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PRETERM BIRTH AND RISK OF MEDICALLY TREATED HYPOTHYROIDISM IN YOUNG ADULTHOOD

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SUMMARY

Objective—Previous studies suggest that low birth weight is associated with thyroid autoimmunity and hypothyroidism in later life, but the potential effect of preterm birth, independent of fetal growth, is unknown. Our objective was to determine whether preterm birth is independently associated with medically treated hypothyroidism in young adulthood.

Design/Participants—National cohort study of 629,806 individuals born in Sweden from 1973 through 1979, including 27,935 born preterm (<37 weeks).

Measurements—Thyroid hormone prescription during 2005–2009 (ages 25.5–37.0 years), obtained from all outpatient and inpatient pharmacies throughout Sweden.

Results—Preterm birth was associated with increased relative odds of thyroid hormone prescription in young adulthood, after adjusting for fetal growth and other potential confounders. This association appeared stronger among twins than singletons ($P=0.04$ for the interaction). Twins had increased relative odds across the full range of preterm gestational ages, whereas singletons had increased relative odds only if born very preterm (23–31 weeks). Among twins and singletons, respectively, adjusted odds ratios for individuals born preterm (<37 weeks) were 1.54 (95% CI, 1.11–2.14) and 1.08 (95% CI, 0.98–1.19), and for individuals born very preterm (23–31 weeks) were 2.62 (95% CI, 1.30–5.27) and 1.59 (95% CI, 1.18–2.14), relative to full-term births.

Conclusions—This national cohort study suggests that preterm birth is associated with an increased risk of medically treated hypothyroidism in young adulthood. This association was independent of fetal growth and appeared stronger among twins than singletons. Additional studies are needed to confirm these new findings in other populations and to elucidate the mechanisms.

Key terms

hypothyroidism; premature birth; thyroid hormones

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DISCLOSURE STATEMENT

The authors have nothing to declare.

There were no conflicts of interest for any authors.

INTRODUCTION

Hypothyroidism is a common disorder resulting from a complex interaction of genetic and environmental factors.^{1–2} Previous reports of an association between low birth weight and thyroid autoimmunity or hypothyroidism in adulthood have suggested an early life origin for these conditions. Some of these studies have reported that low birth weight is associated with an increased prevalence of thyroid peroxidase and thyroglobulin antibodies, markers of autoimmune thyroid disease,^{3–4} or with spontaneous (non-iatrogenic) hypothyroidism in later life.⁵ Other studies, however, have failed to confirm these findings.^{6–7} Low birth weight may be the consequence of either delayed fetal growth or preterm birth. The previous studies to date were generally small and either were unable or had insufficient power to examine the specific effect of preterm birth on hypothyroidism in later life. In addition, differences in effect between singletons and twins have not been previously examined. Twins are exposed to a more adverse intrauterine environment which may potentially modify the risk of developing autoimmunity.

To address these gaps in the current knowledge, we conducted the largest study to date to examine the potential effect of preterm birth on the risk of medically treated hypothyroidism in young adulthood. We used nationwide outpatient and inpatient pharmacy data to determine whether preterm birth, independent of fetal growth, is associated with thyroid hormone prescription in a national cohort of young Swedish adults (ages 25.5–37.0 years), including twins as well as singletons.

SUBJECTS AND METHODS

Study population

We identified 648,276 individuals in the Swedish Medical Birth Register who were born from 1973 through 1979. Of this total, we excluded 6,553 (1.0%) individuals who were no longer living in Sweden at the time of follow-up (2005–2009); 180 (0.03%) who had congenital hypothyroidism; 112 (0.02%) who had evidence of hypopituitarism, based on prescription of a combination of 1) sex hormones, gonadotropins, or gonadotropin-releasing hormones; 2) glucocorticoids for systemic use; and 3) thyroid hormones; 7,921 (1.2%) who had significant congenital anomalies (i.e., other than undescended testicle, preauricular appendage, congenital nevus, or hip dislocation); and 1,882 (0.3%) who had missing information on birth weight. In order to remove possible coding errors, we also excluded 6 (<0.01%) individuals who had a reported gestational age <23 weeks, and 1,816 (0.3%) who had a reported birth weight more than four standard deviations above or below the mean birth weight for gestational age and sex from a Swedish reference growth curve.⁸ A total of 629,806 individuals (97.2% of the original cohort) remained for inclusion in the study.

