MANAGEMENT OF ENDOCRINE DISEASE

Hypoparathyroidism in pregnancy: review and evidence-based recommendations for management

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Abstract

Purpose: Review calcium homeostasis in pregnancy and provide evidence-based best practice recommendations for the management of hypoparathyroidism in pregnancy.
Methods: We searched MEDLINE, EMBASE and Cochrane databases from January 2000 to April 1, 2018. A total of 65 articles were included in the final review.
Conclusions: During pregnancy, calcitriol levels increase by two- to—three-fold resulting in enhanced intestinal calcium absorption. The renal filtered calcium load increases leading to hypercalciuria. PTHrP production by the placenta and breasts increases by three-fold, and this may lower the doses of calcium and calcitriol required during pregnancy in mothers with hypoparathyroidism. The literature however describes a wide variation in the required doses of calcium and calcitriol during pregnancy in hypoparathyroid mothers, with some women requiring higher doses of calcitriol, whereas others require lower doses. Close monitoring is necessary as hypercalcemia in the mother may suppress the fetal parathyroid gland development. Also hypocalcemia in the mother is harmful as it may result in secondary hyperparathyroidism in the fetus. This may be associated with demineralization of the fetal skeleton and the development of intrauterine fractures. Inadequate treatment of hypoparathyroidism may also result in uterine contractions and an increased risk of miscarriage. Treatment targets during pregnancy are to maintain a low normal serum calcium. Calcium, calcitriol and vitamin D supplements are safe during pregnancy. Close monitoring of the mother with a multidisciplinary team is advised for optimal care. If calcium homeostasis is well controlled during pregnancy, most women with hypoparathyroidism have an uncomplicated pregnancy and give birth to healthy babies.

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Introduction and methodology

Hypoparathyroidism is a rare condition and when it occurs in pregnancy it maybe associated with significant maternal and fetal morbidity (1, 2). Physiologic changes in the calcium regulating hormones, which occur during pregnancy impact calcium homeostasis and necessitate close monitoring of serum calcium during pregnancy in hypoparathyroid mothers. Frequent adjustments in the dose of calcium and calcitriol may be required in order to avoid both hypocalcemia and hypercalcemia. Both these conditions impact fetal parathyroid development and may result in maternal and fetal morbidity. We reviewed the literature and provided evidence-based

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recommendations guiding clinical practice today. MEDLINE, EMBASE and CENTRAL databases were searched from January 1, 2000 to April 1, 2018 using the MeSH search terms hypoparathyroidism, pregnancy, physiology, complications and management. A total of 1449 articles were found. These were reduced to 123 articles based on abstract and title. We excluded letters and editorials and only included English language papers dealing with humans. Case reports and case series were also included due to the limited evidence available in the literature today. The final review included 65 articles.

Impact of pregnancy on calcium homeostasis

During pregnancy serum albumin decreases with the expansion of intravascular volume. This reduction in serum albumin results in a reduction in the measured total albumin-bound calcium. Longitudinal studies have demonstrated that serum ionized calcium as well as calcium corrected for albumin remain in the normal reference range (3, 4, 5). Serum phosphorus is unchanged during pregnancy (3, 4, 5). Parathyroid hormone (PTH) is suppressed into the low normal reference range and may actually decline below the normal reference range in the 1st trimester (3, 4, 5, 6, 7, 8, 9, 10). PTH subsequently rises into the midnormal reference range by the third trimester as observed in longitudinal studies. PTH is affected by maternal dietary calcium intake as well as maternal vitamin D levels (11).

Calcitriol rises in the first trimester and increases by two- to three-fold by term as noted in longitudinal studies (4, 5, 12, 13, 14, 15). This significant rise in calcitriol increases intestinal calcium absorption and suppresses PTH (11, 16, 17). The kidney is the main source for the rise in calcitriol with some contribution from the placenta and the fetus. Pregnancy is associated with an increase in renal expression of Cyp27b1 (1-alpha hydroxylase) with levels of Cyp27b1 being 35-fold higher in the kidneys than that found in the placenta (18). The kidney therefore appears to be the major source of the significant rise in serum calcitriol levels. This is also supported by the fact that anephric women on dialysis do not demonstrate significant rises in calcitriol during pregnancy (19).

