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Use of thyroid hormones in relation to pregnancy: a Danish nationwide cohort study

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Key words
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Conflict of interest
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Abstract

Objective. To determine the rate of exposure of pregnant women to levothyroxine and to assess changes in these rates before, during and after pregnancy. *Design.* Register-based cohort study. *Setting.* Danish nationwide registers. *Population.* All women having a live birth in Denmark between 1 January 1997 and 31 December 2010 (n = 912 342). *Methods.* All pregnant women in the study period were identified from the Danish Medical Birth Register. Exposed women were identified from the Danish National Prescription Register, based on redemption of levothyroxine prescriptions before, during or after pregnancy. *Main outcome measures.* The rate of pregnant women redeeming levothyroxine prescriptions and maternal characteristics. *Results.* We identified a fourfold increase in levothyroxine prescription redemption during the study period, from 0.34% in 1997 to 1.39% by 2010. A mean of 0.79% of our cohort received levothyroxine. Most of the women who were using levothyroxine before pregnancy continued the therapy during their pregnancy, but 9.4% stopped redeeming their prescriptions. Overall, 0.28% of our cohort received a levothyroxine prescription for the first time within 9 months after pregnancy. *Conclusions.* Fewer women than expected received levothyroxine treatment during pregnancy even though a fourfold increase was observed during the study period. Furthermore, one of 10 discontinued treatments during pregnancy. These findings all indicate that too few women are treated for hypothyroidism during pregnancy. Further research is needed to determine whether hypothyroid pregnant women are suboptimally treated and the possible consequences for the mother and fetus.

Abbreviation: BMI, body mass index.

Introduction

Up to 2.8% of women of reproductive age are estimated to have hypothyroidism (1,2). Untreated maternal thyroid disorder is associated with adverse neonatal outcomes such as preterm birth, low birthweight and neonatal respiratory distress (3,4). Clinical studies have also shown that children born to mothers with inadequately treated hypothyroidism have significantly lower intelligence

Key Message

About 1% of pregnant women and their unborn children may be exposed to levothyroxine during pregnancy. Use of the drug during pregnancy increased fourfold from 1997 to 2010. A considerable proportion of women discontinue the drug in pregnancy and fewer women than optimal may receive treatment in pregnancy.

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quotients than children born to euthyroid mothers (5,6). Maternal hypothyroidism is also associated with an increased incidence of obstetric complications such as anemia, placental abruption, postpartum hemorrhage and severe preeclampsia (7–9). Proper management of hypothyroidism with thyroid hormones during pregnancy is therefore of the utmost importance, and many pregnant women consequently receive treatment with levothyroxine, as recommended in current USA and European guidelines (10–12). National guidelines, similar to the international ones, have been available for Danish clinics since 2008. These guidelines include recommendations about which pregnant women should be tested for thyroid disease (for example, women with a personal history or family disposition to hypo- or hyperthyroidism), but there is no national or universal screening program for hypothyroidism in Denmark.

Little has been published concerning the prevalence of levothyroxine exposure among pregnant women, or about changes in exposure related to pregnancy. As a public health issue, it is important to know the exposure prevalence in order to estimate the extent of levothyroxine use and to assess whether current guidelines are being followed.

Material and methods

For the present study we established a cohort based on information from Danish nationwide registers, including all births between 1 January 1997 and 31 December 2010, inclusive. The study period was chosen on the basis of available data. For this period we identified 912 342 pregnant women who had a live delivery. In Denmark, every newborn or immigrant is assigned a unique personal identification number, which makes it possible to construct databases linking personal identification numbers across different registers. In the present study, we used information from Statistics Denmark (13), the Danish Medical Birth Register (14), the Danish National Prescription Register (15) and the Danish National Patient Register (16). In Denmark, the Processing of Personal Data Act does not require ethical permission or written informed consent to be obtained for anonymized retrospective register studies. All personal identification numbers were encrypted before analysis. The study was approved by the Danish Data Protection Agency (No. 2008-41-2517).

The study cohort was drawn from the Danish Medical Birth Register (14), which contains information about all women of reproductive age in Denmark and their children. We included all women giving birth in Denmark during the study period and gathered information on maternal age, parity, conception date and delivery date. We excluded records with missing data for any of these variables. Conception date was estimated using the date of the first day of the last menstrual period plus 14 days, or from the gestational length inferred from early ultrasound fetal measurements. The Danish National Prescription Register (15) includes information from all Danish community pharmacies. Pharmacies have been obliged by law since 1995 to register every prescription they dispense, linking them to patients' unique personal identification numbers. In our study, we used the information from every prescription about trade name, pharmaceutical form, strength, package size and redemption date.

