CASE SERIES

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Primary Hyperparathyroidism during Pregnancy: Two Tales with Different Outcomes

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Abstract

Primary hyperparathyroidism (PHPT) is rare in pregnancy. This condition is challenging to diagnose and manage due to the limited diagnostic and therapeutic options that are safe during pregnancy. If not diagnosed and managed in a timely manner, serious maternal and foetal complications may occur. We report two cases, one with surgical intervention and one without, to show the importance of timely surgical intervention and discuss the challenges in the management of PHPT in pregnancy.

Key words: endocrine disorders in pregnancy, primary hyperparathyroidism, pregnancy, hypercalcaemia

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a bone and mineral metabolism disorder caused by the autonomous secretion of parathyroid hormone (PTH). PHPT is rare in pregnancy, with a quoted incidence of less than 1% of all women with PHPT.[1,2] PHPT is caused by an increased secretion of parathyroid hormone (PTH) by one or more of the four parathyroid glands resulting in hypercalcaemia. Most commonly, PHPT is due to a parathyroid adenoma (85–95%), followed by parathyroid hyperplasia and rarely parathyroid carcinoma (less than 1%). PHPT poses serious complications for the mother and foetus. PHPT during pregnancy is challenging to diagnose and difficult to manage. The diagnosis of PHPT in pregnancy is often delayed due to the non-specific and subtle symptoms of the disorder, such as fatigue, nausea and vomiting which are frequently demised as symptoms commonly present during pregnancy. Moreover, as opposed to diagnosing PHPT outside of pregnancy where a battery of tests can be done including imaging involving ionising radiation and nuclear isotopes, the safest imaging for diagnosing PHPT in pregnancy is confined to an ultrasound of the neck which has a lower yield. Furthermore, many therapeutic options for the medical management of PHPT are not recommended in pregnancy, making parathyroidectomy the standard-of-care approach in the treatment of PHPT including PHPT during pregnancy.[3]

Prior to the recent expert consensus released by the European Society of Endocrinology (ESE) in 2022 which remains the only well-recognised international consensus,[4] there were no guidelines or consensus on the management of PHPT during pregnancy that could be widely implemented globally. The ESE expert consensus recommended parathyroidectomy in the second trimester of pregnancy for pregnant women with PHPT and serum-corrected calcium levels >2.85 mmol/L and/or >0.25 mmol/L above ULN and/or an ionised calcium >1.45 mmol/L.[4] For calcium levels below the above-mentioned thresholds, therapeutic options of surgery versus conservative management should be offered to the patient, and a shared decision should be made.[4]

We present two cases of PHPT diagnosed in pregnancy, one with a favourable maternal and foetal outcome after a timely parathyroidectomy and another with a fatal foetal complication when surgery is refused. Through the two cases described below, the authors would like to show the importance of timely surgical intervention in the management of PHPT during pregnancy. The authors emphasize the importance of having a high index of suspicion for serious diseases and the need for further investigations when there is an atypical presentation of symptoms. The management described in both cases adheres to the ESE consensus.

CASES

Case 1

A 35-year-old female in her third pregnancy presented at 27 weeks of gestation with prolonged nausea and vomiting up to her second trimester of pregnancy. There was no