The key stimulators of renal Cyp27b1 during pregnancy are not known and may be PTHrP. It is also possible that estradiol and prolactin may be contributing to the rise in Cyp27b1. PTHrP is known to be a weak stimulator of Cyp27b1 in comparison to PTH (20). The levels of 25hydroxyvitamin D levels appear to be stable during pregnancy despite increased conversion to calcitriol in addition to transfer of 25hydroxyvitamin D to the fetus (11).

Serum calcitonin rises during pregnancy and may protect the maternal skeleton from demineralization during pregnancy (3, 5, 11, 21, 22). Other investigators have not observed rises in serum calcitonin during pregnancy (9, 13). The source of the calcitonin appears to be the thyroid C-cells in addition the breast and placenta contribute to rises in serum calcitonin (23, 24). These rises in calcitonin have been observed in women who have previously had a total thyroidectomy (23, 24, 25).

Calcitonin levels may also increase in association with the rises in estradiol, estrone and estriol in pregnancy. Rises in calcitonin have also been observed in women using oral contraceptives and this may be secondary to the rises in estrogen (11, 26). Postmenopausal women on estrogen supplementation have also demonstrated rises in serum calcitonin (27).

PTHrP begins to rise from the third to the thirteenth week of gestation and increases by three-fold in comparison to the baseline pre-pregnancy level by term as noted in longitudinal studies (5, 8, 25, 28, 29) The significant rise in PTHrP may upregulate calcitriol and suppress PTH (11).

An important source for PTHrP appears to be the placenta. In a case report of a pregnant woman with severe hypercalcemia and very high levels of PTHrP, serum calcium normalized following cesarean section and delivery of the placenta (30). Post cesarean section the PTHrP levels also became undetectable (30). The breasts appear to be an important source of PTHrP. In a case of a pregnant woman with severe hypercalcemia and very high levels of PTHrP in the breast tissue, serum calcium normalized following bilateral mastectomy in the second trimester of pregnancy (31, 32). PTHrP also decreased post bilateral mastectomy and become undetectable following surgery (31, 32). High levels of estradiol may also increase PTHrP. *In vitro* studies have demonstrated that estradiol increases PTHrP mRNA expression in human endometrial cells (33).

In conclusion, rises in calcitriol during pregnancy lead to enhanced intestinal calcium absorption, which in turn increases renal filtered calcium load and results in increases in urine calcium (34; Fig. 1). The reductions in PTH (secondary to rises in calcitriol and PTHrP) also contribute to the hypercalciuria (16, 17, 34). The hypercalciuria observed during pregnancy has been associated with an increased risk of renal stones during pregnancy. The rises in calcitriol and PTHrP seen in

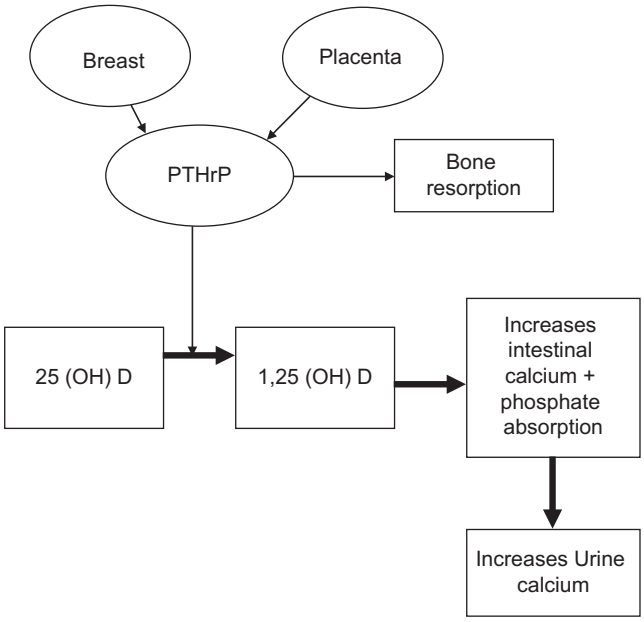

Figure 1
Calcium homeostasis during pregnancy.

pregnancy in women with hypoparathyroidism may result in lower requirements for calcium and calcitriol supplements during pregnancy as noted in many case reports. However, the literature also contains many case reports of hypoparathyroid mothers in whom the calcium and calcitriol requirements have actually increased during pregnancy (35). Variations in requirements for calcium and calcitriol may be a reflection of variations in dietary calcium intake. Many of the patients in the reported cases requiring higher doses of calcitriol did not receive calcium supplements or had inadequate or unknown calcium intake (36, 37, 38, 39, 40). Inadequate calcium intake in the first trimester may contribute to inadequate mineral accrual necessary for the last trimester in order to meet the calcium requirements of the developing fetus. Also there may be variations in the production of PTHrP from the placenta and breast as well as the formation of calcitriol from the maternal kidneys and these variations may contribute to differences in dose requirements during pregnancy in women with hypoparathyroidism. Close monitoring is required during pregnancy to ensure that serum calcium is maintained in the normal reference range.