We gathered information from the Danish National Patient Register concerning smoking habits during pregnancy, coded according to the International Classification of Diseases, 10th revision (ICD-10, Danish revision). We identified the pregnant women's educational level and annual household income during their birth year from Statistics Denmark (13).

The women were classified as having been or having not been exposed to levothyroxine during pregnancy, enabling us to compare the characteristics of maternal age, parity, smoking habits, annual household income, education level and body mass index (BMI). The numbers of missing values for each variable are presented in Table 1. Age was divided into five groups: <20, 20–24, 25–29, 30–35 and >35 years. Parity was presented as no (0), one (1) or two or more previous births (≥2). Smoking during pregnancy was categorized by the self-reported number of cigarettes smoked daily as 0, 1–10, 11–20, 21–30 or >30. Annual household income during the year of birth was split into quartiles. BMI was divided into four groups: <18.5, 18.5–24.9, 25–29.9 and ≥30 kg/cm^2. The highest educational level attained was categorized as low, medium or high.

Exposure was defined as redeeming a prescription for levothyroxine [Anatomic Therapeutic Chemical classification system-code H03AA01] during pregnancy.

To estimate changes in redemptions in relation to pregnancy, we evaluated the variation in prescription redemption not only during the 9-month period of pregnancy but also during the 9 months before and 9 months after each pregnancy, thereby ensuring three comparable periods of equal duration. Seven groups can therefore be defined on the basis of the combinations of periods in relation to pregnancy in which at least one prescription for levothyroxine was redeemed:

- *all periods*: defined as women who redeemed at least one prescription for the drug in each of the periods from nine to zero months before conception ("before pregnancy"), during pregnancy, and zero to nine months after delivery ("after pregnancy");

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Table 1. Maternal characteristics of women exposed and unexposed to levothyroxine during pregnancy between 1997 and 2010. BMI values only cover the period between 2004 and 2010. Chi-squared tests were used to assess the differences between exposed and unexposed women, adjusting for the other variables in the table.

	Exposed (n = 7164)		Unexposed (n = 905 178)		
	n	%	*n*	%	Adjusted *p*
Age (years)					
Missing values	0	–	0	–	<0.0001
<20	46	0.64	25 001	2.76	
20–24	512	7.15	138 009	15.25	
25–29	2204	30.76	339 615	37.52	
30–35	2835	39.57	289 505	31.98	
>35	1567	21.87	113 048	12.49	
Parity					
Missing values	83	1.16	5632	0.62	0.159
0	2565	35.80	395 882	43.74	
1	2778	38.78	330 867	36.55	
>1	1738	24.26	172 797	19.10	
Income					
Missing values	264	3.69	17 249	1.91	0.156
Quartile 1	1421	19.83	222 286	24.56	
Quartile 2	1655	23.10	222 052	24.53	
Quartile 3	1735	24.22	221 972	24.52	
Quartile 4	2089	29.16	221 619	24.48	
Education					
Missing values	290	4.05	40 706	4.50	0.015
Low	1979	27.62	298 178	32.94	
Medium	2029	28.32	269 057	29.72	
High	2866	40.00	297 237	32.84	
Smoking (cigarettes per day)					
Missing values	7	0.10	834	0.09	<0.0001
0	6123	85.47	712 421	78.71	
1–10	622	8.68	134 704	14.88	
11–20	25	0.35	5565	0.61	
21–30	136	1.90	22 926	2.53	
>30	251	3.50	28 728	3.17	
BMI (kg/m^2)					
Missing values	2511	35.05	488 109	53.92	<0.0001
<18.5	211	2.95	28 464	3.14	
18.5–24.9	2482	34.65	251 784	27.82	
25.0–29.9	1125	15.70	87 609	9.68	
≥30.0	835	11.66	49 212	5.44	

- *before pregnancy only*: women who redeemed at least one prescription before pregnancy, but not during or after pregnancy;
- *before and during pregnancy*: women who redeemed a prescription for the drug at least once nine to zero months before pregnancy and at least once during pregnancy, but not zero to nine months after delivery;
- *paused during pregnancy*: defined as women who redeemed the drug at least once nine to zero months before pregnancy, and at least once zero to nine months after delivery, but not during pregnancy;
- *during and after pregnancy*: defined as women who redeemed the drug at least once during pregnancy, and at least once zero to nine months after delivery, but not nine to zero months before pregnancy;
- *only during pregnancy*: defined as women who redeemed the drug at least once during pregnancy, but not nine to zero months before or zero to nine months after pregnancy;
- *only after pregnancy*: defined as women who redeemed the drug zero to nine months after delivery, but not zero to nine months before pregnancy or during pregnancy.

