MANAGEMENT OF HYPOPARATHYROIDISM AND PSEUDOHYPOPARATHYROIDISM DURING PREGNANCY: A RETROSPECTIVE OBSERVATIONAL STUDY

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Introduction and Objective

Parathyroid hormone (PTH) is essential for calcium homoeostasis, and pregnancy is known for an increased calcium requirement. During pregnancy and breastfeeding, physiological changes of maternal calcium metabolism take place to ensure both an adequate fetal skeleton mineralization, with approximately 80% of the mineral accruing in the fetus in the third trimester, and a sufficient amount of calcium in the breast milk.

A status of chronic maternal hypocalcemia, due to hypoparathyroidism (HypoPT) or pseudo-hypoparathyroidism (pseudo-HypoPT) not properly treated with calcium supplements and active vitamin D metabolites (calcitriol) or analogues (alfacalcidol), can cause a reduction of placental transfer of calcium to the fetus. However, fetal hypocalcemia does not develop until the maternal serum calcium level is severely reduced. The maternal calcitriol level in HypoPT or pseudo-HypoPT tends to be low because 1-alpha hydroxylase is activated insufficiently by inadequate serum PTH, or a resistance to PTH; therefore, calcitriol should be adequately supplemented. In pregnancy, either maternal hypercalcemia or hypocalcemia may impact fetal development of the parathyroid glands.

During pregnancy, the challenge of pharmacological management is to maintain normal calcium and phosphate levels in both plasma and urine, periodically evaluating these levels and the variable individual responses to treatment. Calcium and active vitamin D requirements can change dramatically during pregnancy, which may cause frequent adjustments in their doses. This problem is well presented in the recently published evidence-based best practice recommendations by experts of HypoPT. The clinical course and therapeutic management of HypoPT during pregnancy is still not fully clarified, due to the few, and sometimes conflicting, case reports published in literature.

The aim of the present study was to conduct a large retrospective observational investigation on pregnant women affected by HypoPT or pseudo-HypoPT, followed by nine referral endocrinology centers that are part of the research group "HypoparaNet" (HypoPT working group) of the Italian Society of Endocrinology (Società Italiana di Endocrinologia S.I.E.).

Patients and Methods

This is a large retrospective, observational, multicentric study conducted in women affected by HypoPT or pseudo-HypoPT, who had one or more pregnancies. This project involved nine Italian referral centers for endocrine diseases, affiliated with S.I.E. and involved in the "HypoparaNet" research group.

The inclusion criteria included: 1) history of chronic HypoPT for ≥ 12 months post-diagnosis; or pseudo-HypoPT diagnosis; 2) history of one or more pregnancies, followed at specialized endocrinology centers; and 3) capability of providing written informed consent.

All clinical data were collected anonymously with the initials of the name and date of birth of each patient, using an electronic Excel sheet

Analysis of frequencies and descriptive statistics were performed using the IBM Statistical Package for Social Sciences (SPSS 20.0) for Windows (IBM, Armonk, NY, USA). Data are presented as mean ± SD (Standard Deviation), unless otherwise stated. Repeated measures-related differences were evaluated by using Student's t-test for paired sample. P value of less than or equal to 0.05 was considered statistically significant. For all the variables that did not meet the assumptions for parametric analysis, the Wilcoxon Signed-Rank Test was employed to assess paired data. Due to sample size constraints, inferential analyses for repeated measures were performed only on the chronic HypoPT sample.

The study was approved by the Institutional Review Board (Florence, Italy) [number: 10641_oss]. Informed consent was collected in accordance with General Authorization to Process Personal Data for Scientific Research Purposes (Authorization no. 9/2013, The Italian Data Protection Authority).

Results

Thirty-four women with chronic HypoPT and six with pseudo-HypoPT, who had at least one pregnancy, were identified. The results presented are focused on the first pregnancies, since the analysis conducted in the small subgroup with second and third pregnancies showed no differences.

Most of the chronic HypoPT cases were affected by postsurgical HypoPT, with the exception of two autoimmune HypoPT cases, and two idiopathic HypoPT cases. Three women with pseudo-HypoPT type 1B had GNAS gene (Guanine Nucleotide binding protein, Alpha Stimulating) methylation alterations, two women with pseudo-HypoPT type 1A had GNAS gene mutation (GNAS c.568_571del), whereas no mutations were found in one case with clinical pseudo-HypoPT type 1A. Among the six cases of women with pseudo-HypoPT, only for three (two with pseudo-HypoPT type 1B and one with pseudo-HypoPT type 1A) was it possible to collect all clinical, biochemical and therapeutic data.

