Primary Hyperparathyroidism in Pregnancy: Maternofetal Outcomes at a Quaternary Referral Obstetric Hospital, 2000 Through 2015

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Context: Primary hyperparathyroidism (PHPT) in pregnancy has historically been associated with substantial maternofetal morbidity and mortality rates. The optimal treatment and timing of surgical intervention in pregnancy remain contested.

Objective: To compare maternofetal outcomes of medically and surgically treated patients with PHPT in pregnancy.

Design: Retrospective chart review.

Setting: Quaternary referral hospital.

Patients: Women with PHPT in pregnancy treated between 1 January 2000 and 31 December 2015.

Interventions: Medical therapy or parathyroid surgery.

Main Outcomes Measured: Timing of diagnosis; maternal corrected serum calcium concentrations; gestation, indication and mode of delivery; complications attributable to PHPT; birth weight; and admission to the neonatal intensive care unit (NICU).

Results: Twenty-two pregnancies were managed medically, and six patients underwent parathyroidectomy in pregnancy (five in trimester 2, and one at 32 weeks gestation). Most patients treated medically either had a corrected serum calcium concentration $<$2.85 mmol/L in early pregnancy or had PHPT diagnosed in trimester 3. Of viable medically managed pregnancies, 30% were complicated by preeclampsia, and preterm delivery occurred in 66% of this group. All preterm neonates required admission to the NICU for complications related to prematurity. All surgically treated patients delivered their babies at term, and there were no complications of parathyroid surgery.

Conclusion: Maternofetal outcomes have improved relative to that reported in early medical literature in patients treated medically and surgically, but the rates of preeclampsia and preterm delivery were higher in medically treated patients. The study was limited by its retrospective design and small sample sizes. **(*J Clin Endocrinol Metab* 104: 721–729, 2019)**

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Abbreviations: CD, cesarean delivery; K28, before 28 weeks gestation; K32, before 32 weeks gestation; NICU, neonatal intensive care unit; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone; RBWH, Royal Brisbane and Women's Hospital.

Primary hyperparathyroidism (PHPT) has an estimated incidence of 8 per 100,000 population per year in women of childbearing age (1). In a case series of patients treated for PHPT, 1.4% of cases occurred in pregnancy (2).

Maternal complications of PHPT include nephrolithiasis, radiographic bone disease, pancreatitis, hyperemesis gravidarum, and urinary tract infections (3, 4). There is also an association between parathyroid adenomas and preeclampsia (5). A rare but feared complication of PHPT is hyperparathyroid crisis (also termed hypercalcemic crisis), in which patients develop nausea, vomiting, weakness, and mental status change in association with serum calcium concentrations typically >3.5 mmol/L (4). These patients can rapidly progress to uremia, coma, and death (4).

The most serious fetal complications are neonatal hypocalcemia (that can result in seizures or tetany), stillbirth, and miscarriage (3, 6). Premature birth, intrauterine growth restriction, and low birth weight have also been reported to occur in association with maternal PHPT (6, 7).

Increased detection and management of PHPT in pregnancy during the 1970s led to a decline in perinatal morbidity and mortality rates (8) but no clear consensus about the role of medical therapy vs parathyroidectomy in pregnancy. Various threshold maternal serum calcium concentrations above which surgery should be pursued have been proposed on the basis of data that suggest the risk of complications increases with increasing maternal serum calcium concentrations.

This study reviewed treatment of patients with PHPT in pregnancy at the Royal Brisbane and Women's Hospital (RBWH) to compare maternofetal outcomes of medically vs surgically treated patients.

Methods

Ethics

The study was approved by the RBWH Research Ethics Committee prior to commencement.

Case identification

Queensland Health Pathology Services data were interrogated to identify female patients aged 14 to 50 years (inclusive) who had a parathyroid hormone (PTH) assay performed between 1 January 2000 and 31 December 2015 (inclusive). Health Information Services data were used to identify patients with a PTH assay in the same year or year prior to a miscarriage or birth of a baby, such that a minimum of 12 months of laboratory data before the study pregnancy for each patient were scrutinized. Charts of patients who had hypercalcemia in association with an inappropriately normal or elevated PTH assay and normal renal function were reviewed to identify those with PHPT. Patients with secondary or tertiary hyperparathyroidism were excluded. A diagnosis of PHPT was considered definite if histologically proven or serum calcium concentration and PTH level normalized after surgery, and probable if chart records listed this as the working diagnosis, or if hypercalcemia was persistent and other investigations supported a diagnosis of PHPT.

