Maternal thyroid disease in pregnancy and timing of pubertal development in sons and daughters

Lea L. H. Lunddorf, M.D.,[a] Andreas Ernst, Ph.D.,[a,b] Nis Brix, Ph.D.,[a,c] Linn H. Arendt, Ph.D.,[a,d] Stine L. Andersen, Ph.D.,[e,f] Jørn Olsen, Ph.D.,[a,g] and Cecilia H. Ramlau-Hansen, Ph.D.[a]

[a] Department of Public Health, Research Unit for Epidemiology, Aarhus University, Aarhus, Denmark; [b] Department of Urology, [c] Department of Clinical Genetics, and [d] Department of Obstetrics and Gynecology, Aarhus University Hospital, Aarhus, Denmark; [e] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; [f] Department of Clinical Biochemistry, Aalborg University Hospital, Aalborg, Denmark; and [g] Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark

Objective: To study whether maternal thyroid disease in pregnancy is associated with pubertal timing in sons and daughters.
Design: Cohort study.
Setting: National birth cohort and health registers.
Patient(s): A total of 15,763 mothers and children from the Danish National Birth Cohort and its Puberty Cohort.
Intervention(s): Register-based and self-reported information on maternal thyroid diseases during pregnancy (hyperthyroidism, hypothyroidism, benign goiter, or no thyroid disease [reference group]).
Main Outcome Measure(s): The adjusted mean age difference (months) at attaining several self-reported pubertal milestones collected every 6 months using an interval-censored regression and the average difference in age at attaining all pubertal milestones using the Huber-White robust variance estimation (primary outcome).
Result(s): Sons of mothers with hyperthyroidism had earlier pubertal development (average difference, −2.9 [95% confidence interval (CI), −5.0 to −0.7] months) than unexposed sons. Maternal hypothyroidism was not associated with pubertal development in sons (average difference, −1.2 [95% CI, −5.1 to 2.7] months). We observed nonstatistically significant indications of earlier pubertal development in sons of mothers with benign goiter (average difference, −1.9 [95% CI, −4.6 to 0.9] months). Maternal thyroid disease was not associated with pubertal development in daughters (average difference (months), hyperthyroidism, −0.8 [95% CI, −2.8 to 1.2]; hypothyroidism, 0.3 [95% CI, −3.1 to 3.8]; and benign goiter, 0.7 [95% CI, −2.0 to 3.4]).
Conclusion(s): We found indications of earlier pubertal development in sons of mothers with hyperthyroidism. More research is needed to further investigate the observed sex-specific association. (Fertil Steril® 2022;118:136-46. ©2022 by American Society for Reproductive Medicine.)
El resumen está disponible en Español al final del artículo.

Key Words: Puberty, fetal programming, hyperthyroidism, hypothyroidism, goiter

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Reprint requests: Lea Lykke Harrits Lunddorf, M.D., Department of Public Health, Research Unit for Epidemiology, Aarhus University, Bartholins Allé 2, 8000 Aarhus C, Denmark (E-mail: llbl@ph.au.dk).

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The potential causes of the secular trend in pubertal timing observed throughout the last century in girls, and perhaps also in boys, remain to be identified (1). Associations have been reported between earlier age at pubertal development and several diseases in adult life, such as type 2 diabetes mellitus, obesity, cardiovascular traits, asthma, and testicular and breast cancers, although the causality of these associations is not yet well established (2–7). Fetal programming by some intrauterine exposures has been considered important for the decline in age at pubertal onset (8).

Thyroid hormones play a crucial role during fetal brain development (9), which is initiated in the early pregnancy weeks and continues throughout pregnancy as well as after birth. Prenatally, fetal brain development is dependent on maternal thyroid hormones in the first half of pregnancy, but maternal thyroid hormones play an important role in fetal brain development during the entire pregnancy (10). It remains unknown whether maternal thyroid hormones affect the development of the fetal hypothalamus and pituitary gland, which are essential structures of the hypothalamus-pituitary-gonadal (HPG) axis. The HPG axis is responsible for the initiation and progression of puberty. Crosstalk between the hypothalamus-pituitary-thyroid gland (HPT) axis and HPG axis is well established, perhaps because of structural similarities between the hormones and receptors and interactions at receptor level (11). Thus, thyroid hormones during childhood are crucial for normal growth, pubertal development, and reproductive function (12–15). We speculate whether maternal thyroid disease in pregnancy could interfere with fetal brain development, including the development and function of the HPG axis and, thereby, timing of puberty. No human studies have addressed the possible association between maternal thyroid disease in pregnancy and pubertal development in sons and daughters. We hypothesize that both excess and deficit of thyroid hormones during fetal life program might alter pubertal timing in sons and daughters.

MATERIALS AND METHODS

Data Source and Study Population

The Danish National Birth Cohort (DNBC) included pregnant women and their live-born children, recruited at the first antenatal visit in general practice (around gestational weeks 6–12) from 1997 to 2002 (16). A total of 101,042 pregnancies in 91,661 women constitute the DNBC (participation rate, 60%). The women were invited to be interviewed twice during pregnancy (around gestational weeks 17 and 32) using a computer-assisted telephone setup. The children and parents were asked to fill out web-based questionnaires at 7 years (participation rate, 58% of all participants in the DNBC) and 11 years (participation rate, 60% of all participants in the DNBC). The latter included questions on their current stage of pubertal development identical to those asked in the Puberty Cohort.

