Management of hypoparathyroidism during pregnancy – report of twelve cases

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Abstract

There is no established therapeutic regimen for treatment of hypoparathyroidism during pregnancy. This is due particularly to uncertainty about the use of vitamin D or its analogues, as in animal experiments teratogenic side-effects have been reported. Nevertheless, vitamin D or its analogues are required to control tetany predisposing to abortion and preterm labour. We herein report the course of two pregnancies in a hypoparathyroid woman treated with calcitriol (1,25(OH)₂D₃). Additionally, we describe the outcome of pregnancy in ten women receiving calcitriol, reported to the Drug Safety Department (DSD), Hoffmann-La Roche AG.

A 29-year-old hypoparathyroid woman receiving chronic treatment with calcitriol (0.25 µg/day) and calcium (1.5 g/day) was referred in the 6th week of her first pregnancy. Calcitriol was initially discontinued, but during the 20th week of pregnancy recurrent tetany occurred (serum calcium 1.74 mmol/l). Calcitriol (0.25 µg/day) was added, stabilizing serum calcium around 2.15 mmol/l with 1,25(OH)₂D₃ concentrations around 60 ng/l (normal range 35–80 ng/l). To maintain normocalcaemia the calcitriol dose was increased to 0.5 µg/day during the 33rd week and to 0.75 µg/day shortly before delivery of a healthy girl in the 37th week. During her second pregnancy calcitriol was given initially at a dose of 0.25 µg/day with further adaptation to 0.5 µg/day during the 20th and to 1.00 µg/day in the 31st week. Serum calcium and 1,25(OH)₂D₃ were continually within the lower normal range. She gave birth to another healthy girl during the 39th week. In eight of the ten pregnancies reported to the DSD no adverse effects of calcitriol (0.25–3.25 µg/day) were seen and healthy babies were delivered.

In two retrospectively reported cases, serious adverse events were described: premature closure of the frontal fontanelle, and stillbirth in the 20th week due to complex fetal malformation respectively. However, in both cases the causative role of calcitriol administration remains highly questionable.

We conclude that, during pregnancy, management of maternal hypoparathyroidism with calcitriol and calcium is feasible, if the 1,25(OH)₂D₃ concentrations are adapted to the physiological needs during pregnancy and serum calcium levels are kept in the lower normal range.

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Introduction

In 1966 O'Leary *et al.* (1) reported two cases of hypoparathyroid pregnant women. At that time there was medical controversy concerning hypoparathyroidism as a contraindication to pregnancy. They proposed giving high doses of calcium lactate powder (1000–1500 mg/day), a low phosphate diet and vitamin D (50 000–100 000 IE). Both women gave birth to healthy babies after uncomplicated pregnancies.

In experimental animals high doses of vitamin D have been shown to be teratogenic, causing craniofacial abnormalities and supravalvular aortic stenosis syndrome (2). As vitamin D is able to increase the calcium concentration in the human fetus, it is suspected of causing similar changes to those described in idiopathic hypercalcaemia of infancy (3). The complete features of

this syndrome are characteristic elfin facies, mental and growth retardation, strabismus, enamel defects, craniosynostosis, supravalvular aortic and pulmonary stenosis, inguinal hernia, cryptorchism in males, and early development of secondary sexual characteristics in females (2).

Insufficient supplementation of vitamin D, on the other hand, predisposes to con-natal reactive hyperparathyroidism (4). This may lead to intracranial bleeding (5) and neonatal rickets, with intrauterine fractures (6). In addition, hypocalcaemia could cause uterine irritability, reducing the resting potential and spike frequency of the muscle fibres (7), possibly leading to preterm labour or abortion (8).

Despite the introduction of new vitamin D analogues, management of hypoparathyroidism during pregnancy remains a challenge. It has been reported that nearly

half of hypoparathyroid pregnancies showed serious adverse events (9). These were mainly due to under-treatment or no treatment at all. Compared with cholecalciferol and tachysterol, which have a small therapeutic range with a long half-life, increasing the risk of over- and underdosage (10), maintenance of normocalcaemia with the more recently developed active forms of vitamin D, 1,25(OH)₂D₃ (calcitriol) and 1 α -calcidol, is much easier. However, the clinical experience with calcitriol for hypoparathyroidism during pregnancy is still very limited. We herein report the management and outcome of 12 pregnancies in hypoparathyroid women treated with calcium and calcitriol.

