Case Report

Management of hypoparathyroidism in pregnancy and lactation — A report of 10 cases

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A B S T R A C T

Introduction: Hypoparathyroidism in pregnancy is rare, but important, as it is associated with maternal morbidity and foetal loss. There are limited case reports and no established management guidelines. Optimal maintenance of calcium levels during pregnancy is required to minimise the risk of related complications. This study aims to identify causes and examine outcomes of hypoparathyroidism in pregnancy in a cohort of women delivering at a large referral centre.
Design and method: The Monash Health maternity service database captures pregnancy and birthing outcomes in over 9000 women each year. We audited this database between 2000 and 2014 to examine the clinical course, treatment and outcomes of pregnant women with hypoparathyroidism.
Results: We identified 10 pregnancies from 6 women with pre-existing hypoparathyroidism secondary to idiopathic hypoparathyroidism (n = 3), autosomal dominant branchial arch disorder with hypoparathyroidism (n = 3) and autosomal dominant hypocalcaemia (n = 1), surgery for thyroid cancer (n = 2) and Graves' disease (n = 1). Maternal calcium levels were monitored through pregnancy and management adjusted to maintain normocalcaemia. One woman was delivered by caesarean section at 34 weeks' gestation because of intrauterine growth restriction, and oligohydramnios complicated two other pregnancies. The postpartum period was complicated by severe hypercalcaemia in one woman and by symptomatic, labile serum calcium levels during lactation in another woman, requiring close monitoring over a 6 month period.
Conclusion: Although rare, hypoparathyroidism in pregnancy poses a management challenge for clinicians, and co-ordinated care is required by obstetricians and endocrinologists to ensure optimal outcomes for both mother and baby. Continued monitoring of maternal calcium levels during lactation and weaning is essential to avoid the potential complications of either hypercalcaemia or hypocalcaemia.

1. Introduction

Hypoparathyroidism is rarely encountered during pregnancy but is important, however, as it is associated with maternal morbidity and foetal loss. There are limited case reports and no established management guidelines. Physiological adaptations to maternal calcium metabolism occur during pregnancy and lactation to facilitate mineralisation of the foetal skeleton and ensure adequate calcium in breast milk, whilst maintaining normal ionised and albumin-corrected serum calcium levels (Kovacs, 2011). The challenge of managing hypoparathyroidism in pregnancy is to maintain normocalcaemia in the setting of variable individual responses to calcitriol and calcium supplementation, as well as altered calcium homeostasis.

Inadequate management of hypoparathyroidism during pregnancy can result in miscarriage (Eastell et al., 1985), stillbirth (Callies et al., 1998), preterm labour, and acute neonatal morbidity such as respiratory distress syndrome (Kaneko et al., 1999). Maternal hypocalcaemia can also be complicated by neonatal secondary hyperparathyroidism which in turn causes skeletal demineralization, subperiosteal bone resorption and osteitis fibrosa cystica. Conversely, overtreatment with calcitriol causes maternal hypercalcaemia and suppression of the foetal and neonatal parathyroid glands, and there is the additional concern of teratogenicity using older vitamin D preparations (Roth, 2011).

Studies examining the management of hypoparathyroidism in pregnancy and lactation are few, with the majority of data stemming from single case reports. Only two case reports have been published since 2000 (Krysiak et al., 2011; Sweeney et al., 2010). The largest case series, published in 1998, described twelve women with maternal hypoparathyroidism (Callies et al., 1998). Reports thus far have demonstrated that whilst some women have reduced symptoms and

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decreased calcium and calcitriol requirement during pregnancy, others require increased doses. However, the physiological decline in serum calcium due to haemodilution in pregnancy has sometimes been misinterpreted as worsening hypocalcaemia resulting in the treatment of women based on their laboratory results rather than clinical symptoms (Kovacs, 2011; Eastell et al., 1985; Krysiak et al., 2011; Markestad et al., 1983; Caplan and Beguin, 1990; Rude et al., 1984; Mather et al., 1999; Sadeghi-Nejad et al., 1980; Wright et al., 1969). There is consistent evidence that calcitriol requirements decrease during lactation.