This study was approved by the Ethics Committee of Lund University in Malmö, Sweden.

Study period

Study participants were followed for medication prescriptions from July 1, 2005 through December 31, 2009, the first 4.5 years that the Swedish national pharmacy register was kept. These individuals were between 25.5 and 37.0 years of age during the follow-up period.

Outcome measurement

Medication data were obtained using a national pharmacy register maintained by the Swedish National Board of Health and Welfare.⁹ This register contains a record of each medication prescribed by a health care provider and dispensed to a patient by any outpatient or inpatient pharmacy in Sweden. For inpatients, the register includes all medications

prescribed and dispensed to a patient upon discharge from the hospital. All medication data are categorized according to the Anatomical Therapeutic Chemical (ATC) Classification System developed by the WHO Collaborating Centre for Drug Statistics Methodology.¹⁰ We obtained all outpatient and inpatient prescriptions for thyroid hormone medications (ATC code H03AA), which include both levothyroxine and liothyronine. These data were linked to the Medical Birth Register using an anonymous identification number. The outcome was defined as an average of at least one thyroid hormone prescription per year during the follow-up period. Because hypothyroidism typically requires long-term maintenance therapy, defining the outcome in terms of multiple prescriptions is expected to improve the positive predictive value for this condition.

Exposure measurement

The exposure of interest was gestational age at birth, which was based on maternal report of last menstrual period. This information was obtained from nationwide prenatal and birth records in a national research database, WomMed, located at the Center for Primary Health Care Research, Lund University, Sweden. To allow for a non-linear effect, gestational age at birth was categorized as 23–31 weeks, 32–36 weeks, 37–42 weeks (full-term), and ≥ 43 weeks. Cutpoints were chosen in order to have adequate numbers in each category for statistical analysis.

Adjustment variables

The WomMed Database also contains sociodemographic information for the parents, including age, marital status, and socioeconomic indicators, collected annually starting in 1990. For the current study, sociodemographic characteristics were obtained using the Swedish Population and Housing Census of 1990, the most recent census when the young adults in this study (who were then 11 to 17 years of age) were still likely to be residing in the same household as their mothers. This information was used to identify maternal characteristics that would reflect the social and environmental conditions of these young adults during their upbringing that may be associated with subsequent risk of hypothyroidism.¹¹ An anonymous, serial-number version of the personal identification number (similar to the U.S. social security number but nearly 100% complete) was used to link the mothers to their children. The following variables were included as potential confounders:

Age—Modeled as a continuous variable by infant's date of birth.

Gender—Female or male.

Maternal age at delivery— < 20 years, 20–24 years, 25–29 years, 30–34 years, or ≥ 35 years. This was alternatively modeled as a continuous variable and the results were unchanged.

Maternal marital status in 1990—Married/cohabiting, never married, divorced, or widowed.

Maternal education in 1990—Compulsory high school or less (≤ 9 years), practical high school or some theoretical high school (10–11 years), or theoretical high school and/or college (≥ 12 years).

Family income in 1990—Calculated as the annual family income divided by the number of people in the family, or family income per capita, using a weighted system whereby small

children were given lower weights than adolescents and adults. The final variable was categorized in quartiles.

Maternal prescription of thyroid hormones—Prescription of thyroid hormones (ATC code H03AA) to the mothers of the study participants during the follow-up period, dichotomized as <1 or ≥ 1 prescriptions/year. Maternal hypothyroidism is a potentially important confounder because hypothyroidism or autoimmune thyroid disease is associated with preterm delivery,¹² and because thyroid autoimmunity appears to be under strong genetic influence.^{4, 13}

Fetal growth—Birth weight for gestational age and sex was used as a measure of fetal growth, categorized into six groups according to the number of standard deviations from the mean birth weight for gestational age and sex from a Swedish reference growth curve (<-2 SD; -2 SD to <-1 SD; -1 SD to <0 SD; 0 SD to <1 SD; 1 SD to <2 SD; ≥ 2 SD).⁸ This was alternatively modeled as a continuous variable and the results were unchanged.