Data collection

Maternal charts were reviewed to collect demographic information (patient age and ethnicity), gravidity, and parity. Body mass index at admission, gestation (single or multiple pregnancy), smoking status, maternal history of hypertension, gestational diabetes mellitus, type 1 diabetes mellitus, and type 2 diabetes mellitus were recorded.

The date of PHPT diagnosis (either as documented in the patient's chart or when the first elevated or inappropriately normal PTH assay was performed) was recorded. Biochemical information collected included corrected serum calcium concentration at diagnosis or the earliest concentration in pregnancy if the diagnosis was not made during the study pregnancy. Few patients had frequent ionized calcium concentrations measured, hence corrected serum calcium concentrations were used.

Peak serum calcium, serum PTH, and 25-hydroxy vitamin D (hereafter, vitamin D) concentrations; results of imaging; and 24-hour urinary calcium concentrations were also recorded. If other biochemical or genetic investigations were performed, the results were reviewed to ensure they were consistent with a diagnosis of PHPT. Details of medical treatment and parathyroid surgery were recorded, as well as the number of admissions and total length of stay over the course of the pregnancy.

Pregnancy outcomes assessed included gestation at delivery, indication for and mode of delivery, and the development of complications attributable to PHPT (*i.e.*, miscarriage, pregnancy-induced hypertension or preeclampsia, pancreatitis, and hypercalcemic crisis). Neonatal outcomes assessed included birth weight, admission to the neonatal intensive care unit (NICU), and neonatal hypocalcemia (with or without tetany or seizures).

Data analysis

The decision to pursue surgery may have been affected by the timing of PHPT diagnosis (*i.e.*, before or after the end of trimester 2), thus patients were divided into three groups: medically treated patients with PHPT diagnosed before 28 weeks gestation (K28), medically treated patients with PHPT diagnosed after K28, and patients treated surgically during pregnancy (only one surgically managed patient received a PHPT diagnosis after K28). Data are presented using simple summary statistics. Where there were missing data points, the sample size for calculations is indicated separately.

Results

Study population and timing of diagnosis

Twenty-eight pregnancies among 23 patients with PHPT were included in the analysis. In 22 pregnancies (including two that ended in early miscarriage), PHPT was managed medically, with 12 of these diagnosed before K28 and 10 after K28. Six patients underwent

parathyroid surgery during pregnancy; of these, PHPT was diagnosed in five before K28 and these women underwent surgery during trimester 2. One patient received a PHPT diagnosis after K28 and underwent surgery at 32 weeks gestation K32. Baseline characteristics of patients are shown in Table 1.

Maternal serum calcium concentrations

The mean initial maternal serum calcium level among medically treated patients was 2.7 mmol/L for those diagnosed before K28 and 2.9 mmol/L among those diagnosed after K28 (Table 2). Among those in whom PHPT was diagnosed before K28, initial serum calcium level was <3 mmol/L in 11 of 12 patients and < 2.85 mmol/L in 10 of 12 patients.

Four medically treated patients had several pregnancies during the study period. The mean peak serum calcium level of these patients across all pregnancies was 2.71 mmol/L, which was lower than that of the remaining viable medically managed pregnancies (3.10 mmol/L).

Table 1. Population Characteristics of Patients With PHPT in Pregnancy Treated at the RBWH, 1 January 2000 Through 31 December 2015

	Medical, Diagnosed <K28 (n = 12)	Medical, Diagnosed >K28 (n = 10)	Surgical (n = 6)
Age, mean (SD), y	36 (5)	30 (7)	31 (6)
Body mass index at admission, mean (SD), kg/m^2	31 (9) (n = 11)	30 (5) (n = 9)	30 (7)
Gravida			
1	1	1	3
2–5	10	7	3
≥6	1	2	0
Parity			
0	3	3	4
1–5	9	7	2
Ethnicity			
Indian	1	1	1
White	9	8	5
White/black	1	0	0
Aboriginal	1	1	0
Smoker			
Yes	0	2	0
No	12	7	6
Unknown	0	1	0
Chronic hypertension			
Yes	2	4	0
No	10	6	5
Unknown	0	0	1
Gestational diabetes			
Yes	1	1	2
No	11	9	4
T1DM or T2DM			
Yes	1	1	1
No	11	9	5

Data given as no. unless otherwise indicated.

