


## CASE REPORT OPEN ACCESS

# Pregnancy Complicated by Primary Hyperparathyroidism—A Case Report on the Use of Cinacalcet

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## ABSTRACT

Adverse outcomes are common in pregnant women with primary hyperparathyroidism, but no established guidelines are available. Parathyroidectomy is advised in the second trimester. Cinacalcet, though category C, appears to be safe and may be used for moderate to severe hypercalcemia. Aspirin should be considered for preeclampsia prevention.

## 1 | Introduction

Primary hyperparathyroidism (PHPT) is a rare condition during pregnancy, accounting for roughly 1% of all PHPT patients [1]. Several studies have reported a significantly increased risk of adverse maternal and fetal/neonatal outcomes [1–9]. This risk is strongly correlated with serum calcium levels, particularly when the total calcium concentration exceeds 2.85 mmol/L (11.42 mg/dL) [4]. Pregnant women with PHPT frequently experience symptoms related to hypercalcemia, such as malaise, nausea, vomiting, fatigue, polyuria, and muscle weakness [10]. Additionally, the risk of pancreatitis and nephrolithiasis is increased [2, 10]. Complications such as hyperemesis gravidarum, gestational hypertension, preeclampsia/eclampsia, miscarriages, and premature birth may also occur [1–9]. Fetal and neonatal complications include oligohydramnios, intrauterine growth restriction, kidney and myocardium calcifications, arrhythmias, stillbirth, neonatal hypocalcemia, and neonatal death [1–9, 11].

Scientific evidence on managing PHPT during pregnancy is scarce. The recommendations of the ESE (European Society Endocrinology) Educational Program of Parathyroid Disorders (PARAT 2021) suggest that pregnant women with PHPT and an albumin-adjusted total calcium level > 2.85 mmol/L (> 11.42 mg/dL) and/or > 0.25 mmol/L (> 1 mg/dL) above the upper limit normal (ULN) and/or an ionized calcium > 1.45 mmol/L (> 5.81 mg/dL) should undergo parathyroidectomy (PTX) in the second trimester [10]. For those with calcium levels below these thresholds, conservative treatment, involving hydration and avoiding excessive calcium intake, is advised [10, 12]. If surgery is not an option, cinacalcet may be considered for women with moderate hypercalcemia (albumin-adjusted serum calcium > 3.0 mmol/L [> 12 mg/dL]) [12–14]. The United States Food and Drug Administration (FDA) classifies cinacalcet as a category C drug, indicating that it has been used by a limited number of pregnant and childbearing-age women, without an increased risk of malformations or other harmful effects on the fetus [15].

Juliana Gonçalves and Gonçalo Freitas should be considered co-first authors and have contributed equally to this work.

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We describe a case of a pregnant woman with moderate hypercalcemia due to PHPT who was treated with cinacalcet until PTX could be performed in the second trimester, detailing the treatment and outcomes.

2 | Case History

In February 2023, a 25-year-old pregnant Caucasian woman at 8th week of gestation was referred to the outpatient, multidisciplinary department of Endocrinology–Obstetrics for the management of PHPT.

The identification of the diagnosis of PHPT associated with moderate hypercalcemia (serum calcium 3.25 mmol/L [13 mg/dL]) was made in October 2022. The patient presented a one-year history of recurrent bilateral nephrolithiasis, complicated by acute pyelonephritis, and had received bilateral stone extraction l through retrograde intrarenal surgery (RIRS). At that moment, she showed no additional symptoms, signs, or complications like bone fractures, and was not taking any medications. She reported a smoking history of 2.5 pack-years, and her family history showed no calcium or parathyroid diseases. Laboratory results verified PHPT, a vitamin D deficiency, and normal kidney function (Table 1). A neck ultrasound (Figure 1A) and a 99mTc-sestamibi scan (Figure 1B), conducted at the request of the Surgery department, revealed an anomalous left inferior parathyroid gland. Hypercalcemia was treated with oral fluids, and cholecalciferol supplementation started. A left inferior PTX was intended; however, the patient later became pregnant.