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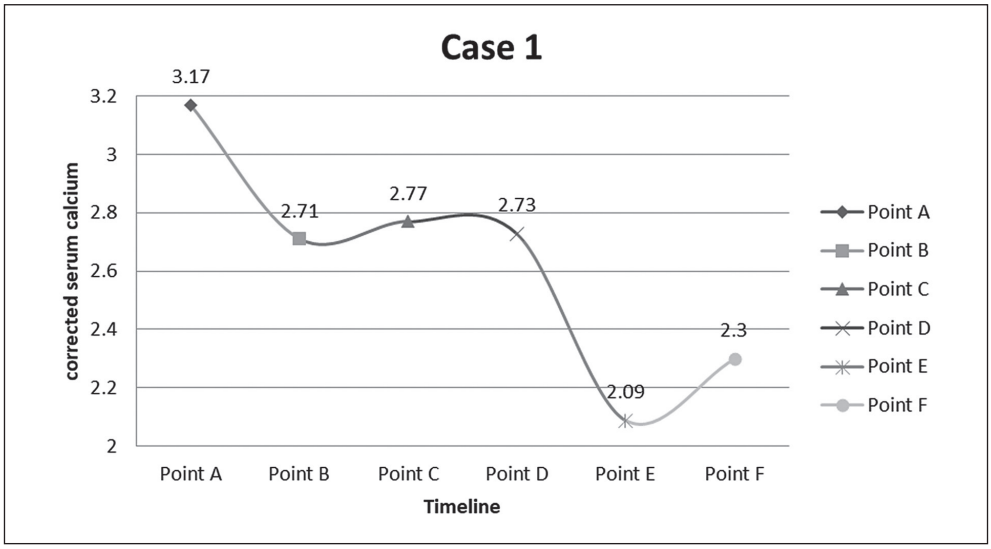

Figure 1. Serial corrected serum calcium levels for Case 1.

Point A: Upon initial admission; Point B: After inpatient intravenous rehydration with forced diuresis; Point C: After outpatient oral rehydration; Point D: Upon elective admission for parathyroidectomy; Point E: Post parathyroidectomy (when not requiring IV Calcium infusion); Point F: Upon outpatient follow-up (more than 2 months post parathyroidectomy).

history of miscarriage. Given the atypically prolonged symptoms, further workup was done. Blood results showed a raised corrected serum calcium of 3.17 mmol/L (reference range: 2.20-2.65 mmol/L) and normal renal function. Other blood investigations are shown in Table 1. Ultrasound of the neck showed an enlarged left superior parathyroid gland measuring 8 x 9 x 19 mm. She was admitted to the ward, and her corrected serum calcium levels reduced to 2.71 mmol/L after 7 days of intravenous rehydration with forced diuresis. She requested discharge against medical advice because of home commitments. Repeated corrected serum calcium increased after a 1-week trial of outpatient oral rehydration (Figure 1). Given failed conservative therapy and the huge adverse implications of hypercalcemia on the mother and foetus, a multi-disciplinary discussion and a family conference were conducted. A decision was reached to perform a left superior parathyroidectomy, which was done at 29 weeks of gestation. Histopathological examination was consistent with a left parathyroid adenoma. Her serum calcium returned to normal following parathyroidectomy, and her nausea and vomiting resolved. Subsequently, she presented at 38 weeks of gestation in the latent phase of labour and an emergency caesarean section was done for poor progress of labour. She delivered a healthy male infant with a birth weight of 3.35 kg.

Case 2

A 39-year-old female in her fifth pregnancy presented at 19 weeks of gestation with a recurrent urinary tract infection (UTI). There was no history of miscarriage. Given recurrent UTI in pregnancy, further investigations were done to try to ascertain the cause. Blood results during admission revealed corrected serum calcium of 2.87 mmol/L and normal renal function. Other blood investigations are shown in Table 1. Ultrasound of the neck showed an enlarged left inferior parathyroid gland measuring 17 x 12 x 22 mm and multiple American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) category 4 thyroid nodules. After 9 days of inpatient intravenous rehydration with forced diuresis, repeated corrected serum calcium normalized (Figure 1). Parathyroidectomy with hemithyroidectomy was advised after fine needle aspiration cytology (FNAC) of thyroid lesions. She refused FNAC and was desirous for discharge, and refused any further intervention. She was advised to drink 3 litres of fluid per day. A follow-up appointment was scheduled 1 week later to decide on further management after a multi-disciplinary discussion. Six days after discharge, she noticed no foetal movement while at home and decided to seek medical attention. A diagnosis of intrauterine death was made, and she was admitted to the obstetric ward for termination of pregnancy. Her corrected serum calcium

