Hipoparatiroid Gebelik: Yirmi Olgunun Retrospektif Analizi

Hypoparathyroid Pregnancy: Retrospective Analysis of Twenty Cases

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ÖZ

GİRİŞ ve AMAÇ: *Kalıcı hipoparatiroidisi olan gebe kadınların klinik ve laboratuar özelliklerini ortaya koymayı amaçladık.*

YÖNTEM ve GEREÇLER: *Herhangi bir komorbid hastalığı olmayan kalıcı hipoparatiroidi tanısı olan gebe kadınları retrospektif olarak analiz ettik. Yaş, gravida, parite, hipoparatiroidi etiyolojisi ve süresi, ilaçlar, laboratuar testleri, önceki hipoparatiroid gebelik veya gestasyonel diyabet öyküsü, hipokalsemi sebebiyle hastanede yatış, düzenli takip (klinik takip olup olmadığı), gebelikte en az bir kez ciddi hipokalsemi (düzeltilmiş kalsiyum <7.5 mg/dL) olup olmadığı analiz edildi.*

BULGULAR: *Hastaların (n=20) ortalama yaşı 35.10(±4.83) idi, ortalama hipoparatiroidi süresi 74.55 aydı. Yalnız 1 hastada idiyopatik hipoparatiroidi tanısı mevcuttu. Toplamda hastaların %55'inde (n=11) ve gebelikte kalsitriol kullanmayan 4 hastanın 1'inde ciddi hipokalsemi tespit edildi. Gebelikte hastaların %80'i (n=16) kalsitriol, %40'I (n=8) kolekalsiferol, %65'I (n=13) kalsiyum karbonat ve %20'si (n=4) magnezyum kullanımına devam etti. İki hasta gebe kaldığında kalsitriol kullanımını bıraktı ve sadece kalsiyum karbonat kullanımına devam etti. Üçüncü trimesterde kalsitriol dozu pregestasyonel döneme göre daha yüksek saptandı (p=0.001), ancak kalsiyum karbonat dozu, düzeltilmiş kalsiyum veya fosfor düzeyleri açısından fark bulunamadı.*

TARTIŞMA ve SONUÇ: *Bildiğimiz kadarıyla, bizim çalışmamız, bu kadar yüksek sayıda hipoparatiroidi tanılı gebe kadını analiz eden ilk çalışmadır. Biz, klinik özelliklere dayanarak gebelikte sıkı doz ayarlanmasını önermekteyiz.*

Anahtar Kelimeler: *Hipoparatiroid gebelik, hipokalsemi, hipoparatiroidizm, gebelik, gebelikte hipoparatiroidizm*

ABSTRACT

INTRODUCTION: *We aimed to reveal the clinical and laboratory features of pregnant women with permanent hypoparathyroidism.*

METHODS: *We retrospectively analyzed the pregnant women with permanent hypoparathyroidism and without any comorbid illness. Age, gravida, parity, etiology and duration of hypoparathyroidism, medications, and laboratory tests, history of previous hypoparathyroid pregnancy, gestational diabetes mellitus, hospitalization due to hypocalcemia, regular follow-up (presence of clinical controls or not), severe hypocalcemia at least once in pregnancy (corrected Ca(CCa)<7.5 mg/dL) were analyzed.*

RESULTS: *Mean age of the patients (n=20) was 35.10 (±4.83). Mean duration of hypoparathyroidism was 74.55 months. Only 1 patient had idiopathic hypoparathyroidism. Severe hypocalcemia was detected in 55% (n=11) in total, and in only 25% (n=1) of 4 patients who did not use calcitriol in pregnancy. In pregnancy, 80% (n=16) of the patients used calcitriol, 40% (n=8) cholecalciferol, 65% (n=13) calcium carbonate, and 20% (n=4) magnesium. Two patients left off calcitriol and used only CaCO3 when became pregnant. Calcitriol dosage was higher in 3rd trimester of pregnancy comparing to pregestational period (p=0.001), but no change was found in CaCO3 dosage, CCa or phosphorus level.*