At the first antenatal visit, she was at 9 weeks of gestation and reported fatigue, constipation, and back pain, which had been

TABLE 1 | Laboratory results at diagnosis of primary hyperparathyroidism.

Analytical parameter	Value	Normal range
Albumin-adjusted total calcium	3.25 mmol/L	2.10–2.55
Intact parathormone	20.5 pmol/L	1.06–6.89
Phosphorous	0.77 mmol/L	0.87–1.45
Magnesium	0.80 mmol/L	0.76–1.03
25-OH-vitamin D	47.5 nmol/L	> 75 nmol/L
Creatinine	0.05 mmol/L	0.06–0.08
eGFR	125 mL/min/1.73m <sup>2</sup>	—
24-h urinary calcium	8.55 mmol	2.5–7.5
TSH	0.68 mUI/L	0.35–4.94
Free T4	13.0 pmol/L	9.01–19.1
Calcitonin	<0.58 pmol/L	<1.46

Note: eGFR: Estimated Glomerular Filtration Rate—was calculated using the CKD-EPI equation.  
Abbreviation: TSH, thyroid stimulating hormone.

present for 5 weeks. She was on daily folic acid 5 mg, cholecalciferol 5328 IU, magnesium 520 mg, and a prenatal vitamin supplement. The physical examination showed no findings. Her weight was 71 kg, and the blood pressure was 122/77 mmHg.

3 | Investigation

An initial evaluation at 10 weeks and 1 day of gestation revealed an albumin-adjusted total calcium of 3.13 mmol/L (12.5 mg/dL) and an intact parathormone (iPTH) of 17.8 pmol/L (167.4 pg/mL). Detailed analytical results are provided in Table 2. A Next Generation Sequencing (NGS) panel for PHPT was requested, but no variants were identified in the analyzed genes (*AP2S1*, *CASR*, *CDC73*, *CDKN1A*, *CDKN1B*, *CDKN2B*, *CDKN2C*, *GCM2*, *GNA11*, *MEN1*, *PTH*, *RET*, *TRPV6*).