There are very limited data evaluating the effects of pregnancy in hypoparathyroid women on urinary calcium excretion. The limited data suggest that renal calcium excretion increases further with pregnancy in hypoparathyroidism (41).

What is the impact of maternal hypoparathyroidism on the developing fetus?

The endochondral skeleton of the embryo gradually mineralizes with approximately 80% of the mineral accruing in the third trimester (42, 43). The placenta is essential for the delivery of essential minerals namely calcium, phosphate and magnesium to the fetus from the maternal circulation. Even in the presence of inadequate maternal serum calcium the placenta will extract calcium to meet the fetal requirements at the expense of the maternal skeleton (44, 45, 46, 47). Fetal hypocalcemia does not develop until the maternal serum calcium is severely reduced. In severe hypoparathyroidism with severe hypocalcemia, the fetus can develop hypocalcemia. This will result in the stimulation of the fetal parathyroid glands and development of hyperparathyroidism and demineralization of the fetal skeleton (48, 49, 50, 51). Calcitriol does not cross the placenta and circulating calcitriol in the fetus is synthesized in the fetal kidneys or placenta (52, 53, 54). Maternal PTH also does not cross the placenta and PTH is synthesized in low concentrations in the fetal parathyroid glands (44, 54, 55, 56, 57, 58).

Calcitonin is synthesized in the fetal thyroid as well as the placenta (23, 59, 60). Cord blood has high levels of PTHrP from the placenta (61, 62). The serum calcium is normally maintained at a higher level in the fetus in comparison to the mother, and calcium, phosphorus and magnesium are actively transported against a concentration gradient by the placenta (63). These high levels of minerals may contribute to optimal skeletal calcification of the fetus (63). In the presence of maternal hypercalcemia, transfer of calcium to the fetus is increased and will result in the suppression of the fetal parathyroid glands (64). Similarly, in the presence of maternal hypocalcemia, placental transfer of calcium is decreased and will result in fetal parathyroid gland stimulation and the development of fetal hyperparathyroidism, with severe cases presenting with subperiosteal bone resorption, bowing of the long bones, osteitis fibrosa cystica, intrauterine rib and limb fractures, low birth weight, spontaneous abortion and possibly fetal death (65, 66, 67, 68).

What are the treatment targets for serum calcium during pregnancy?

During pregnancy, careful monitoring of serum calcium is required with maintenance of serum calcium in the

low normal reference range. It is recommended to avoid hypocalcemia in order to prevent stimulation of the fetal parathyroid glands (69). Hypercalcemia should also be avoided in order to prevent suppression of the fetal parathyroid glands, which can result in hypocalcemia in the newborn. Although several case reports have described normalization of serum calcium and PTH within the first months after birth, intrauterine hyperparathyroidism has been associated with skeletal demineralization and intrauterine fractures as mentioned above. Also intrauterine hypoparathyroidism has been associated with neonatal tetany (70, 71). Furthermore, untreated hypoparathyroidism has been associated with an increased risk of abortion (2). Therefore, it is important to maintain serum calcium in the low normal reference range during pregnancy and monitor closely to ensure that both hypocalcemia and hypercalcemia are avoided.

The lactating breast is a significant source of PTHrP and impacts bone resorption as well as enhances renal calcium reabsorption (12, 72). Calcitriol levels normalize postpartum, following delivery of the placenta. Also reductions in estradiol which are elevated by 100-fold in pregnancy and may have stimulated Cyp27b1 and this may contribute to the reductions in calcitriol levels (11). The effects of these changes on calcium homeostasis postpartum are variable and close monitoring of serum calcium is advised. However, care should be taken not to titrate (change) doses of calcitriol and calcium supplements too frequently, as this may contribute to wide fluctuations in serum calcium while adapting to the postpartum state. Serum albumin corrected or ionized calcium levels should be measured within the first week postpartum followed by measurement once-weekly during the first month postpartum. In the presence of breastfeeding we advise measuring calcium levels once a month. Calcium levels should be targeted in the low normal reference range similar to non-breastfeeding levels. More frequent measurements may of course be needed if calcium levels are out of the target range. If calcium levels have been fairly well controlled during pregnancy and the newborn thrives well, biochemical tests may not be needed. However, the newborn should be carefully monitored clinically and calcium levels should be evaluated in the baby if the baby is not well (e.g. does not suckle well) or if long periods of hypo- or hypercalcemia occurred during pregnancy, as this may have affected the development of the parathyroid glands of the newborn causing hypo- or hyper-calcemia.