Monash Health's maternity service is the largest maternity provider in Victoria, Australia, with an associated database that captures birthing outcomes in over 9000 women each year. In this retrospective audit, we outline the available cases and present the results of an audit of the birthing outcomes database, examining ten pregnancies with pre-existing maternal hypoparathyroidism over a fifteen year period.

2. Subjects and methods

Ethics approval was obtained from the Monash Health Human Research Ethics Committee to review the Birthing Outcomes System database and identify all pregnancies presenting to the Obstetrics Department between 2000 and 2014 with the concurrent diagnosis of hypoparathyroidism. The diagnosis of hypoparathyroidism was confirmed with the biochemical findings of hypocalcemia and a low serum parathyroid hormone (PTH) level. Subsequent review of medical and biochemical records was performed to record clinical course, treatment, and maternal and foetal outcomes of these pregnancies.

3. Results

The Birthing Outcomes System database identified twelve pregnancies with pregnancy-associated hypoparathyroidism. Two were excluded due to lack of available data. The remaining ten pregnancies from six women with a diagnosis of hypoparathyroidism will be described.

3.1. Cases

3.1.1. Pregnancy 1

A 37 year old woman attended pre-pregnancy counselling for idiopathic hypoparathyroidism diagnosed two years earlier, following episodic muscle twitching after the birth of her first child. She denied a family history of calcium disorders and had no clinically or biochemical evidence of other associated endocrinopathies.

The patient was managed with calcitriol 0.50 mcg twice daily and calcium carbonate 600 mg twice daily, with a corrected serum calcium of 2.13 mmol/L (normal 2.15–2.65 mmol/L). Once pregnancy was confirmed, her corrected calcium levels were monitored every 3 weeks with the aim of maintaining her corrected serum calcium at the lower end of the normal range. Calcitriol requirements increased during the second trimester and early third trimester to a maximum dose of 1.00 mcg mane and 0.75 mcg nocte required to maintain normocalcaemia. Serum calcium levels were maintained between 2.13 mmol/L and 2.38 mmol/L during pregnancy. Calcitriol doses were able to be reduced in the latter part of the third trimester to 0.75 mcg twice daily.

Following an uncomplicated pregnancy, the patient had a normal labour and delivery of a healthy female baby weighing 3660 g at term (75th percentile for gestation and sex (Dobbins et al., 2013)). Calcitriol supplementation was decreased to pre-pregnancy levels of calcitriol 0.50 mcg twice daily by day 3 post-partum. The baby had normal serum calcium when measured within a week of birth and at 4 months of age. Breast-feeding was continued for 6 months. During lactation, maternal serum calcium levels were maintained at 2.10 to 2.30 mmol/L with no complications.

3.1.2. Pregnancy 2 and 3

A 34 year old woman with idiopathic hypoparathyroidism, seronegative arthritis and congenital limb hypoplasia presented in the first trimester of her second pregnancy for monitoring of her calcium levels.

Her initial management during pregnancy consisted of caltrate 2400 mg and calcitriol 0.75 mcg daily. To maintain normocalcaemia, this was adjusted to caltrate 600 mg and calcitriol 1.00 mcg daily in the third trimester. Her serum calcium levels were maintained between 2.17 mmol/L and 2.46 mmol/L during pregnancy with no noted complications. At 41^{+6} weeks' gestation she had induced onset of labour and assisted vaginal birth of a healthy baby boy weighing 3435 g (50th percentile for gestation and sex (Dobbins et al., 2013)).

During her first pregnancy two years earlier, her serum calcium levels had been maintained around 2.15 mmol/L with a peak serum calcium level of 2.67 mmol/L in the second trimester. This necessitated a decrease of her medications from calcitriol 0.75 mcg and caltrate 1800 mg daily to calcitriol 0.50 mcg and caltrate 1200 mg daily. The pregnancy was complicated by vasa praevia and when born at 38^{+1} weeks' gestation by elective caesarean, the baby developed transient tachypnoea of the newborn, which resolved without therapy. Medication dose was appropriately decreased postpartum to maintain eucalcaemia.

3.1.3. Pregnancy 4, 5 and 6

A 23 year old woman with a history of autosomal dominant branchial arch disorder with hypoparathyroidism presented for review in the 13th week of her fifth pregnancy. Her hypoparathyroidism was diagnosed when she presented with neonatal seizures and was noted to have facial weakness, malformed external ears, pre-auricular pits and deafness. Her renal function was normal. Her father was similarly affected. She had previously had two early pregnancy miscarriages and two pregnancies complicated by symptomatic hypocalcemia, though these deliveries were normal.