The Puberty Cohort is part of the DNBC (Fig. 1). First, we identified all live-born singletons born between 2000 and 2003 whose mothers had responded to the first interview during pregnancy and had not withdrawn their consent of participation by May 2012 (n = 56,641). Second, among those, we sampled participants from 27 sampling frames within 12 exposures of interest, hypothesized to be predictors of pubertal timing, including thyroid diseases, in addition to a random sample of 8,000 children (17). Overall, 22,439 children were sampled and invited to participate in the Puberty Cohort (Fig. 1). Third, we asked the 22,439 children to report their current stage of pubertal development every 6 months from the age of 11.5 years and onward. The follow-up of the individual child ended at full sexual maturation (Tanner stage 5 in both pubic hair [sons and daughters] and genital [sons] or breast [daughters] development (18, 19)) or when the child turned 18 years of age. Of the 22,439 invited children, 15,819 (7,696 sons and 8,123 daughters [response rate, 70%]) responded to at least 1 pubertal questionnaire – either in the 11-year follow-up only (n = 1,063), in the Puberty Cohort only (n = 5,154), or in both (n = 9,602) (Fig. 1).

Children whose mothers had a register-based diagnosis of thyroiditis (E06-E06.9) or unspecified thyroid disease (E07-E07.9 and E350) and no self-reported thyroid disease were excluded (n = 21). Additionally, children whose mothers had self-reported thyroiditis or unspecified thyroid disease and no thyroid diagnosis in the registers were excluded (n = 35), making the total number of mother-child pairs included in this study 15,763 (Fig. 1)

Assessment of Maternal Thyroid Disease in Pregnancy

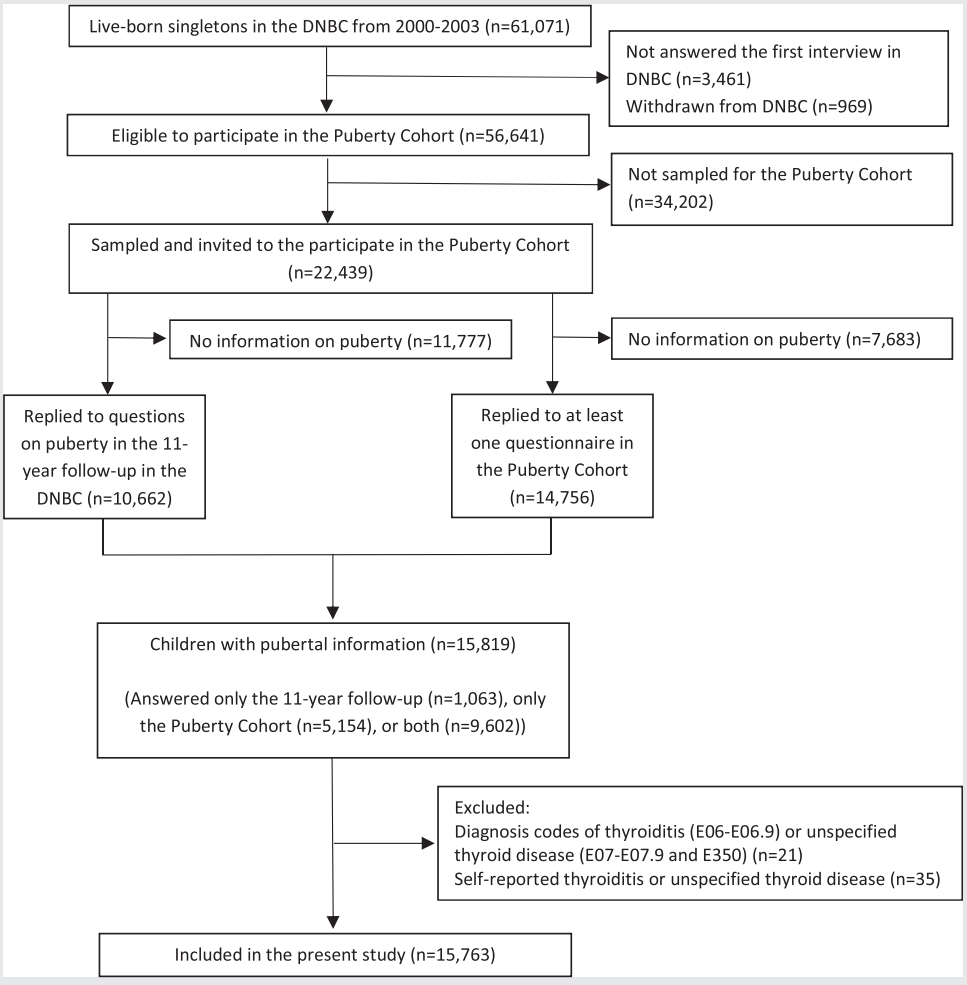
We assessed maternal thyroid disease in pregnancy (hyperthyroidism, hypothyroidism, and benign goiter) using register-based diagnostic codes and self-reported information on thyroid disease in the DNBC.

From the Danish National Patient Registry (DNPR), we first obtained register-based information on maternal thyroid disease from 1996 and onward (20). The DNPR contains information and dates of all diagnostic codes classified according to the International Classification of Diseases Version 10 in Denmark. We considered the children exposed if the mothers had a thyroid diagnosis at any time before pregnancy, during pregnancy, and up to 5 years after birth of the child. Women with known thyroid disease may not be adequately treated by the time of conception and throughout pregnancy (21, 22). Additionally, symptoms of thyroid disease are often unspecific and may persist for a period of time before the diagnosis is made. Thus, women diagnosed with thyroid disease in the years after a pregnancy may have had undiagnosed and untreated abnormal thyroid function in the pregnancy (21).