4 | Treatment

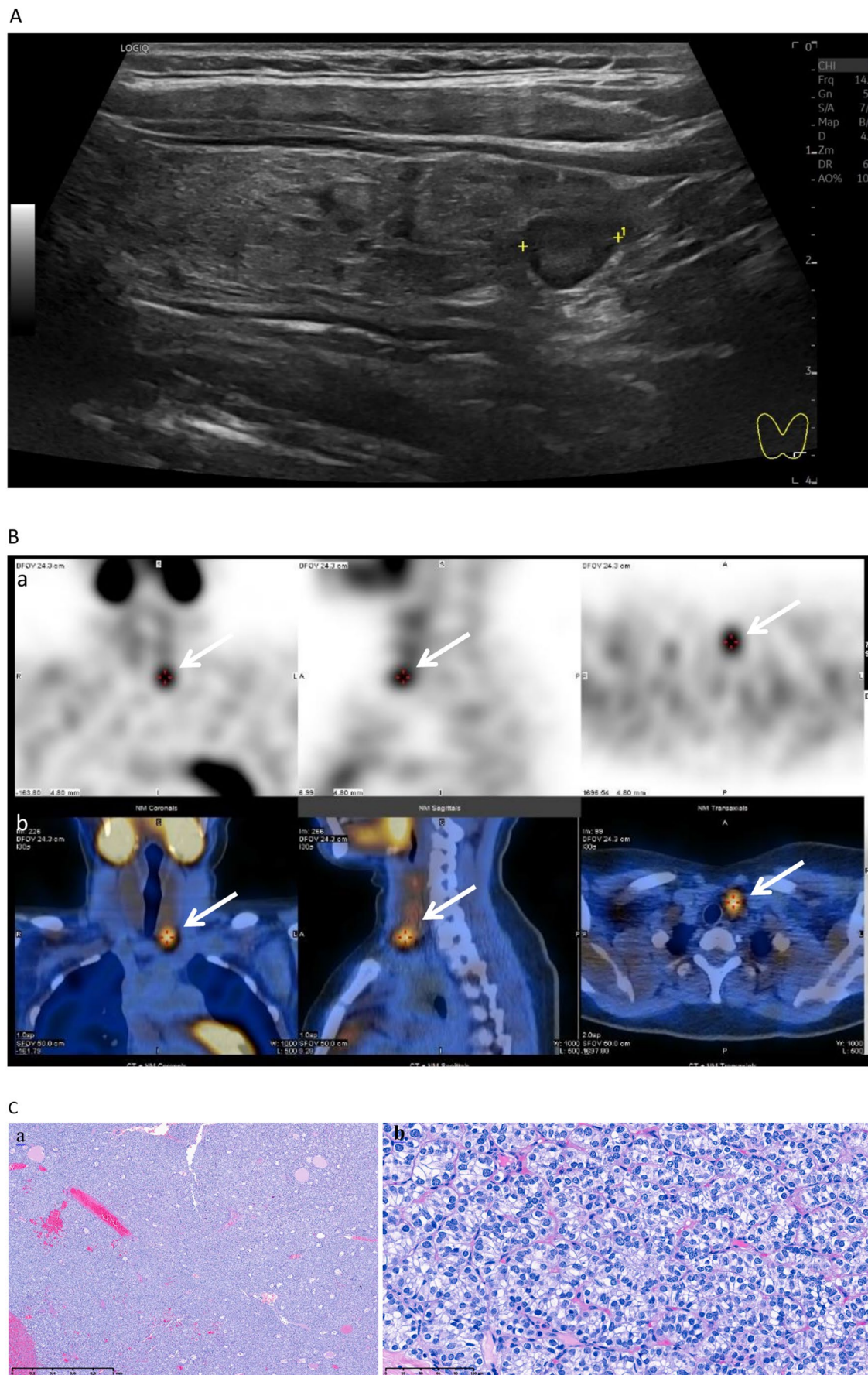
High oral fluid intake was recommended, and aspirin 150 mg was prescribed for preeclampsia prevention. After discussing the risks and benefits with the patient, and obtaining approval from our Ethics Committee, cinacalcet was initiated until PTX could be performed in the second trimester. An initial dose of 30 mg daily started at 12 weeks and 1 day of gestation and increased to 60 mg daily after 3 weeks (Figure 2). The cinacalcet dose was adjusted due to an increase in albumin-adjusted total calcium levels to 3.52 mmol/L (14.1 mg/dL), which subsequently decreased to 3.39 mmol/L (13.6 mg/dL) (Figure 2). The patient did not report any gastrointestinal symptoms.

At 16 weeks and 1 day of gestation, left inferior PTX was successfully performed. One day after PTX, iPTH decreased to 0.37 pmol/L (3.5 pg/mL) and albumin-adjusted total calcium to 2.63 mmol/L (10.5 mg/dL) (Table 2, Figure 2). After PTX, calcium carbonate 1500 mg, three times per day, and calcitriol 0.25 µg, twice daily, were started. Histology was consistent with parathyroid adenoma measuring 15 × 14 × 7 mm (Figure 1C). Serum calcium levels remained within normal range (2.3–2.5 mmol/L [9.2–10.0 mg/dL]), and doses of calcium carbonate and calcitriol were gradually tapered until 1500 mg daily and 0.25 µg daily, respectively (Figure 2).

Due to symptomatic nephrolithiasis complicated by right uretero-hydronephrosis, stone fragmentation with holmium: YAG laser via RIRS and placement of a ureteral double J stent were performed at 20 weeks gestation.

5 | Outcome and Follow-Up

Labor was induced at 39 weeks gestation. She delivered a 2.856 kg healthy male newborn with an Apgar score of 9 at 1 min and 10 at 5 and 10 min. The newborn did not require neonatal intensive care and had no neonatal complications. The patient’s serum albumin-adjusted total calcium remained within the normal range (2.4 mmol/L [9.6 mg/dL]) (Figure 2). At hospital discharge, calcium supplementation was discontinued, but calcitriol 0.25 µg and cholecalciferol were maintained.