The patient presented in the 13th week of her fifth pregnancy with peripheral cramping and peri-oral tingling, however, her corrected serum calcium was normal at 2.20 mmol/L. Initial doses of calcitriol 0.25 mcg daily and calcium carbonate 1500 mg daily were titrated to calcitriol 0.50 mcg twice daily and caltrate 1200 mg twice daily by 15 weeks' gestation. Though a documented calcium level of 2.09 mmol/L was noted 18 weeks' gestation, a corrected calcium level of 2.94 mmol/L was measured a week later. Following titration of her calcitriol dose, normocalcaemia was maintained for the remainder of the pregnancy with no noted complications. She had a normal labour and vaginal delivery at term. The baby was small for gestational age (SGA) with birth weight of 2440 g, <3rd percentile for gestation and sex (Dobbins et al., 2013). Of note, a maternal corrected calcium level of 2.87 mmol/L was noted post-delivery, with titration of doses and normalisation of maternal serum calcium levels by 1 week postpartum.

Fluctuating calcium levels were reported by the patient following breastfeeding her child and she had three hospital admissions with hypocalcaemic crises requiring IV calcium.

3.1.4. Pregnancy 7

A 38 year old woman with autosomal dominant hypocalcaemia presented in the second trimester of her sixth pregnancy for review of calcium levels. She had a past history of three miscarriages and two healthy pregnancies and children with no reported antenatal complications. Throughout the pregnancy, her calcium levels were maintained with calcitriol 1.50 mcg daily and calcium carbonate. A maximum corrected calcium level of 2.41 mmol/L was noted in week 28 with a minimum corrected calcium level of 1.98 mmol/L in week 36, with no noted complications throughout the pregnancy. At 39 weeks' gestation, she had an elective caesarean on a background of previous caesarean delivery, and a healthy boy was born weighing 2840 g (10th percentile for gestation and sex (Dobbins et al., 2013)). In the first 3 weeks postpartum, the mother developed hypercalcaemia up to 3.01 mmol/L and her calcitriol dose was reduced to 1.00 mcg daily.

3.1.5. Pregnancy 8 and 9

A 28 year old woman presented one week post-partum with vomiting, dizziness and malaise. Her medical history included hypoparathyroidism following thyroidectomy for papillary thyroid carcinoma in 2008. She was initially managed with thyroxine 100 μg daily, calcitriol 0.50 mcg twice daily and calcium carbonate 1200 mg twice daily. During pregnancy, she was reviewed with titration of thyroxine doses up to 100 μg daily and 200 μg daily on alternate days, calcitriol 0.50 mcg three times daily and calcium carbonate 1200 mg three times daily to maintain eucalcaemia and thyroid function tests within trimester-appropriate reference ranges. The birth was uncomplicated and she had a normal vaginal birth of a healthy infant weighing 3620 g (90th percentile for gestation and sex (Dobbins et al., 2013)) at term.

On presentation 1 week postpartum, the patient was vomiting and was volume deplete. She had a serum calcium of 4.16 mmol/L (normal 2.15–2.65 mmol/L), with an ionised calcium of 2.04 mmol/L (normal 1.14–1.29 mmol/L). Renal function was normal but her serum phosphate was mildly elevated at 1.53 mmol/L, PTH was undetectable, and her 25(OH) vitamin D was normal at 75 nmol/L. Her dose of calcitriol and calcium carbonate had not been reduced following delivery and she had been maintained on calcitriol 0.50 mcg three times daily and calcium carbonate 1200 mg three times daily for one week postpartum. The patient was breast-feeding. She was admitted for fluid replacement and cardiac monitoring. Calcitriol and calcium carbonate were ceased for one week, during which time serum calcium levels were monitored. A serum calcium normalised after nine days.

In her first pregnancy, corrected calcium levels within the normal range had been maintained throughout pregnancy, reaching maximum of 2.39 mmol/L in week 9. This pregnancy was complicated by preterm labour at 36 weeks' gestation with intrapartum bleeding and an abnormal foetal heart rate on cardiotocogram. A healthy infant weighing 2820 g (50th percentile for gestation and sex (Dobbins et al., 2013)) was born. No issues of hypercalcaemia were noted post-partum.