The mothers were categorized on the basis of their first diagnosis as having either hyperthyroidism (E05-E05.9 or O992C) (n = 345), hypothyroidism (E00-E03.9, E06-E06.9, or O992B) (n = 103), benign goiter (E04-E04.9) (n = 170), or no thyroid disease registered (reference group) (n = 15,145).

As the diagnostic codes were considered superior to the self-reported, we second checked if any of whose without a

FIGURE 1



Flowchart of participation in the Puberty Cohort, Denmark, 2000–2020. DNBC = Danish National Birth Cohort.

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diagnostic code (reference group) had provided self-reported information on thyroid disease collected in the 2 interviews during pregnancy in the DNBC. Here, the mothers were asked to report if they had ever had a thyroid disease, including the type of disease, and whether a doctor had confirmed the disease. The following were added to the exposure groups: hyperthyroidism (n = 61); hypothyroidism (n = 48); and benign goiter (n = 19).

After combining these data sources, the exposure groups were as follows: hyperthyroidism (n = 406); hypothyroidism (n = 151); benign goiter (n = 189); and no thyroid disease (reference group, n = 15,017).

Assessment of Pubertal Development

We collected information on pubertal development every 6 months using a web-based questionnaire assisted by explanatory text and drawn pictures of each Tanner stage (18, 19). Sons were asked to state their current Tanner stages 1–5 (pubic hair and genital development). Additionally, they were asked whether they had had their first ejaculation (if yes, they were asked to state the exact age in years and months), voice break (sometimes changed, completely changed, or not changed), axillary hair development (yes/no), and acne occurrence (yes/no). Daughters were asked to state their current Tanner stages 1–5 (pubic hair and breast development). Furthermore, they were asked whether they had had their first menstrual bleeding (if yes, they were asked to state the exact age in years and months), axillary hair development (yes/no), and acne occurrence (yes/no).

Covariates

We identified potential confounders on the basis of existing literature and directed acyclic graphs (Supplemental Fig. 1, available online) (23). We adjusted all analyses for the following potential confounders: maternal prepregnancy body mass index (BMI) (restricted cubic splines with 5 knots); maternal type 1 or 2 diabetes mellitus; highest social economic class of the parents on the basis of education and occupational level; maternal age at menarche; maternal age (restricted cubic splines with 4 knots); parity; maternal

smoking during the first trimester; maternal alcohol consumption during the first trimester; cohabitation of the parents during pregnancy; birth year of the child because of the mandatory iodine fortification of salt since the year 2000 in Denmark; and place of residence of the mother at the time of birth because of regional differences in population iodine intake levels (Table 1).

Data on maternal BMI, highest social economic class of the parents, maternal age at menarche, and maternal smoking and alcohol consumption in addition to cohabitation of the parents were available from the baseline interviews in the DNBC. Maternal age, parity, and birth year of the child were retrieved from the Danish Medical Birth Register (24). Maternal diabetes mellitus was obtained using both self-reported from the DNBC and register-based information from the DNPR as described in detail previously (25). Place of residence was retrieved from Statistics Denmark. Information on each covariate was missing for <1.5% of the study population (Table 1).

From the 7-year follow-up in the DNBC, we retrieved self-reported height (cm) and weight (kg) of the children and calculated the BMI (continuous variable). Information on the 7-year BMI was missing for 4,762 (30.2%) children (Table 1).

Data Analyses

The children provided information on current pubertal development every 6 months. Therefore, data on age at attaining the different pubertal milestones were either left-, interval-, or right-censored. Data were left-censored if the pubertal milestones were attained before the first questionnaire, interval-censored if attained between 2 questionnaires, and right-censored if still not attained at the time of the last questionnaire. Consequently, we analyzed data using an interval-censored regression on the basis of the normal distribution fitted by maximum likelihood estimation (the -intreg- command in Stata 15.0 software [Stata Corporation, College Station, TX]) (26). These models enable inclusion of all individuals in the analyses regardless of the number of questionnaires returned (27).

We estimated the crude and adjusted mean age difference (months) with 95% confidence interval (CI) at attaining the pubertal milestones in children prenatally exposed to hyperthyroidism, hypothyroidism, or benign goiter compared with those in children born of mothers without thyroid disease as the secondary outcomes of the study.

On the basis of these results, we used the Huber-White robust variance estimation to estimate the association between maternal thyroid diseases and the average difference in age at attaining all pubertal milestones for each sex as the primary outcomes of the study (28, 29). Thereby, we accounted for the correlation in age at attaining the different pubertal milestones within individuals and limited the risk of type 1 errors due to multiple testing. We obtained the crude and adjusted mean age difference (months) with 95% CI at attaining the average difference of pubertal development, which is the average of the estimates from the models with the individual pubertal milestones.

We checked the model assumption of normally distributed residuals by plotting the nonparametric cumulative incidence function on the basis of the Turnbull estimator against the normal distribution using the *icenreg* package in R (ver. 1.0.136). Thereafter, we visually inspected the assumption of constant variance across explanatory variables by stratifying these plots on the levels of explanatory variables, and the data were deemed compatible with these assumptions.