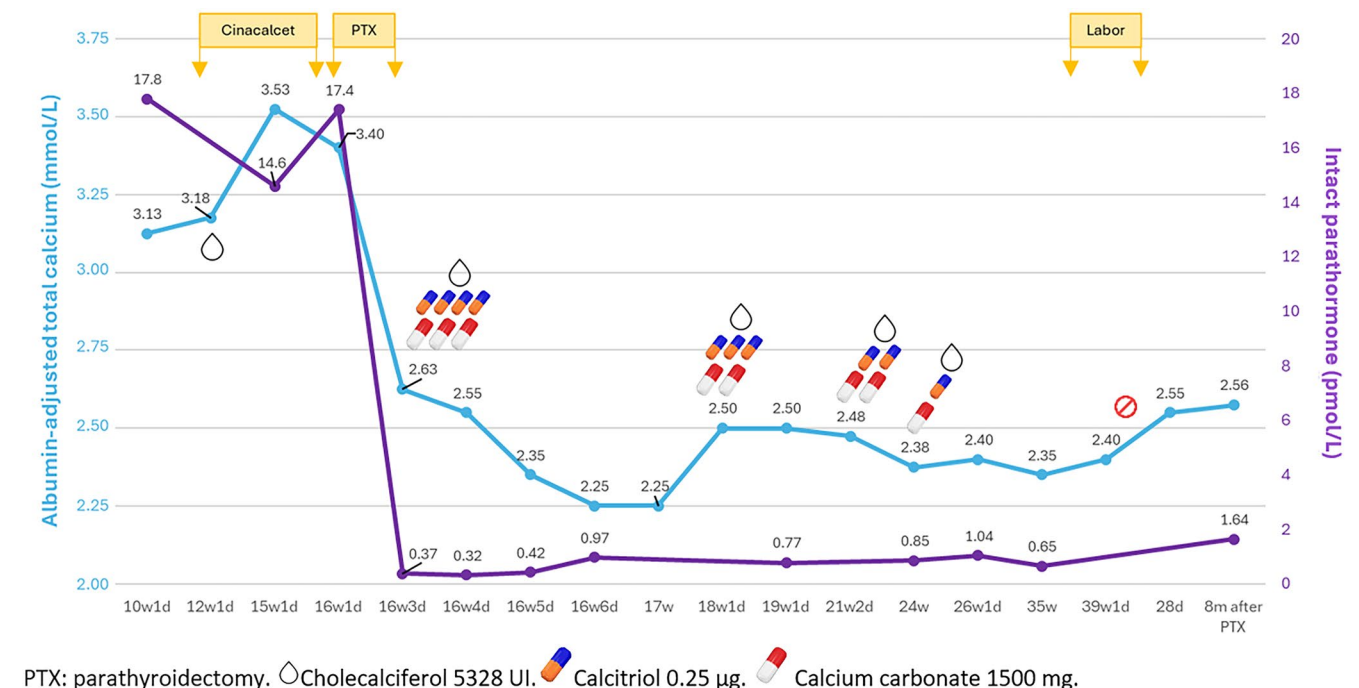
**FIGURE 1** | Legend on next page.

**FIGURE 1** | (A) Neck ultrasound images showing a hypoechogenic nodule (arrow) measuring 9×7 mm, located posterior to and separate from the inferior third of left thyroid lobe. (B) The 99 m Tc-sestamibi scan (a) and axial computed tomography fusion with sestamibi (b) showed a radio-tracer uptake focus (arrow) located inferior to the left thyroid lobe. (C) Histopathological examination revealing a parathyroid adenoma. A well-circumscribed tumor, without stromal fat (a), composed of chief cells (b) arranged in sheets or nests in a delicate capillary network.

