Cinacalcet for Hyperparathyroidism in Pregnancy and Puerperium

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ABSTRACT

The efficacy and safety of various modes of medical treatment for primary hyperparathyroidism (PHPT) in pregnancy is largely unknown. This report describes two cases of PHPT in pregnancy that were temporarily treated with the calcimimetic cinacalcet. The first case was diagnosed in the 31st week of pregnancy. The patient was asymptomatic and had an albumin-corrected total calcium level (Ca_{corr}) of 3.24 mmol/l. As serum calcium was only mildly elevated it was decided to postpone surgery to the postpartum period. Cinacalcet was started immediately after delivery to prevent a postpartum surge in serum calcium. The second patient presented with hypertension and symptomatic hypercalcemia (Ca_{corr} 3.96 mmol/l) in the 32nd week of pregnancy. Surgery was postponed because of suspected pheochromocytoma. Treatment with a combination of cinacalcet and calcitonin reduced serum Ca_{corr} to 3.0 mmol/l. This report describes the monitoring of mother and child, and explores the pros and cons of the use of calcimimetics during pregnancy and puerperium.

KEY WORDS

hyperparathyroidism, pregnancy, cinacalcet

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INTRODUCTION

The prevalence of primary hyperparathyroidism (PHPT) in women of childbearing age is about 5 per 10,000[1-3]. A diagnosis of PHPT is notoriously difficult during pregnancy because it rarely presents with classical symptoms. Most often the symptoms are non-specific and easily mistaken for common pregnancy-related symptoms. In addition, the pregnancy-induced fall in serum albumin reduces the total serum calcium and tends to mask hypercalcemia unless ionized calcium is measured. These are probably the main reasons why PHPT is rarely diagnosed during pregnancy. Since the first case was reported in 1932, only about 200 cases have been published in the medical literature[4].

PHPT is typically a disease of middle-aged and elderly women. It usually runs a relatively benign clinical course and rarely needs immediate, lifesaving interventions. In contrast, during pregnancy PHPT may have serious clinical implications for mother and child[5-8]. It may lead to hyperemesis gravidarum, pre-eclampsia, nephrolithiasis, recurrent urinary tract infections, pancreatitis, hypercalcemic crisis, intrauterine growth retardation, miscarriage, stillbirth, preterm labor, neonatal tetany and neonatal death[4-8]. Pregnancy may also develop uneventfully but even in cases of mild PHPT severe fetal/neonatal complications have been reported. At present there are no evidence-based parameters that reliably predict the outcome of PHPT in pregnancy, but most experts suggest that severe complications are less likely if the total serum calcium remains below 3.0 mmol/l.

Because the outcome cannot be accurately predicted, it is not surprising that the optimal management of PHPT during pregnancy is unresolved. Most authors advocate parathyroidectomy

(PTx) during pregnancy as the treatment of choice in the second trimester[7]. The safety of surgery in the first and third trimesters is debated because of the associated risks for the fetus[9]. Experience with medical treatment for PHPT in pregnancy is very limited and poorly documented. In less than 20% of reported cases were adequate details provided about the medical interventions and outcome. So far, only intravenous hydration with or without forced diuresis, and intravenous or subcutaneous calcitonin have emerged as safe treatments[10]. Both will lower serum calcium only temporarily, and additional treatment of the underlying cause will always be needed to prevent recurrent hypercalcemia. $MgSO_4$ may be used to increase urinary calcium excretion[11]. Oral or intravenous phosphate is not recommended because it may cause extensive intra- and extravascular calcium phosphate deposits which may lead to severe organ failure[12]. Bisphosphonates cross the placenta and have been shown in some animal models to interfere with normal endochondral bone development. They should only be used in emergencies as a short-term intervention to stabilize severe hypercalcemia prior to surgery[13,14].

Calcimimetics are effective in reducing serum calcium in PHPT; however, their use in pregnancy has not yet been reported[15,16]. To our knowledge, this is the first report describing the effects of the calcimimetic cinacalcet during pregnancy and puerperium.