3.1.6. Pregnancy 10

A 34 year old woman presented in her third pregnancy with a known diagnosis of hypoparathyroidism secondary to thyroidectomy for Graves' disease. She had an obstetric history of intrauterine growth restriction (IUGR), preterm delivery, oligohydramnios, and caesarean birth. During the first trimester she was treated with caltrate 600 mg and calcitriol 0.75 mcg daily. This was titrated down to calcitriol 0.25 mcg daily in the third trimester. Maximum corrected calcium reading was 2.46 mmol/L in week 28. The antenatal period was complicated by oligohydramnios, maternal hypertension, and suspected IUGR. A severely growth restricted female baby weighing 1355 g (<1st percentile for gestation and sex (Dobbins et al., 2013)) was born at 34^{+6} weeks' gestation by elective caesarean. She required management of jaundice, SGA, and suspected sepsis. Mild maternal hypocalcaemia (2.04 mmol/L) was incidentally noted on biochemistry on a post-partum review.

3.2. Review of cases

Two of the women in this series had hypoparathyroidism as a result of thyroidectomy performed prior to becoming pregnant; one for treatment of Graves' disease (pregnancy 8, 9) and the other for papillary thyroid cancer (pregnancy 10). Two women were diagnosed with idiopathic hypoparathyroidism at the age of 33 (pregnancy 1) and 23 (pregnancy 2, 3). Congenital hypoparathyroidism accounted for the remaining two women. One was diagnosed with a branchial arch anomaly with hypoparathyroidism at 3 weeks of age (pregnancy 4, 5, 6), and the other diagnosed with autosomal dominant hypocalcaemia at the age of 27 (pregnancy 7).

Of note, 2/6 women had a history of multiple miscarriages. These women were known to have labile serum calcium levels during pregnancy (see Table 1). IUGR was suspected in 2/10 pregnancies (pregnancy 6 and 10) and 3/10 newborns were SGA (pregnancy 6, 7 and 10). In addition, 2/10 pregnancies had preterm births (<37 weeks' gestation).

Of concern, significant antepartum hypocalcaemia (corrected calcium <2.15 mmol/L) occurred in 3/10 pregnancies. Postpartum hypercalcaemia (corrected calcium >2.65 mmol/L) was documented in 2/10 pregnancies, with a peak serum of 3.01 mmol/L (pregnancy 7) and 4.16 mmol/L (pregnancy 9) in the setting of lack of adjustment of calcitriol doses post-partum.

4. Discussion

During pregnancy, a term foetus acquires approximately 30 g of calcium, with the majority acquired during the third trimester (Kovacs, 2011). To accommodate this, the mother undergoes several adaptations to calcium handling (Kovacs, 2011; Cooper, 2011; Parkes et al., 2013). Throughout the first and second trimester, parathyroid hormone (PTH) levels are normal or suppressed, and then gradually increase during the third trimester.

From the 12th week of pregnancy, the earliest time point for which data are reported, intestinal calcium absorption doubles. This is thought to be associated with increased 1,25-dihydroxyvitamin D levels. Urinary calcium excretion also increases, exceeding the normal range (>275 mg/24 h) (Kovacs and Kronenberg, 1997). There is evidence demonstrating increased bone resorption from early pregnancy to mid-pregnancy (estimated by bone markers), in conjunction with suppressed bone formation which then increases to normal in the third trimester (Kovacs and Kronenberg, 1997). Serum calcitonin, parathyroid hormone-related protein (PTHrP), prolactin, placental lactogen and insulin-like growth factor 1 are other hormones contributing to calcium homeostasis. When breastfeeding, women typically lose 210 mg of calcium through breast milk each day (Kovacs, 2011). This is primarily attributed to mammary-derived PTHrP and low oestradiol, both of which stimulate bone resorption from the maternal trabecular

Table 1
Summary of case findings.