DISCUSSION AND CONCLUSION: *To our knowledge, our study is the first to analyze such a high number of pregnant women with hypoparathyroidism. We recommend delicate dose adjustment based on the clinical background.*

Keywords: *Hypoparathyroid pregnancy, hypocalcemia, hypoparathyroidism, pregnancy, hypoparathyroidism in pregnancy.*

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INTRODUCTION

Etiology of hypoparathyroidism in pregnancy is similar to that of nonpregnant adults, but the management may be somehow different due to physiological changes in pregnancy (1-3). In late pregnancy, especially, hormones other than parathormone (PTH), such as PTH-related protein (PTHrP), placental growth hormone or prolactin, may have some effect to increase calcitriol level (1,4,5). PTHrP activate vitamin D, and increased calcitriol level enhances the absorption of calcium and phosphorus (6-8). Estrogen may increase PTHrP level, and PTH may be suppressed by elevated PTHrP and calcitriol (9). Increased renal filtration of calcium and reduced PTH may lead hypercalciuria (10,11). Calcitriol requirement was shown to decrease in postpartum period (1,4). The placenta actively extracts sufficient calcium to maintain fetal calcium level in the normal range, even in the presence of maternal hypocalcemia (12,13). Phosphorus and magnesium are also actively transported to fetus by the placenta, so that calcification of fetal skeleton may be optimal (14). If maternal hypocalcemia is severe, it may cause fetal hypocalcemia, overstimulation of fetal parathyroid glands, low birth weight, spontaneous abortion and possibly fetal death (15-17). Maternal hypercalcemia leads to increase in spontaneous active transport of calcium to the fetus, and hence results in the suppression of the fetal parathyroid glands (18). Course of hypoparathyroidism in pregnancy was studied in only small patient populations. We aimed to analyze the clinical and laboratory features in twenty pregnant women with permanent hypoparathyroidism.

MATERIAL and METHOD:

Study Design

The pregnant women with a known diagnosis of permanent hypoparathyroidism who were referred to Endocrinology Clinics of Kocaeli Derince Training and Research Hospital between January 2015 and October 2019 were included in our study. Our study was designed as retrospective, observational, cross-sectional manner in a single center. We performed our study in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Participants and Data Collection

Hypoparathyroidism was diagnosed as a persistence of serum calcium levels lower than normal limits, and low or inappropriately normal levels of PTH in the presence of serum magnesium level in the normal range (19). We defined the etiology as idiopathic hypoparathyroidism if no cause was detected, and as surgical hypoparathyroidism if thyroid, parathyroid or neck surgery led to the development of hypoparathyroidism for longer than 6 months (19). We used total serum calcium level corrected for serum albumin level in the diagnosis and follow-up of hypoparathyroidism. Data were obtained from the electronic files. The patients who could not complete pregnancy for any cause, or who had surgical transient hypoparathyroidism for <6 months were excluded. Those with any comorbid illness other than hypothyroidism, or lacking data were also excluded.

Age, gravida, parity, the duration of hypoparathyroidism (months), and the type and dosage of medications used in pregestational and pregnancy period, such as levothyroxine (LT4), calcitriol, cholecalciferol, calcium carbonate ($CaCO_3$) and magnesium, were recorded and analyzed. The dosage of $CaCO_3$ and calcitriol was analyzed separately for each trimester of pregnancy,

but only the average dosage in pregnancy was recorded for the other medications.

Laboratory evaluation included the level of corrected total serum calcium (CCa; mg/dL) and phosphorus (P; mg/dL) at each trimester and in pregestational and postpartum period, and also the level of vitamin D (25(OH)D3; ng/mL), PTH (pg/mL), magnesium (Mg; mg/dL), TSH (mIU/L), free T4 (fT4; ng/dL), free T3 (fT3; pg/mL) measured once in pregnancy. Serum albumin (g/dL) was not analyzed itself but used to calculate corrected total serum calcium level with a formula of "CCa=Serum calcium+0.8*(4-patient albumin)". According to patient data which we could acquire, we could define pregestational period until 3 months before pregnancy, postpartum period until 3 months after pregnancy.