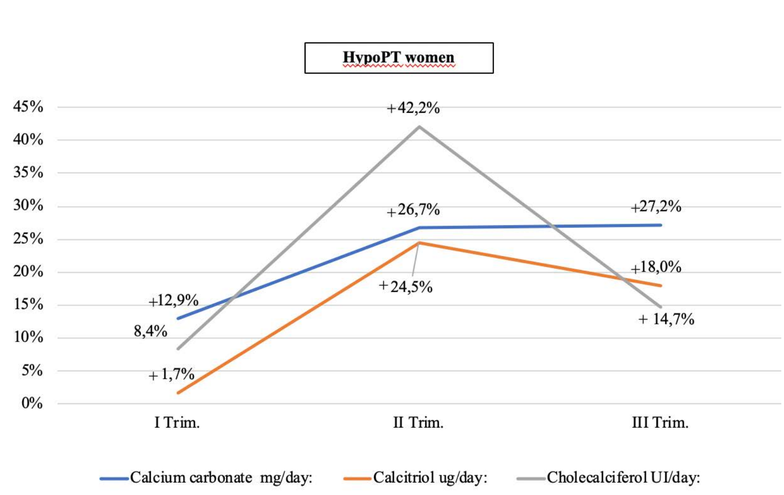
History of spontaneous miscarriages was present in 26.5% (9/34) women with HypoPT, and in 66.7% (4/6) women with pseudo-HypoPT. Only three women with HypoPT (12.9%, 3/31), aged 29-35 years, underwent assisted reproduction treatment; in 1/3, the reason was infertility of the partner. Most of the women with HypoPT had a term birth (82.1%, 23/28); only 2 women (7.1%) had a post-term birth; 3 (10.7%) women had a preterm birth. Among women with pseudo-HypoPT, 5 out of 6 had term pregnancies.

During pregnancy, 8 women with HypoPT (26.6%, 30/34) reported maternal complications, including: pre-eclampsia (n = 2), premature rupture of membranes (n = 2), polyhydramnios (n=1), 1 case of placenta previa (n = 1), and gestational diabetes (n = 3). One woman had gestational diabetes and pre-eclampsia during a triplet pregnancy. No patient with pseudo-HypoPT reported maternal complications.
One case of interventricular septal defect was reported as a neonatal complication among the newborns of women with HypoPT, whereas 1 case of transient hypocalcemia and 1 case of respiratory distress with pulmonary hypertension were described in 2 newborns of women with pseudo-HypoPT.

This table shows the supplementation with calcium and vitamin D (analogues and metabolites) and biochemical exams during pre-pregnancy semester and three trimesters of the pregnancy in women with HypoPT and in women with pseudo-HypoPT (not all data are present data due to missing data)