All analyses were reweighted using sampling and selection weights. Sampling weights were computed as the inverse probability of being sampled according to the sampling regime in the Puberty Cohort (17, 29). Selection weights were calculated using multivariable logistic regression as the inverse probability of participation in the Puberty Cohort on the basis of a priori specified factors related to participation (30). Robust standard errors were added to account for the use of weights and the clustering of siblings in the cohort.

We performed three subanalyses. In subanalysis 1, we explored the potential influence from the onset of maternal thyroid disease (before or after birth of the child) on pubertal development in sons and daughters as the exploratory outcomes of the study. Thus, we sought to investigate the effects of detected, likely treated disease diagnosed before birth and undetected, untreated disease diagnosed after birth. Onset was defined as the date of the first hospital visit with a diagnosis of thyroid disease or self-reported thyroid disease and categorized as before or after birth of the child. The onset was "before birth" if the date of the first diagnosis of thyroid disease was before birth of the child or if the mother reported to have previous or current thyroid disease in the pregnancy interviews. On the other hand, the onset of thyroid disease was "after birth" if the date of the first diagnosis of thyroid disease was after birth of the child and the mother did not self-report any thyroid disease during pregnancy.

In subanalysis 2, we excluded mothers with only self-reported thyroid diseases (hyperthyroidism [n = 61], hypothyroidism [n = 4], and benign goiter [n = 19]) to explore potential misclassification due to self-report as the exploratory outcomes of the study.

In subanalysis 3, we performed a mediation analysis with the 7-year BMI as a potential intermediate factor using interval-censored regression, G-computation, and nonparametric bootstrap with 1,000 replications to obtain 95% CIs (31). Here, we estimated the natural indirect effect through the mediator as well as the natural direct effect as exploratory outcomes of the study.

Details of Ethics Approval

The Committee of Biomedical Research Ethics in Denmark (KF 01-471/94) and the Steering Committee of the DNBC (2012-04 and 2015-47) approved the study, and it is registered by the Danish Data Protection Agency (2012-41-0379 and 2015-57-0002). The mothers provided written informed consent of participation on behalf of themselves and their child when entering the DNBC. This consent can be withdrawn at any time.

TABLE 1

Maternal and child characteristics according to the type of maternal thyroid disease among 15,763 sons and daughters in the Puberty Cohort, Denmark, 2000–2020.

Characteristics	No thyroid disease	Hyperthyroidism	Hypothyroidism	Benign goiter	Missing
n (%)	15,017 (95.3)	406 (2.6)	151 (1.0)	189 (1.2)	
Sex of child, n (%)					0 (0.0)
Sons	7,306 (48.7)	205 (50.5)	76 (50.3)	86 (45.5)	
Daughters	7,711 (51.4)	201 (49.5)	75 (49.7)	103 (54.5)	
Maternal prepregnancy BMI, n (%)					217 (1.4)
Mean (95% CI)	23.8 (23.7 to 23.9)	23.8 (23.4 to 24.3)	24.3 (23.5 to 25.0)	23.5 (22.9 to 24.1)	
Maternal type 1 or 2 diabetes mellitus, n (%)					0 (0.0)
No	14,790 (98.5)	396 (97.5)	144 (95.4)	< 189[a]	
Yes	226 (1.5)	10 (2.5)	7 (4.6)	<5[b]	
Socioeconomic status of parents					0 (0.0)
High-grade professional	3,523 (23.5)	82 (20.2)	30 (19.9)	40 (21.2)	
Low-grade professional	4,891 (32.6)	155 (38.2)	64 (42.4)	67 (35.5)	
Skilled worker	4,152(27.7)	102 (25.1)	30 (19.9)	53 (28.0)	
Unskilled worker	2,451 (16.3)	67 (16.5)	27 (17.9)	29 (15.3)	
Maternal age at menarche, n (%)					123 (0.8)
Earlier than peers	3,815 (25.4)	<105[a]	39 (25.80)	<45[a]	
Same time as peers	8,525 (56.8)	<240[a]	85 (56.3)	<110[a]	
Later than peers	2,558 (17.0)	67 (16.5)	27 (17.9)	36 (19.1)	
Maternal age at delivery in y					6 (0.0)
Mean (95% CI)	30.6 (30.5 to 30.6)	31.1 (30.7 to 31.6)	32.1 (31.4 to 32.8)	32.4 (31.7 to 33.0)	
Parity, n (%)					0 (0.0)
First child	7,620 (50.7)	191 (47.0)	56 (37.1)	68 (36.0)	
Second or more child	7,397 (49.3)	215 (53.0)	95 (62.9)	121 (64.0)	
Maternal smoking during the first trimester, n (%)					53 (0.4)
No	10,764 (71.7)	287 (70.7)	115 (76.2)	139 (73.5)	
1–10 cigarettes per d	3,329 (22.2)	99 (24.4)	30 (19.9)	43 (22.8)	
>10 cigarettes per d	871 (5.8)	20 (4.9)	6 (4.0)	7 (3.7)	
Cohabitation of parents, n (%)					<10 (0.1)
Live together	14,7000 (97.9)	396 (97.5)	144 (95.4)	<189[a]	
Do not live together	308 (2.1)	10 (2.5)	7 (4.6)	<5[b]	
Residence, n (%)					0 (0.0)
Eastern Denmark	5,641 (37.6)	138 (34.0)	57 (37.8)	65 (34.4)	
Western Denmark	9,375 (62.4)	268 (66.0)	94 (62.3)	124 (66.6)	
Birth y					0 (0.0)
<2001	5,405 (36.0)	141 (34.7)	50 (33.1)	69 (36.5)	
≥2001	9,612 (64.0)	265 (65.3)	101 (66.9)	120 (63.5)	
7-y BMI					4,762 (30.2)
Mean (95% CI)	15.6 (15.6 to 15.7)	15.7 (15.5 to 15.9)	15.8 (15.5 to 16.2)	15.7 (15.4 to 16.1)	

Note: BMI = body mass index; CI = confidence interval.