Statistical analysis

Generalized estimating equations were used to estimate odds ratios and 95% confidence intervals for the association between gestational age at birth (as defined above) and thyroid hormone prescription in young adulthood. Analyses were conducted unadjusted for covariates, and then were adjusted in two different models. Adjusted model 1 included the following variables as potential confounders: age, gender, maternal age at delivery, maternal marital status, maternal education, family income, and maternal prescription of thyroid hormones during the follow-up period. Adjusted model 2 included the same set of covariates as well as fetal growth. Models were run for the entire cohort and then separately for singletons and twins. Robust standard errors were used in all models to account for correlation among siblings. We also explored first-order interactions between gestational age at birth and each of the covariates with respect to thyroid hormone prescription in young adulthood, using a likelihood ratio test to evaluate for statistical significance. All analyses were conducted using Stata statistical software, version 11.0.¹⁴

RESULTS

Of the 629,806 study participants, 27,935 (4.4%) were born prematurely (<37 weeks), including 2,062 (0.3%) born at 23–31 weeks, and 25,873 (4.1%) born at 32–36 weeks. Compared to individuals who were born full-term, those who were born prematurely were more likely to be male and/or a twin; and their mothers were more likely to be either <20 or ≥ 35 years old at delivery, divorced or never married, and to have the lowest educational attainment and/or the lowest family incomes (Table 1). The average birth weight was 3504 grams for singletons and 2629 grams for twins.

A total of 11,159 (1.8%) individuals were prescribed at least one thyroid hormone medication/year during the follow-up period, including 3.2% of women and 0.5% of men (Table 2). Individuals who were born very preterm (23–31 weeks) had a higher prevalence of thyroid hormone prescription than those who were born full-term ($P=0.001$). Among individuals born prematurely (<37 weeks), twins had a higher prevalence of thyroid hormone prescription than singletons (2.3% compared to 1.8%, respectively; $P=0.02$).

Young adults who were born very preterm (23–31 weeks) had an increased relative odds of thyroid hormone prescription relative to those born full-term (Table 3). Adjustment for potential confounders, with or without fetal growth, had only modest effects on the odds ratios. In the fully adjusted model, comparing all individuals born very preterm (23–31

weeks) to those born full-term, the odds ratio for thyroid hormone prescription was 1.70 (95% CI, 1.29–2.23).

Among twins, the association appeared to be stronger than among singletons and an increased relative odds was observed across the full range of preterm gestational ages. In the fully adjusted model for twins, the odds ratios were 2.62 (95% CI, 1.30–5.27) and 1.44 (95% CI, 1.02–2.03) for those born at 23–31 weeks and 32–36 weeks, respectively, relative to full-term births (Table 3). The magnitude of association was constant across the 32–36 week gestational age range, including at 35–36 weeks.

Table 4 presents odds ratios for the association between the model covariates and thyroid hormone prescription for the entire cohort of young adults. After adjusting for the other variables included in the model, the only strong predictors of thyroid hormone prescription were female gender (adjusted OR 7.29; 95% CI, 6.90–7.71) and maternal prescription of thyroid hormones (adjusted OR 3.07; 95% CI, 2.92–3.22). A very weak association was found between high educational attainment and thyroid hormone prescription. The association between poor fetal growth and thyroid hormone prescription was very weak or nonexistent, with or without adjusting for gestational age at birth. Odds ratios in the 1.00–1.10 range were observed for the smallest fetal growth categories (<–2 SD; –2 to <–1 SD; or –1 to <0 SD), relative to individuals with fetal growth ≥ 0 and <1 SD from the reference using a standard Swedish growth curve.⁸

We found a significant first-order interaction between preterm birth and multiple gestation status, with a stronger association observed among twins, as noted above and in Table 3 ($P=0.04$). No other interactions were statistically significant at the $P<0.05$ level, including no interaction between preterm birth and gender ($P=0.56$) or between preterm birth and fetal growth ($P=0.23$).

