Women With Chronic Hypoparathyroidism Have Low Risk of Adverse Pregnancy Outcomes

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Women with chronic hypoparathyroidism have low risk of adverse pregnancy outcomes.

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Abstract

Objective: The aim of this study was to evaluate pregnancy outcome and total number of births in chronic hypoparathyroidism (hypoPT).

Patients: The Swedish National Patient Register, The Swedish Prescribed Drug Register, Swedish Medical Birth Register and the Total Population Register were used to identify 97 women with chronic hypoPT and 1030 age-matched controls who delivered 139 and 1577 singleton infants, respectively, following diagnosis between 1997 and 2017.

Results: Women in the chronic hypoPT group had more frequent diabetes (DM) and chronic kidney disease (CKD) compared to women in the control group ($p=0.043$ and $p<0.001$, respectively). After adjusting for DM, CKD, maternal age at delivery and calendar year of delivery, chronic hypoPT cases were associated with increased risk of induction of labor (OR 1.82; 95% CI 1.13-2.94) and giving birth to infants with lower birth weight (β-coefficient -188 g; 95% CI -312.2- -63.8) compared to controls. No difference was found in infant length, small for gestational age or head circumference after adjustments. Mean gestational age at delivery after controlling for DM, CKD and pre-eclampsia, was not significantly younger ($p=0.119$). There was no difference in congenital malformations or perinatal death. There was no difference in the total number of infants born to women with chronic hypoPT and controls ($p=0.518$).

Conclusion: The majority of women with chronic hypoPT had normal pregnancy outcomes, and the overall risks appear to be low. Maternal chronic hypoPT, is however, associated with a higher risk of induction of labor and slightly lower infant birth weight.

Introduction

Chronic hypoparathyroidism (hypoPT) is a rare disorder characterized by low serum calcium, increased serum phosphorus, and deficient production of parathyroid hormone (1). The majority of patients with chronic hypoPT are women and the most common cause is anterior neck surgery responsible for about 75% of cases (2). During pregnancy, levels of calcitriol increase two- to three-fold due to increased renal production, resulting in enhanced intestinal calcium and phosphate absorption (3). Consequently, the renal calcium load may increase, often leading to hypercalciuria. Parathyroid hormone-related peptide (PTHrP) increases three-fold during pregnancy due to production by the placenta and the breasts, most significantly in the third trimester (3). These physiologic changes in the calcium regulating hormones may lower the dose requirements of calcium and calcitriol during pregnancy in women with chronic hypoPT. Interestingly, the literature describes a wide variation in required doses of calcium and calcitriol during pregnancy with some women requiring higher doses and others lower (4, 5).

Close monitoring in women with chronic hypoPT during pregnancy is important as hypercalcemia in the mother may suppress fetal parathyroid gland development and the neonate may develop hypocalcemia. In contrast, if the mother is hypocalcemic, it may result in secondary hyperparathyroidism in the fetus leading to fetal skeletal demineralization and intrauterine fractures (6). Inadequate treatment of hypoparathyroidism may also result in premature uterine contractions and an increased risk of second trimester miscarriage (7, 8). The management of chronic hypoPT during pregnancy represents a challenge for endocrinologists as there are scarce data on this topic. Published work are mainly based on case reports or small case series which have shown that chronic hypoPT in pregnancy is associated with significant maternal and fetal morbidity as well as early fetal loss and preterm

delivery (9-11). Treatment decisions are usually based on expert opinion bearing in mind the physiological changes in calcium metabolism during pregnancy.

Sweden offers excellent possibilities for research in this area, with high-quality population-based registers covering essentially all inpatient care and all birth records. In this study, data were linked from national registries to examine the potential influence of maternal chronic hypoPT on outcome of pregnancy.