HypoPT women (n:34)												
	Pre-pregnancy semester			I° trimester			II° trimester			III° trimester		
Medications	N.	Mean ± SD	Range	N.	Mean ± SD	Range	N.	Mean ± SD	Range	N.	Mean ± SD	Range
Calcium carbonate, mg/day	25	1.416 ± 876	500- 4000	25	1600 ± 1050	500-4000	25	1795 ± 1265.6	250 - 6000	25	1802 ± 1242	500 - 6000
Calcitriol, µg/day	28	0.79 ± 0.51	0.25-3	30	0.8 ± 0.4	0-2	28	1 ± 0.7	0 - 3	28	0.94 ± 0.62	0-3
Cholecalciferol, IU/day	9	977 ± 423	400-1600	10	1059.7 ± 522.4	400-2000	8	1389.6 ± 1063.6	400 - 3666.7	7	1121 ± 653	400 - 2000
Biochemistry *												
Albumin-corrected calcium, mg/dl [8.510.1]	25	8.2 ± 0.7	6.8-9.1	25	8.6 ± 0.8	7.2 – 9.8	25	8.5 ± 0.8	6.9 - 9.6	25	8.5 ± 0.8	6.3 - 9.2
Phosphate serum, mg/dl [2.5-4.9]	19	4.3 ± 1.3	0.9-6.4	15	4.3 ± 1.2	1.1 – 6.3	17	4.2 ± 1.2	1.3 - 5.8	15	4.3 ± 1.1	1.8 - 5.8
Urinary calcium, mg/24h [100-300]	10	201 ± 87.2	68-353.8	5	231.9 ± 119	69 - 350	5	301 ± 224.4	166 - 698	5	378.3 ± 167.5	260 - 570
Creatinine, mg/dl [0.5-1.3]	16	0.7 ± 0.1	0.5-0.9	15	0.7 ± 0.1	0.5 – 0.9	9	0.6 ± 0.1	0.4 - 0.8	12	0.7 ± 0.1	0.5 - 0.8
25 (OH) vitamin D, ng/dl [30-100]	23	29 ±11.1	13.4-50.2	9	31.9 ± 10.3	13 - 44	7	38.5 ± 19.9	15 - 79.7	4	21.5 ± 13.3	7 - 36.1
Magnesium, mg/dl [1.5-2.6]	12	1.8 ± 0.4	0.8-2.2	8	1.7 ± 0.4	0.7 - 2	5	1.5 ± 0.4	0.7 - 1.9	3	1.9 ± 0.1	1.8 - 1.9
Pseudo-HypoPT women (n:3)												
	Pre-pregnancy semester			I° trimester			II° trimester			III° trimester		
Medications	N.	Mean ± SD	Range	N.	Mean ± SD	Range	N.	Mean ± SD	Range	N.	Mean ± SD	Range
Calcium carbonate, mg/day	3	500 ± 0	500 - 500	3	875 ± 530	500 - 1250	3	875 ± 530	500 - 1250	3	1125 ± 177	1000 - 1250
Calcitriol, µg/day	3	0.7 ± 0.1	0.5-0.8	3	0.67 ± 10	50 - 80	3	0.67 ± 10	50 - 80	3	0.83 ± 29	50 - 100
Cholecalciferol, IU/day	3	1600 ± 0	1600 - 1600	3	2466 ± 1225	1600 - 1333	3	2466 ± 1225	1600 - 3333	3	2466 ± 1225	1600 - 3333
Biochemistry *												
Albumin-corrected calcium, mg/dl [8.5-10.1]	3	9.3 ± 0.7	8.8 – 9.8	3	9.3 ± 0.8	8.7 – 9.8	3	9.2 ± 0.2	9 – 9.4	3	9.1 ± 0.7	8.6 – 9.6
Phosphate serum, mg/dl [2.5-4.9]	3	4.5 ± 0.6	3.8 – 5.1	2	4.1 ± 0.4	3.8 – 4.4	3	4.0 ± 0.7	3.5 – 4.8	3	3.9 ± 0.1	3.8 - 4
Urinary calcium, mg/24h [100-300]	3	122 ± 96.3	36 - 226	1	86 ± 0	86 - 86	1	215 ± 0	215 - 215	1	156 ± 0	156 - 156
Creatinine, mg/dl [0.5-1.3]	3	0.7 ± 0.1	0.6 – 0.8	2	0.7 ± 0.1	0.6 – 0.7	2	0.6 ± 0	0.6 – 0.6	2	0.5 ± 0	0.5 – 0.5

This figure shows the percentage differences of mean dosage of calcium carbonate, calcitriol and cholecalciferol during pregnancy compared to the pre-pregnancy semester in HypoPT women.



Abbreviations: Trim: trimester

Most women of both groups increased significantly calcium supplementation and calcitriol dosage during the pregnancy compared to the pre-pregnancy period. During pregnancy, the average calcium supplement doses were mostly maintained or increased, and the average calcitriol doses were mostly maintained at same dosage. During the breastfeeding in HypoPT women, the average dose of calcium supplements and calcitriol decreased significantly compared to the third trimester. A general improvement in HypoPT-related clinical manifestations, such as cramps, tetany, and paresthesia, was shown during pregnancy compared to the previous six months. In most of cases the average serum albumin-corrected calcium levels were monitored and maintained in the low/normal reference range in the HypoPT women and in the normal reference range in the pseudo-HypoPT women throughout pregnancy and breastfeeding.

Conclusions

This study included all cases with HypoPT or pseudo-HypoPT wom followed in pregnancy by 9 Italian referral centers for endocrine diseases, between 2005 and 2018. Most women of both groups had a natural pregnancy with a full-term birth, however the 26.5% of women with HypoPT reported a previous history of spontaneous miscarriages, and the 66.7% of women with pseudo-HypoPT. In addition, maternal / fetal complications and fluctuations of blood and urinary calcium levels were described. With the limitations of a retrospective study, we show that, in the clinical practice at the participating centers, serum calcium levels were monitored during pregnancy and post-pregnancy period in most of women, while other biochemical parameters, such as urinary 24h calcium, serum phosphate, 25-OH vitamin D and seum magnesium tended to be poorly controlled.

Therefore, also in light of the new guidelines, an accurate biochemical monitoring, in addition to the evaluation of clinical manifestations and monitoring of therapy, needs to take place in pregnant/lactating hypoparathyroid women, in order to further reduce biochemical fluctuations and maternal/fetal complications. As a corollary, prospective investigations in women with HypoPT and pseudo-HypoPT during pregnancy and breastfeeding are necessary in order to increase knowledge about biochemical alterations, maternal and fetal clinical complications, and to improve the quality of care available today.

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