As urinary calcium in hypoparathyroidism is closely related to serum calcium levels (34, 73), it is advised to maintain serum calcium levels in the lower part of the normal reference interval in order to avoid further rises in renal calcium excretion. Calcium, calcitriol and vitamin D supplements are safe to use during pregnancy. PTH has not been adequately evaluated in pregnancy and is classified as a pregnancy risk category C drug (74). Thiazide diuretics should be discontinued during pregnancy and are considered FDA pregnancy risk category B drugs (75).

What are the best treatment strategies for the management of hypoparathyroidism in pregnancy?

Since the publication of the first case of hypoparathyroidism in pregnancy (76) treatment options have not really improved despite a significant increase in our understanding of calcium homeostasis in both the mother and the fetus (1, 36, 37, 41, 68, 70, 77, 78, 79, 80, 81, 82, 83, 84, 85). As noted previously the rises in calcitriol and PTHrP which occur in hypoparathyroid women during pregnancy may result in lower requirements for calcium and calcitriol supplementation; however, this may not always be the case and in some women calcium and calcitriol requirements may actually increase during pregnancy (35, 86). Close monitoring is required during pregnancy to ensure that serum calcium is maintained in the low normal reference range in order to avoid potential maternal and fetal complications. Calcium and calcitriol supplements are safe during pregnancy and lactation.

Recommendations

- In order to avoid adverse effects on the development and function of the fetal parathyroid glands and to avoid worsening of renal calcium losses, serum calcium (albumin corrected or ionized) levels should be targeted toward the lower part of the normal reference range.

Quality of evidence – very low

- We recommend monitoring serum calcium every 3–4 weeks during pregnancy to ensure that hyper or hypocalcemia do not develop. If changes in the dose of calcium or calcitriol are advised, then the lab profile with serum calcium corrected for albumin should be repeated in 1–2 weeks. The half-life of calcitriol is 4–6 h and steady state is reached in five half-lives. Waiting for 1–2 weeks provides us with an opportunity to observe the real-world response in the individual patient as

serum calcium will also be dependent on other factors including dietary and lifestyle factors such as exercise.

Quality of evidence – very low

- We recommend serum phosphate, magnesium, 25hydroxyvitamin D and the 24-h urine for calcium should be maintained in the normal reference range.

Quality of evidence – very low

- We recommend stopping treatment with thiazides during pregnancy.

Quality of evidence – moderate

- We recommend stopping replacement therapy with PTH (1–84) and PTH (1–34) during pregnancy.

Quality of evidence – low

- We recommend educating the patient regarding the symptoms of hypercalcemia and hypocalcemia and advice that they have their serum calcium (corrected for albumin or ionized) checked urgently if they are experiencing symptoms of hypo or hypercalcemia. Optimal care outcomes for both the mother and baby are achieved with coordinated care among the endocrinologist, obstetrician as well as the pediatrician. We advise informing the pediatrician prior to delivery to ensure the neonate can be immediately assessed with appropriate monitoring of the serum calcium.

Quality of evidence – very low

In conclusion, hypoparathyroidism may result in severe adverse pregnancy outcomes if not adequately treated. Calcium, calcitriol and vitamin D supplements are safe to use during pregnancy. Serum calcium should be monitored every 3–4 weeks during pregnancy. Although only limited data are available in the form of case reports and case series most women with hypoparathyroidism have an uncomplicated pregnancy and give birth to healthy babies if serum calcium levels are maintained within the low-to-mid normal reference range throughout pregnancy. A coordinated approach to care among the treating endocrinologist, obstetrician, pediatrician and nursing staff is highly recommended. There is an urgent need for prospective studies in hypoparathyroidism in pregnancy in order to enhance the quality of care available today.

Declaration of interest

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Author contribution statement

Aliya Khan completed the literature search with Hajar Abu Alrob MSc candidate, Health Research Methodology, McMaster University and all authors shared in developing the manuscript.

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