Abbreviations: T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

The mean initial serum calcium level among surgically treated patients was 2.9 mmol/L (Table 2). Four of the five patients treated surgically who received a PHPT diagnosis before K28 had serum calcium concentrations >2.85 mmol/L before pursuing surgery.

Medical treatment

Medical treatment was required in 8 of 22 medically managed pregnancies, with the most common therapy being IV fluid and/or antihypertensive medication (Table 2). Five of the six patients who received antihypertensive medications had preeclampsia. Two patients received pamidronate postpartum and had serum calcium concentrations >3 mmol/L.

Medical treatment was required in three of six surgically managed pregnancies, and these patients had serum calcium concentrations >3 mmol/L. The most common therapy used was IV fluid (Table 2). One patient received phosphate and cinacalcet with no adverse outcomes. One patient received antihypertensive medications for pregnancy-induced hypertension.

Surgery

Surgically managed pregnancies tended to be more recent, with all surgeries conducted between 2011 and 2014 (five surgeries by surgeon 1, one surgery by surgeon 2). The mean gestation at the time of surgery was K24 [range, K18 to K32]. The reasons for pursuing surgery were not consistently documented. Two patients were referred directly to endocrine surgeons by the patients' general practitioners. Three other patients had serum calcium concentrations >3 mmol/L. The remaining patient had serum calcium concentrations between 2.82 and 2.92 mmol/L, and the reason for surgery was not documented. Four patients underwent minimally invasive surgery, and two patients underwent bilateral neck exploration. Three of the four patients who underwent minimally invasive surgery had target lesions identified on imaging performed within RBWH, whereas imaging was not conclusive for those who underwent bilateral exploration. Histology confirmed the presence of single parathyroid adenomas in four patients, one patient had hyperplastic parathyroid tissue consistent with an adenoma, and another had a possible parathyroid adenoma. Serum calcium and PTH concentrations normalized in all patients after surgery (including those with probable histological findings). There were no maternal or fetal complications of parathyroidectomy in pregnancy.

Admissions

The mean number of inpatient hospital admissions during pregnancy was 1.5 for viable medically treated

Table 2. Mean Maternal Corrected Serum Calcium Concentrations and Medical Treatment of Women With PHPT in Pregnancy Treated at the RBWH, 1 January 2000 Through 31 December 2015

	Medical, Diagnosed <K28 (n = 12)	Medical, Diagnosed >K28 (n = 10)	Surgical (n = 6)
Patients receiving diagnosis outside of study pregnancy	7	0	1
Gestation at diagnosis for those receiving diagnosis during pregnancy, mean (SD), wk	15.9 (6.4)	33.1 (3.4)	15.8 (9.1)
Initial serum calcium level in pregnancy[a], mean (SD), mmol/L	2.7 (0.2)	2.9 (0.2)	2.9 (0.3)
Peak serum calcium level, mean (SD), mmol/L	2.8 (0.2)	3.1 (0.4) (n = 9)	3.0 (0.3)
Treatment			
IV fluid	3	3	3
Furosemide	0	1	0
Antihypertensive medication	2	4	1
Pamidronate	0	2	0
Phosphate	0	0	1
Cinacalcet	0	0	1

Data given as no. unless otherwise indicated.

[a]At the time of diagnosis or earliest serum calcium concentration in pregnancy.

patients regardless of complications and 1.3 for surgically treated patients, excluding the admission for parathyroid surgery (Table 3). The mean total length of stay was 8.8 days for medically treated patients who developed preeclampsia compared with 4.3 days for those who did not, and 3.3 days for surgically treated patients, excluding the admission for surgery (Table 3).

