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Low Birth Weight in Children Born to Mothers with Hyperthyroidism and High Birth Weight in Hypothyroidism, whereas Preterm Birth Is Common in Both Conditions: A Danish National Hospital Register Study

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Key Words

Thyroid disease · Hyperthyroidism · Hypothyroidism · Iodine · Pregnancy · Gestational age · Birth weight · Birth length · Danish National Hospital Register

Abstract

Objectives: Maternal hyper- and hypothyroidism have been associated with increased risk of adverse pregnancy outcomes, but studies have led to inconsistent results. We aimed to identify children born to mothers with a hospital-recorded diagnosis of thyroid dysfunction in Denmark and to study the association with gestational age at delivery and birth weight of the child. ***Study Design:*** Population-based cohort study using Danish nationwide registers. All singleton live births in Denmark between January 1, 1978 and December 31, 2006 were identified and stratified by maternal diagnosis of hyper- or hypothyroidism registered in the Danish National Hospital Register before January 1, 2007. ***Results:*** Maternal first-time diagnosis of thyroid dysfunction before, during or after pregnancy was registered in 32,809 (2.0%) of the singleton live births (n = 1,638,338). Maternal diagnosis of hyperthyroidism (adjusted OR 1.22, 95% CI 1.15–1.30) and hypothyroidism (adjusted OR 1.17, 95% CI 1.08–1.27) were associated with increased risk of preterm birth. Moreover, birth weight in children born to mothers with a diagnosis of hyperthyroidism was lower (adjusted difference –51 g, 95% CI –58 to –43 g) and higher in relation to maternal hypothyroidism (adjusted difference 20 g, 95% CI 10–30 g). Hyperthyroidism was associated with small-for-gestational-age (adjusted OR 1.15, 95% CI 1.10–1.20) and hypothyroidism with large-for-gestational-age children (adjusted OR 1.24, 95% CI 1.17–1.31). ***Conclusions:*** Based on Danish nationwide registers, both maternal hyper- and hypothyroidism were associated with increased risk of preterm birth. Actual birth weight of the child and birth weight for gestational age were low if the mother had a diagnosis of hyperthyroidism and high if the diagnosis was hypothyroidism.

Introduction

Thyroid hormones are essential for fetal growth and development [1] and several studies have reported an association between maternal thyroid dysfunction and pregnancy outcomes [2].

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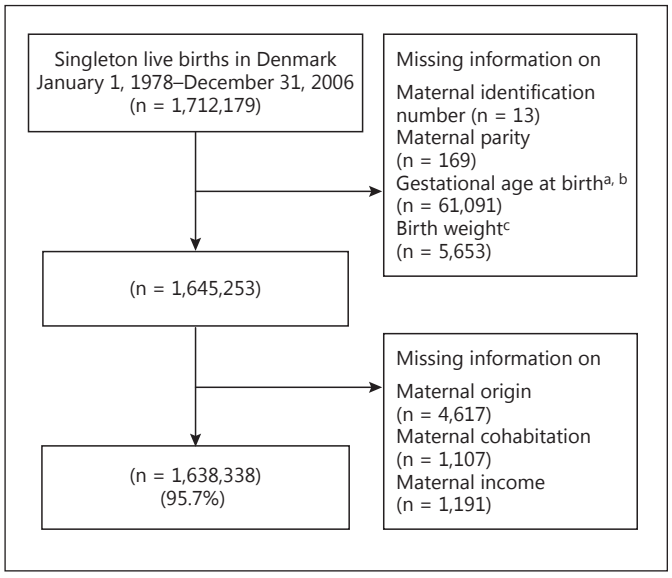

Fig. 1. Flowchart illustrating the selection of the singletons under study and the exclusion due to missing values. [a] Including registration of gestational age <20 weeks (n = 95, range 4–19 weeks) and >45 weeks (n = 22, range 46–55 weeks). [b] Distribution of missing values: 1978 (n = 18,218), 1979 (n = 15,111), 1980 (n = 11,187), 1981 (n = 6,683), 1982–2006 (n = 9,775). [c] Including registration of birth weight <500 g (n = 122, range 3–496 g), >6,000 g (n = 657, range 6,004–7,253 g) and birth weight registration considered too large for gestational week 20–33 (n = 582).

Gestational age at delivery and birth weight are important predictors of neonatal mortality and morbidity [3], and it has been proposed that some of the complications associated with maternal thyroid disease may be secondary to preterm birth [4].

Evidence suggests an increased risk of preterm birth in relation to both maternal hyperthyroidism and hypothyroidism [2]. Concerning birth weight, maternal hyperthyroidism has been associated with an increased risk of low birth weight and small-for-gestational-age (SGA) children [5–8], whereas results in relation to maternal hypothyroidism are more diverse. Some studies reported an increased risk of low birth weight or SGA [9–12], whereas others found no association [4, 13]. Finally, maternal isolated hypothyroxinemia in the first trimester has been associated with increased risk of fetal macrosomia [14], and in another study, thyroid peroxidase antibody-positive mothers had more often large-for-gestational-age (LGA) children [15].