The most common package of levothyroxine redeemed in Denmark contains 100 pills with 50 μg levothyroxine

per pill. The daily dose is 50–200 μg, which is equivalent to a treatment period for each prescription of 25–100 days.

To estimate changes in exposure rates from 1997 to 2010, we explored the annual incidences of levothyroxine prescription redemptions.

SAS 9.2 (SAS Institute Inc., Cary, NC, USA) was used for managing data and for all statistical analyses. Adjusted chi-squared tests were applied to assess differences in basic characteristics between the exposed and unexposed groups of women. Linear regression was used to estimate changes in the rate of drug use during the study period.

Results

The maternal characteristics of exposed and unexposed women are compared in Table 1. Exposed women tended to be older ($p < 0.001$), to have a higher level of education ($p = 0.02$), to smoke less ($p < 0.001$) and to have a higher BMI ($p < 0.001$) than unexposed women. There was no difference in annual household income ($p = 0.16$) or parity ($p = 0.12$) between the exposed and unexposed groups.

Of the 912 342 pregnant women who had a live birth identified in the defined period, 7164 (0.79%) of them redeemed a levothyroxine prescription at least once during pregnancy. These women constitute the exposed cohort (Figure 1).

We also analyzed changes in redemption in relation to pregnancy. A total of 10 318 women (1.13% of all women) redeemed levothyroxine at least once during any of the three periods (nine to zero months before pregnancy, the 9 months during the pregnancy, and zero to nine months after pregnancy). Most (5380, 52.0%) redeemed the drug during all three periods. In all, 592 women (9.4% of those who had redeemed a prescription nine to zero months before pregnancy) stopped redeeming the drug during pregnancy and 139 women paused redemption during pregnancy (2.2% of those who had redeemed a prescription before pregnancy). The rate of women discontinuing treatment during pregnancy decreased during the study period from 18.5% in 1997 to 5.1% in 2010 ($p < 0.001$). A total of 2562 women (24.8% of those redeeming the drug in any of the three periods) redeemed the drug for the first time, zero to nine months after delivery. The rates of exposure from 1997 to 2010 are shown in Figure 2. The increase in exposure during the study period was linear ($\beta = 0.08$, $p < 0.05$; $r^2 = 0.97$), from 0.34% in 1997 to 1.39% in 2010.

Discussion

We identified a fourfold increase in levothyroxine use during the study period, from 0.34% to 1.39%. A total of 0.79% of the women in our cohort were exposed to levothyroxine at some point during their pregnancy and 0.28% of our cohort commenced levothyroxine treatment within 9 months after pregnancy.

A comparable study of the prevalence of levothyroxine exposure during pregnancy was done in Sweden (17) using the Swedish birth register and information on drug exposure from prescription registers and interviews during the first trimester of pregnancy. Overall, 1.16% of pregnant women used thyroid hormone. In a study based on the Collaborative Perinatal Project in the USA, which included information collected in the 1950s and 1960s, it was found that 1% of mother–child pairs were exposed to levothyroxine during the first trimester (18). These results also correspond closely with those of our study.

It has been estimated that up to 2.8% of women of reproductive age suffer from hypothyroidism (1,2). In 1991, Klein (1) found that 2.5% of pregnant women had elevated thyroid-stimulating hormone levels, which could indicate a hypothyroid state. Bjøro et al. (2) found that 1.5–2.8% of women of reproductive age were or had been