Pregnancy	Cause	Pregnancy cCalcium range (mmol/L)[+]	Range of calcitriol dose (mcg)	Gestation at birth	Current pregnancy complications
1(A)	Idiopathic	2.13(1)–2.38(3)	1.00–1.75	37.1	Nil
2(B)	Idiopathic	2.17(3)–2.46(2)	0.75–1.00	41.6	Nil
3(B)	Idiopathic	2.15(3)–2.67(2)	0.50–0.75	38.1	Vasa praevia
4(C)	Branchial arch disorder	1.97(3)–2.30(3)	0.75	38	2× miscarriage
5(C)	Branchial arch disorder	1.77(1)–2.09(3)	1.50	39	2× miscarriage Presented with pre-epileptic aura
6(C)	Branchial arch disorder	2.09(2)–2.94(2)	0.25–1.00	39.4	2× miscarriage Suspected IUGR; SGA (3rd centile) Several presentations with peripheral paraesthesia Postpartum hypercalcaemia (2.61 mmol/L)
7(D)	Congenital	1.98(3)–2.41(3)	1.00–1.50	39	3× miscarriage; SGA (10th centile) Postpartum hypercalcaemia (3.01 mmol/L)
8(E)	Secondary	2.38(1)–2.39(3)	N/A	36	Preterm (36/40)
9(E)	Secondary	2.25(1)–2.56(1)	1.00–1.50	40.1	Postpartum hypercalcaemic crisis (4.16 mmol/L)
10(F)	Secondary	2.04(pp)–2.46(3)	0.25–0.75	34.6	Preterm (34/40); suspected IUGR; SGA (3rd centile)

Ten deliveries from 6 women (A, B, C, D, E, F) were identified and the aetiology, corrected calcium (cCalcium), calcitriol dose, gestational age and complications were summarised. Normal range for cCalcium = 2.15–2.65 mmol/L; Preterm delivery = delivery prior to 37 weeks gestation; SGA = small for gestational age; IUGR = intrauterine growth restriction.

skeleton. Loss of bone density continues during the period of lactation but is compensated after weaning (More et al., 2001).

PTH is normally responsible for maintaining calcium homeostasis. Absence of this hormone in conjunction with the increased calcium demands during pregnancy can result in hypocalcaemia if inadequately supplemented (Kovacs, 2011; Mestman, 1998; Kovacs, 2014). During lactation, however, PTH is not required for calcium mobilisation, and supplementation must be reduced to prevent hypercalcaemia.

The most common cause of hypoparathyroidism in the general population is thyroid surgery, posing a risk of 0.50–6.60%, depending on the baseline thyroid disorder, thyroid volume, the extent of thyroid ablation, and experience of the surgeon (Shoback, 2008). Postoperative hypoparathyroidism is most commonly associated with surgery for substernal goitre, head or neck malignancies, or Graves' disease (Bilezikian et al., 2011). The highest incidence of Graves' disease is between the ages of 40–60 (Tunbridge et al., 1977), whilst the median age of diagnosis of thyroid cancer is 40–45 (Gimm, 2001). As many women conceive in younger years, this may explain why hypoparathyroidism is rarely encountered during pregnancy. In our study, the most common causes were idiopathic hypoparathyroidism and congenital hypoparathyroidism.

Branchial arch disorders (also referred to as pharyngeal or aortic arch disorders) develop during the 2nd to 6th week of gestation and are due to abnormal development of the branchial apparatus (Prasad et al., 2014). DiGeorge syndrome is a 22q11 deletion syndrome resulting in 3rd and 4th branchial pouch anomalies. It is characterised by the presence of cardiac anomalies, immunological abnormalities, cleft lip and palate, hypoparathyroidism, learning disabilities, and schizophrenia (Botto et al., 2003). Though one of the mothers in our case study (pregnancy 4, 5, 6) was initially labelled with DiGeorge syndrome, this was subsequently excluded due to normal karyotype and fluorescent in situ hybridization as well as absence of cardiac and immune anomalies. She was referred to geneticists for further evaluation and results of further investigations were not available.

Hypocalcaemia increases uterine irritability, reduces the resting potential, and affects spike frequency of the muscle fibres (Mitchell and Jüppner, 2010), which may have contributed to the incidence of 2/10 preterm deliveries and history of multiple miscarriages in the two women with congenital hypoparathyroidism. The usual rate of preterm delivery is 0.80/10 of all pregnancies in Australia (Laws et al., 2006).