If a disease is related to adverse pregnancy outcomes, it may be caused by the disease itself, its treatment (or lack of treatment) or the causes or correlates of the disease. If the causes are of a genetic nature, maternal diseases diagnosed after pregnancy could also be related to the pregnancy outcome, and an association with paternal disease might be observed as well. The same can be seen if the preclinical state of a disease is present during pregnancy with subsequent diagnosis of disease after the birth of the child.

Based on Danish nationwide registers, we aimed to identify children born to mothers diagnosed with thyroid dysfunction in a Danish hospital before, during or after the birth of a child, and to examine predictors of a first-time diagnosis of thyroid dysfunction during pregnancy, which might possibly confound an association between maternal thyroid dysfunction and adverse pregnancy outcomes. Finally, we aimed to investigate the impact of a diagnosis of maternal thyroid dysfunction on gestational age at delivery and the birth weight of the child.

Methods and Materials

Study Population and Design

We conducted a population-based cohort study using Danish nationwide registers. All Danish citizens are assigned a unique ten-digit personal identification number which is used in all national registers and enables linkage between the different registers. In the Danish Civil Registration System [16], we identified all singleton live births in Denmark between January 1, 1978 and December 31, 2006 (fig. 1).

Maternal Thyroid Dysfunction

The Danish National Hospital Register (DNHR) [17] holds nationwide data on all admissions to any Danish Hospital since 1977 and all hospital outpatient visits since 1995. For every admission, the register contains date of admission and discharge, and diagnoses classified according to the 8th revision of the International Classification of Disease (ICD-8) from 1977 to 1993 and the 10th revision (ICD-10) from 1994 and onwards.

We included all in- and outpatient visits (except emergency room visits) with a main or additional first-time diagnosis of hyper- or hypothyroidism after January 1, 1977 and before January 1, 2007. Hyperthyroidism was defined as ICD-8: 242.00–242.29 and ICD-10: E05–E05.9 [excluding thyrotoxicosis factitia (E05.4), overproduction of thyroid-stimulating hormone (E05.8A) and thyrotoxic heart disease (E05.9A)]. Hypothyroidism was defined as ICD-8: 243.99, 244.00–244.09 (excluding secondary hypothyroidism 244.02) and ICD-10: E03–E03.9 and E89.0 [excluding unspecified congenital goitre (E03.0A) and atrophy of the thyroid (congenital E03.1B, acquired E03.4)]. ICD codes of thyroiditis (ICD-8: 245.00–245.09 and ICD-10: E06–E06.9 including postpartum thyroiditis 090.5) were not included.

The 'onset' of disease was defined as the day of admission to hospital and categorized as before, during and after pregnancy. Pregnancy period was defined by subtracting gestational age at birth from the date the child was born.

Gestational Age, Birth Weight and Covariates

From the Danish Medical Birth Registry [18], we obtained information on gender of the child, gestational age at delivery, birth weight and length, maternal parity and maternal age. Gestational age was previously based on last menstrual period, but ultrasound estimation has been increasingly used over time [19]. We excluded singletons with a registration of gestational age and/or birth weight considered incorrect records (fig. 1). Similarly, very preterm births with a registration of unlikely large birth weight for gestational age were excluded, as previously suggested [20]. Children were categorized as SGA if they had a birth weight ≤ the 10th percentile and LGA if they had a birth weight ≥ the 90th percentile of birth weight distribution according to gestational week at birth and gender. Preterm birth was defined as gestational age at delivery <37 weeks.

From Statistic Denmark, we obtained information on maternal cohabitation, income, origin and residence at birth of the child. Information was only available from 1980 and we used data from 1980 to substitute the missing values in 1978 and 1979. For maternal cohabitation and origin, we replaced additional missing values by available information in the preceding or following 5 (origin) or 3 (cohabitation) years, whichever came first. We used information on maternal residence as a proxy variable for maternal iodine intake. Iodine is essential for thyroid hormone synthesis and Denmark was previously iodine deficient with regional differences; moderate iodine deficiency in West Denmark and mild iodine deficiency in East Denmark (divided by the Great Belt). The mandatory iodine fortification of salt was introduced in the year 2000 and had increased urinary iodine to a lower recommended level in 2004–2005 [21].

From the DNHR, we obtained information on maternal first-time diagnosis of diabetes (ICD-8: 249.00–250.09 and ICD-10: E10.0–E14.9, O24–O24.9). Information on maternal smoking during pregnancy was available in the DNHR from 1996.