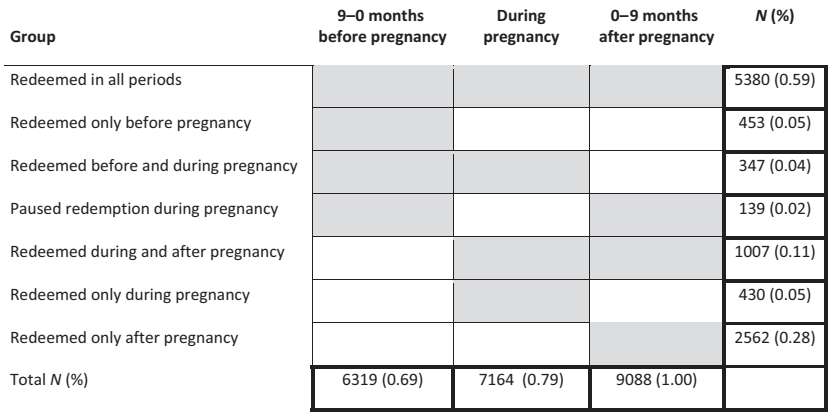

Figure 1. Redemption patterns of levothyroxine in relation to pregnancy. The gray area indicates redemption of a prescription for levothyroxine. The base of each column shows the number of exposed pregnant women for each period.

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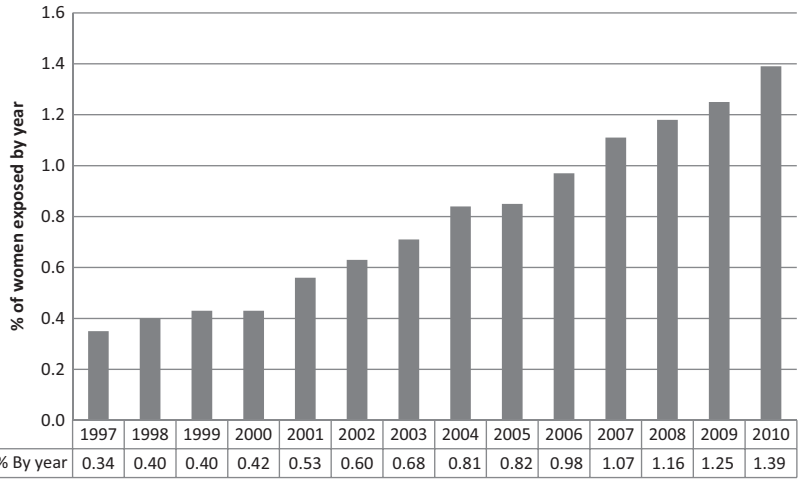

	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
% By year	0.34	0.40	0.40	0.42	0.53	0.60	0.68	0.81	0.82	0.98	1.07	1.16	1.25	1.39

Figure 2. Percentage of women redeeming a prescription for levothyroxine during pregnancy between 1997 and 2010 (n = 7164). The increase in exposure over time was linear ($\beta = 0.08$, $p < 0.05$; $r^2 = 0.97$).

receiving treatment for hypothyroidism. Compared with the aforementioned studies, our findings may suggest suboptimal treatment of hypothyroidism during pregnancy. Further research is needed to evaluate the potential consequences of this during pregnancy.

No national screening program had been set up to identify unrecognized thyroid disease in all pregnant women in Denmark during the study period, nor indeed is one currently running. Guidelines from 2008 recommend tracing and screening of relevant patients, comprising women with: a history of hyper- or hypothyroidism, postpartum thyroiditis or thyroidectomy; a family disposition to thyroid disease; goiter; thyroid antibodies or symptoms or clinical signs of thyroid disease; type 1 diabetes; other autoimmune disorders; fertility problems; previous radiation therapy of the head and neck region; prior history of preterm delivery (12). There has been no substantial change in the national recommendations during the study period that could explain the increase in the rate of redemptions of prescriptions for thyroid hormones. The first Danish national guidelines about the treatment of pregnant women with thyroid diseases was released in 2008, and so these could only have been effective during the last 3 years of the study period. Before 2008, only local recommendations for each clinic were available, although they were very similar to the 2008 national guidelines. Therefore, we do not believe that the introduction of the national guidelines explains the increase in the prevalence of prescription redemptions. This has been confirmed in a study by Granfors et al. (19), who reported that the recommendations are followed only to a limited extent, despite the implementation of the international guidelines. The medical profession may have become more aware of the potential for thyroid disease among pregnant women during the study period, which may have contributed to the increased exposure rates seen over time.