[a] Rounded up or down because of other cells with <5 or missing <5, due to the General Data Protection Regulation and Danish Data Protection Act.

[b] The cell contains <5 individuals, which cannot be shown according to the General Data Protection Regulation and Danish Data Protection Act.

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TABLE 2

Mean age differences (in months) at pubertal development according to maternal thyroid diseases in pregnancy among 15,763 sons and daughters in the Puberty Cohort, 2000–2020.

			No thyroid disease (reference)[b]	Hyperthyroidism[c]		Hypothyroidism[d]		Benign goiter[e]	
				Mean age difference (mo)		Mean age difference (mo)		Mean age difference (mo)	
Puberty outcomes		**No.[a]**	**Crude mean age (y)**	**Crude[f,g]**	**Adjusted[f,g,h] (95% CI)**	**Crude[f,g]**	**Adjusted[f,g,h] (95% CI)**	**Crude[f,g]**	**Adjusted[f,g,h] (95% CI)**
Sons									
Tanner stage									
Pubic hair	2	7,472	11.3	−4.0 (−6.7 to −1.2)	−4.0 (−6.8 to −1.3)	3.4 (−1.9 to 8.7)	3.4 (−1.9 to 8.7)	−1.3 (−5.0 to 2.4)	−1.5 (−5.2 to 2.2)
	3	7,472	12.7	−2.5 (−5.2 to 0.2)	−2.6 (−5.3 to 0.1)	−0.2 (−4.3 to 3.9)	−0.1 (−4.3 to 4.0)	−0.1 (−3.3 to 3.0)	−0.7 (−3.9 to 2.5)
	4	7,472	13.5	−2.3 (−5.0 to 0.5)	−2.6 (−5.4 to 0.3)	−1.1 (−5.6 to 3.5)	−1.1 (−5.8 to 3.5)	−2.6 (−6.3 to 1.1)	−3.3 (−6.9 to 0.3)
	5	7,472	14.8	−2.6 (−5.6 to 0.4)	−2.9 (−6.1 to 0.2)	−2.3 (−7.8 to 3.2)	−2.3 (−7.9 to 3.3)	−5.1 (−8.9 to −1.2)	−5.6 (−9.3 to −1.9)
Genitals	2	7,468	10.9	−4.9 (−8.1 to −1.8)	−5.0 (−8.1 to −1.9)	0.9 (−4.3 to 6.1)	0.9 (−4.3 to 6.1)	−2.7 (−7.0 to 1.5)	−2.8 (−7.1 to 1.5)
	3	7,468	12.5	−4.0 (−7.0 to −1.1)	−4.3 (−7.2 to −1.4)	0.2 (−4.6 to 5.1)	0.1 (−4.8 to 5.0)	−1.8 (−5.6 to 2.0)	−2.3 (−6.1 to 1.4)
	4	7,468	13.7	−2.8 (−6.1 to 0.6)	−3.2 (−6.5 to 0.2)	−1.2 (−6.1 to 3.8)	−1.1 (−6.3 to 4.0)	−1.4 (−6.0 to 3.1)	−2.1 (−6.7 to 2.5)
	5	7,468	15.8	−4.5 (−9.5 to 0.5)	−5.0 (−10.2 to 0.1)	−5.1 (−13.1 to 2.8)	−5.3 (−13.3 to 2.8)	−1.4 (−8.3 to 5.6)	−1.8 (−8.5 to 5.0)
Ejaculation		7,464	13.3	0.7 (−2.1 to 3.5)	0.4 (−2.5 to 3.2)	3.1 (−1.1 to 7.3)	3.1 (−1.1 to 7.3)	−2.3 (−6.0 to 1.4)	−2.8 (−6.5 to 1.0)
Voice break		7,274	13.0	−3.6 (−6.7 to 0.6)	−3.8 (−6.9 to −0.7)	−0.9 (−5.5 to 3.7)	−0.9 (−5.4 to 3.7)	−0.3 (−4.7 to 4.0)	−0.9 (−5.1 to 3.4)
Axillary hair		7,476	13.3	−0.5 (−3.2 to 2.2)	−0.7 (−3.54 to 2.1)	−4.1 (−10.0 to 1.8)	−3.9 (−10.0 to 2.1)	0.9 (−3.8 to 5.5)	0.1 (−4.5 to 4.7)
Acne		7,476	12.2	−0.8 (−3.6 to 2.0)	−1.3 (−4.2 to 1.7)	−7.0 (−11.6 to −2.4)	−7.6 (−12.1 to −3.0)	−1.5 (−6.4 to 3.3)	−2.5 (−7.4 to 2.4)
Average difference		7,273	–	−2.6 (−4.7 to −0.6)	−2.9 (−5.0 to −0.7)	−1.2 (−5.0 to 2.6)	−1.2 (−5.1 to 2.7)	−1.3 (−4.1 to 1.5)	−1.9 (−4.6 to 0.9)
Daughters									
Tanner stage									
Pubic hair	2	7,870	11.2	−2.2 (−4.2 to −0.2)	−2.0 (−4.0 to −0.1)	0.8 (−3.5 to 5.0)	1.0 (−3.4 to 5.4)	−0.8 (−3.7 to 2.2)	−0.3 (−3.2 to 2.7)
	3	7,870	12.5	0.2 (−2.0 to 2.4)	0.4 (−1.8 to 2.6)	−0.6 (−4.5 to 3.3)	−0.4 (−4.5 to 3.7)	0.0 (−2.7 to 2.7)	0.5 (−2.0 to 3.0)
	4	7,870	13.5	−0.7 (−3.0 to 1.5)	−0.5 (−2.7 to 1.7)	2.3 (−3.2 to 7.7)	2.3 (−3.3 to 7.8)	2.6 (−2.5 to 7.7)	2.9 (−2.0 to 7.9)
	5	7,870	15.6	−2.8 (−7.1 to 1.5)	−2.3 (−6.7 to 2.1)	−1.5 (−7.6 to 4.7)	−1.2 (−7.4 to 4.9)	0.8 (−6.0 to 7.6)	1.3 (−5.3 to 7.9)
Breasts	2	7,869	9.9	−0.1 (−3.8 to 3.7)	0.9 (−2.7 to 4.5)	2.0 (−4.9 to 8.8)	2.2 (−4.7 to 9.1)	−0.9 (−7.5 to 5.7)	−0.7 (−7.0 to 5.6)
	3	7,869	11.6	−1.2 (−4.0 to 1.6)	−0.5 (−3.2 to 2.3)	−1.1 (−5.0 to 2.8)	−0.9 (−5.0 to 3.2)	−2.4 (−6.3 to 1.5)	−1.9 (−5.5 to 1.7)
	4	7,869	13.1	−0.9 (−3.4 to 1.5)	−0.4 (−2.9 to 2.2)	−1.4 (−5.3 to 2.5)	−1.2 (−5.0 to 2.7)	−3.2 (−7.5 to 1.1)	−2.7 (−7.0 to 1.6)
	5	7,869	16.1	−4.1 (−8.9 to 0.6)	−3.3 (−8.0 to 1.5)	−0.4 (−8.3 to 7.5)	0.3 (−7.7 to 8.2)	−2.0 (−10.7 to 6.8)	−0.7 (−9.2 to 7.9)
Menstruation		7,867	13.0	−0.9 (−3.4 to 1.6)	−0.4 (−2.8 to 2.1)	0.0 (−3.2 to 3.3)	0.1 (−3.4 to 3.5)	0.2 (−4.0 to 4.3)	0.6 (−3.5 to 4.8)
Axillary hair		7,875	11.9	−2.9 (−5.5 to −0.3)	−2.6 (−5.2 to −0.1)	−2.2 (−6.9 to 2.5)	−1.9 (−6.8 to 2.9)	0.5 (−3.3 to 4.4)	0.9 (−2.8 to 4.6)
Acne		7,875	11.4	0.9 (−2.9 to 4.6)	1.3 (−2.4 to 5.0)	3.6 (−3.5 to 10.7)	3.6 (−3.2 to 10.4)	5.3 (0.9 to 9.6)	5.2 (0.9 to 9.5)
Average difference		7,278	–	−1.3 (−3.4 to 0.8)	−0.8 (−2.8 to 1.2)	0.1 (−3.3 to 3.5)	0.3 (−3.1 to 3.8)	0.3 (−2.5 to 3.1)	0.7 (−2.0 to 3.4)