Statistical Analyses

First-time diagnoses of maternal thyroid dysfunction during pregnancy over time and characteristics of singletons born to mothers with and without a diagnosis of thyroid dysfunction (hyper- or hypothyroidism) were compared using the χ^2 test for categorical variables and one-way ANOVA for continuous variables.

Predictors of maternal diagnosis of thyroid dysfunction during pregnancy and the risk of preterm birth, SGA and LGA in children born to mothers with a diagnosis of hyper- or hypothyroidism were studied in univariate and multivariate logistic regression models. Also, birth weight and length of the child and ponderal index [birth weight (kg) divided by the cube of birth length (m^3)] [22] were examined in linear regression models with and without adjustment for gestational age at delivery.

Analyses were stratified according to time of maternal diagnosis, and parallel analyses according to paternal diagnosis of thyroid dysfunction were performed. Analyses were restricted to firstborn child and repeated after adjustment for maternal smoking during pregnancy in the cohort of singletons born after December 31, 1995 (n = 626,606).

Statistical analyses were performed using STATA version 11 (Stata Corp., College Station, Tex., USA) and a 5% level of significance was chosen.

The study was approved by the Danish Data Protection Agency.

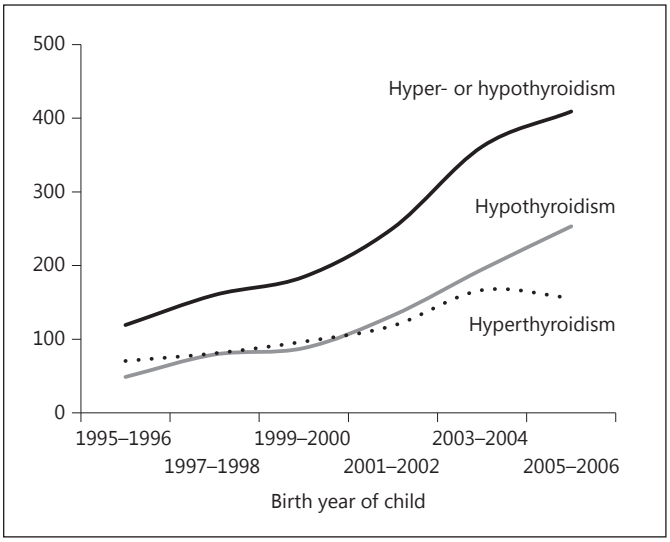

Fig. 2. Maternal first-time diagnosis of hyper- or hypothyroidism during pregnancy registered in the DNHR per 100,000 singleton live births. Curves are smooth fitted lines.

Results

Maternal Diagnosis of Thyroid Dysfunction

Among the 1,638,338 singleton live births between January 1, 1978 and December 31, 2006 included, we identified 32,809 (2.0%) singleton pregnancies with a maternal first-time hospital diagnosis of hyper- or hypothyroidism before (n = 6,268), during (n = 2,503) or after (n = 24,038) pregnancy and registered in the DNHR before January 1, 2007.

From 1995 to 2006, during which period both in- and outpatients were included in the DNHR and when ICD-10 was used for classification of disease, there was a steep increase in the registered number of maternal first-time diagnoses of hyper- and hypothyroidism during pregnancy ($p < 0.001$); however, hyperthyroidism seemed to reach a plateau in 2003–2004, whereas hypothyroidism continued to increase (fig. 2). From 1978 to 1995, when only inpatients were included in the register and ICD-8 was the classification of choice, the number of first-time diagnoses of thyroid dysfunction (hyper- or hypothyroidism) during pregnancy was stable ($p = 0.462$, data not shown).

Predictors of Maternal First-Time Diagnosis of Thyroid Dysfunction during Pregnancy

Singleton pregnancies with a maternal diagnosis of thyroid dysfunction before or after the birth of a child had higher maternal parity, mothers were older at the birth of