Subjects and Methods

Registries

The Swedish National Patient Register (SNPR) encompasses both inpatients and outpatients. Inpatient data have been available since 1964 in parts of Sweden and became available nationwide in 1987. In 2001 the National Board of Health and Welfare also began to collect data on outpatient diagnoses from hospitals to include in the register. Data in the SNPR can be linked to other registries through the unique personal identity number assigned to all Swedish residents (12). The Swedish Prescribed Drug Register (SPDR) has collected data since July 2005 on all drugs dispensed by prescription to the Swedish population (13). The SPDR does not include information about drugs sold over the counter or for use during hospital care, nor clinical information on diagnosis/indication for treatment. All drugs are classified according to the Anatomical Therapeutic Chemical (ATC) classification system. It is mandatory for all pharmacies in Sweden to register all prescribed and dispensed drugs into the SPDR. We linked data to the Swedish Medical Birth Register, which includes prospectively collected and validated information from the pregnancy, delivery, and neonatal period on more than 98% of all births in Sweden since 1973 (14). Maternal characteristics are recorded in a standardized manner at the first visit to antenatal care, which occurs before the 12th week of gestation in more than 95% of the pregnancies.

Participants

We used inpatient and outpatient data from the SNPR to identify all women with a main or secondary diagnosis of hypoPT, according to the international classification of diseases, the 10^{th} revision (ICD-10), including the diagnostic codes, E20.0 and E20.2-9 (hypoparathyroidism) and E89.2 (postsurgical hypoparathyroidism)) between 1997 and 2017. This interval was chosen because the diagnosis of hypoparathyroidism did not have specific

ICD-10 codes until 1997. The SPDR was used to further increase the diagnostic accuracy of hypoPT and to make sure we only included women with chronic hypoPT. As this register started in 2005, women diagnosed with hypoPT before 2004 had to have at least 2 dispensations of active vitamin D ((dihydrotachysterol (ATC A11CC02), alfacalcidol, (ATC A11CC03), or calcitriol (ATC A11CC04)) with or without calcium between 2005-2006 to be included. Women diagnosed after 2005 had to have at least 2 dispensations of active vitamin D with or without calcium 13-24 months after first time entered with hypoPT diagnosis in the SNPR. We preferred to define chronic hypoparathyroidism as treatment with active vitamin D with or without calcium for more than 12 months after first entered in the SNPR as some patients recover from transient hypoPT within 6 months after surgery (15). To minimize the risk of misclassification we excluded all women with a diagnosis of a kidney disease (ICD-10: E10.2: Type 1 diabetes mellitus with kidney complications, E11.2: Type 2 diabetes mellitus with kidney complications, I12.0 and I12.9: Hypertensive chronic kidney disease, N00-08: Glomerular diseases, N10-16: Renal tubulo-interstitial diseases, N18-19: Chronic Kidney Disease and Unspecified kidney failure, N25-29: Other disorders of kidney and ureter, Q61: Cystic kidney disease, Z49: Encounter for care involving renal dialysis, Z99.2: Dependence on renal dialysis, Z94.0: Kidney transplant status) prior or 12-months post first time entered with the hypoPT diagnosis in the SNPR. Due to Swedish reimbursement regulations, each prescription generally mandates a time window of three months between two dispensations. Therefore, we excluded women if they did not have at least two dispensations of active vitamin D the last year of follow up. The date of first enrollment in the registry with hypoPT diagnoses does not have to be the same as the date of diagnosis as there can be a delay from the date of diagnosis until the patient is entered for the first time in the SNPR. For each woman with chronic hypoPT, we randomly identified 10 control women matched by maternal birth year and county of residence using the Register of Total Population

including all female Swedish residents alive at the end of each year (Figure 1). Study entry for the controls began when their matched cases were for the first time registered with hypoPT in the SNPR. The follow-up time for cases and controls was until the end of the study period (December 31, 2017) or death, whichever came first. All women with chronic hypoPT and matched controls were individually linked to the Swedish Medical Birth Register during the period 1997-2017.