We also grouped the patients according to the history of previous hypoparathyroid pregnancy (absence vs presence), the etiology (idiopathic vs surgical) and duration (<24months vs ≥24months) of hypoparathyroidism, medications (absence vs presence), dose of LT4 (<100 vs ≥100mcg/day) or calcitriol (<0.5 vs ≥0.5mcg/day), gestational diabetes mellitus (GDM, absence vs presence) in the current pregnancy, previous hospitalization due to hypocalcemia (absence vs presence), regular follow-up (absence vs presence), severe hypocalcemia at least once in pregnancy (CCa<7.5 mg/dL, absence vs presence), TSH level comparing to trimester-specific range in which TSH was measured (low vs normal vs high). We defined regular follow-up as at least two medical visits to endocrinology clinics at each trimester. Due to the limited recordings of patient files, we could not analyze the clinical manifestations of hypocalcemia or hypoparathyroidism, or maternal or fetal complications of hypoparathyroidism.

Statistical Analysis

SPSS 22.0 (IBM Corporation, Armonk, New York, United States) program was used in the analysis of data. We used Shapiro-Wilk test to assess whether the data showed normal distribution or not. Homogeneity of variance was evaluated by Levene test. We used descriptive statistics to reveal clinical and laboratory parameters of the patients. Paired samples T test was used to assess the change in dosage of calcitriol or CaCO3, and CCa or P level between pregestational period and 3rd trimester of pregnancy. Quantitative variables were defined as mean(X)±standard deviation(SD), and median (minimum-maximum) in the tables. Categorical variables were demonstrated as number(n) and percent(%), and p value of <0.05 was accepted as statistically significant.

RESULTS

Mean age of patients(n=20) was 35.10(±4.83). Mean duration of hypoparathyroidism was 74.55 months. First pregnancy was found in 4, idiopathic hypoparathyroidism in 1 patients. No patients had GDM. Severe hypocalcemia was detected in 11 patients(Table 1). Severe hypocalcemia was found in 6, 4, and 7 patients in 1st, 2nd, and 3rd trimester of pregnancy, respectively.

Eighteen(90%) patients used calcitriol in pregestational period. In pregnancy, 16 patients(80%) used calcitriol, 19 patients(95%) LT4, 8 patients(40%) cholecalciferol, 13 patients(65%) calcium carbonate, and 4 patients(20%) magnesium(Table 2). Two patients left off calcitriol and used only CaCO3 in pregnancy. Severe hypocalcemia was detected in only one of 4 patients who did not use calcitriol in pregnancy. She developed severe hypocalcemia in only 3rd trimester.

Laboratory values of the patients were demonstrated in (Table 3).

Calcitriol dosage was significantly higher in 3rd trimester of pregnancy comparing to pregestational period (1.23(±0.44) vs 0.82(±0.41), p=0.001). There was no significant change in CaCO3 dosage, or serum levels of CCa or P between pregestational period and 3rd trimester of pregnancy (not shown on the table).

Table 1.Clinical features of pregnant women with permanent hypoparathyroidism.

Clinical parameters	X(±SD)
Age	35.10(4.83)
Duration of hypoparathyroidism (months)	74.55(62.1)
	Median(min.-max.)*
Gravida	3(1-9)
Parity	1(0-8)
	n
First pregnancy (no/yes)	16/4
Previous hypoparathyroid pregnancy (no/yes)	12/8
Etiology of hypoparathyroidism (idiopathic/surgical)	1/19
Duration of hypoparathyroidism (<24/≥24months)	5/15
GDM (absence/presence)	20/0
Previous hospitalization due to hypocalcemia (absence/presence)	17/3
Regular follow-up (absence/presence)	5/15
Severe hypocalcemia in pregnancy (absence/presence)	9/11
TSH (low/normal/high)	4/9/7

**min.:minimum max.:maximum*

Table 2.Preference and dosage of medications used in pregestational and pregnancy period in women with permanent hypoparathyroidism.