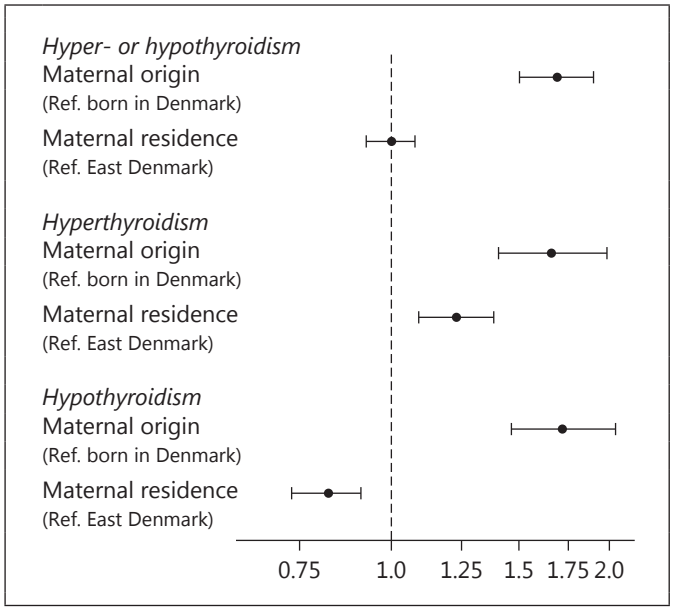

Fig. 3. Adjusted OR with 95% CIs for maternal first-time diagnosis of hyper- or hypothyroidism during singleton pregnancy January 1, 1978 to December 31, 2006. Reference is singleton pregnancies in which the mother was born in Denmark (maternal origin) and singleton pregnancies in which the mother was living in East Denmark (maternal residence) at the time of the child's birth. Model included the following variables obtained at the time of the child's birth: maternal origin (born in Denmark/not born in Denmark), maternal residence (West Denmark/East Denmark), maternal age (<20, 20–24, 25–29, 30–34, 35–39, ≥40 years), calendar year (<1980, 1980–1982, 1983–1985, 1986–1988, 1989–1991, 1992–1994, 1995–1997, 1998–2000, 2001–2003, 2004–2006), parity including index pregnancy (1, 2, 3, ≥4), maternal cohabitation (married/not married) and maternal income (1st, 2nd, 3rd, 4th quartile).

a child and were more often foreign-born (table 1). Maternal first-time diagnosis of hyperthyroidism was most common in West Denmark with previously moderate iodine deficiency, and a diagnosis of hypothyroidism occurred more often in East Denmark with previously mild iodine deficiency.

Figure 3 focuses on maternal first-time diagnosis of thyroid dysfunction during pregnancy alone. Pregnancies, in which the mother was not born in Denmark had a higher risk of maternal first-time diagnosis of hyper- or hypothyroidism during pregnancy, whereas the odds ratio differed in relation to maternal residence revealing an increased risk of hyperthyroidism and a reduced risk of hypothyroidism during pregnancy in West Denmark compared to East Denmark. In addition, higher maternal age at the birth of a child was a significant risk factor (data not shown).

Gestational Age at Delivery and Birth Weight of the Child

Preterm birth was more frequent in children born to mothers with a diagnosis of thyroid dysfunction before or after the birth of a child; hyperthyroidism 5.40% versus hypothyroidism 5.50% versus no maternal diagnosis of thyroid disease 4.40%, $p < 0.001$ (table 1).

Mean birth weight was lower in children born to mothers with a diagnosis of hyperthyroidism and higher in children born to mothers with a diagnosis of hypothyroidism (table 1). This also appeared in the distribution of SGA and LGA children with a higher percentage of children classified as SGA in relation to maternal hyperthyroidism, whereas more children were classified as LGA in relation to maternal hypothyroidism (table 1).

In a logistic regression model including potential confounders, both a maternal diagnosis of hyperthyroidism and hypothyroidism before or after the birth of a child were associated with increased risk of preterm birth (fig. 4). On the other hand, maternal diagnosis of hyperthyroidism was associated with an increased risk of SGA and hypothyroidism with an increased risk of LGA children (fig. 4). The adjusted model changed the estimates slightly; however, the association was still the same. Gestational age at birth was not included in the adjusted model as it was already included in the birth weight variable (SGA, appropriate for gestational age and LGA).

In a linear regression model adjusting for the same variables, but not including gestational age at delivery, differences in birth weight according to maternal diagnosis of thyroid dysfunction were almost the same. Children born to mothers with a diagnosis of hyperthyroidism had lower birth weight (adjusted birth weight difference –51 g, 95% CI –58 to –43 g), whereas birth weight in children born to mothers with a diagnosis of hypothyroidism was higher (adjusted birth weight difference 20 g, 95% CI 10–30 g). Including gestational age in the model diminished the impact of maternal hyperthyroidism (adjusted birth weight difference –39 g, 95% CI –45 to –32 g) and exaggerated the impact of maternal hypothyroidism (adjusted birth weight difference 29 g, 95% CI 20–38 g).

Stratifying the analyses by time of maternal first-time diagnosis before, during or after pregnancy also revealed the same association (table 2). However, the number of singletons exposed to maternal hypothyroidism diagnosed before or during pregnancy was rather low, and birth weight difference in the adjusted model not in-

Table 1. Characteristics of singletons born between January 1, 1978 and December 31, 2006 and their mothers at birth of child stratified by maternal diagnosis of thyroid dysfunction