Several studies have shown that children born to mothers with inadequately treated hypothyroidism have lower scores in measures of intelligence, language ability, school performance, attention, and reading ability (5,6), and maternal hypothyroidism has been associated with severe obstetric complications (7–9). Therefore, the proper management of hypothyroidism during pregnancy is of utmost importance. This should involve initiating treatment with thyroid hormones as soon as possible to avoid the aforementioned complications. Studies addressing the risks associated with hypothyroidism during pregnancy, such as those mentioned above, were published just before and during the study period considered here. Knowing more about the importance of treatment may have focused attention more on the treatment benefits and thereby prompted the more frequent use of thyroid hormones during pregnancy. Disease rates (possibly due to changes in diagnostic criteria) might have increased over time and led to an increase in redemptions. Furthermore, maternal age at conception, which is associated with an increased risk of hypothyroidism, rose during the study period (20).

A quarter of women who had redeemed a prescription before, during and/or after their pregnancy had redeemed a prescription for the first time during the 9 months following pregnancy. This could be explained by the presence of postpartum thyroiditis, which occurs in approximately 3.3% of women after pregnancy in Denmark, which may give rise to a period of hypothyroidism

after delivery (21). We found that exposed women were generally older, had a higher level of education, smoked less and had a higher BMI than the unexposed women. The older age of exposed women could be explained by the increased risk of hypothyroidism with advancing age (20).

Guidelines of the American Thyroid Association, the Endocrine Society and the Danish Thyroid Association recommend that pregnant women with hypothyroidism should not merely maintain but rather increase the dose of their thyroid substitution therapy during pregnancy (10–12). Our results show that most women who redeemed prescriptions for levothyroxine before pregnancy continued the therapy during pregnancy, although some (9.4%) stopped redeeming the drug during pregnancy. This suggests that these pregnant women and their doctors may not adhere to the current guidelines that recommend continuation of thyroid substitution therapy during pregnancy, which may be a serious health issue for these women and their fetuses. However, our results indicate that the trend has changed over the years, since the rate of women discontinuing treatment decreased during the study period from 18.5% in 1997 to 5.1% in 2010.

To our knowledge there have been no previous studies that have sought a possible association between over-use of thyroid hormones and malformations. Use of levothyroxine during pregnancy has been associated with a slightly higher risk of malformations (17,22). Also, even though most recommendations aim to facilitate the benefits of treatment with levothyroxine in pregnant women with hypothyroidism, several studies have shown that women are reluctant to use any medications during pregnancy, even those that are probably harmless and potentially necessary (23,24). These arguments may be a complicating factor in the treatment of hypothyroidism during pregnancy and may help explain the potential suboptimal treatment of hypothyroidism during pregnancy.

Our study has two particular strengths. First, we analyzed prescription redemption data from all three trimesters of the pregnancy, rather than just the first. Secondly, we used information solely from nationwide registers, which made it possible to consider all pregnant women in Denmark who gave birth to a live baby. The registers are very complete; 97.5% of all redeemed prescriptions are recorded in the Danish National Prescription Register (15) and 99.7% of all births are registered in the Danish Medical Birth Registry (14). The use of these registers largely eliminates any selection bias, and since the information is collected prospectively rather than by interview or questionnaire, the risk of recall bias is also avoided. A limitation of register studies based on redeemed prescriptions is that they contain no information about adherence. We used redemption of a prescription as a surrogate measure of the ingestion of the prescribed drug. However, in reality, this may not be the case, which would tend to lead to the overestimation of exposure rates. However, when prescriptions are redeemed, especially when done so regularly, it is very likely that the drug is taken (25). Conversely, there is a risk of underestimating exposure if women redeemed the drug prescription outside the study period but actually took the drug during the period examined.

Conclusion

We used nationwide registers of all pregnancies of women in Denmark to determine the prevalence of redemption of prescriptions for levothyroxine and thereby to evaluate drug exposure in relation to pregnancy. The results show that fewer than 1% of women and their unborn children were exposed to levothyroxine during pregnancy. This proportion is significantly lower than the estimated rate of women with hypothyroidism (2.8%) found by earlier studies. These results may indicate lack of treatment of the disease during pregnancy. However, exposure increased fourfold from 0.34% in 1997 to 1.39% in 2010. Most women tended to continue their thyroid substitution therapy during pregnancy, but almost one in 10 women who had redeemed a prescription for the drug at least once zero to nine months before pregnancy did not do so during their pregnancy. A quarter of all women who redeemed a prescription in relation to pregnancy did so for the first time in the 9 months following pregnancy. Despite the increased use of levothyroxine during pregnancy, we believe that many women with hypothyroidism are not identified and are therefore not treated, which could be a serious health issue to these women and their fetuses. Further studies are needed to analyze whether there is an ongoing suboptimal treatment of hypothyroid pregnant women and the consequences of this.

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