Outcome measures

Data from the first visit for antenatal care in the Medical Birth Register includes family status (living with the child´s father or other), smoking status and use of oral tobacco in early pregnancy, working status (full-time, part-time or not working) and chronic conditions such as maternal pre-gestational diabetes, kidney disease, epilepsy and chronic hypertension. Gestational age was determined by second trimester ultrasound examination, which is offered to all pregnant women in Sweden since 1990 with more than 95% having accepted the offered test (16). When this information was not available, gestational age was estimated from the date of the woman's last menstrual period. Further data from the Medical Birth Register includes maternal age at delivery (years), calendar year of delivery (between 1997 and 2017), gestational length at delivery, mode of delivery (vaginal non-instrumental, vaginal instrumental, or cesarean section), stillbirth, infant sex, birth length (cm), birth weight (grams), head circumference (cm), small for gestational age, large for gestational age and Apgar score at 1, 5 and 10 minutes (<7, 7–10), ICD-10 diagnosis of all types of congenital malformations, pre-gestational and gestational diabetes, preeclampsia (ICD-10: O11, O 14 and O15), and postpartum hemorrhage (ICD-10: O72, defined as hemorrhage > 1000 ml). Through the SPDR we analyzed the thyroxine use (ATC H03AA01) during pregnancy in women with chronic hypoPT and controls. The total number of singleton childbirths from the

start of follow-up until the end of 2017 was further retrieved from the Medical Birth Register. Multiple pregnancies were excluded from the study since they carry an increased risk of adverse pregnancy outcome. Biochemical data from cases and controls were not available in the registries used in this study.

Statistical analysis

Categorical variables were summarized using frequency and percentage and compared between cases and matched controls using a McNemar chi-square test. Continuous variables were summarized using mean and standard deviation (SD) or median and inter-quartile range (IQR) and compared using a paired t-test or signed-rank test as appropriate. Clustered univariable and multivariable linear mean regression was used to analyze the association between chronic hypoPT and continuous outcomes including infant birth length and weight, pregnancy length and Apgar scores. Overall model fit was assessed via analysis of residuals and the coefficient of determination. Conditional logistic regression was used to analyze associations between chronic hypoPT and binary outcomes including pre-eclampsia, induction, pre-term birth, pharmacological pain relief and post-partum hemorrhage. Goodness-of-fit was assessed using a Hosmer & Lemeshow test. A conditional approach to the regression modelling was used to adjust for the matched design of the study. For all outcomes, the models were clustered on the mother to adjust for individual mothers contributing multiple births to the analysis. All analyses were conducted in Stata version 16 (StataCorp, College Station, Texas).

Research permits

This registry-based study was approved by the Research Ethics Committee of Stockholm, Sweden (Dnr: 2017/476-31/4).

Results

Characteristics of women with chronic hypoPT and controls

With our strict enrollment criteria, we identified 1520 women with chronic hypoPT and 15200 controls. In the chronic hypoPT cohort, 97 (6.4 %) gave birth to 139 singleton infants after the diagnosis of chronic hypoPT while 1030 (6.8 %) of controls gave birth to 1577 singleton infants during the study period (Figure 1). The mean (SD) age for women first recorded in the SNPR with chronic hypoPT diagnosis was 26.9 (6.5) years. 76.4 % of women had postsurgical and 23.6 % had nonsurgical chronic hypoPT. Of those 97 women who gave at least one birth after diagnosis of chronic hypoPT, 55 (56.7 %) were nulliparous as were 574 (55.7 %) of the controls. There was no significant difference in mean (SD) age at delivery for women with chronic hypoPT (31.7 (5.0) years) and controls (32.4 (5.0) years), (Table 1). Maternal weight at delivery in chronic hypoPT women did not differ from controls (p=0.119). No difference was observed in smoking or use of oral tobacco in early pregnancy between the groups. There was no difference in family (p=0.472) or working status (p=0.609) for women with chronic hypoPT compared to controls. No difference was found in calendar year of delivery between the groups (p=0.964). There were more pregnancies in the chronic hypoPT group where the mother received thyroxine (64%) compared to controls (5.1%), (p<0.001). There were three women with type 1 diabetes (two with postsurgical and one with nonsurgical hypoPT) and one woman with gestational diabetes (postsurgical hypoPT) in the chronic hypoPT group (2.9%) compared to 10 women with type 1 diabetes and one with type 2 diabetes and one with gestational diabetes in the control group (0.8%), (p=0.043). Five women with chronic hypoPT (3.6%) had CKD (four with postsurgical and one with nonsurgical hypoPT) compared to 8 women in the control group (0.5%) (p<0.001). There was no overlap of the women with maternal diabetes and chronic kidney disease. No difference

was seen in the diagnosis of epilepsy (p=0.253) or chronic hypertension (p=1.0) between the groups.