	No thyroid dysfunction[a]		Hyperthyroidism[b]		Hypothyroidism[b]	
	n	%	n	%	n	%
Singletons	1,605,529	98.0	21,623	1.3	11,186	0.7
Maternal characteristics						
Parity[c]						
1	729,818	45.5	9,022	41.7	4,820	43.1
2	611,259	38.1	8,399	38.8	4,259	38.1
3	202,847	12.6	3,124	14.5	1,541	13.8
≥4	61,605	3.8	1,078	5.0	566	5.0
Age						
<20 years	41,368	2.6	489	2.3	212	1.9
20–24 years	315,523	19.6	4,121	19.0	1,994	17.8
25–29 years	617,115	38.4	7,776	36.0	3,997	35.7
30–34 years	452,446	28.2	6,204	28.7	3,349	30.0
35–39 years	155,626	9.7	2,588	12.0	1,396	12.5
≥40 years	23,451	1.5	445	2.0	238	2.1
Cohabitation						
Married	984,389	61.3	13,785	63.7	7,283	65.1
Not married	621,140	38.7	7,838	36.3	3,903	34.9
Income						
1st quartile (lowest)	78,429	4.9	1,095	5.1	653	5.8
2nd quartile	426,130	26.5	5,871	27.1	3,189	28.5
3rd quartile	862,097	53.7	11,734	54.3	5,726	51.2
4th quartile	238,873	14.9	2,923	13.5	1,618	14.5
Origin						
Born in Denmark	1,463,930	91.2	19,456	90.0	9,713	86.8
Not born in Denmark	141,599	8.8	2,167	10.0	1,473	13.2
Residence[d]						
West Denmark	903,254	56.3	13,074	60.5	6,002	53.7
East Denmark	702,275	43.7	8,549	39.5	5,184	46.3
Child characteristics						
Gender						
Boy	824,152	51.3	10,890	50.4	5,792	51.8
Girl	781,377	48.7	10,733	49.6	5,394	48.2
Gestational age						
20–27 weeks	1,666	0.1	24	0.1	16	0.1
28–32 weeks	10,424	0.7	176	0.8	97	0.9
33–36 weeks	58,577	3.6	968	4.5	504	4.5
37–41 weeks	1,396,234	87.0	18,743	86.7	9,630	86.1
42–45 weeks	138,628	8.6	1,712	7.9	939	8.4
Birth weight (mean ± SD), g	3,488±559		3,429±573		3,507±587	
Birth weight categories						
SGA	165,603	10.3	2,642	12.2	1,083	9.7
AGA	1,275,175	79.4	16,902	78.2	8,618	77.0
LGA	164,751	10.3	2,079	9.6	1,485	13.3

[a] No maternal diagnosis of hyper- or hypothyroidism registered in the DNHR before January 1, 2007. [b] Maternal first time diagnosis of hyper- or hypothyroidism registered in DNHR before January 1, 2007. [c] Number of births (live- and stillbirths) including index pregnancy. [d] Divided into regions by the Great Belt; West Denmark previously moderate iodine deficiency, East Denmark previously mild iodine deficiency. AGA = Appropriate for gestational age. χ^2 test for categorical variables, one-way ANOVA for continuous variables: no maternal thyroid disease vs. maternal hyperthyroidism vs. maternal hypothyroidism, $p < 0.001$ for all variables except gender of the child ($p = 0.011$).