DISCUSSION

These findings from a large national cohort suggest that individuals who were born very prematurely have an increased risk of medically treated hypothyroidism in young adulthood. Among twins, the association appeared stronger than among singletons and extended across the full range of preterm gestational ages (<37 weeks). These associations were independent of fetal growth. In contrast, only a weak association, if any, was observed between poor fetal growth and thyroid hormone prescription after adjusting for gestational age at birth.

This is the first study with sufficient power to examine the association between preterm birth and hypothyroidism in later life, and the first that was able to evaluate for differences in effect between singletons and twins. Previous smaller studies of low birth weight and either subclinical or clinically overt hypothyroidism have produced inconsistent results. The first of these reported that low birth weight was associated with an increased prevalence of thyroid peroxidase or thyroglobulin antibodies, but not with overt hypothyroidism, among 305 women in the U.K., aged 60 to 71 years.³ Another U.K. study of 372 twin individuals (including 44 monozygous and 91 dizygous twin pairs) born from 1950 to 1955, reported that in monozygous twin pairs with discordant birth weight, the smaller twin had a higher prevalence of thyroid peroxidase antibodies.⁴ A Finnish study of 293 women born from 1934 to 1944 reported that low birth weight and small size during childhood were associated with spontaneous (non-iatrogenic) hypothyroidism.⁵ Other studies, however, have failed to confirm these findings. A Danish study of 131 twin pairs born from 1953 to 1972 reported that neither low birth weight nor prematurity was associated with clinically overt thyroid disease at follow-up in 1996 (ages 24 to 43 years).⁷ Another Danish study of 512 twin pairs, median age 36 years, failed to confirm an association between low birth weight and thyroid

peroxidase or thyroglobulin antibody levels.⁶ Only two of these studies examined gestational age at birth but statistical power was quite limited,^{5, 7} and none was able to explore for effect modification by multiple gestation status.

The current study's findings are consistent with some of the previous evidence for perinatal influences on hypothyroidism in later life, but they suggest that premature birth may be a more important factor than fetal growth. The mechanisms underlying these findings are not well established but may involve hormonal effects on autoimmunity. Low birth weight is known to be associated with lifelong alterations in glucocorticoid and sex steroid secretion, which have strong immunomodulatory effects and may predispose to the development of autoimmune disease.^{15–16} Common genetic determinants may also be involved: Twin studies have reported a strong genetic influence on autoimmune thyroid disease,^{4, 13} and maternal hypothyroidism and autoimmune thyroid disease in euthyroid women are associated with preterm delivery.¹² Further research is needed to elucidate the specific pathways involved, including the possibility of different mechanisms among twins, and the relative contributions of premature birth and fetal growth.

A limitation of this study is the unavailability of clinical diagnostic data including thyroid function tests and autoantibody levels. We were unable to distinguish between clinically overt and subclinical hypothyroidism, or between autoimmune and non-autoimmune causes. We excluded individuals with congenital hypothyroidism or with evidence of hypopituitarism, but were unable to identify other specific minor causes of hypothyroidism in these data. Instead we examined all medically treated hypothyroidism using nationwide thyroid hormone prescription data, resulting in greatly improved statistical power. Sweden is an iodine-replete area and the prevalences of thyroid hormone prescription in women and men in this cohort were comparable to the prevalence of clinically overt thyroid disease reported for other non-endemic areas.^{17–19}

Information on twin zygosity and postnatal growth patterns was unavailable for this cohort. It is possible that the effect of preterm birth on hypothyroidism in later life is stronger among monozygous than dizygous twins due to a more adverse intrauterine environment associated with the high proportion of shared placentas, or may be modified by postnatal growth patterns. Information on maternal thyroid disease during pregnancy was also unavailable, although the analyses were adjusted for maternal thyroid hormone prescription during the follow-up period. Gestational age was based on maternal report of last menstrual period rather than by ultrasound, which was not yet widely used at the time these study participants were born (1973–1979). We also are unable to fully exclude the possibility of differential ascertainment and treatment of hypothyroidism among individuals who were born preterm.