Patients and methods

A 29-year-old hypoparathyroid woman after subtotal thyroidectomy for cold nodules was followed up during two pregnancies by the outpatient clinic of the Department of Endocrinology (Würzburg). She was on long-term treatment with calcitriol and calcium. The patient was monitored throughout the pregnancies with regular assessment of the clinical status, serial measurements of calcium and determination of 1,25(OH)₂D₃ by an established immunoassay (Limbach, Heidelberg, Germany).

In cooperation with the Drug Safety Department (DSD), Hoffmann-La Roche AG, all cases of pregnant women who received calcitriol for hypocalcaemia during pregnancy and were reported to the Unit were reviewed. Only patients with a medical history, information on calcitriol dosage, concomitant medication and reported outcome were evaluated.

Results

Case report

In her first pregnancy calcitriol (0.25 μ g/day) was initially discontinued in the 6th week of pregnancy because of its potential teratogenicity, while the oral calcium dose was maintained (1.5 g/day). The patient developed hyperemesis gravidarum and diarrhoea, possibly induced by increased calcium supplementation. In addition, recurrent tetanic episodes, paraesthesia and muscle cramps occurred, impairing daily life activities as well as job performance. After the 20th week of gestation calcitriol (0.25 μ g/day) was added and the symptoms disappeared. Serum calcium concentrations were stabilized and kept between 2.00 and 2.20 mmol/l (normal range 2.00–2.75 mmol/l), while 1,25(OH)₂D₃ concentrations ranged between 22 and 59 ng/l (normal range 35–80 ng/l). In the 33rd week the patient again complained of recurrent tetany and calcitriol was increased to 0.50, and eventually to 0.75 μ g/day. At the end of the 37th week of pregnancy she gave birth to a healthy girl (3370 g, 50 cm). The lactation period was

characterized by severe nocturnal tetany, despite the administration of 1.0 μ g calcitriol and 4–6 g of calcium per day (Fig. 1).

During the first trimester of her second pregnancy, calcitriol and calcium administration (1.5 g/day) remained unchanged. Calcitriol was given initially at a dose of 0.25 μ g/day with further adaptation to 0.50 μ g/day during the 20th and to 1.00 μ g/day in the 31st week of pregnancy. Serum calcium and 1,25(OH)₂D₃ were continuously within the lower normal range of healthy pregnant women, while 25(OH)D₃ was slightly decreased (47 nmol/l, normal range 50–300). The urine excretion rate ranged between 3.56 mmol/day at the beginning to 11.53 mmol/day (normal range in non-pregnant women 3.25–8.25 mmol/day) in late pregnancy. In comparison to her first pregnancy she clearly suffered less from tetanic episodes, paraesthesia and muscle cramps. She gave birth to another healthy girl during the 39th week of pregnancy. Immediately after delivery she received calcitriol in a dose of 0.75 μ g/day together with 3.0 g/day of oral calcium throughout the lactation period (Fig. 2).

Pregnancies reported to the DSD of Hoffmann-La Roche

Of 13 reported cases, 3 were excluded because of loss to follow up. A total of five prospective and five retrospective cases of pregnant women receiving chronic calcitriol treatment have been reported to the DSD. In eight cases receiving 0.25–3.25 μ g/day of calcitriol no adverse effects were seen and the pregnancies resulted in the delivery of healthy babies. In two retrospectively reported cases serious adverse events were described. In the first case a 30-year-old woman with parathyreoprive hypoparathyroidism delivered an otherwise healthy baby who later was shown to have premature closure of the frontal fontanelle. She took calcitriol in a changing dose between 1 and 5 μ g/day during pregnancy and lactation. Unfortunately no serum calcium concentrations were reported. The second patient received 0.50 μ g/day calcitriol and co-medication with fluoxetine for major depression. She had a stillbirth in the 20th week of pregnancy. The fetus was shown to have a complex malformation of the palate and the left kidney.

Discussion

In normal human pregnancy maternal serum concentrations of 1,25(OH)₂D₃ rise early in the first trimester of pregnancy, remain high and show a further increase during the third trimester. On the third day after delivery they fall to non-pregnant levels (11–13). The increased synthesis of 1,25(OH)₂D₃ in the mother may represent an adjustment to the high fetal uptake of calcium into the skeleton, especially in the third trimester (14–16).

In normal pregnancy, ionized calcium is actively transported across the placenta (17). Fetal total and dialysable serum calcium values appear to be slightly higher than maternal values (17).

It has recently been demonstrated in animals that parathyroid hormone (PTH)-related protein (PTHrP) is the fetal equivalent of PTH (18). It is believed that fetal PTHrP, which is mainly derived from the placenta during early gestation and from the fetal parathyroid glands during further development (18), helps maintain the maternal-fetal calcium gradient either alone or in

concert with $1,25(\text{OH})_2\text{D}_3$ (18). In mice in which the PTHrP gene has been ablated by homologous recombination, fetal circulating ionized calcium levels are significantly lower (19).