Pregestational period	
Medication preference	N
LT4 (absence/presence)	1/19
Calcitriol (absence/presence)	2/18
Cholecalciferol (absence/presence)	13/7
Calcium carbonate (absence/presence)	4/16
Magnesium (absence/presence)	16/4
Medication dosage	X(±SD)
LT4 (mcg/day)	131.58(58.23)
Calcitriol (mcg/day)	0.82(0.41)
Cholecalciferol (unit/day)	2951.92(3438.58)
Calcium carbonate (mg/day)	2272.73(1348.40)
Magnesium(mg/day)	365(0.0)
Pregnancy	
Medication preference	N
LT4 (absence/presence)	1/19
Dosage of LT4 (<100/≥100mcg/day)	9/10
Calcitriol (absence/presence)	4/16
Dosage of calcitriol (<0.5/≥0.5mcg/day)	5/11
Cholecalciferol (absence/presence)	12/8
Calcium carbonate (absence/presence)	7/13
Magnesium (absence/presence)	16/4
Medication dosage	X(±SD)
LT4 (mcg/day)	142.11(58.95)
Calcitriol overall (mcg/day)	1.13(0.38)
Calcitriol 1st trimester (mcg/day)	1.03(0.35)
Calcitriol 2nd trimester (mcg/day)	1.15(0.38)
Calcitriol 3rd trimester (mcg/day)	1.23(0.44)
Cholecalciferol (unit/day)	2499.93(1111.97)
CaCO3 overall (mg/day)	3115.38(2550.76)
CaCO3 1st trimester (mg/day)	3000(2466.44)
CaCO3 2nd trimester (mg/day)	3076.92(2572.66)
CaCO3 3rd trimester (mg/day)	3269.23(2642.72)
Magnesium (mg/day)	1.25(0.50)

Table 3.Laboratory values of pregnant women with permanent hypoparathyroidism.

Laboratory values	X(±SD)
Pregestational CCa (mg/dL)	7.66(0.98)
1st trimester CCa (mg/dL)	7.78(0.66)
2nd trimester CCa (mg/dL)	7.72(0.62)
3rd trimester CCa (mg/dL)	7.92(0.72)
Postpartum CCa (mg/dL)	7.25(1.05)
Pregestational P (mg/dL)	4.97(0.81)
1st trimester P (mg/dL)	4.57(0.98)
2nd trimester P (mg/dL)	4.60(0.76)
3rd trimester P (mg/dL)	4.87(0.75)
Postpartum P (mg/dL)	4.79(0.93)
25(OH)D3 (ng/mL)	16.4(8.82)
PTH (pg/mL)	6.24(5.70)
Mg (mg/dL)	1.75(24.0)
TSH (mIU/L)	10.8(23.1)
fT4 (ng/dL)	1.20(0.37)
fT3 (pg/mL)	2.52(0.52)

DISCUSSION

Severe hypocalcemia occurred throughout pregnancy in more than half of the patients. Higher calcitriol dosage in late pregnancy comparing to pregestational period was probably associated with severe hypocalcemia in 3rd trimester. Failure to increase the dosage of CaCO3 towards late pregnancy might have a role in a high frequency of severe hypocalcemia in 3rd trimester.

Medication adherence might be effective in the occurrence of severe hypocalcemia. Regular follow-up in most patients might be an indicator for good adherence. Somehow long duration of the disease and advanced maternal age in our patients might decrease the patient compliance. History of previous hypoparathyroid pregnancy in nearly half of the patients also might affect medication adherence. We could not employ a medication adherence scale.