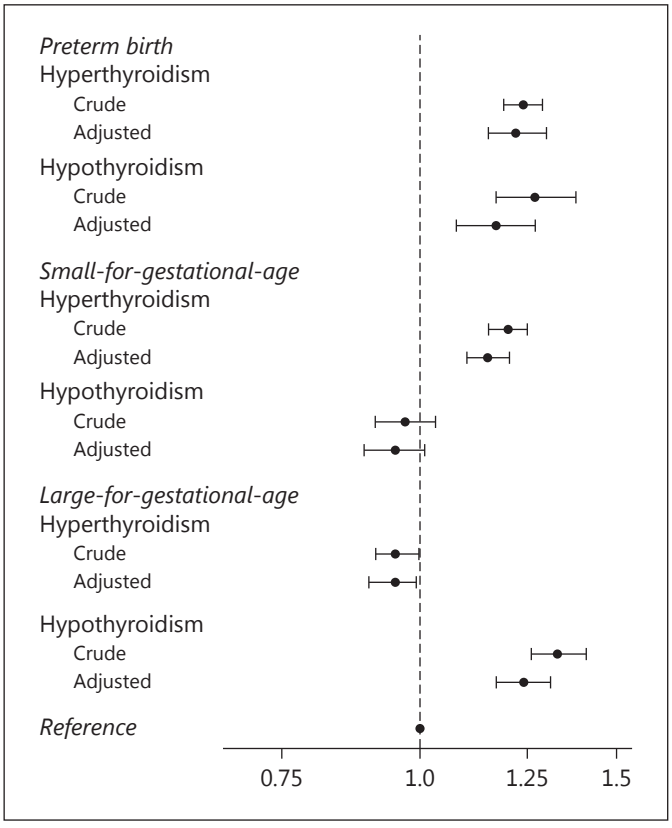

Fig. 4. OR with 95% CIs for preterm birth, SGA and LGA in singleton pregnancies between January 1, 1978 and December 31, 2006 with a maternal first-time diagnosis of thyroid dysfunction (hyper- or hypothyroidism) before, during or after pregnancy and registered in the DNHR before January 1, 2007. Reference is singleton live births in the same period with no registered maternal diagnosis of thyroid dysfunction before January 1, 2007. Adjusted model included the following variables obtained at the time of the child's birth: maternal age (<20, 20–24, 25–29, 30–34, 35–39, ≥40 years), calendar year (<1980, 1980–1982, 1983–1985, 1986–1988, 1989–1991, 1992–1994, 1995–1997, 1998–2000, 2001–2003, 2004–2006), parity including index pregnancy (1, 2, 3, ≥4), maternal cohabitation (married/not married), maternal income (1st, 2nd, 3rd, 4th quartile), maternal origin (born in Denmark/not born in Denmark), maternal residence (East/West Denmark) and maternal diagnosis of diabetes registered in the DNHR before January 1, 2007 (yes/no).

cluding gestational age did not reach statistical significance in these groups. The risk of SGA and lower birth weight in relation to maternal hyperthyroidism seemed higher when maternal first-time diagnosis had been registered before or during pregnancy compared to maternal diagnosis after pregnancy (95% CI marginally or not overlapping).

Additional Analyses

To evaluate if changes in birth weight were associated with disproportional fetal growth, birth length of the child and ponderal index were studied in the same linear regression models as for birth weight. Birth length of the child was significantly shorter or longer if the mother had a diagnosis of hyperthyroidism or hypothyroidism, respectively [adjusted birth length difference (cm) in the model including gestational age: hyperthyroidism –0.16, 95% CI –0.19 to –0.13; hypothyroidism: 0.12, 95% CI 0.073–0.16]. Ponderal index did not differ significantly [adjusted ponderal index difference (kg/m^3) in the model including gestational age: hyperthyroidism –0.028, 95% CI –0.080 to 0.023; hypothyroidism 0.028, 95% CI –0.043 to 0.099].

Paternal diagnosis of thyroid disease occurred in relation to 5,407 of the singleton births (0.33%) and mainly with a paternal diagnosis after the child's birth (n = 4,134). A paternal diagnosis of hyper- or hypothyroidism was not associated with increased risk of preterm birth (adjusted OR 1.00, 95% CI 0.88–1.14) or birth weight not appropriate for gestational age (adjusted OR SGA 1.04, 95% CI 0.95–1.13; LGA 0.99, 95% CI 0.91–1.09).

Results were considerably the same as presented above when restricting the cohort to firstborn child and when adjusting for maternal smoking during pregnancy in the cohort of singletons born between 1996 and 2006 (data not shown).

Discussion

Main Findings

Based on Danish nationwide registers we found a steep increase in the number of maternal first-time hospital diagnoses with thyroid dysfunction during pregnancy from 1995 and onwards. Maternal age, country of birth and geographical residence at time of child's birth were predictors of maternal diagnosis of thyroid dysfunction. Children born to mothers with a diagnosis of thyroid dysfunction before, during or after pregnancy had increased risk of preterm birth, deviation from average birth weight and length and birth weight not appropriate for gestational age. Our findings in relation to birth weight and length indicated that maternal hyperthyroidism was associated with lower birth weight and length and increased risk of small (SGA) children, whereas maternal hypothyroidism was associated with higher birth weight and length and increased risk of large (LGA) children.

Table 2. Mean birth weight, adjusted birth weight difference and OR with 95% CIs for preterm birth, SGA and LGA in singletons born to mothers with a first-time diagnosis of hyper- or hypothyroidism before, during or after pregnancy

	None[a]	Maternal diagnosis of hyperthyroidism[b]			Maternal diagnosis of hypothyroidism[b]		
		before	during	after	before	during	after
Singletons, n	1,605,529	4,381	1,262	15,980	1,887	1,241	8,058
Birth weight (mean ± SD), g	3,488±559	3,448±588	3,426±600	3,425±567	3,558±607	3,529±574	3,492±584
Linear regression model[c]							
Birth weight difference, not including gestational age, g							
Adjusted difference (95% CI)	ref.	–88 (–105 to –72)	–91 (–121 to –61)	–37 (–46 to –29)	7 (–18 to 32)	11 (–19 to 42)	24 (12 to 36)
Birth weight difference, including gestational age[d], g							
Adjusted difference (95% CI)	ref.	–67 (–82 to –53)	–65 (–92 to –39)	–29 (–36 to –21)	26 (4 to 48)	30 (3 to 57)	29 (19 to 40)
Logistic regression model[c]							
Preterm birth							
Adjusted OR (95% CI)	ref.	1.36 (1.20–1.54)	1.43 (1.14–1.79)	1.17 (1.09–1.25)	1.26 (1.04–1.53)	1.27 (1.01–1.60)	1.13 (1.02–1.25)
Small-for-gestational-age							
Adjusted OR (95% CI)	ref.	1.27 (1.15–1.40)	1.43 (1.20–1.69)	1.11 (1.05–1.16)	1.05 (0.88–1.24)	1.02 (0.83–1.25)	0.93 (0.86–1.00)
Large-for-gestational-age							
Adjusted OR (95% CI)	ref.	0.92 (0.83–1.01)	0.94 (0.79–1.13)	0.96 (0.91–1.02)	1.15 (1.02–1.31)	1.22 (1.04–1.43)	1.27 (1.19–1.36)

