Primary Hyperparathyroidism in Pregnancy

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Contributor: Dalal Ali

Parathyroid disease is uncommon in pregnancy. During pregnancy, multiple changes occur in the calcium regulating hormones which may make the diagnosis of primary hyperparathyroidism more challenging. Close monitoring of serum calcium during pregnancy is necessary in order to optimize maternal and fetal outcomes.

hyperparathyroidism pregnancy calcium homeostasis parathyroidectomy gestational hyperparathyroidism cinacalcet nephrolithiasis preeclampsia hypercalcemia

1. Introduction

Primary hyperparathyroidism (PHPT) is a relatively common endocrine disorder and represents the most common cause of hypercalcemia in the non-pregnant population [1]. The prevalence of PHPT in pregnancy was examined in one retrospective study conducted between 2005 and 2013. Among 292,042 women of reproductive age, PHPT was present in 0.05%. Seventy-four women with untreated PHPT conceived, representing 0.03% of the entire cohort [2]. Two case series performed before 2000 reported on a total of 1600 parathyroidectomies, with 0.8 to 1.4% of them being carried out in pregnant women [3][4]. The diagnosis of PHPT in pregnancy can be confirmed in the presence of hypercalcemia (elevated serum ionized calcium or calcium adjusted for albumin) with a non-suppressed parathyroid hormone (PTH) level. PHPT is usually caused by a solitary parathyroid adenoma (~85%), hyperplasia is less frequent, and carcinoma is extremely rare with only eight cases reported in pregnancy [5][6][7][8][9][10][11][12]. In individuals below the age of 40 years, PHPT may be due to an underlying genetic mutation which occurs in approximately 10% of the cases [13]. Since pregnant women represent a considerably younger population, the presence of an underlying genetic mutation may be expected to be greater than 10%. Genetic mutations can present as part of a syndrome, such as multiple endocrine neoplasia (MEN 1, MEN2A or MEN4) or hyperparathyroidism-jaw tumor syndrome (HPT-JT), or it may be isolated as in familial isolated hyperparathyroidism (FIHP). Familial hypocalciuric hypercalcemia (FHH) should also be considered in the differential diagnosis of hypercalcemia along with a non-suppressed PTH. Appropriate evaluation is required prior to confirming the diagnosis of PHPT (see details in Section 4).

PHPT in pregnancy is associated with a number of maternal complications including hyperemesis gravidarum, nephrolithiasis and/or pancreatitis [14][15][16]. While neonatal hypocalcemia, tetany, intrauterine growth retardation (IUGR) and fetal demise have been previously reported with PHPT in pregnancy [17][18][19], milder forms of PHPT being diagnosed nowadays do not seem to carry the same degree of maternal or fetal mortality or morbidity [2][20]. Early recognition of PHPT has been associated with a lower rate of complications when compared to the older

literature. However, medically managed PHPT still appears to be associated with an increased risk of preeclampsia and miscarriage rates [18][20]. The postpartum hypercalcemic crisis has been reported in the literature as a potential complication of PHPT in pregnancy, and this likely happens when the active transplacental transfer of calcium from the mother to the fetus is lost after delivery of the placenta [6][21][22].

2. Impact of PHPT on Mother and Fetus during Pregnancy

Several maternal and fetal adverse outcomes have been associated with PHPT in pregnancy. Mothers can present with nephrolithiasis [16][23], hyperemesis gravidarum [15], and in severe cases acute pancreatitis [9][15][24][25][26][27][28][29]. Preeclampsia and hypertension have been frequently reported with PHPT in pregnancy [30][31][32][33][34]. PTH may stimulate the renin–angiotensin–aldosterone system and contribute to hypertension and preeclampsia [35][36][37][38][39][40]. Women with PHPT may develop a hypertensive crisis or HELLP syndrome which is characterized by hemolysis, elevated liver enzymes, low platelets and eclampsia or preeclampsia [37].

As for the non-pregnant population, PHPT may result in bone loss, especially at sites rich in cortical bone, such as the distal third radius, with relative sparing of the spine [41][42]. However, it should be noted that data pertaining to bone loss in pregnant women are limited as Dual-energy X-ray absorptiometry (DXA) assessment is seldom performed in such a population. In rare cases, fragility fractures may occur, and vertebral compression fractures, rib fractures as well as bilateral femur fractures have been reported in association with PHPT in pregnancy [43][44].

Neonatal hypocalcemia has been widely reported in the literature in association with maternal PHPT [45][46][47][48]. Other complications may include polyhydramnios [49], as well as fetal and maternal mortality [4][34][50].