In pregnancy, renal 1-alpha hydroxylase expression was shown to be much higher than in placenta (20). PTHrP, estradiol and PRL may stimulate renal 1-alpha hydroxylase in pregnancy (21) It was shown that increased PTHrP, and calcitriol synthesis might decrease calcium or calcitriol requirement in pregnancy, and dose decrement might be necessary in the late pregnancy (1). Studies indicating increased calcitriol requirement also were reported (2,3,22). Therefore, rather than a routine dose decrement in late pregnancy, we should meticulously follow-up the clinical and laboratory parameters along pregnancy to adjust the dosage of medications. Unfortunately, we significantly increased the dosage of calcitriol until late pregnancy. Given the fact that the importance of calcitriol is obvious in the management of hypoparathyroidism, we could not explain why our 2 patients left off calcitriol when became pregnant. Together with this, only one of 4 patients who did not take calcitriol in pregnancy developed severe hypocalcemia in 3rd trimester.

Several case reports indicated that inadequate calcium intake might lead to an increase in calcitriol requirement (23). Adequate calcium intake is important both for developing fetus, and the normal regulation of calciotropic hormones. In our study, we could not evaluate dietary calcium intake due to lacking data. Similar to calcium, magnesium is actively transported by placenta to optimize fetal skeletal development (24). Hypomagnesemia may impair PTH secretion, and also cause PTH resistance (25,26). It may also affect renal effects of PTH. In one study analyzing 10 patients with postoperative hypoparathyroidism, magnesium supplementation of 3-week period was shown not to increase serum calcium level significantly (27). Theoretically, due to lack of PTH, it might be expected that magnesium replacement did not exert any effect on serum calcium level in the patients with hypoparathyroidism. There is no consensus; but magnesium supplementation is suggested for hypomagnesemia with very low quality of evidence in the patients with hypoparathyroidism (19,27). There is no prospective study concerning that magnesium supplementation has any effect on the course of hypoparathyroidism in pregnant women. In our study, only 4 patients did take magnesium salts in pregnancy. It was recommended that serum magnesium level should be maintained in the reference range in pregnant women with hypoparathyroidism, with a very low quality of evidence (24).

It is known that hypercalciuria occurs in pregnancy as a physiological change (10,11). Renal calcium excretion was shown to be higher in hypoparathyroid pregnancy than normal pregnancy in one report (28). In our study, we could not

analyze urinary calcium excretion due to lacking data.

A couple of hormones were shown to affect calcium metabolism in pregnancy (1,4,5). PTHrP and PRL increase calcitriol level, and estrogen may increase PTHrP level (6-9). Placenta and breast appear to be the main sources of PTHrP in pregnancy (29,30). It may be suggested that PTHrP and calcitriol increase in hypoparathyroid pregnancy (24). PTHrP was not adequately studied in hypoparathyroid pregnancy. We could not analyze PTHrP, calcitonin, placental growth hormone, prolactin or estrogen.

Strength and Limitations

To our knowledge, there is a limited number of studies analyzing such a high number of pregnant women with hypoparathyroidism. Due to the retrospective nature of the study, we could not assess medication adherence. Due to limited data, we could not analyze dietary calcium intake, urinary calcium excretion or other hormones which might have any effect on calcium metabolism in pregnancy.

Ethics Committee Approval: Ethical approval was obtained.

Conflict of Interest: There is no conflict of interest.

Funding: There is no financial support.

Informed Consent: This a retrospective study

CONCLUSIONS

The number of reports analyzing such a high number of pregnant women with hypoparathyroidism is limited. Rather than routine dose adjustment, we recommend a meticulous titration of dose of medications based on follow-up along pregnancy. Personalized dose adjustment of calcitriol, calcium and magnesium would be beneficial. Prospective studies will reveal the effectiveness of calcitriol, CaCO3 or magnesium in pregnant women with hypoparathyroidism. The association between the causative factors, medication adherence, dietary calcium intake, urinary calcium excretion, or PTHrP level and the course of hypoparathyroidism in pregnancy remains to be explained.

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