Maternal immunoreactive PTH, like other polypeptide hormones, does not cross the placenta (17). Conflicting results of the PTH concentrations during pregnancy have been reported. Seki *et al.* (20) measured low PTH in maternal serum associated with elevated fetal PTHrP. Others (21) found unchanged PTH with a significant rise postpartum. In a prospective longitudinal

Figure 1 Daily dose of calcitriol and oral calcium, and serum calcium and $1,25(\text{OH})_2\text{D}_3$ concentrations in our patient during her first pregnancy and after delivery. In the two lower panels, shaded areas are serum concentrations of calcium and $1,25(\text{OH})_2\text{D}_3$ measured in pregnant women (modified after Reddy *et al.* (11)).

study (12) PTH concentrations increased from the first to the second trimester, declining again in the third trimester to the levels of the first trimester. However, PTH significantly increased postpartum. In contrast, PTHrP concentrations increased continuously throughout pregnancy and lactation. Whether PTH decreases in late pregnancy due to an increasing PTHrP production by the placenta is not known. The increased requirement of calcitriol in women with hypoparathyroidism in the third trimester of pregnancy, which has been observed not only in our case but also in other patients (16, 22, 23), clearly suggests

that the increase in the placenta-derived PTHrP is unable to compensate for the lack of PTH in patients with hypoparathyroidism.

After delivery the placental supply of calcium ceases abruptly, stimulating the secretion of PTH and production of $1,25(\text{OH})_2\text{D}_3$ in the newborn, and these are the main regulators of postnatal calcium metabolism (18). The main synthesis of $1,25(\text{OH})_2\text{D}_3$ takes place in the maternal kidney, although the enzymatic ability of the placenta and the fetal kidney does also produce some (24, 25). In addition, other hormones elevated during gestation, such as prolactin, human growth hormone

Figure 2 Daily dose of calcitriol and oral calcium, and serum calcium and $1,25(\text{OH})_2\text{D}_3$ concentrations in our patient during her second pregnancy and after delivery. In the two lower panels, shaded areas are serum concentrations of calcium and $1,25(\text{OH})_2\text{D}_3$ measured in pregnant women (modified after Reddy *et al.* (11)).

and oestradiol, may also directly promote the synthesis of $1,25(\text{OH})_2\text{D}_3$ (26).

Concerning the treatment of hypoparathyroidism during pregnancy, the absence of PTH impairs the metabolism of endogenous vitamin D to $1,25(\text{OH})_2\text{D}_3$. Substitution therapy of hypoparathyroidism in this situation requires a compound with immediate and predictable bioavailability. In contrast to prodrugs like cholecalciferol and to tachysterol, calcitriol has a much shorter, dose-independent half-life. For example, 50% of intravenously given radioactive $1,25(\text{OH})_2\text{D}_3$ is eliminated within 8 min from the blood, and 4 h after administration only 10–16% is still detectable (27). Studies using tritium-labelled and unlabelled calcitriol have demonstrated that after oral administration peak plasma concentrations are achieved between 3 and 6 h after administration (27). Thus, in a case of over-treatment, hypercalcaemia will resolve within 2 to 7 days. In contrast, alfacalcidol (1- α -hydroxycholecalciferol), a prodrug which is metabolized to $1,25(\text{OH})_2\text{D}_3$ by hepatic hydroxylation, has its peak plasma concentration after 6 to 16 h and therefore a more delayed effect (28).

The risk of vitamin D overdosage and subsequent teratogenicity in humans and animals seems to be small as long as the serum calcium and the $1,25(\text{OH})_2\text{D}_3$ concentrations remain in the lower normal range. The outcome of a total of nine pregnancies complicated by hypoparathyroidism or vitamin D-resistant rickets requiring treatment with vitamin D or its analogues has been published in the literature (Table 1). No toxicity or teratogenicity was observed, although in some cases very high doses were given.

Additionally we herein report ten new cases of calcitriol treatment during pregnancy reported to the DSD, Hoffmann-La Roche AG. A normal outcome was found for eight newborns. In two cases, serious adverse events concerning the fetus were documented. However the causal relationship to calcitriol treatment remains questionable, as the observed changes were not suggestive of vitamin D toxicity. Moreover, both cases were reported retrospectively, probably reflecting a

reporting bias. So far in prospectively reported cases no serious adverse events were noted. This suggests, based on the still limited available data, that treatment with calcitriol is rather safe.