Maternal Outcomes

Hypertensive disorders of pregnancy

Six (30%) viable medically managed pregnancies were complicated by preeclampsia (Fig. 1) and there were three cases of pregnancy-induced hypertension among medically treated patients. Maternal hypertension was listed as either the sole indication or a contributing indication for delivery in seven (35%) viable medically managed pregnancies.

In four (20%) viable medically managed pregnancies, the babies were delivered before K37 because of preeclampsia (Fig. 1). Each of the four mothers had a history of chronic hypertension. One patient had a prior pregnancy complicated by PHPT. Peak serum calcium concentration during the first pregnancy was 2.63 mmol/L and the patient underwent induction of labor at K38 for type 2 diabetes mellitus and hypertension. Peak serum calcium concentration during the second pregnancy was 2.71 mmol/L and the patient underwent cesarean delivery (CD) at K36 because of preeclampsia and fetal distress. Mean peak serum calcium level for the remaining patients whose babies were delivered preterm because of preeclampsia was 3.37 mmol/L (SD, 0.42 mmol/L). PHPT was diagnosed in these patients between K28 and K32.

In surgically treated patients, there were no cases of preeclampsia and two cases of pregnancy-induced hypertension. All surgically treated patients delivered their babies after K37 (Fig. 1).

Delivery

Fifty percent of viable medically and surgically treated patients underwent CD. CD for hypertensive disorders was performed in three medically treated patients before K37. No CDs were performed because of hypertensive disorders in surgically treated patients.

Miscarriage

Two medically treated patients had early miscarriages (Fig. 1). One occurred at K12 and was a twin pregnancy.

Table 3. Mean Number of Admissions and Total Length of Stay for Women With Viable Pregnancies Complicated by PHPT and Treated at the RBWH, 1 January 2000 to 31 December 2015

	Medical Patients		Surgical Patients (n = 6)	Surgical Patients (excluding admission for surgery) (n = 6)
	PE (n = 6)	No PE (n = 14)		
Admissions, mean (SD), No.	1.5 (1.2)	1.5 (1.1)	2.3 (0.5)	1.3 (0.5)
Total length of stay, mean (SD), d	8.8 (4.2)	4.3 (3.7)	6.3 (3.0)	3.3 (1.4)

Two miscarriages excluded.

Abbreviation: PE, preeclampsia.

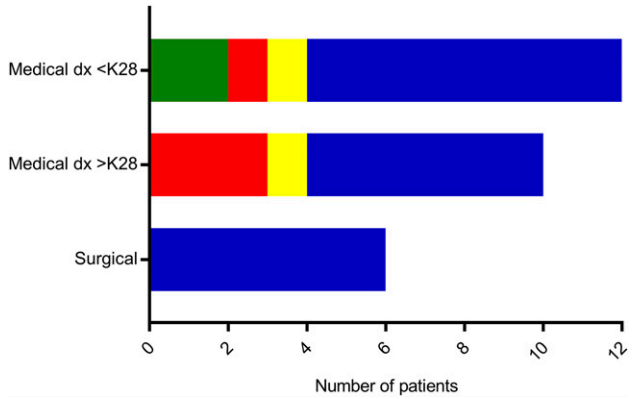

Figure 1. Pregnancy outcomes for women with primary hyperparathyroidism treated at the RBWH, 1 January 2000 through 31 December 2015. dx, diagnosed. Blue denotes delivery >K37 no PE; yellow, delivery >K37 PE; red, delivery <K37 PE; and green, miscarriage. PE, preeclampsia.

Serum calcium concentration was 2.57 mmol/L at the time of the miscarriage and cytogenetics were normal. This patient had normal pregnancies before and after the miscarriage. Another patient had a missed miscarriage at K13, at which time her serum calcium level was 2.78 mmol/L. She was also taking warfarin for a thrombophilia and previous thrombosis.

Other complications

There were no cases of maternal pancreatitis or hypercalcemic crisis.

Neonatal outcomes

Admission to NICU

The four neonates born to medically treated patients before K37 required admission to the NICU for complications related to prematurity (Table 4). The mean length of stay in NICU was 19.8 days (range, 2 to 42 days). One of these babies had mild hypocalcemia (serum calcium concentration, 1.94 mmol/L) that did not require treatment.