**TABLE 2** | Laboratory results during pregnancy.

Analytical parameter	10w1d Initial evaluation	16w1d Before PTX	16w3d 1 day after PTX	39w Labor
Albumin-adjusted total calcium, mmol/L	3.13	3.39	2.63	2.40
Intact parathormone, pmol/L	17.8	17.4	0.37	—
Phosphorous, mmol/L	0.74	0.77	0.67	0.81
Magnesium, mmol/L	0.87	0.67	0.60	0.65
25-OH-vitamin D, nmol/L	92.5	—	—	—
Creatinine, mmol/L	0.05	—	—	0.05
eGFR, mL/min/1.73m <sup>2</sup>	130	—	—	122

Note: eGFR: Estimated Glomerular Filtration Rate—was calculated using the CKD-Equation.



**FIGURE 2** | Trend of serum albumin-adjusted total calcium (blue line) and serum PTH (purple line figure) at various stages of pregnancy and the postpartum period.

At the postpartum visit on the 35th day of puerperium, the patient had discontinued calcitriol and exhibited normal calcium levels (2.55 mmol/L [10.2 mg/dL]). Eight months after PTX, calcium (2.65 mmol/L [10.3 mg/dL]) and iPTH (1.64 pmol/L [15.5 pg/mL]) levels were normal (Figure 2). The infant showed normal growth, as well as normal motor and cognitive development at 10 months of age.

## 6 | Discussion

The management of PHPT during pregnancy is challenging. A recent systematic review analyzing 382 cases of PHPT during pregnancy found that 108 (28.3%) were diagnosed while pregnant, and 274 (71.7%) were treated conservatively (hydration, oral phosphate, magnesium sulfate and/or cholecalciferol



supplementation) [5]. Those who underwent PTX experienced fewer maternal, fetal, or neonatal complications (9.1% vs. 28.9%), a lower stillbirth rate (2.4% vs. 33.8%), and a lower caesarean section rate (2.8% vs. 6.9%) compared to those managed conservatively [5]. PTX performed in the second trimester was associated with a lower complication rate than when performed in the third trimester (4.5% vs. 22.1%) [5].

Therefore, PTX is a safe and effective treatment option, particularly when performed in the second trimester, as was observed in our case report. Concerns about PTX during pregnancy are largely outdated [5]. Modern anesthesia techniques are associated with fewer teratogenic effects [16], and current surgery approaches, such as unilateral neck exploration and minimally invasive PTX, have reduced surgery duration and the risks of preterm labor, teratogenicity, or fetal loss [5]. Although this recommendation is based solely on observational data with the potential risk of confounding and bias, current literature and practice strongly support surgery over conservative treatment in this setting [4, 10]. After PTX, it is essential to maintain calcium levels within the normal range. Therefore, in our case, we prescribed calcium and active vitamin D following PTX to prevent severe and long-standing maternal hypocalcemia, which may lead to fetal secondary hyperparathyroidism, skeletal demineralization, and an increased risk of intrauterine fractures, low birth weight, and fetal death [10, 12]. Therefore, during PHPT management, vigilant fetal monitoring is crucial to detect early complications. Ultrasounds should focus on fetal growth, amniotic fluid levels, fetal movements, and the detection of any abnormal structures or calcifications. Regular assessments, including Doppler studies and biophysical profiles, are essential to ensure the well-being of the fetus and to determine the appropriate timing of delivery.

Since the diagnosis was made before pregnancy and the patient presented with hypercalcemia, further action was required before reaching the second trimester. For symptomatic patients and/or those with moderate to severe hypercalcemia, medical treatment can be an option, either until PTX can be performed or when surgery is declined [10, 12]. While cinacalcet and calcitonin can be used during pregnancy, bisphosphonates and denosumab should be avoided as they cross the placenta [10]. Although calcitonin does not cross the placenta, it only transiently decreases calcium levels due to tachyphylaxis [10].