The most important strength of this study is its ability to examine the association between preterm birth and medically treated hypothyroidism in a large national cohort using nationwide medication data. These data are remarkably complete because they were obtained from all outpatient and inpatient pharmacies from all health care settings throughout Sweden, thus avoiding bias that may result either from self-reporting or from the sole use of hospital-based data. As the largest study to date, it was the first with sufficient statistical power, and the first with the ability to examine effect modification by multiple gestation status. Information on maternal prescription of thyroid hormones during the study period enabled adjustment for the potentially important confounding effect of maternal history of hypothyroidism.

In summary, this national cohort study suggests that preterm birth is associated with an increased risk of medically treated hypothyroidism in young adulthood. This association was

independent of fetal growth and appeared stronger among twins than singletons. Additional studies are needed to confirm these new findings in other populations and to elucidate the etiologic mechanisms.

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Table 1

Infant and maternal characteristics by gestational age at birth (1973–1979)

	Gestational Age, %			
	23–31 weeks (N=2,062)	32–36 weeks (N=25,873)	37–42 weeks (N=583,322)	≥43 weeks (N=18,549)
Gender				
Female	44.6	44.6	48.8	49.9
Male	55.4	55.4	51.2	50.1
Multiple gestation status				
Singleton	85.4	88.4	98.8	99.4
Twin	14.6	11.6	1.2	0.6
Maternal age at delivery (years)				
<20	9.0	9.0	6.3	8.4
20–24	30.0	29.0	30.0	34.9
25–29	32.1	34.0	38.3	37.4
30–34	20.9	19.9	19.4	15.8
≥35	8.1	8.1	6.0	3.5
Maternal marital status in 1990				
Married/cohabiting	70.7	71.6	76.3	72.9
Never married	12.9	12.0	9.5	11.5
Divorced	15.5	15.0	13.0	14.6
Widowed	0.9	1.4	1.2	1.0
Maternal education in 1990 (years)				
Compulsory high school or less (≤9)	31.9	31.2	27.0	29.5
Practical high school or some theoretical high school (10–11)	47.2	46.6	47.2	47.5
Theoretical high school and/or college (≥12)	20.9	22.2	25.8	23.0
Family income in 1990				
Lowest quartile	28.7	26.5	23.0	24.1
Second quartile	25.3	25.5	25.8	25.3
Third quartile	24.4	25.0	25.7	25.8
Highest quartile	21.6	23.0	25.5	24.8
Maternal prescription of thyroid hormones (≥1/year) during follow-up period				
	8.2	9.3	8.9	8.6

Table 2Thyroid hormone prescription (≥ 1 /year) in young adulthood (ages 25.5–37.0 years) by gestational age at birth (1973–1979)

	Gestational Age, n (%)						All (N=629,806)
	<37 weeks (N=27,935)	23–31 weeks (N=2,062)	32–36 weeks (N=25,873)	37–42 weeks (N=583,322)	≥ 43 weeks (N=18,549)		
All individuals (N=629,806)	510 (1.8)	56 (2.7)	454 (1.8)	10,296 (1.8)	353 (1.9)	11,159 (1.8)	
Women (N=306,157)	429 (3.4)	48 (5.2)	381 (3.3)	8,965 (3.2)	308 (3.3)	9,702 (3.2)	
Men (N=323,649)	81 (0.5)	8 (0.7)	73 (0.5)	1,331 (0.4)	45 (0.5)	1,457 (0.5)	
Singletons (N=619,668)	433 (1.8)	45 (2.6)	388 (1.7)	10,192 (1.8)	349 (1.9)	10,974 (1.8)	
Twins (N=10,138)	77 (2.3)	11 (3.6)	66 (2.2)	104 (1.5)	4 (3.3)	185 (1.8)	

Table 3

Odds ratios for association between gestational age at birth (1973–1979) and thyroid hormone prescription (≥ 1 /year) in young adulthood (ages 25.5–37.0 years)