One baby, born at K38 to a mother who underwent parathyroid surgery at K32, required 32 days in the NICU because of persistent pulmonary hypertension of the newborn. The baby was born via CD after decreased fetal movements were noted and an abnormal fetal cardiotocograph was recorded (Table 4).

Other neonatal outcomes

The mean birthweights of babies of medically and surgically treated patients are shown in Table 4 and reflect the timing of delivery. Other than the case of asymptomatic neonatal hypocalcemia outlined previously, there were no cases of hypocalcemia among neonates born to medically or surgically treated mothers. However, neonatal calcium concentrations were not measured in 12 medically treated neonates and four surgically treated neonates.

Discussion

Key findings

Most patients with PHPT in pregnancy between 2000 and 2015 at RBWH were treated medically. This appeared to be due to the gestational age at diagnosis as well as the degree of elevation of serum calcium concentrations: All but one patient with PHPT diagnosed in trimester 3 were treated medically, and most (83%) patients with PHPT diagnosed before the end of trimester 2 who pursued medical treatment had serum calcium concentrations <2.85 mmol/L in early pregnancy.

The findings from the cohort in this study suggest the major morbidity associated with medical management of PHPT with mild to moderate hypercalcemia may be increased rates of preeclampsia. Preeclampsia developed in 30% of viable medically managed pregnancies, compared with 3% to 7% among the general population (9, 10). Other authors also have reported increased rates of preeclampsia in up to 25% of patients with PHPT during pregnancy (7). Three of the patients delivering preterm because of preeclampsia had serum calcium concentrations >3 mmol/L. This suggests an

Table 4. Outcomes of Neonates Born to Women With PHPT Treated at the RBWH, 1 January 2000 Through 31 December 2015

	Medical, Diagnosed <K28 (n = 10)	Medical, Diagnosed >K28 (n = 10)	Surgical (n = 6)
Birthweight, mean (SD), g			
<K37	2180[a] (n = 1)	1633 (738) (n = 3)	N/A
>K37	3477 (445) (n = 9)	3725 (475) (n = 7)	3368 (575)
NICU stay >1 d, No.			
<K37	1	3	0
>K37	0	0	1
Neonatal hypocalcemia, No.	0	1	0

Two miscarriages excluded.

Abbreviations: K37, 37 weeks gestation; N/A, not applicable.

[a]SD incalculable, n = 1.

association between severity of maternal hypercalcemia and preeclampsia risk; however, the data must be interpreted with caution owing to the small sample size and lack of adjustment for other risk factors.

A history of chronic hypertension was present in all patients who delivered their babies before K37 in this study and chronic hypertension is a known risk factor for preeclampsia. Twenty percent of viable medically managed pregnancies in this study were delivered before K37, because of preeclampsia, and 75% of these neonates required prolonged NICU admission. Rates of preterm delivery in Australia in 2012 were 9% (11) and between 9.5% and 10.5% in the United States between 2007 and 2015 (12).

Preeclampsia was associated with an increased need for hospitalization and medical interventions, although whether this was statistically significant is unknown. The CD rate was also high at 50% of deliveries in our study, compared with the general rate across Australia, which is ~33% (13). If CDs performed for hypertensive disorders are excluded, then the rate approaches that of the general population, at 35% for medically treated patients. Estimates of CD rates should be interpreted with caution given the small number of patients.

The two miscarriages managed at RBWH could not be attributed to PHPT: One was a twin pregnancy and occurred in a mother who had successful pregnancies before and after the miscarriage; the other occurred in a patient taking warfarin who had multiple medical comorbidities.

Guidelines for management of PHPT in pregnancy

The literature on PHPT in pregnancy comprises case reports and retrospective cohort studies, making it difficult to establish when the risks of medical management outweigh the risks of surgery in pregnancy. Recommendations for threshold maternal serum calcium concentrations above which surgery should be pursued vary. Some authors suggest surgery in trimester 2 for all pregnant patients with PHPT regardless of the serum calcium concentration (4, 14, 15). Others suggest surgery only if patients are symptomatic with serum calcium concentration >12 mg/dL (2.99 mmol/L) (3). Kelly (2) proposed that patients with serum calcium levels >11.5 mg/dL (2.87 mmol/L) be treated surgically, preferably in trimester 2. Many authors are unsure when to pursue surgery for patients in trimester 3 (2, 4, 15, 16).