Table 1. Other relevant blood investigations

	Serum phosphate (reference range 0.81-1.45 mmol/L)	Alkaline phosphatase (reference range 30-120 U/L)	Intact PTH (reference range 14.9-56.9 pmol/L)	25-Hydroxy Vitamin D (nmol/L)	Calcium clearance to creatinine clearance ratio*
Case 1	0.56	601	346.0	28.03	0.016
Case 2	0.67	121	139.4	17.74	0.013

PTH: Parathyroid hormone.
*Calculated using the Hammersmith urine calcium to creatinine ratio [urine calcium (mmol/L) × (serum creatinine (μmol/L)/1000 divided by serum calcium (mmol/L) × urine creatinine (mmol/L)].

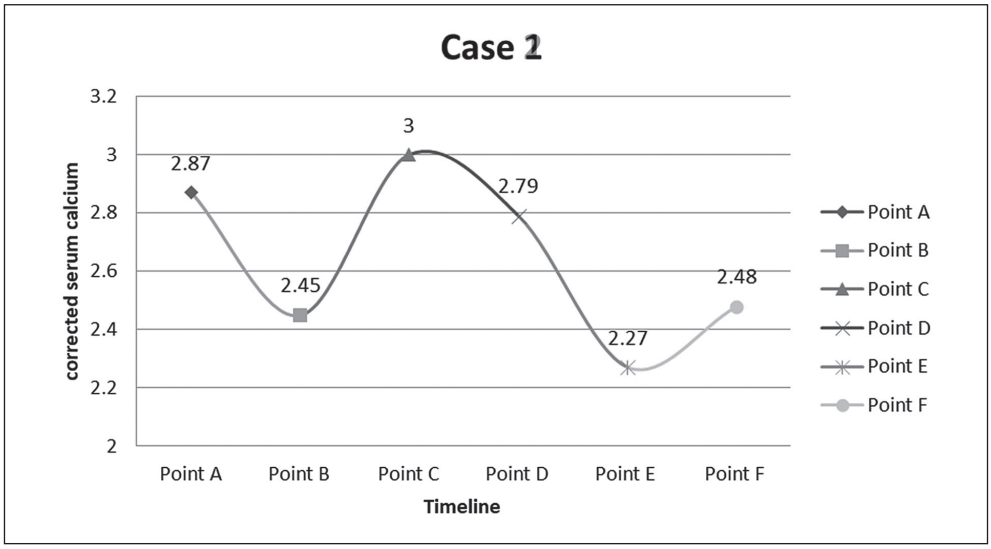

Figure 2. Serial corrected serum calcium levels for Case 2.

Point A: Upon initial admission; Point B: After inpatient intravenous rehydration with forced diuresis; Point C: After outpatient oral rehydration; Point D: Upon elective admission for parathyroidectomy; Point E: Post parathyroidectomy (when not requiring IV Calcium infusion); Point F: Upon outpatient follow-up (more than 2 months post parathyroidectomy).

was markedly raised on admission and normalised after 4 days of intravenous rehydration with forced dieresis and 1 dose of intravenous bisphosphonate (pamidronate). She was sad but aware of the risk of miscarriage, which was explained to her prior to being discharged home during the first admission, and she accepted the outcome. After the postpartum period, hemithyroidectomy and left inferior parathyroidectomy were done. Histopathological examination was consistent with a left inferior parathyroid adenoma and micropapillary carcinoma of the thyroid, and treatment was given accordingly.