SGA is defined as having a birth weight more than 2 standard deviations below the mean, or less than the 10th percentile for the gestational age (Dobbins et al., 2013). Given that 3/10 neonates met the classification for SGA, this suggests that there may be an association of SGA with hypoparathyroidism in pregnancy and warrants further study.

In our audit, calcium levels throughout pregnancy demonstrated a peak calcium reading during the 3rd trimester for 6/10 pregnancies. 2/6 of these exceeded the maximum recommended corrected calcium range (>2.65 mmol/L). Postpartum hypercalcaemia was present in 2 of the pregnancies, pregnancy 7 and 9, and both were associated with unchanged medication following delivery. Pregnancy 7 reached a peak of 3.01 mmol/L on day 21, on which day calcitriol dose was noted to be decreased from 1500 mcg to 1000 mcg. Pregnancy 9 presented in hypercalcaemic crisis (corrected calcium 4.16 mmol/L) on day 9 postpartum. She had maintained eucalcaemia throughout pregnancy but calcitriol doses were not decreased following delivery. This highlights the importance of closely monitoring serum calcium levels postpartum and managing accordingly.

During the immediate postpartum period, serum calcium levels in neonates are decreased in response to decreased PTHrP and maternal supplementation. Calcium levels then stabilise over the proceeding 24–48 h with stimulation of PTH secretion (Blackburn, 2013). Maternal calcium disorders may alter calcium homeostasis and parathyroid function in the newborn if calcium levels are not maintained within the normal range (Thomas et al., 1999). Infants are at risk of

hyperparathyroidism if their mothers have hypoparathyroidism, which may be associated with several skeletal deformities and respiratory difficulties (Hsu and Levine, 2004). Given these complications, it has been suggested in the literature that neonatal calcium levels are monitored in the first few weeks of life (Wright et al., 1969). Our study was limited by the retrospective collection of data, with varied postpartum follow up with transfer of care out of a tertiary referral centre to local doctors. Data were also only available on neonatal calcium levels in three pregnancies and these levels were normal.

Currently there are no best practice guidelines for management of maternal hypoparathyroidism during pregnancy. Our study highlights the need to monitor serum calcium levels during pregnancy and in the postpartum period. We have identified the varying aetiologies of hypoparathyroidism in young women of reproductive age and highlighted the known association of recurrent miscarriage with this condition. Whether there is a potential association of SGA with hypoparathyroidism in pregnancy is an important consideration and needs further evaluation.

In pregnancy, ionised calcium or albumin-corrected serum calcium is maintained in the low to mid normal range. The calcitriol dose should be adjusted based on the ionised calcium or corrected serum calcium level. Calcitriol has a shorter half-life compared with the older preparations including high-dose cholecalciferol. Cholecalciferol requires high levels of 25-hydroxyvitamin D of greater than 250 nmol/L: the associated toxicity of high dose preparations makes calcitriol the preferred medication. However, studies examining calcitriol in pregnancy are limited.

4.1. Conclusion

The requirements for exogenous calcitriol vary during the second half of pregnancy but are expected to decrease substantially (if not completely) during lactation. We recommend monitoring calcium levels every three to four weeks throughout pregnancy, and within one week post-partum to ensure normocalcaemia in both mother and baby. During lactation, monitoring should occur every 4 to 6 weeks, with review during weaning to ensure stability of maternal calcium levels. Expecting and lactating mothers should be made aware of the symptoms of both hypercalcaemia and hypocalcaemia and given instructions to urgently seek medical care if these symptoms occur. Written information given to the patient during pregnancy is recommended to ensure understanding of the condition, the need for monitoring and reduction of calcitriol following delivery. Education of medical and nursing staff about this rare condition in pregnancy is essential to avoid complications. Coordinated care between endocrinologists and obstetricians is essential to ensure optimal outcomes and the establishment of a multi-centred database to prospectively study hypoparathyroidism and pregnancy outcomes is warranted.

Author contributions

FM and BLH conceived the study; FM, CAA and BLH designed and conducted the study, PJF, FM, EMW, CA, PRE, PW and JT interpreted the data and reviewed the manuscript; FM and BLH wrote the manuscript.

Declaration of interest

All authors declare that they have no conflicts of interest that could be perceived as prejudicing the impartiality of the research reported.

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