Complications of PHPT in pregnancy relative to maternal serum calcium concentrations

Some authors have raised concerns that that the risk of miscarriage in mothers with PHPT is elevated relative to the general population, even at low maternal serum calcium concentrations (17, 18). However, these studies are limited by selection bias and had no control group to account for other causes of fetal demise. Hirsch *et al.* (19) provided more reassuring data with regard to the miscarriage risk associated with mild maternal hypercalcemia. Their retrospective cohort study of 74 pregnant women with a mean serum calcium concentration of 2.72 mmol/L showed no increase in spontaneous abortions relative to control participants without PHPT (19). Abood and Vestergaard (20) also performed a retrospective cohort study of 1057 Danish women with PHPT compared with matched control women and found no difference in the rate of abortions. Maternal serum calcium concentrations were not documented in their study.

The risk of stillbirth has declined over time, most likely because of earlier detection and better management (8). Shangold *et al.* (8) identified 11 stillbirths among 159 PHPT pregnancies, comprising 10 cases between 1930 and 1970 and 1 case in 1975. Wagner *et al.* (21), compared maternal serum calcium concentrations of women with PHPT who suffered stillbirth with those who delivered live infants. There was no significant difference in maternal serum calcium concentrations, but the mean calcium concentration in both groups was high, at 15 to 15.9 mg/dL (3.74 to 3.97 mmol/L).

Most reports of neonatal tetany due to hypocalcemia also precede 1980, with rates declining well before then (8). Limited data suggest the risk of neonatal tetany is proportional to the degree of maternal hypercalcemia. Wagner *et al.* (21) identified 11 cases of neonatal tetany in which mean peak maternal serum calcium concentration was 15.7 mg/dL (3.92 mmol/L), compared with 12.3 mg/dL (3.07 mmol/L) in two women among whom there were three neonates without tetany. However, it should be noted that neonatal tetany has occurred at serum calcium concentrations <3 mmol/L (22, 23) and that there is a case report of dichorionic twins born to a mother with PHPT in which only one twin suffered neonatal seizures (23). There are also case reports of neonatal hypocalcemia persisting to 3 months (24) and 12 months (25) of age, although the latter case was complicated by kidney disease in the neonate, and maternal serum calcium concentrations during pregnancy were unknown.

Other life-threatening complications, such as maternal pancreatitis and hypercalcemic crisis, are rare and occur at high maternal serum calcium concentrations. There have been 13 reported cases of pancreatitis in patients with PHPT during pregnancy (15, 26, 27) and of the 10 cases published in English or German, only one had a serum calcium level <3 mmol/L (28). Hypercalcemic crisis usually occurs when serum calcium level is >3.5 mmol/L (4, 29) and can be precipitated by the loss

of placental transfer of calcium to the fetus at delivery and high levels of PTH-related peptide during lactation (6, 16). However, there are seven documented cases of hypercalcemic crisis occurring during pregnancy, sometimes in association with pancreatitis (29).

Risks and benefits of medical therapy

First-line medical therapy to lower maternal serum calcium level is IV hydration with or without furosemide (7, 30). This is thought to be relatively safe provided iatrogenic dehydration that can lead to placental hypoperfusion and oligohydramnios is avoided (31). The efficacy of these measures is variable (4, 16). Vitamin D replacement therapy, if maternal stores are low, can also help reduce the parathyroid reaction to vitamin D deficiency and reduce the risk of hypocalcemia in the newborn (6).

Calcitonin, which opposes the effects of PTH on bone resorption, is also thought safe because it does not cross the placenta (7), but it only provides short-term improvement in serum calcium level (3). Other medical options include magnesium sulfate, which can lower serum calcium by multiple mechanisms (32), and cinacalcet, a calcimimetic, for which there are limited safety data in pregnancy. There have been no teratogenic adverse effects of cinacalcet identified in animal models, to our knowledge, but decreased fetal body weight in conjunction with decreased maternal food consumption and body weight gain were observed in rats (33). There are three published human case reports of cinacalcet therapy in the third trimester of pregnancy with no adverse fetal effects, but patient tolerance was variable (30). One surgically treated patient in this series received cinacalcet with no adverse maternal or infant effects noted (30). Due to the limited published experience with cinacalcet, there are insufficient data to recommend its use in pregnancy. We would encourage others to report cases of use to enhance the literature in this area.