Cinacalcet crosses the placenta, but no significant safety concerns have been reported [10]. However, acute neonatal hypocalcemia can occur due to the drug's interference with the calcium-sensing receptor (CaSR) in the placenta, which can inhibit transplacental calcium transport and suppression of fetal PTH secretion [12]. In animal studies, teratogenic effects were observed only at human dose equivalents equal to or exceeding 180 mg/dL [17]. The effect on calcium levels was variable, likely due to varying severity of hypercalcemia, lack of CaSR sensitivity at adenoma, and/or limitation in dose escalation due to gastrointestinal adverse effects [18]. In our case, the use of cinacalcet was safe, with no reported maternal or fetal adverse events; however, its impact on calcium levels was modest, likely due to the first two factors. We found at least 17 detailed cases of women with PHPT due to benign pathology who were treated with cinacalcet during pregnancy [13, 14, 18–29] (Table 3).

The median age was 32.0 [26.5; 37.0] years, and the median dose of cinacalcet was 30 [30; 60] mg. Calcium levels decreased by  $0.45 \pm 0.22$  mmol/L ( $1.80 \pm 0.88$  mg/dL) to reach levels of  $2.69 \pm 0.26$  mmol/L ( $10.76 \pm 1.04$  mg/dL). Normalization of calcium was only achieved in four (28.6%) cases. The most common adverse effects were nausea and vomiting, reported by 8 (53.3%) patients. Premature birth occurred in six (35.3%) cases, and one (6.25%) newborn was small for gestational age. Neonatal hypocalcemia was observed in three (18.8%) newborns.

In animal studies, cinacalcet concentration in milk was higher than in plasma [30]; however, there is no data on whether it is transferred to human breast milk [10]. In such situations, a careful benefit/risk assessment should be conducted to decide whether to discontinue breastfeeding or the treatment with cinacalcet [10, 12].

PHPT can have complications beyond the elevation of calcium levels and its direct effects that can lead to adverse maternal and fetal outcomes. PTH raises cytosolic free calcium concentration in vascular smooth muscle through the PTH receptor 1, leading to vasoconstriction, which, in turn, increases peripheral vascular resistance and enhances responsiveness to sympathetic stimuli and the renin-angiotensin-aldosterone system (RAAS). Additionally, PTH may stimulate RAAS, further increasing vascular volume [31, 32]. A study involving 52 pregnant women with PHPT and 519 healthy pregnant women found that parathyroid adenoma was associated with an increased risk of preeclampsia (adjusted OR 6.89 [95% CI, 2.30, 20.58]) [33]. While PHPT may increase the risk of hypertensive disorders during pregnancy, the use of aspirin in this context, according to ACOG [34], would be based on the presence of other recognized high-risk factors rather than PHPT alone. However, we prescribed aspirin 150 mg daily from 12 weeks of gestation until delivery. The use of aspirin should be started at 12–16 weeks and maintained until delivery to provide continuous protection against preeclampsia [34]. The decision to continue or discontinue should be based on individual risk assessment by the healthcare provider, but for most women at high risk of preeclampsia, the benefits of continuing aspirin outweigh the risks, primarily for women with a lack of disease stabilization in the first trimester of pregnancy [34].

Given the potential complications during pregnancy, women with PHPT should be advised not to conceive until curative surgery has been performed and calcium levels have been normalized [10, 12]. Thus, effective contraception and comprehensive patient education are essential for women of childbearing age. This was a shortcoming in the management of our patient.

## 7 | Conclusion

This case highlights the complexities of managing PHPT with hypercalcemia during pregnancy, in which it is crucial to avoid associated complications. Our patient, who got pregnant after being diagnosed with PHPT, had a favorable outcome after PTX during the second trimester. Cinacalcet can be an option during the first trimester until surgical intervention. Medical treatment with cinacalcet can play an important role in managing moderate to severe hypercalcemia until PTX can be performed. Given the strong association between PHPT and preeclampsia/