DISCUSSION

PHPT in pregnancy presents either asymptomatically or with symptoms such as lethargy, hypertensive disorders in pregnancy, thirst, abdominal pain, constipation, nephrolithiasis, pancreatitis, hyperemesis gravidarum, and hypercalcaemic crisis. The symptoms mentioned above are very non-specific and some of them are frequently dismissed as symptoms commonly present during pregnancy, resulting in a delayed or missed diagnosis. Compared to other case reports, there was a delay in establishing the diagnosis of PHPT in both cases. Both patients were not symptomatic pre-pregnancy, were not known to have PHPT prior to pregnancy, and did not have significant past medical or family histories. Case 1 presented with non-specific symptoms of prolonged nausea and vomiting until late into the second trimester and the symptoms were dismissed as pregnancy symptoms, while Case 2 had an atypical presentation as she was asymptomatic but presented with a recurrent UTI that was not investigated before. Both cases had elevated serum calcium levels. A high level of clinical suspicion is required for further investigations to confirm the diagnosis of PHPT.

When left untreated, PHPT poses many serious complications to the mother and foetus ranging from hyperemesis gravidarum, hypercalcaemic crises in the mother, preterm delivery or miscarriage, to neonatal hypocalcaemia. Hence, PHPT should be given prompt and effective treatment.

Local practices and expert opinions still dictate a large part of the management of PHPT in pregnancy.[5] This is because prior to the recent expert consensus released by the European Society of Endocrinology in 2022,[4] there was a lack of guidelines or consensus on management of PHPT particularly during pregnancy. Moreover, there are no randomized control trials to guide management decisions for PHPT during pregnancy, and recommendations are based on limited evidence from observational studies and personal experience.[4] Parathyroidectomy is the only curative treatment for PHPT.[6] Advances in the effectiveness and safety of surgical techniques have added confidence to its recommendation,[7] and first-time cure rates have been reported to be over 95% in experienced hands.[8] Conservative treatment is viewed as a stopgap measure until surgery is performed.[4] Conservative treatment options are limited during pregnancy because many therapeutic options are not approved for use in pregnancy; management is mainly confined to oral and intravenous rehydration with or without forced diuresis. The use of medications such as cinacalcet,[9–12] calcitonin[12,13] and bisphosphonates[14,15] in PHPT during pregnancy has been reported but is not widely used due to insufficient data to recommend its wide usage, safety concerns in pregnancy, or lesser efficacy.

Prior to surgery, localization of abnormal parathyroid glands is needed. In both cases described, ultrasound of the neck was the only imaging modality used and was adequate to aid in establishing the diagnosis of PHPT. In cases where ultrasound of the neck fails to localise the lesion, contrast-

enhanced magnetic resonance imaging (MRI), ^{99m}Tc-methoxyisobutylisonitrile (^{99m}Tc-MIBI) scans, sestamibi single-photon emission computer tomography (SPECT/CT), 18F-Fluorocholine positron emission tomography (PET)/CT, or methionine PET/CT can be offered after weighing risks and benefits.[4]

There have been different opinions as to the indications and the best timing for performing parathyroidectomies in pregnant women. Unless contraindicated, international guidelines recommend surgery in PHPT patients under the age of 50.[7] The ESE expert consensus recommended parathyroidectomy in the second trimester of pregnancy for pregnant women with PHPT and serum-corrected calcium levels >2.85 mmol/L and/or >0.25 mmol/L above ULN and/or an ionised calcium >1.45 mmol/L[3,4] and all patients with symptomatic PHPT.[3] For calcium levels below the above-mentioned thresholds, therapeutic options of surgery versus conservative management should be offered to the patient, and a shared decision should be made.[4] It has been traditionally suggested that the second trimester of pregnancy is the best timing for parathyroidectomy, as surgery in the first trimester may involve a consequence of anaesthetic medications on incomplete organogenesis, while surgery in the third trimester may risk inducing preterm labour.[3,4] The patient's condition should be optimised and calcium levels brought down to normal prior to surgery, and the surgery does not necessarily need to be done during the same admission where the diagnosis was established. If the ideal timing of the second trimester is missed and conservative therapy fails, there are reports of third-trimester parathyroidectomy being performed safely.[16–18]