Note: CI = confidence interval.

[a] The numbers in analyses vary because not all children gave information on all pubertal milestones.

[b] Number of unexposed: sons, 7,306; daughters, 7,711.

[c] Number of exposed to hyperthyroidism: sons, 205; daughters, 201.

[d] Number of exposed to hypothyroidism: sons, 76; daughters, 75.

[e] Number of exposed to benign goiter: sons, 86; daughters, 103.

[f] Mean monthly difference in age at achieving each pubertal milestone compared with the reference group.

[g] Reweighted using sampling and selection weights.

[h] Adjusted for maternal prepregnancy body mass index, maternal diabetes mellitus, socioeconomic status, maternal age at menarche, maternal age at birth, parity, maternal smoking during the first trimester of pregnancy, cohabitation of the parents, year of birth, and place of residence in Denmark.

Lunddorf. Maternal thyroid disease and puberty. Fertil Steril 2022.

RESULTS

Overall, 15,763 mother-child pairs were included in the study, whereof 746 (4.7%) mothers had thyroid disease diagnosed before, during, or up to 5 years after pregnancy, including hyperthyroidism, hypothyroidism, and benign goiter (Table 1). Mothers with hyperthyroidism tended to be nulliparous in the index pregnancy and older than the reference group. Mothers with hypothyroidism were more often low-grade professionals, older, multiparous, and nonsmokers. Mothers with benign goiter tended to be older and multiparous.

Overall, maternal hyperthyroidism was associated with earlier pubertal onset in sons (average difference, −2.9 [95% CI, −5.0 to −0.7] months) than in sons of mother without thyroid disease (Table 2). This association was mostly driven by the age differences for Tanner stages 2–5 for pubic hair and genital development of up to 5 months earlier pubertal development as well as first voice break episode. Maternal hypothyroidism was not associated with pubertal development in sons (average difference, −1.2 [95% CI, −5.1 to 2.7] months). We observed nonstatistically significant indications of earlier pubertal development in sons of mothers with benign goiter (average difference, −1.9 [95% CI, −4.6 to 0.9] months) than in the reference group.