	Gestational Age, OR (95% CI)				
	<37 weeks (N=27,935)	23–31 weeks (N=2,062)	32–36 weeks (N=25,873)	37–42 weeks (N=583,322)	≥ 43 weeks (N=18,549)
All individuals (N=629,806)					
Unadjusted	1.0 (0.95, 1.13)	1.55 (1.18, 2.03)	0.99 (0.90, 1.09)	1.00	1.08 (0.97, 1.20)
Adjusted Model 1*	1.11 (1.01, 1.21)	1.71 (1.30, 2.24)	1.06 (0.96, 1.17)	1.00	1.04 (0.94, 1.16)
Adjusted Model 2†	1.11 (1.01, 1.21)	1.70 (1.29, 2.23)	1.06 (0.96, 1.17)	1.00	1.03 (0.92, 1.14)
Singletons (N=619,668)					
Unadjusted	1.00 (0.90, 1.10)	1.46 (1.08, 1.96)	0.96 (0.87, 1.06)	1.00	1.08 (0.978, 1.20)
Adjusted Model 1*	1.08 (0.97, 1.19)	1.60 (1.19, 2.15)	1.04 (0.93, 1.15)	1.00	1.04 (0.93, 1.16)
Adjusted Model 2†	1.08 (0.98, 1.19)	1.59 (1.18, 2.14)	1.04 (0.94, 1.15)	1.00	1.02 (0.91, 1.13)
Twins (N=10,138)					
Unadjusted	1.53 (1.11, 2.11)	2.36 (1.19, 4.65)	1.44 (1.03, 2.02)	1.00	2.32 (0.84, 6.42)
Adjusted Model 1*	1.54 (1.11, 2.14)	2.69 (1.34, 5.38)	1.44 (1.02, 2.03)	1.00	2.06 (0.72, 5.87)
Adjusted Model 2†	1.54 (1.11, 2.14)	2.62 (1.30, 5.27)	1.44 (1.02, 2.03)	1.00	2.03 (0.68, 6.049)

* Adjusted for age, gender, maternal age at delivery, maternal marital status, maternal education, family income, and maternal prescription of thyroid hormones (≥ 1 /year) during the follow-up period (7/1/2005 through 12/31/2009).

† Adjusted for the same variables included in Adjusted Model 1, and fetal growth.

Table 4

Adjusted odds ratios* for association between categorical model covariates and thyroid hormone prescription (≥ 1 /year) in young adulthood (ages 25.5–37.0 years; N=629,806)

	OR	95% CI	P value
Gender			
Male	1.00		
Female	7.29	6.90, 7.71	<0.0001
Fetal growth (SD)			
<-2	1.04	0.93, 1.17	0.45
-2 to <-1	1.09	1.03, 1.16	0.004
-1 to <0	1.04	1.00, 1.09	0.07
0 to <1	1.00		
1 to <2	1.00	0.94, 1.07	0.89
≥ 2	1.01	0.91, 1.12	0.90
Maternal age (years)			
<20	1.00		
20–24	0.94	0.87, 1.02	0.13
25–29	0.95	0.88, 1.03	0.24
30–34	0.91	0.83, 0.99	0.04
≥ 35	0.89	0.80, 1.00	0.05
Maternal marital status in 1990			
Married/cohabiting	1.00		
Never married	0.96	0.90, 1.03	0.27
Divorced	1.01	0.95, 1.07	0.76
Widowed	1.12	0.94, 1.32	0.20
Maternal education in 1990 (years)			
Compulsory high school or less (≤ 9)	1.00		
Practical high school or some theoretical high school (10–11)	1.06	1.01, 1.11	0.02
Theoretical high school and/or college (≥ 12)	1.10	1.04, 1.16	0.002
Family income in 1990			
Lowest quartile	1.00		
Second quartile	0.97	0.92, 1.03	0.36

	OR	95% CI	P value
Third quartile	0.99	0.94, 1.05	0.85
Highest quartile	0.99	0.94, 1.06	0.85
Maternal prescription of thyroid hormones (≥ 1/year) during follow-up period			
0	1.00		
≥ 1	3.07	2.92, 3.22	<0.0001

*The model included gestational age at birth, fetal growth, age, gender, maternal age at delivery, maternal marital status, maternal education, family income, and maternal prescription of thyroid hormones (≥ 1 /year) during the follow-up period (7/1/2005 through 12/31/2009). The reference category for all odds ratios is indicated by an OR of 1.00.