It is generally recommended that phosphate be avoided because it has limited efficacy (4) and may cause intra- and extravascular calcium phosphate deposition, resulting in organ failure (34). Bisphosphonate therapy is also contraindicated because of possible adverse effects on fetal endochondral bone development (35); although there have been some case reports of use during pregnancy without adverse effects, it is recommended bisphosphonate therapy only be used in pregnancy if hypercalcemia is life threatening (7). Receptor Activator of Nuclear Factor-κ B Ligand antagonists are also teratogenic in animals and contraindicated in pregnancy.

Risks and benefits of parathyroid surgery in pregnancy

Provided residual parathyroid function is retained, parathyroid surgery restores serum calcium concentrations to normal. It is important to note that although parathyroid surgery has been shown to decrease cardiovascular death rates in the nonpregnant population (36), there is no evidence that parathyroid surgery negates the risk of subsequent preeclampsia attributable to PHPT: This risk remains elevated relative to the general population 2 to 5 years after parathyroidectomy (5). The reason for surgery, therefore, needs to be carefully considered.

Most authors recommend surgery be performed during trimester 2 if possible, to minimize the risk of precipitating preterm delivery and to avoid fetal exposure to anesthetic agents during organogenesis (6, 7). In experienced hands, the risk of maternal complications, such as laryngeal nerve palsy and postoperative hypocalcemia, is low, at 1% to 3% (7). Surgery during pregnancy also ensures surgical treatment is not delayed during busy parental years, and minimizes long-term complications of PHPT.

Surgical techniques and anesthesia appear to have improved over time. There were no complications of parathyroid surgery in our study or among five patients treated between 2009 and 2013 described by Walker *et al.* (37). In contrast, Kristofferson *et al.* (14) identified 23 pregnancies complicated by PHPT between 1947 and 1983 who underwent parathyroid surgery during pregnancy. There were two stillbirths and three cases of neonatal tetany among those who underwent surgery, giving a total fetal complication rate of 22% (14). Notably, none of these complications occurred in women with asymptomatic PHPT (14).

Schnatz and Thaxton (38) reviewed outcomes among 16 women who underwent parathyroid surgery during trimester 3 between 1970 and 2004. Women in this study had either symptomatic disease or severe hypercalcemia (>3 mmol/L) (38). Two fetal complications potentially attributable to surgery were identified: premature rupture of membranes, leading to delivery of a preterm infant and respiratory distress syndrome; and stillbirth associated with preterm labor (38). These early studies suggest that parathyroid surgery in the setting of severe hypercalcemia carries added risk.

Limitations

The current study was retrospective and may not have identified all patients with PHPT if they did not have a PTH assay performed at RBWH in the same year or year prior to miscarriage or delivery. Biochemistry is not part of routine antenatal testing, so asymptomatic cases of PHPT may also have gone undiagnosed. The study included 11 patients with probable PHPT, and although we consider the likely diagnosis to be PHPT, it is possible that some cases of familial hypocalciuric hypercalcemia may have been included in the study.

The small sample size, particularly of the surgically treated group, precluded extensive examination of risk factors contributing to adverse outcomes. Surgically treated cases were also relatively recent. We do not consider that medical treatment changed significantly over the study period, but it is possible that surgical outcomes have improved with time.

In conclusion, most patients with PHPT in pregnancy at RBWH between 2000 and 2015 were treated medically. There were no maternal or late fetal deaths attributable to PHPT during this time. The major morbidity associated with medical treatment was preterm delivery, because of preeclampsia. It is not known whether parathyroid surgery negates the risk of preeclampsia due to PHPT, but surgery in trimester 2 appears to be safe. Surgery was uncomplicated for the one patient who underwent surgery in trimester 3, but more information is needed on the risks of surgery in late pregnancy.

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