PATIENT 1

A 35 year-old pregnant women, G2P1, was referred to the Department of Endocrinology because of recently discovered mild primary hypothyroidism: free T4 11 pmol/l (normal range [NR]: 11-25 pmol/l), TSH 4.87 mU/l (NR: 0.3-4.0 mU/l), anti-TPO antibodies negative. Thyroid replacement therapy was started and euthyroidism was soon established with thyroxin at a dose of 50 µg once per day. She had used multivitamins on a daily basis since gastric banding for morbid obesity 5 years earlier. Additional blood tests were performed in the 31st week of pregnancy to rule out hypo- or hypervitaminosis. The results were compatible with PHPT: serum total calcium 3.06

mmol/l, albumin 29.5 g/l, albumin-corrected total calcium level (Ca_{corr}) 3.32 mmol/l, ionized calcium (Ca^{2+}) 1.60 mmol/l, phosphate 0.71 mmol/l, parathyroid hormone (PTH) 6.1 pmol/l (NR in non-pregnant women: 1.6-6.9 pmol/l), 25-hydroxy-vitamin D 41 nmol/l (NR: 50-100 nmol/l), 1,25-dihydroxy-vitamin D 269 pmol/l (NR: 48-161 pmol/l), and urinary calcium excretion 25.1 mmol/24 h. Five years previously, serum total calcium and phosphate levels had been within the normal range (Ca^{2+} 2.43 mmol/l, phosphate 0.89 mmol/l). Ultrasonography of the neck revealed a right inferior parathyroid adenoma of 0.9 x 1.6 cm. Abdominal ultrasonography of the kidneys was normal.

The patient was hospitalized in the 32nd week of pregnancy to monitor calcium and phosphate metabolism. She was advised to maintain a fluid intake of 4 liters per day to ensure high urinary calcium excretion. Serum Ca^{2+} levels and urinary calcium excretion remained stable during the first week (Fig. 1). Fetal ultrasound showed normal fetal development without growth retardation. In a multidisciplinary discussion it was concluded that PTx was not the option of choice in this phase of pregnancy because of the associated risk of preterm labor. It was decided to perform a preterm delivery at 36 weeks, either by induction of labor or by Cesarean section. At 36 weeks labor induction with oxytocin i.v. and dinoprostone gel treatment was not successful. Therefore, a Cesarean section was carried out as planned. A healthy son was delivered, body weight 3,390 g (>90th percentile), height 52 cm, head circumference 35.5 cm, Apgar score 8-9, umbilical cord serum Ca^{2+} 1.77 mmol/l. i.e. 0.37 mmol/l higher than that of the mother (Fig. 1). Macroscopic and microscopic examination of the placenta did not reveal any abnormalities.