As to our management approach for both cases, intravenous rehydration and forced diuresis were initiated immediately in both cases, which successfully lowered the corrected serum calcium levels. However, corrected serum calcium levels remain elevated and refractory to outpatient oral rehydration. Other therapeutic options commonly prescribed in non-pregnant PHPT cases such as bisphosphonate,[14,15] cinacalcet,[9–12] and calcitonin,[12,13] were not prescribed for both cases as there are limited data for use in pregnancy. As a result, parathyroidectomy was planned for both cases, but only Case 1 had it done successfully during the third trimester of her pregnancy. After parathyroidectomy, her serum calcium returned to normal, her symptoms subsided, and her pregnancy was relatively uneventful, except for a caesarean section for obstetric indication. Unfortunately for Case 2, a delay in parathyroidectomy and conservative management with oral rehydration while awaiting for her decision for surgery resulted in suboptimal control of her serum calcium levels, as evidenced by an increasing serum calcium trend, eventually leading to an unwanted outcome—intrauterine death (IUD) in the second trimester of her pregnancy. The event of the IUD was attributed to hypercalcaemia as it coincided with the peak of the calcium level (3 mmol/L), and it is a known complication of hypercalcaemia beyond serum calcium levels of 2.85 mmol/L.[19] This could have been prevented with adequate inpatient intravenous hydration to bring the calcium levels down, followed by a parathyroidectomy.

CONCLUSION

Clinicians should have a high index of suspicion for PHPT in pregnancy and manage the condition with a multidisciplinary team consisting of an endocrinologist, an endocrine surgeon, an obstetrician, a paediatrician, and an anaesthesiologist promptly due to its potential serious maternal and foetal adverse outcomes if left untreated.

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Ethical Consideration
Patient consent was obtained before submission of the manuscript.

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All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
YDL: Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – original draft preparation, Visualization, Project administration; **MHMA:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – review and editing, Supervision, Project administration

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References

1. Kort KC, Schiller HJ, Numann PJ. Hyperparathyroidism and pregnancy. Am J Surg. 1999;177(1):66-8. PMID: 10037311. https://doi.org/10.1016/s0002-9610(98)00302-x.
2. Heath H 3rd, Hodgson SF, Kennedy MA. Primary hyperparathyroidism. Incidence, morbidity, and potential economic impact in a community. N Engl J Med. 1980;302(4):189-93. PMID: 7350459. https://doi.org/10.1056/NEJM198001243020402.
3. Shifrin A. Advances in diagnosis and management of primary hyperparathyroidism during pregnancy. Advances in treatment and management in surgical endocrinology. Elsevier Inc.; 2019.
4. Bollerslev J, Rejnmark L, Zahn A, et al. European expert consensus on practical management of specific aspects of parathyroid disorders in adults and in pregnancy: Recommendations of the ESE Educational Program of Parathyroid Disorders (PARAT 2021). Eur J Endocrinol. 2022;186(2):R33-63. PMID: 34863037. PMCID: PMC8789028. https://doi.org/10.1530/EJE-21-1044.
5. Bollerslev J, Marcocci C, Sosa M, Nordenström J, Bouillon R, Mosekilde L. Current evidence for recommendation of surgery, medical treatment and vitamin D repletion in mild primary hyperparathyroidism. Eur J Endocrinol. 2011;165(6):851-64. PMID: 21964961. https://doi.org/10.1530/EJE-11-0589.
6. Hassan-Smith ZK, Criseno S, Gittoes NJL. Mild primary hyperparathyroidism—to treat or not to treat? Br Med Bull. 2019;129(1):53-67. PMID: 30576424. https://doi.org/10.1093/bmb/ldy042.
7. Bilezikian JP, Khan AA, Potts JT. Guidelines for the management of asymptomatic primary hyperparathyroidism: Summary statement from the third international workshop. J Clin Endocrinol Metab. 2009;94(2):335–9. PMID: 19193908. PMCID: PMC3214274. https://doi.org/10.1210/jc.2014-1413.
8. Udelsman R, Lin Z, Donovan P. The superiority of minimally invasive parathyroidectomy based on 1650 consecutive patients with primary hyperparathyroidism. Ann Surg. 2011;253(3):585-91. PMID: 21183844. https://doi.org/10.1097/SLA.0b013e318208fed9.
9. Horjus C, Groot I, Telting D, et al. Cinacalcet for hyperparathyroidism in pregnancy and puerperium. J Pediatr Endocrinol Metab. 2009;22(8):741-9. PMID: 19845125. https://doi.org/10.1515/jpem.2009.22.8.741.