An interesting case of twin pregnancy in a mother with PHPT was reported. The findings were discordant, with one of the babies presenting with neonatal hypocalcemia and a seizure, while the other was normocalcemic despite similar exposure to maternal hypercalcemia during pregnancy [51]. Therefore, it seems that the impact of maternal hypercalcemia on the developing fetus cannot be predicted by the degree of hypercalcemia alone.

Neonatal complications have been reported in women treated medically for PHPT throughout pregnancy [52]. Fetal mortality in medically treated pregnant women was estimated to be one in five fetuses (16%) while fetal mortality and morbidity in those who were treated surgically for PHPT were estimated to be 3% and 10%, respectively, based on data published from case reports from 1930 to 1990 [3]. Older literature is believed to represent more severe cases of PHPT in pregnancy with worse associated outcomes. Early recognition of PHPT with a milder degree of hypercalcemia has been associated with a lower rate of fetal and neonatal outcomes [20][53].

In another case series involving 17 pregnant women with PHPT, parathyroidectomy (PTX) was performed in the 2nd trimester with no maternal or fetal adverse outcomes and a 100% cure rate. One patient out of the 17 cases declined surgery during pregnancy and suffered from severe preeclampsia and delivered a baby with IUGR [17].

3. Clinical Management of PHPT in Pregnancy

There is no consensus on the management of PHPT during pregnancy, however, an individualized approach is required for women with PHPT. This approach is dependent on the severity of symptoms, gestational age at presentation, age, associated features, and complications. Mild PHPT (serum corrected calcium less than 2.85 mmol/L (11.42 mg/dL)) in pregnancy may be managed conservatively.

Medical management includes adequate hydration and cessation of thiazide diuretics, calcium supplements and lithium if possible [54][55]. Pharmacologic options are severely limited with no safety data with any of the available treatment strategies.

Calcitonin is reserved for refractory hypercalcemia. It is classified as category C in pregnancy and it does not cross the placenta [56]. It has been used in a number of case reports [54][57]. Associated tachyphylaxis may limit its long-term efficacy.

Calcimemetics, namely cinacalcet, increases the sensitivity of the parathyroid CaSR to extracellular calcium, resulting in a reduction in PTH secretion [58]. It is categorized as class C in pregnancy and has been shown to cross the placenta. Data on long-term safety in pregnancy are unfortunately lacking. There are six published case reports describing cinacalcet use during pregnancy in patients with PHPT [5][23][54][57][59][60]. Neonatal hypocalcemia was reported in three out of the six cases treated with cinacalcet [5][23][57]. This, however, may be in association with maternal hypercalcemia and a causal relationship with cinacalcet has not been confirmed. Cinacalcet has also been used in a pregnant woman with PHPT due to parathyroid carcinoma with no reported maternal or fetal unfavorable outcomes [5].

Bisphosphonates should be avoided during pregnancy as they cross the placenta and adverse fetal skeletal outcomes have been observed in animal studies [61]. Similarly, denosumab is classified as category D in pregnancy, it crosses the placenta and has been associated with skeletal fetal adverse outcomes in animal studies and should be avoided in pregnancy [62][63].

Oral phosphate has been previously used to lower serum calcium levels, however, safety and efficacy data during pregnancy are very limited and use should not be recommended [64][65][66][67].

Surgery remains the only curative option for PHPT. It is well-tolerated during pregnancy and adverse events are minimal [43]. Timely surgical intervention in the 2nd trimester has been associated with favorable outcomes in patients with moderate to severe hypercalcemia during pregnancy (calcium adjusted for albumin greater than 3 mmol/L (12.02 mg/dL)) [68][69]. This has shown to be an effective approach in several case reports and case series [17][28][31][70][71][72].

Surgical intervention in the 3rd trimester of pregnancy has been reported in patients who have failed medical therapy. In the majority of these cases, surgery was safe and did not result in any harmful maternal or fetal outcomes [21][30][69][70][73][74][75][76][77][78][79]. Some cases, however, reported associated preeclampsia, preterm labor and severe neonatal hypocalcemia with surgery in the 3rd trimester [21][34][80][81]. These complications may be

attributed to delayed presentation and prolonged exposure to maternal hypercalcemia. Parathyroidectomy has also been performed successfully in the 1st trimester [82].

Intraoperative PTH measurement is recommended to confirm successful resection of the hyperfunctioning parathyroid adenoma [1]. It can be of a great value in pregnant women in whom preoperative localization of abnormal parathyroid tissue is not conclusive or in those with the multiglandular disease.

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