Total number of births

The total number of births did not differ significantly between women with chronic hypoPT and the controls during the study period (p=0.518).

Pregnancy outcomes

The mean gestational age at delivery in women with chronic hypoPT was slightly albeit significantly shorter (38.7 weeks (2.4)) compared to controls (39.2 (2.1)) (p= 0.009). After adjusting for maternal diabetes, CKD and preeclampsia this difference was no longer significant (p= 0.119) (Table 2). Preeclampsia was more commonly seen in chronic hypoPT cases vs controls (5.8% vs 2.5%) (p=0.023). After adjusting for maternal diabetes, CKD, maternal age at delivery and calendar year of delivery, the difference was not significant (p= 0.091) (Table 3). Chronic hypoPT was associated with 1.82-fold increased risk of induction of labor after adjusting for DM, CKD, maternal age at delivery and calendar year of delivery (OR 1.82; 95% CI 1.13-2.94). Chronic hypoPT remained significantly associated with a 1.79-fold increased risk of induction of labor independent of both preeclampsia and gestational age (p= 0.018). When stratifying induction of labor by gestational age it was only significantly increased in women with gestational length 40-41 weeks + 6 days. When controlling for thyroxine exposure during pregnancy the effect of chronic hypoPT on the risk of induction of labor did not remain significant (OR 1.58; 95% CI 0.95-2.61). There was no difference in proportion of cesarean delivery (p=0.681) or postpartum haemorrhage (p=0.788) between the groups.

The mean (SD) birth weight was significantly lower at 3329 g (620) in case neonates compared to controls 3506 g (624), (p=0.001). The association between chronic hypoPT and low birth weight was still significant after adjustment for maternal diabetes, CKD, maternal age at delivery and calendar year of delivery (OR -188 g; 95% CI -312.2- (-63.8)) compared to controls. Chronic hypoPT remained significantly associated with a mean 89.68 g reduction in birth weight after additionally controlling for preeclampsia and gestational age. Low birth weight was significant even after controlling also for thyroxine exposure during pregnancy (p=0.032). However, there was no difference in the incidence of small for gestational age (SGA) between the groups (p=0.829). No difference was found in infants' length or head circumference after adjustments (Table 2). Women with chronic hypoPT delivered more female babies compared to controls (p=0.05). There were no differences between groups with respect to Apgar scores at 1, 5 and 10 minutes, congenital malformations or stillbirths.

When comparing surgical and non-surgical chronic hypoPT there was no significant difference in pregnancy outcomes, but this could be due to the small numbers in each group (data not shown).

Discussion

This Swedish national cohort study comparing 139 singleton births of 97 mothers with chronic hypoPT with 1577 births of matched controls demonstrates that the majority of women with chronic hypoPT have normal pregnancy outcome, and that the overall risk for adverse pregnancy outcome is low. Women with chronic hypoPT gave birth to a similar number of children as the control group, strongly suggesting that there was no reduction in fecundity. Women with chronic hypoPT gave birth at the same age, and had a similar socioeconomic status compared to controls. The vast majority of infants born to mothers with chronic hypoPT were healthy and born at term, and no evidence was found for an increased risk of congenital malformations, stillbirth or neonatal complication represented by Apgar score. This is important information when counselling women of child-bearing potential with chronic hypoPT and planning the management of their pregnancies. Compared to women without chronic hypoPT, preeclampsia was more common in women with hypoPT and there was more than a 2-fold increased risk in adjusted analysis, but with a confidence interval of 0.88 to 5.52. This may indicate an increased risk of hypertensive disease during pregnancy, including preeclampsia, that was not possible to demonstrate due to lack of power in the current study.

We found an increased proportion of chronic kidney disease and diabetes in the chronic hypoPT group, but the absolute numbers were small, limiting the generalizability of this finding.