We found no statistically significant difference in pubertal development among daughters whose mothers had hyperthyroidism (average difference, −0.8 [95% CI, −2.8 to 1.2] months), hypothyroidism (average difference, 0.3 [95% CI, −3.1 to 3.8] months), or benign goiter (average difference, 0.7 [95% CI, −2.0 to 3.4] months) compared with that among daughters of mothers without thyroid disease (Table 2).

In subanalysis 1 (Supplemental Table 1, available online), we repeated the analyses according to onset of maternal thyroid disease. In line with the overall findings, associations were observed among sons but not in daughters. In sons of mothers with hyperthyroidism, we observed tendencies of earlier pubertal development when maternal hyperthyroidism was detected both before and after birth of the child but only statistically significant after birth. In sons of mothers with hypothyroidism or benign goiter, we observed tendencies of earlier pubertal development only when the disease was diagnosed before birth of the child. In subanalysis 2, we observed similar results as in the main analysis when excluding mothers with only self-reported thyroid diseases (Supplemental Table 2, available online). In subanalysis 3, little or none of the effect of maternal thyroid diseases was mediated through the 7-year BMI (Supplemental Table 3, available online).

DISCUSSION

Main Findings

In this large population-based cohort study, we found earlier pubertal development in sons of mothers with hyperthyroidism. We observed nonstatistically significant indications of earlier pubertal development in sons of mothers with benign goiter, whereas no association with hypothyroidism was noted in the main analysis. Furthermore, the results did not indicate that maternal thyroid disease was associated with pubertal development in daughters in both the main analysis and subanalyses.

Strengths and Limitations

We had detailed information on pubertal development collected every 6 months throughout puberty. We included a large number of children with a participation rate of 70%.

We used self-assessment of the pubertal development to achieve a higher participation rate than that in studies using clinical examinations. We have previously studied the risk of selection bias due to nonparticipation within the Puberty Cohort and found that timing of puberty was not associated with participation in the Puberty Cohort (32). Additionally, in the present study, maternal thyroid disease was not associated with participation in the Puberty Cohort as 4.9% of the nonparticipants had mothers with a thyroid disease in pregnancy, as opposed to 4.7% among participants. Additionally, the frequency of maternal thyroid disease was rather similar in the different rounds of follow-up. Overall, 4.3% had a mother with a thyroid disease in the group only answering the 11-year follow-up, 4.8% among those answering only the Puberty Cohort, and 4.8% for those answering both. Thus, the exposure of interest did not relate to the participants' willingness to participate in the different rounds of follow-up. Furthermore, we applied selection weights in all analyses.

A study within the DNBC found that 3.9% of the pregnant women were diagnosed with a thyroid disease (33). Because of the sampling regime of the Puberty Cohort, we had a slightly larger prevalence in the present study. Nonetheless, the number of exposed children was limited, leading to wide 95% CIs, especially in subanalysis 1, which challenged the interpretation of the results. In addition, there was a risk of misclassification of the exposure, for which reason we used 2 sources of information on exposure to increase accuracy. A study within the DNBC has previously evaluated the self-reported information of thyroid disease and compared this to information in the DNPR (33). If the 2 data sources did not agree, the self-reported information was more often misleading. Thus, we considered the DNPR as the most valid data source and only added the self-reported if no diagnostic code was provided. In subanalysis 2, we found that the results were similar when comparing those observed in the main analysis and when restricting to mothers with a diagnostic code. This indicates that the potential misclassification by self-reported thyroid disease is likely minimal. Information on medical and surgical treatment of thyroid disease and biochemical assessment of maternal thyroid function in pregnancy would be of interest to substantiate the findings and extend the hypothesis. Because all information on thyroid disease was provided long before the children entered puberty, any misclassification of the exposure will most likely be unrelated to the pubertal development and, therefore, nondifferential and expected to cause bias toward the null if present.

There might also be a risk of misclassification of the outcome because we used self-reported data on pubertal development (34). To improve the ability to self-assess the

current pubertal status, each Tanner stage was supplemented by pictures drawings and a simple descriptive text. Studies have previously evaluated the agreement between self-reported assessment Tanner stages and clinical assessment by medical professionals to be fair to substantial and usable in large etiologic studies (35, 36). Both sons and daughters were asked to state the exact age in years and months at first ejaculation and menarche, respectfully, which could reduce the accuracy. However, because they were asked every 6 months, the recall time was minimal. Nonetheless, the children were unaware of the hypotheses of ongoing or future studies as they filled out the questionnaires. We expect any misclassification of pubertal development to be unrelated to maternal thyroid disease in pregnancy and, thereby, nondifferential if present.

We adjusted for potential confounders; however, there is a risk of residual confounding. Among the included confounders were prepregnancy BMI and maternal diabetes mellitus (Supplemental Fig. 1). These variables are most like confounders, but we cannot completely exclude that they may act as intermediates on the causal pathway. However, results did not change when these variables were omitted from the adjusted model. This suggests that prepregnancy BMI and diabetes mellitus are neither important confounders nor intermediary variables.