At the time of delivery, the mother's serum Ca^{2+} of 1.40 mmol/l was rather low. This was attributed to extensive fluid infusion which had been necessary to maintain blood pressure during the Cesarean section. To prevent a rapid surge of serum calcium in the postpartum period, cinacalcet 30 mg twice per day was started immediately after delivery, in combination with infusion of 0.9% NaCl at a rate of 4 l/24 h. During the subsequent days Ca^{2+} gradually decreased, and 7 days after the Cesarean
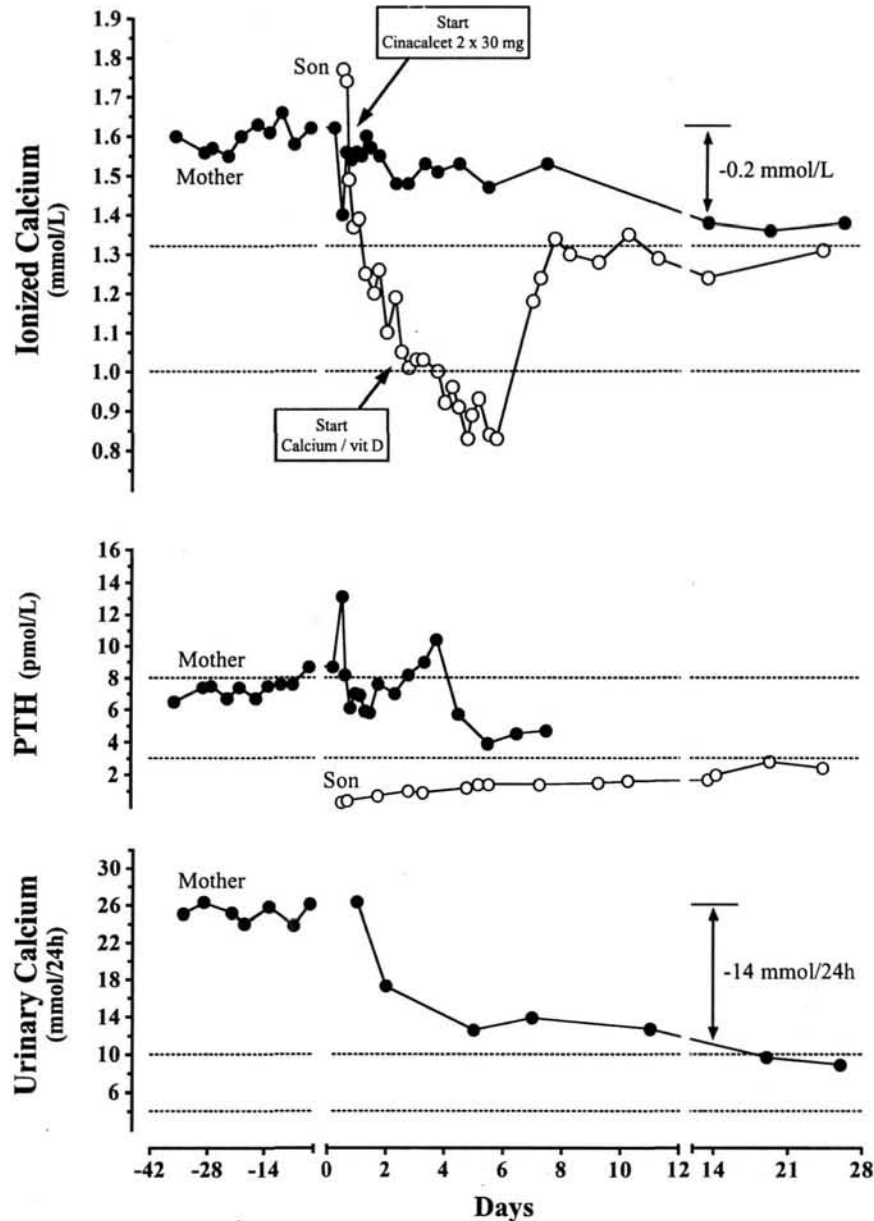
Fig. 1: Patient 1. Serum ionized calcium in mother and child during pregnancy and puerperium (0 = delivery).

section the mother was discharged. Serum Ca^{2+} stabilized between 1.30 and 1.40 mmol/l on cinacalcet. Six weeks after delivery a right inferior parathyroid adenoma of 2 cm was removed, and this completely normalized serum calcium.

The neonate

Immediately after delivery, the infant was transferred to the neonatal intensive care unit. Labora-tory results from cord blood samples are summarized in Table 1. The son's serum Ca^{2+} level was 0.37 mmol/l higher than that of his mother. Serum phosphate was markedly higher in the neonate, whereas serum PTH and PTH-related protein (PTHrp) were suppressed. Serum calcitonin was nearly 20-fold higher than in the mother. The neonate's 1,25-$(OH)_2$-vitamin D was half the level observed in the mother, whereas 25-OH-vitamin D levels were comparable. Vitamin D binding protein