In experimental rats a dosage of $0.30 \mu\text{g}/\text{kg}$ per day calcitriol (equivalent to $25 \mu\text{g}/\text{day}$ in a human subject of 70 kg body weight) did not induce any embryo or fetus toxic effects. This contrasts with experiments in rabbits which exhibited signs of maternal and fetal toxicity with the same dose (29). In humans, there is only one report of a pregnant woman suffering from vitamin D-resistant rickets who received very high doses of calcitriol ($17\text{--}36 \mu\text{g}/\text{day}$). Serum calcium levels of the infant were high after birth, but otherwise the newborn was healthy (30). In our case the maximum calcitriol dose was $1.00 \mu\text{g}/\text{day}$ in the 35th week of pregnancy. Pitkin (31) recommends a daily dosage of calcitriol ranging between 0.5 and $3.0 \mu\text{g}/\text{day}$ with advancing gestation to maintain a normal maternal serum calcium level.

It is important to note that not only hypercalcaemia, but also hypocalcaemia is dangerous for the development of the fetus. *In vitro* experiments with the uteri of pregnant rats have shown that hypocalcaemia tends to increase uterine irritability, possibly leading to preterm labour (7). If the plasma calcium concentration is reduced to levels $<1.7 \text{ mmol}/\text{l}$ in humans, the pregnancy is at considerable risk (8).

Summarizing the data from the literature and our own experience, we propose the following regimen for the treatment of hypoparathyroidism during pregnancy: treatment of choice is the combination of oral calcium supplementation with calcitriol. The serum calcium concentration should be kept within the lower normal range (between 2.00 and $2.20 \text{ mmol}/\text{l}$), which generally requires a calcitriol dose between 0.25 and $3.00 \mu\text{g}/\text{day}$. Starting from $0.25 \mu\text{g}/\text{day}$ calcitriol and a calcium supplementation of $1 \text{ g}/\text{day}$, the dosage has to be adjusted to the physiological requirements during pregnancy, increasing the dosage after the 20th week of gestation with further elevation in the last trimester. Because of the short half-life of calcitriol, symptomatic tetany at night time may become a problem, which can

Table 1 Vitamin D derivatives used for the treatment of hypoparathyroidism during pregnancy.

Vitamin D derivatives	Year (reference)	Cases (n)	Maximum daily dosage	Maximum plasma calcium (mmol/l)	Maximum $1,25(\text{OH})_2\text{D}_3$ (ng/l)	Toxic effects
Calciferol	1966 (1)	2	150 000 IE	1.77	—	None
Calciferol	1969 (35)	3	100 000 IE	1.47	—	None
Calcitriol	1980 (30)	1	$36.00 \mu\text{g}$	2.40	680	None
Calcitriol	1980 (22)	1	$3.00 \mu\text{g}$	2.00	—	None
Calcitriol	1981 (16)	1	$2.00 \mu\text{g}$	2.59	—	None
Alfacalcidol	1985 (8)	1	$2.00 \mu\text{g}$	2.25	—	None
Calcitriol	1985 (31)	1	$3.00 \mu\text{g}$	—	—	None
Calcitriol	1980 (23)	2	$3.25 \mu\text{g}$	2.25	—	None
Calcitriol	1994 (9)	1	$1.50 \mu\text{g}$	2.50	—	None

Normal ranges: serum calcium $2.00\text{--}2.75 \text{ mmol}/\text{l}$; serum $1,25(\text{OH})_2\text{D}_3$ $35\text{--}80 \text{ ng}/\text{l}$.

be controlled by dividing the dose (32). Serum calcium levels should not fall below 1.70 mmol/l to avoid preterm labour or midtrimester abortion (8). Monitoring possible overtreatment by measuring the urinary calcium excretion is difficult, as in third trimester pregnancy 20% of healthy women have values exceeding the normal range (13, 33), probably due to an increase in the glomerular filtration rate. Moreover, even with optimum substitution therapy, hypoparathyroidism may be associated with an increased urinary calcium excretion. Thus, the short-lasting deviation of urinary calcium excretion observed in our case seems to be of minor clinical relevance.

After delivery the calcium homeostasis is changing (22). Probably due to the effect of PTH-rP, the calcitriol dose should be reduced during lactation. Thus, both mother and infant should be monitored during breast-feeding to detect hypercalcaemia (22, 34).

In conclusion, during pregnancy, management of maternal hypoparathyroidism with calcitriol is feasible, if the 1,25(OH)₂D₃ concentrations are adapted to the physiological needs and serum calcium levels are kept in the lower normal range.

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