Previous Studies

No human studies have investigated whether intrauterine excess or deficit of maternal thyroid hormones affects the pubertal development in sons and daughters. Overall, 5 animal studies have previously investigated maternal hypothyroidism induced by propylthiouracil treatment and reproductive health in offspring with inconclusive results (37–41). Zertashia et al. (37) found increased body weight in female offspring but no difference in ovarian development or estradiol levels in rats. Park et al. (38) found lower body weight but no difference in timing of vaginal opening in rats. Radovanovic et al. (41) found impaired ovarian development in rats. Additionally, Gifford et al. (40) found no difference in female puberty in lambs. These results correspond with the present study. No animal studies have investigated whether maternal hyperthyroidism affects reproductive development in offspring.

Interpretation

We observed an association between maternal hyperthyroidism and pubertal development in sons. We speculate whether the mothers with hyperthyroidism were either inadequately treated (diagnosed either before or during pregnancy) or had unknown and untreated disease (diagnosed after birth), thereby exposing the fetus to abnormal thyroid levels. Thyroid disease in women of fertile age is predominantly of autoimmune origin and associated with the presence of thyroid autoantibodies (42). Thus, we expect thyroid autoimmunity as a potential underlying mechanism both when maternal thyroid disease was known and when it was later diagnosed. The hyperthyroidism of Graves' disease is associated with the presence of thyroid-stimulating hormone receptor antibodies that stimulate the thyroid gland to increase the production of thyroid hormone. It remains enigmatic how these autoimmune mechanisms may affect fetal development, but it may signal an underlying persistent autoimmune or genetic mechanism.

We observed nonstatistically significant indications of earlier pubertal development in sons of mothers with benign goiter, which is a more unspecific marker of thyroid disease. It has previously been observed that women diagnosed with benign goiter before or during pregnancy were more likely to have biochemical hyperthyroidism in the early pregnancy (21). Thus, our finding in relation to maternal benign goiter may support an overall link between hyperthyroidism and pubertal development in sons.

Maternal thyroid hormones are important for early fetal growth, and thyroid diseases in pregnancy are associated with preterm birth and low birth weight (42, 43). This may increase the risk of catch-up growth and childhood obesity potentially leading to early pubertal development (44–47). Therefore, we performed a mediation analysis examining childhood BMI as a potential confounder. Here, we found that none or little of the potential association was mediated (Supplemental Table 3).

Hyperthyroidism caused by a multinodular toxic goiter is less common in women aged <40 years but more common in populations with iodine deficiency (48). The mandatory iodine fortification of salt was implemented in 2000 in Denmark, which led to a transient increase in the incidence of hyperthyroidism in the Danish population (49). We adjusted the analyses for birth year of the child, as well as geographic residence, because of regional differences in iodine levels.

It was noteworthy that we observed associations only in boys. Thus, from a fetal programming hypothesis, it seems as if the male fetus may be more sensitive to an excess of thyroid hormones in relation to pubertal development. Previous studies have identified a similar male-specific effect to an intrauterine exposure perhaps due to an increased vulnerability of the male fetus (50–52). Additionally, we found tendencies of associations between all 3 maternal thyroid diseases and pubertal development in sons when the disease was diagnosed before birth perhaps due to inadequate treatment during pregnancy. However, the 95% CIs were wide, and we hesitate to conclude firmly on these results. More research is needed to further explore this and address the underlying mechanisms and the sex-specific association observed.

In conclusion, we found indications of earlier pubertal development in sons of mothers with hyperthyroidism. We found no evidence to support that maternal thyroid disease programs pubertal development in daughters.

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Enfermedad tiroidea materna en embarazo y momento del desarrollo puberal en hijos e hijas.

Objetivo: Estudiar si la enfermedad tiroidea materna en el embarazo está asociada con el momento de pubertad en hijos e hijas.

Diseño: Estudio de Cohorte.

Paciente(s): Un total de 15,763 madres e hijos del Cohorte Nacional Danés de Nacimiento y su Cohorte de Pubertad.

Intervención(es): Información autoreportada y basada en registros sobre enfermedad tiroidea materna durante el embarazo (hipertiroidismo, hipotiroidismo, bocio benigno, o sin enfermedad tiroidea [grupo de referencia]).

Medida(s) de Resultado(s) Principal(es): La diferencia de la edad media ajustada (meses) al alcanzar varios hitos puberales autoreportados recopilados cada 6 meses usando una regresión censurada por intervalo y la diferencia promedio en la edad al alcanzar todos los hitos puberales usando la estimación de varianza robusta de Huber-White (resultado primario).

Resultado(s): Hijos de madres con hipertiroidismo presentaron un desarrollo puberal más temprano (diferencia promedio, -2.9 [95% intervalo de confianza (CI), -5.0 a -0.7] meses) que hijos no expuestos. El hipotiroidismo materno no se asoció con desarrollo puberal en hijos (diferencia promedio, -1.2 [95% CI, -5.1 a 2.7] meses). Observamos indicaciones no estadísticamente significativas de desarrollo puberal más temprano en hijos de madres con bocio benigno (diferencia promedio, -1.9 [95% CI, -4.6 a 0.9] meses). La enfermedad tiroidea materna no se asoció con desarrollo puberal en hijas (diferencia promedio (meses), hipertiroidismo -0.8 [95% CI, -2.8 a 1.2]; hipotiroidismo, 0.3 [95% CI, -3.1 a 3.8]; y bocio benigno, 0.7 [95% CI, -2.0 a 3.4]).

Conclusión(es): Encontramos indicaciones de desarrollo puberal más temprano en hijos de madres con hipertiroidismo. Se necesitan más estudios para investigar a fondo la asociación específica de sexo observada.