TABLE 1

Laboratory results in mother and infant (Patient 1), just after Cesarean section

	Mother	Infant	Normal range
Ca_{corr} (mmol/l)	3.06	3.45	2.10-2.55
Ca^{2+} (mmol/l)	1.40	1.77	1.10-1.30
Albumin (g/l)	20.8	23.8	35-50
pH	7.46	7.38	7.35-7.45
Phosphate (mmol/l)	0.74	1.83	0.87-1.45
PTH (pmol/l)	13.1	0.3	1.6-6.9
PTHrp (pmol/l)	< 0.3	< 0.3	0-0.6
Calcitonin (pmol/l)	0.7	13.6	0-4.7
25-OH-Vitamin D_3 (nmol/l)	48	40	50-100
1,25-$(OH)_2$-Vitamin D_3 (pmol/l)	362	187	48-161
Vitamin D binding protein (μg/ml)	431	257	217-449

For abbreviations see text. Normal ranges refer to normal values in non-pregnant adults.

was in the low normal range in the neonate and in the high normal range in the mother. Ionized calcium decreased rapidly and two days after delivery a level of 1.10 mmol/l was reached. Infusion of calcium and oral ingestion of 1α-calcidiol was started, but this did not prevent a further decline of serum Ca^{2+} to 0.80 mmol/l. Neonatal tetany did not occur. Six days after the start of treatment a consistent rise in serum calcium was achieved, ending with a Ca^{2+} level around 1.30 mmol/l. The child was discharged in good health on day 15. After 2 months calcium and vitamin D supplementation was stopped permanently.

PATIENT 2

A 40 year-old female, G2P0, was hospitalized in the 32nd week of pregnancy because of progressive hypertension (180/110 mm Hg) not responding to methyldopa. There was no evidence of pre-eclampsia. Polyuria (10-12 liters daily) and poly-dipsia was noted and this prompted further evaluation. Laboratory results were compatible

with a diagnosis of severe PHPT: total calcium 3.57 mmol/l, albumin 24.6 g/l, Ca_{corr} 3.96 7 mmol/l, Ca^{2+} 1.98 mmol/l, phosphate 0.65 mmol/l, PTH 16.1 pmol/l, urinary calcium excretion 32.7 mmol/24 h. Plasma glucose, creatinine, and sodium were within the normal range. Ultrasonography of the neck did not reveal a parathyroid adenoma. Because of the combination of hypertension and PHPT a MEN 2A syndrome could not be ruled out with certainty and thus parathyroid surgery was post-poned pending further analysis. Intravenous hydra-tion with 0.9% NaCl, 6 liter/24 h, did not reduce serum Ca^{2+}. Calcitonin alone was considered ineffective for the long-term Ca^{2+} control needed in this case, and so we chose to start treatment with cinacalcet 30 mg twice daily. The dose was rapidly increased to 240 mg/day, within one week. This resulted in a temporary reduction of maternal serum Ca^{2+} after three days, but after one week of treatment serum Ca^{2+} had increased to its original level. Calcitonin was added, first at a dose of 200 μg subcutaneously, and then 100 μg subcutaneously every other day. The combined regimen reduced

serum Ca^{2+} to a stable level of around 1.50 mmol/l (Fig. 2). After confirmation that urinary catechol-amine excretion was normal, surgery was planned for the 34th week. Cesarean section was performed first, directly followed by a right parathyroid adenomectomy in the same session. A cord blood sample taken immediately after delivery showed elevated neonatal serum Ca^{2+} as compared to the mother, indicating that the physiological Ca^{2+} gradient between mother and child was maintained during the use of cinacalcet (Table 2). Vitamin D and calcium supplementation was started on the

second day when serum Ca^{2+} had decreased to 1.05 mmol/l. Neonatal tetany did not occur. Vitamin D and calcium supplementation was stopped after 11 days.