Because maternal and infant serum biochemistries and other laboratory analyses were not available in the registries used for this cohort study, levels of serum calcium at birth in mothers with chronic hypoPT and their infants were unknown. The same was true for thyroid

hormones and thyroid receptor antibodies, which may affect the interpretation of our findings, since the majority of women with chronic hypoPT in our cohort developed the disease after anterior neck surgery. Graves' disease is an autoimmune condition that may affect women of childbearing potential, and autoimmune conditions in general may affect the risk of pregnancy complications, intrauterine growth, timing of delivery and pregnancy outcomes. It is also known that thyroid receptor antibodies may persist, in spite of thyroidectomy, and that persisting antibodies may affect the pregnancy (17). The background risk of Graves' disease and possible other autoimmune conditions may explain the finding of lower mean birth weights in the chronic hypoPT cohort compared to controls, persisting after adjustments. This is in line with a study from Denmark that showed that mothers with hyperthyroidism had a higher risk of giving birth to children with low birth weight (18). In a case series of hypoPT mothers, 30% of the infants were small for gestational age (19). Even though mean birth weight was lower in our study we did not find any difference in the incidence of small for gestational age between cases and controls.

The reason for the higher frequency of induction of labor is not known and could not be explained by maternal age, increased incidence of hypertensive disorders of pregnancy or fetal growth restriction (small for gestational age). It was only significant for gestational age greater than 40-41 weeks and 6 days, and as labor induction due to late delivery was only recommended for gestational age greater than 42+0 weeks in Sweden during the study period, the most likely reason for the increased induction rate was due to concern for the mother's or the infant´s health. A possible explanation for this finding is that the proportion of women undergoing induction of labor is higher in pregnant women with chronic diseases compared to those without chronic disease due to clinical practice (20).

Previous published case reports have indicated that insufficiently managed maternal hypoPT cause skeletal deformities, neonatal respiratory distress, preterm labor and stillbirth (7). In our cohort of 137 singleton infants, we did not find any of these complications or malformations. No intrinsic reason is known why women with chronic hypoPT would deliver more female babies. This finding is most likely due to relatively small number of neonates.

The strengths of our study include the use and linkage of well-designed, high-quality and detailed registers with the inclusion of virtually all births in Sweden during the study period. Another strength is the previous validation of the hypoPT diagnosis using patients' charts where we found a positive predictive value of 91% for the diagnosis of hypoPT using a similar method as described above. (21). By using strict criteria to minimize the risk of misclassification of chronic hypoPT diagnosis there is a potential risk that we may have left out some women with chronic hypoPT, although with a low risk of differential misclassification. The limitations of this study include lack of information on biochemical data, dosage of pharmacological treatment and dietary intake of calcium during pregnancy. We did not have information on genetic data on nonsurgical hypoPT or if women underwent assisted reproduction treatment. Furthermore, we did not have access to long term outcomes of the children and potential long-term effects of maternal chronic hypoPT could thus not be investigated.

Conclusion: This is the first population-based epidemiological study of pregnancy outcomes in women with chronic hypoPT. The majority of women had normal pregnancy and delivery outcomes with low risk of adverse perinatal outcome. It is however important to coordinate the prenatal care of women with chronic hypoPT between the treating endocrinologist and the maternal-fetal medicine specialist to ensure optimal maternal and neonatal outcomes.

Data availability.

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Figure legend

Figure 1. Flowchart of study participants.

Maternal Characteristics	Pregnancies in women with chronic hypoPT N= 139	Pregnancies in controls N= 1577	p-value
	N (%)	N (%)	
Parity			
0	55 (39.6)	585 (37.1)	
1	57 (41)	641 (40.7)	0.518
2	24 (17.3)	236 (15)	
≥3	3 (2.2)	115 (7.3)	
Age at delivery, years (SD)	31.7 (5.0)	32.4 (5.0)	0.118
Smoking in early pregnancy			
No	121 (87.1)	1402 (88.9)	
Yes	9 (6.5)	92 (5.8)	0.875
Not reported	9 (6.5)	83 (5.3)	
Maternal pre-gestational or gestational diabetes	4 (2.9)	13 (0.8)	**0.043**
Maternal Chronic kidney disease	5 (3.6)	8 (0.5)	**<0.001**
Maternal Epilepsy	2 (1.4)	10 (0.6)	0.253
Maternal chronic hypertension	0 (0)	10 (0.6)	1.0
Family situation			
Living with father	123 (88.5)	1426 (90.4)	
Other	9 (6.5)	67 (4.3)	0.472
Not reported	7 (5.0)	84 (5.3)	
Working status			
Full time	64 (46.0)	816 (51.7)	
Part time	35 (25.2)	367 (23.3)	
Not working	26 (18.7)	247 (15.7)	0.609
Not reported	14 (10.1)	147 (9.3)	