10. Vera L, Oddo S, Di Iorgi N, Bentivoglio G, Giusti M. Primary hyperparathyroidism in pregnancy treated with cinacalcet: A case report and review of the literature. J Med Case Rep. 2016;10(1):361. PMID: 27998296. PMCID: PMC5175373. https://doi.org/10.1186/s13256-016-1093-2.
11. Arshad MF, Arambewela MH, Bennet WM, Sterrenburg M, Balasubramanian SP. Primary hyperparathyroidism in pregnancy: Experience of a tertiary centre. Surg Today. 2023;53(4):470-5. PMID: 36107253. PMCID: PMC10042935. https://doi.org/10.1007/s00595-022-02583-8.
12. Rey E, Jacob C-E, Koolian M, Morin F. Hypercalcemia in pregnancy – a multifaceted challenge: Case reports and literature review. Clin Case Rep. 2016;4(10):1001-8. PMID: 27761256. PMCID: PMC5054480. https://doi.org/10.1002/ccr3.646.
13. Joint Formulary Committee. Calcitonin (salmon). British National Formulary. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; [cited 2023 Feb 21]. https://bnf.nice.org.uk/drugs/calcitonin-salmon/.
14. Djokanovic N, Klieger-Grossmann C, Koren G. Does treatment with bisphosphonates endanger the human pregnancy? J Obstet Gynaecol Can. 2008;30(12):1146-8. PMID: 19175968. https://doi.org/10.1016/S1701-2163(16)34026-9.
15. Patlas N, Golomb G, Yaffe P, Pinto T, Breuer E, Ornoy A. Transplacental effects of bisphosphonates on fetal skeletal ossification and mineralization in rats. Teratology. 1999;60(2):68-73. PMID: 10440778. https://doi.org/10.1002/(SICI)1096-9926(199908)60:2<68::AID-TERA10>3.0.CO;2-H.
16. DiMarco AN, Meeran K, Christakis I, et al. Seventeen cases of primary hyperparathyroidism in pregnancy: A call for management guidelines. J Endocr Soc. 2019;3(5):1009–21. PMID: 31065618. PMCID: PMC6497920. https://doi.org/10.1210/js.2018-00340.
17. Hui E, Osakwe O, Teoh TG, Tolley N, Robinson S. Three case reports of maternal primary hyperparathyroidism in each trimester and a review of optimal management in pregnancy. Obstet Med. 2010;3(1):33–7. PMID: 27582838. PMCID: PMC4989765. https://doi.org/10.1258/om.2009.090040.
18. Schnatz PF, Thaxton S. Parathyroidectomy in the third trimester of pregnancy. Obstet Gynecol Surv. 2005;60(10):672–82. PMID: 16186784. https://doi.org/10.1097/01.ogx.0000180889.23678.fb.
19. Norman J, Politz D, Politz L. Hyperparathyroidism during pregnancy and the effect of rising calcium on pregnancy loss: A call for earlier intervention. Clin Endocrinol (Oxf). 2009;71(1):104–9. PMID: 19138316. https://doi.org/10.1111/j.1365-2265.2008.03495.x.