**TABLE 3** | Summary of cases reported in the literature.

Case	Age years	Parathyroid pathology	Cinacalcet dose mg/day	Cinacalcet exposure time	Variation of calcium on cinacalcet mmol/L	Calcium on cinacalcet mmol/L	Maternal/obstetric complications	Neonatal effect
Rey et al. [19]	40	Adenoma	120	7weeks (until labor)	−0.64	2.04	Nausea Premature birth	No
Vera et al. [13]	34	Adenoma	30	8weeks (until labor)	−0.13	3.00	Nausea Premature birth	Neonatal hypocalcemia and hyperphosphatemia
Gokkaya et al. [20]	29	Adenoma	N.A.	Until PTX in 2nd trimester	No response	N.A.	N.A.	N.A.
Horton et al. [28]	21	Ectopic adenoma	60	4weeks (until PTX)	−0.53	2.68	Nauseas, vomiting	No
Garcia et al. [22]	30	Adenoma	60	2weeks (until labor)	−0.65	3.03	Preeclampsia Premature birth	Neonatal hypocalcemia
Bashir et al. [21]	37	N.A.	45	11 weeks (until labor)	−0.60	2.57	No	No
Arnold et al. [29]	24	Adenoma	N.A.	2 weeks (until PTX)	Partial response	N.A.	No	No
Ning et al. [23]	37	N.A.	90	2weeks (until labor)	< −0.20	> 2.87	Nausea, vomiting Premature birth	No
Pal et al. [24]	25	Multiglandular adenoma	30	Until labor	−0.33	2.78	Nausea, vomiting, anorexia	No
Pal et al. [24]	28	Adenoma MEN1 Syndrome	30	Until labor	−0.40	2.65	Nausea, vomiting, anorexia Premature birth	No
Pal et al. [24]	37	Adenoma	30	Until labor	−0.35	2.65	Nausea, vomiting, anorexia	SAG
Pal et al. [24]	38	Adenoma	30	Until labor	−0.43	2.60	Nausea, vomiting, anorexia	No
Eremkina et al. [18]	36	Adenoma	30	3weeks (until labor)	−0.30	2.64	No	No
Edling et al. [25]	21	Parathyromatosis	30	5 weeks (until labor)	−0.25	2.75	No	No

(Continues)

TABLE 3 | (Continued)

Case	Age years	Parathyroid pathology	Cinacalcet dose mg/day	Cinacalcet exposure time	Variation of calcium on cinacalcet mmol/L	Calcium on cinacalcet mmol/L	Maternal/obstetric complications	Neonatal effect
Horjusz et al. [14]	N.A.	N.A.	240	2 weeks (until labor)	−0.96	3.00	Premature birth	Neonatal hypocalcemia
Foster et al. [26]	28	Adenoma	30	5 weeks (until labor)	−0.58	2.43	No	No
Latif et al. [27]	40	Adenoma	15	5 days (until PTX)	No response	N.A.	N.A.	No

Abbreviations: MEN1, multiple endocrine neoplasia; N.A., not available; PTX, parathyroidectomy; SGA, small for gestational age.

eclampsia, aspirin may be considered as a preventive medication. Managing such an unusual case during pregnancy is always challenging, and treatment options not well studied in this population may be necessary after carefully weighing the risks and benefits.

#### Author Contributions

**Juliana Gonçalves:** conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft. **Gonçalo Freitas:** conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft. **Selma B. Souto:** data curation, investigation, supervision, validation, visualization, writing – review and editing. **Teresa Rodrigues:** data curation, investigation, supervision, validation, visualization, writing – review and editing. **Pedro Sá Couto:** data curation, visualization, writing – review and editing. **Sandra Belo:** data curation, investigation, visualization, writing – review and editing. **Joana Queirós:** validation, visualization, writing – review and editing.

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#### Ethics Statement

Ethical approval for this publication was obtained from our Institutional Review Board (or Ethics Committee).

#### Consent

Written informed consent was obtained from the patient for the publication of this case report.

#### Conflicts of Interest

The authors declare no conflicts of interest.

#### Data Availability Statement

The dataset for this study is available from the corresponding author upon reasonable request and ethical approval.

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