TABLE 1. Characteristics of pregnant women with deliveries during the period 1997–2017 diagnosed with chronic hypoPT and controls.

Pregnancy outcomes	Pregnancies in Women with chronic hypoPT N= 139	Pregnancies in Controls N= 1577	p-value
Preeclampsia, n (%)	8 (5.8)	39 (2.5)	**0.023**
Onset of labor with induction, n (%)	30 (21.6)	209 (13.3)	**0.007**
Gestational length, (weeks), mean (SD)	38.7 (2.4)	39.2 (2.1)	**0.009**
Mode of delivery, n (%)			
Spontaneous vaginal	95 (68.4)	1118 (70.9)	0.527
Instrumental vaginal	13 (9.4)	89 (5.6)	0.076
Cesarean section	24 (17.3)	307 (19.5)	0.528
Postpartum hemorrhage, n (%)	11 (7.9)	115 (7.3)	0.788
Birth weight, (g), mean (SD)	3329 (620)	3506 (624)	**0.001**
Birth length, (cm), mean (SD)	48.9 (2.5)	50.3 (2.8)	0.123
Small for gestational age, n (%)			
No	129 (92.8)	1483 (94)	
Yes	4 (2.9)	35 (2.2)	0.829
Not reported	6 (4.3)	59 (3.7)	
Head circumference, (cm), mean (SD)	34.7 (1.7)	34.9 (1.7)	0.178
Apgar score, mean (SD)			
At 5 minutes	9.6 (0.9)	9.7 (1.0)	0.577
Infant sex, n (%)			
Male	66 (47.5)	814 (51.6)	
Female	72 (51.8)	763 (48.4)	0.05
No Information	1 (0.7)	0 (0.0)	
Congenital malformations, n (%)	5 (3.6)	58(3.7)	0.961

TABLE 2. Pregnancy outcomes in women with chronic hypoPT and controls during the period 1997–2017.

Group	Unadjusted OR (95% CI) p-value	Adjusted* OR (95% CI) p-value
Outcome = Pre-eclampsia		
Women with chronic hypoPT	2.41 (1.10, 5.26) p=0.027	2.21 (0.88, 5.52) p=0.091
Women without chronic hypoPT	Reference group	Reference group
Outcome = Induction of labour		
Women with chronic hypoPT	1.80 (1.11, 2.91) p=0.016	1.82 (1.13, 2.94) p=0.014
Women without chronic hypoPT	Reference group	Reference group
Group	**Unadjusted β-coefficient (95% CI) p-value**	**Adjusted** β-coefficient (95% CI) p-value**
Outcome = Gestational length (weeks)		
Women with chronic hypoPT	-0.47 (-0.92, -0.01) p=0.046	-0.45 (-0.91, 0.01) p=0.054
Women without chronic hypoPT	Reference group	Reference group
Outcome = Birth weight (grams)		
Women with chronic hypoPT	-176.71 (-300.01, -53.41) p=0.005	-187.98 (-312.19, -63.77) p=0.003
Women without chronic hypoPT	Reference group	Reference group

* adjusted for maternal diabetes, chronic kidney disease, maternal age at delivery and calendar year of delivery

** adjusted for maternal diabetes, chronic kidney disease, maternal age at delivery and calendar year of delivery

TABLE 3. Odds ratios and β-coefficients for pregnancy outcomes in women with chronic hypoPT compared to women without chronic hypoPT.