the first[80] and third trimesters.[51,81–83]

Different surgical intervention thresholds have been proposed, ranging from 2.7 mmol/L to 3.0 mmol/L.[7,84,85] No randomized trials have compared medical management with PTX in pregnancy. Older series[86,87] have suggested a higher rate of neonatal complications in medically managed compared with surgically treated women with PHPT (53% vs 12.5%) as well as a higher rate of neonatal death (16.0% vs 2.5%). However, it is felt that these represent more severe presentations than the milder cases that are encountered in the modern era. Data from a more recent cohort, in which the majority of patients had mean serum calcium of less than 2.85 mmol/L, did not demonstrate any maternal or late fetal deaths attributable to medically managed women with PHPT.[88] The major morbidity related to medical management compared with surgical intervention seemed to be preeclampsia leading to preterm delivery (30% vs 0%). A large retrospective study by Hirsch and colleagues[13] examined pregnancy outcomes in women with gestational PHPT compared with normocalcemic pregnant women tested during the same time period. The mean calcium levels of the PHPT group was 2.67 $\pm$ 0.15 mmol/L. No difference was found in miscarriages rate or any pregnancy-related complications between patients with PHPT and controls, suggesting that mild hypercalcemia does not generally carry an increased risk of obstetric complications.

The bulk of the data available to date favors surgical intervention in the second trimester in the presence of total corrected calcium levels of more than 3.0 mmol/L. Pregnant patients with PHPT who are being followed conservatively with medical management require close postpartum monitoring to avoid a potential abrupt rise in serum calcium following cessation of calcium outflow to the fetus with delivery.

SUMMARY

Hypercalcemia in pregnancy may result in significant maternal and fetal morbidity and requires effective and timely intervention. The nonspecific signs and symptoms of hypercalcemia during pregnancy make the identification of this condition challenging. When considering a diagnosis of PTH-dependent hypercalcemia, it is essential to exclude FHH, because surgical intervention is never indicated for this condition. Appropriate management is determined by the degree of hypercalcemia and the presence of symptoms and complications, as well as the gestational age at presentation. PHPT diagnosed in the first trimester of pregnancy should be managed conservatively if at all possible, until PTX can be offered safely in the second trimester. PHPT in the third trimester requires a careful evaluation of risk and benefits of surgery for both the mother and fetus prior to considering surgical intervention. Close monitoring of the mother and the fetus is of particular importance in the postpartum period to avoid or effectively manage a hypercalcemic crisis in the mother or neonatal tetany.

Currently, the literature is limited to case reports and case series and the quality of evidence on which these recommendations are made is unfortunately very low quality. The optimal management of such complex cases involves the close collaboration of the endocrinologist, obstetrician, and pediatrician.

CLINICS CARE POINTS

- Always use albumin-adjusted serum calcium or ionized calcium, because the unadjusted serum calcium is artefactually decreased in pregnancy.
- Changes in calcium homeostasis and the calcium regulating hormones in pregnancy include suppression of PTH. A nonsuppressed PTH in the presence of hypercalcemia is suspicious for PTH-mediated hypercalcemia.
- A 24-hour urine for calcium and creatinine is recommended for evaluation of hypercalciuria. The spot urine sample may be misleading owing to the development of absorptive hypercalciuria.
- The CCCR in pregnancy may not be as reliable in distinguishing PHPT and FHH. DNA analysis should be considered if FHH is a possible diagnosis.
- PHPT is a biochemical diagnosis. Imaging should only be completed to guide the surgical approach and should not be used as a diagnostic tool.
- PTX in the second trimester of pregnancy should be considered in the presence of significant hypercalcemia (albumin-adjusted calcium of $\geq$3.0 mmol mmol) owing to PHPT.
- Hypercalcemia should be carefully evaluated with confirmation of the underlying diagnosis and definitive therapy, if possible, before planning a pregnancy.

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