[a] No maternal diagnosis of hyper- or hypothyroidism registered in the DNHR before January 1, 2007. [b] Maternal first time diagnosis of hyper- or hypothyroidism before, during or after pregnancy and registered in DNHR before January 1, 2007. [c] Model included the following variables obtained at the time of the child's birth: maternal age (<20, 20–24, 25–29, 30–34, 35–39, ≥40 years), calendar year (<1980, 1980–1982, 1983–1985, 1986–1988, 1989–1991, 1992–1994, 1995–1997, 1998–2000, 2001–2003, 2004–2006), parity including index pregnancy (1, 2, 3, ≥4), maternal cohabitation (married/not married), maternal income (1st, 2nd, 3rd, 4th quartile), maternal origin (born in Denmark/not born in Denmark), maternal residence (East/West Denmark) and maternal diagnosis of diabetes registered in DNHR before January 1, 2007 (yes/no). [d] Gestational age at delivery (20–27, 28–32, 33–36, 37–41, 42–45 weeks).

Gestational Age in Children Born to Mothers with Thyroid Dysfunction

In our study population, a maternal hospital diagnosis of hyper- or hypothyroidism was associated with increased risk of preterm birth independent of time of maternal diagnosis in relation to pregnancy period. Evidence from previous studies suggests that maternal thyroid dysfunction as well as thyroid peroxidase antibodies in euthyroid pregnant women might be associated with increased risk of preterm birth [2, 23]. We speculate that a maternal diagnosis of thyroid dysfunction after the birth of a child in our study population might indicate a higher than average frequency of undiagnosed thyroid dysfunction and/or autoimmunity present during the preceding pregnancy. Another possible explanation would be a shared genetic component linking maternal thyroid disease and preterm birth of a child; however, lack of an association with paternal thyroid disease in our study population contradicts a genetic component to some extent.

Birth Weight in Children Born to Mothers with a Diagnosis of Hyperthyroidism

Previous studies evaluating the impact of maternal overt hyperthyroidism rather consistently showed an increased risk of low-birth-weight and SGA children [5–8], which was confirmed in the present study. In addition, birth length of the child was shorter, whereas no difference in ponderal index was observed.

The mechanisms behind an association between maternal hyperthyroidism and SGA children have not been clarified. It could be that hyperthyroidism-induced metabolic changes in the mother subsequently affect growth of the placenta and/or the fetus [24], and in Graves' disease transplacental transport of thyroid-stimulating antibodies may induce fetal hyperthyroidism [25].

Maternal smoking is an important risk factor for low birth weight and preterm birth [26] and also constitutes a potential risk factor for thyroid dysfunction [27]. Our results, however, did not show signs of confounding by smoking.

Birth Weight in Children Born to Mothers with a Diagnosis of Hypothyroidism

In our study population, hypothyroidism in contrast to hyperthyroidism was associated with higher birth weight and an increased risk of LGA, which was observed both when the mother had a diagnosis of hypothyroidism registered before and after the birth of a child.

Previous studies have reported an increased risk of low birth weight or SGA children in relation to maternal overt hypothyroidism or high thyroid-stimulating hormone levels alone [9–12]. One study found an increased risk of LGA children similar to our results in relation to the presence of thyroid peroxidase antibodies [15] and another study reported increased risk of fetal macrosomia [14] in relation to isolated maternal hypothyroxinemia in the first trimester. Our finding of an association with maternal hypothyroidism diagnosed after the birth of a child could indicate subclinical disease being present during the preceding pregnancy or as discussed in relation to hyperthyroidism, a genetic component might exist. However, again no association with paternal thyroid disease was observed.

Overall, mothers diagnosed with hypothyroidism gave birth to children with higher birth weight, but on average, gestational age was lower. Thus, adjusting birth weight for gestational age led to an even more pronounced difference in birth weight. Children were both heavier and longer with unaltered ponderal index. This is different from the disproportionate body composition with a high ponderal index often found in children born to diabetic mothers [28].