DISCUSSION

This paper describes the use of cinacalcet in two cases of PHPT in pregnancy. The first case is an example of asymptomatic, mild hyperparathyroid-ism diagnosed in the third trimester of pregnancy. Decisions about when and how to intervene are
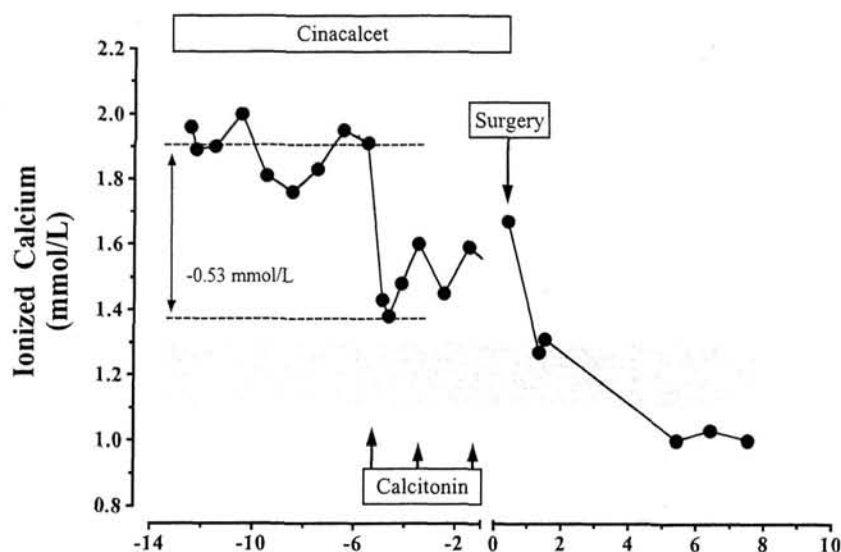

Fig. 2: Patient 2. Effect of cinacalcet monotherapy, combination treatment with cinacalcet and calcitonin, and subsequent surgery on maternal ionized calcium levels in the third trimester of pregnancy.

TABLE 2

Effects of cinacalcet and calcitonin treatment on neonatal calcium homeostasis (Patient 2)

	Mother	**Child**
Total calcium (mmol/l)	3.01	3.28
Ca^{2+} (mmol/l)	1.67	1.85
Albumin (g/l)	22.9	27.2
PTH (pmol/l)	32.5	<1
Phosphate (mmol/l)	1.38	2.52

Laboratory results of samples obtained immediately after delivery.
Normal ranges are shown in Table 1.

difficult in cases like this because systematically analyzed clinical data are not available to guide our judgment. At present, we do not know exactly what threshold level of serum calcium is associated with increased risks of serious complications. As demonstrated by this patient, pregnancy may continue uneventfully in cases of mild PHPT; however, this case also illustrates that even mild maternal hypercalcemia can cause neonatal hypocalcemia and hypoparathyroidism.

Withholding calcium lowering treatment during pregnancy may put the mother and fetus at risk for more severe complications[17]. The use of cinacalcet during pregnancy was discussed at length but eventually rejected because of lack of safety data in humans. Conservative management with watchful waiting until full term was considered too dangerous because any event associated with a decline in renal function might compromise calcium excretion and could thus precipitate a hypercalcemic crisis. It was decided to provide adequate hydration and plan a preterm delivery at 36 weeks to avoid the physiological decline in maternal glomerular filtration rate (GFR) that occurs in the late phase of pregnancy[18]. We also started cinacalcet immediately after delivery to prevent a rise in serum calcium that might occur as a result of the loss of calcium shunting to the fetus, the rapid decline in GFR that follows delivery, and the onset of accelerated bone resorption with early lactation. As shown in Figure 1, cinacalcet gradually lowered serum Ca^{2+} to 1.36 mmol/l in 2 weeks, and parathyroid surgery was safely postponed until the patient had recovered from the Cesarean section.