The mechanisms behind an association between maternal hypothyroidism and LGA children are not clear. The metabolic changes in maternal diabetes are known risk factors of fetal macrosomia [29], and in previous studies maternal thyroid disease was associated with an increased risk of gestational diabetes [12]. Prepregnancy weight and gestational weight gain outside of recommended ranges increase the risk of birth weight not appropriate for gestational age [30] and obesity is associated with higher serum thyroid-stimulating hormone levels [31]. Perhaps maternal obesity is an intermediate linking maternal hypothyroidism with the risk of LGA children. However, we did not have data on maternal weight and height.

Maternal First-Time Diagnosis of Thyroid Dysfunction during Pregnancy

In recent years, there was a steep increase in the number of first-time hospital diagnoses of thyroid dysfunction during pregnancy in Denmark. The transition to registration of both in- and outpatients in DNHR from 1995 is probably of importance, but unlikely to explain the continuing increase. Maternal origin (not born in Denmark) and age at the birth of a child were important predictors in our multivariate model. Maternal age at the birth of a child increased during the period under study (mean 28.7 years in 1995 vs. 30.1 years in 2005). The percentage of foreign-born mothers also increased, but reached a plateau in the middle of the period (2001–2002). Finally, a shift in the detection of thyroid dysfunction including screening of asymptomatic individuals or individuals not at particular risk might have occurred, or a shift in the registration or definition of mild disease might have happened.

The mandatory iodine fortification of salt was introduced in Denmark in 2000 and led to a transient increase in the incidence of hyperthyroidism most pronounced in West Denmark with previous moderate iodine deficiency [32, 33]. Iodization of salt was followed by an increase in the incidence of hypothyroidism most pronounced in East Denmark with previous mild iodine deficiency [34, 35]. Our findings are consistent with these associations; however, further studies are needed to exactly clarify the association of iodine fortification with the occurrence and subtype of thyroid dysfunction during pregnancy in Denmark.

Methodological Considerations

The strength of our study is the population-based design and large study population. We used the time of first diagnosis with thyroid dysfunction to define 'onset' of maternal disease; however, patients are referred to hospital from general practice and might present with clinical disease years before the first hospital visit. Our study only included patients admitted to in- or outpatient hospital care, but we believe that pregnant women with a diagnosis of thyroid dysfunction defined by treatment are in general referred to hospital for diagnosis and therapy [36]. On the other hand, management of thyroid disease diagnosed after the birth of a child might take place in general practice alone, and inclusion in the present study may be incomplete. We cannot exclude that this may have influenced on our findings in the subgroup of women diagnosed after the birth of a child, but the principal findings were quite similar in women diagnosed before or during the pregnancy.

The validity of DNHR in relation to a diagnosis of thyroid dysfunction has not been evaluated in pregnancy; however, a diagnosis of hyper- or hypothyroidism in the

general population only revealed misclassification in less than 2% [37]. The diagnostic validity of DNHR in relation to other medical diseases in women of reproductive age (inflammatory bowel disease, rheumatoid arthritis) has been evaluated providing evidence for the use of DNHR in cohort studies [38, 39]. The validity decreases with the number of digits employed in the ICD [40]; however, we used only three digits to classify hyperthyroidism and hypothyroidism, respectively.

We excluded singletons with missing values on gestational age (mainly singletons born in the years 1978–1981); however, the occurrence of maternal thyroid disease was similar in this group compared to other singletons born in the same period of time and the risk of selection bias due to this exclusion is low, as previously described in detail [41].

Misclassification of exposure and/or outcome exists in our study population including misclassification of maternal thyroid disease onset in relation to pregnancy period [42]; however, we believe any misclassification is nondifferential, which would often create bias towards the null.

We were able to adjust for a number of important possible confounders, but unmeasured confounders might still exist. It has been brought forward that adjustment or even stratification of birth weight by gestational age may introduce bias from such unknown confounders (collider bias) [43]. It seems, however, not likely that such bias had a major impact on our findings, because adjustment for gestational age did not change the results substantially.

Conclusion

Based on Danish nationwide registers, we found a steep increase in the number of first-time diagnoses with thyroid dysfunction during pregnancy since 1995. Children born to mothers with a diagnosis of thyroid dysfunction had an increased risk of preterm birth and deviation from average birth weight and length as well as birth weight not appropriate for gestational age. Notably, the associations were consistent irrespective of time of maternal diagnosis in relation to pregnancy and no association with paternal thyroid disease was observed.

The findings call for additional studies investigating the occurrence and impact of maternal thyroid dysfunction and its therapy during pregnancy in Denmark, especially to see if adverse pregnancy outcomes are associated with nonoptimal therapy of maternal thyroid disease.

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Disclosure Statement

The authors declare no conflict of interest.

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