The second case is, to our knowledge, the first to demonstrate that the use of cinacalcet for PHPT in pregnancy does not compromise fetal blood calcium or apparent placental calcium transport. At birth the neonatal Ca^{2+} level was 0.18 mmol/l higher than in the mother (Table 2). This case also illustrates that cinacalcet monotherapy is not useful for the acute control of serum calcium in severe PHPT (Fig. 2). To some extent this was expected since at least 2 weeks of treatment of non-pregnant patients with PHPT are required to reach the nadir calcium levels for a given dose[15]. We hoped to induce an earlier response by rapidly increasing the

dose up to its maximum. Unfortunately, only a temporary decline was observed, and after one week of treatment serum calcium was again at its peak level. In contrast, the combination of cinacalcet and calcitonin proved highly effective in reducing serum Ca^{2+} to our target level of 1.50 mmol/l. We did not wish to normalize serum calcium because too large a decline in serum calcium might trigger premature labor or compromise fetal calcium metabolism. Serum calcium was monitored every 6 hours, and this permitted careful titration of calcitonin. After an initial dose of 200 µg of calcitonin, a dose of 100 µg every other day in combination with cinacalcet was sufficient to maintain serum calcium at the desired level. Monotherapy with calcitonin every other day would not have achieved this consistent lowering in serum calcium given the rapid tachyphylaxis that occurs in response to calcitonin. We hypothesize that the combination treatment prevents the PTH surges that are likely to occur in response to the calcium lowering effects of calcitonin monotherapy.

Before considering cinacalcet treatment we extensively discussed the pros and cons because its use in human pregnancy had not been previously reported. Cinacalcet is a calcimimetic that activates the calcium sensing receptor (CaSR) present on parathyroid cells, C-cells of the thyroid, and renal distal tubular cells. Activation of the CaSR reduces PTH secretion and increases calcitonin release, whereas activation of the renal tubular cell CaSR reduces renal calcium resorption independently of changes in PTH[19]. Cinacalcet has been used successfully to treat PHPT in non-pregnant women[15,16]. The recommended starting dose is 30 mg twice a day, and it may be increased to up to 180-360 mg/day. It takes about 2 weeks before steady state is reached on a given dose. Safety and efficacy have not been established in patients below the age of 18 years. Animal studies in pregnant rats and rabbits have shown that cinacalcet crosses the placenta; however, embryonal or fetal toxicity or harmful effects with respect to pregnancy or parturition have not been observed[20]. Based on these data, cinacalcet has been classified as a category C drug. Considering the demonstrated efficacy of cinacalcet in non-pregnant women, there is little doubt that cinacalcet will also lower serum

calcium in pregnant women. It should thus reduce the feto-maternal complications of hyperparathyroidism that are due to the hypercalcemia. However, there are two main concerns for its use in pregnancy. First, effects on fetal calcium levels have not been studied previously; secondly, direct frequent monitoring of fetal calcium levels is not feasible. CaSRs are present in the placenta, and thus cinacalcet might alter placental function to cause fetal hypocalcemia, for example by suppressing fetal PTH secretion, placental PTHrp production, or the production of other factors contributing to active placental calcium transport[17]. On the other hand, several lines of evidence suggest that the use of cinacalcet is likely to be safe, as long as the mother is not made hypocalcemic. In normal pregnancy, fetal ionized calcium is about 0.3 mmol/l higher than in the mother, due to active transport of calcium across the placenta[17]. These high fetal calcium levels suppress fetal parathyroid activity, and fetal PTH levels are normally low or even undetectable. In cases of maternal PHPT fetal calcium levels are even higher and this will completely suppress fetal PTH secretion. Thus, it is very unlikely that cinacalcet would adversely affect fetal parathyroid activity during PHPT in pregnancy, simply because fetal PTH production would already be maximally suppressed in response to the maternal hypercalcemia.

Potential adverse effects of cinacalcet on placental active calcium transport are more difficult to predict. To some extent, the safety of CaSR modulation in humans can be deduced from an experiment of nature, i.e. a gain-of-function mutation of the CaSR. In affected children the CaSR is overly sensitive to the effects of calcium to such a degree that even subnormal calcium levels can suppress PTH secretion and renal tubular calcium resorption. This results in a clinical syndrome known as autosomal dominant hypocalcemia (ADH), which is characterized by hypocalcemia and hypercalciuria[21-30]. Most affected individuals are detected during childhood or later in life because of muscle spasms or seizures. A large group is asymptomatic and only detected during family survey, and only a very small number present with tetany in the neonatal period. Table 3 summarizes all reported cases of ADH presenting

with neonatal tetany or with known calcium levels in the neonatal period. All cases had an uneventful pregnancy and delivery, even those from affected mothers. None presented with hypocalcemic seizures on the first day of life. The earliest symptomatic infant had seizures at 3 days of age[26]. This relatively late onset of symptomatic hypocalcemia suggests that calcium levels are likely to have been normal at birth and imply that fetal calcium homeostasis is not adversely affected by an increase in CaSR sensitivity. Even in affected mothers with serum total calcium levels between 1.63 and 1.75 mmol/l the placental calcium pump must have been functioning quite well as neonatal tetany occurred as late as 6-7 days after birth. Apparently, the placental CaSR is not pivotal in the regulation of placental calcium transport.

Adverse effects of cinacalcet on neonatal calcium homeostasis are also unlikely. As cinacalcet has a half life of about 30 hours its effect will be negligible after 3 days. A clinically significant lengthening of the neonatal hypocalcemic period is thus unlikely. The use of cinacalcet could conceivably reduce the neonatal hypocalcemic period, because lowering the maternal serum calcium toward normal may lead to an increase in fetal PTH from the typically undetectable levels associated with maternal hypercalcemia. By reducing the suppressive effects of maternal hypercalcemia on fetal parathyroid development, this may speed up the recovery of normal parathyroid function in the neonatal period. The events in the neonate of Patient 2 support this line of thought.

In conclusion, this report indicates that the combination of cinacalcet and calcitonin may be an effective approach to treat selected cases of PHPT in the third trimester of pregnancy before surgery can be safely performed. Clearly, additional studies are needed to determine this treatment's relative benefits and safety issues with respect to the mother and fetus/neonate. Due to cinacalcet's delayed onset of action, monotherapy is not useful for the rapid correction of severe PHPT in pregnancy unless combined with calcitonin. However, cinacalcet monotherapy may prove useful for mild PHPT in the third trimester of pregnancy to postpone surgery and avoid preterm labor or to prevent severe neonatal hypoparathyroidism.

TABLE 3

Timing of onset of symptoms and biochemical characteristics at the onset of symptoms in newborns with a gain-of-function mutation of the calcium sensing receptor (CaSR) of affected and unaffected mothers

Genetics	Pregnancy	Delivery	First symptoms	Calcium M/N*	Reference
A	uneventful	38 wk	6 days	1.58/1.23	21
A	NR	NR	7 days	1.58/1.48	21
A	NR	NR	5 years	1.63/1.78	22
A	NR	NR	'asymptomatic at birth'	1.63/1.78	22
A	NR	NR	'asymptomatic at birth'	1.63/1.85	22
A	uneventful	term	7 months	1.50/1.65	23
A	uneventful	37 wk	7 days	1.75/1.30	24
A	NR	NR	3 years	1.75/1.75	24
B	NR	NR	'shortly after birth'	NL/1.76	25
B	uneventful	term	3 days	NL/1.45	26
C	uneventful	term	24 days	NL/1.10	27
C	uneventful	38 wk	5 days	NL/1.30	27
C	uneventful	37 wk	21 days	NL/1.54	28
C	twin	34 wk	7 days	NL/1.25	29
C	twin	34 wk	8 days	NL/0.99	29
C	uneventful	37 wk	14 days	NL/1.70	30

Genetics: A = mother and child affected; B = mother not affected, only father and child affected; C = child affected due to *de novo* mutation.
NR = not reported; NL = normal.
* Serum total calcium in mother (M) and neonate (N) at the time of diagnosis in mmol/l.

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