Hyperthyroidism Incidence Fluctuates Widely in and Around Pregnancy and Is at Variance With Some Other Autoimmune Diseases: A Danish Population-Based Study

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Context: Hyperthyroidism in women of reproductive age is predominantly caused by Graves’ disease. Pregnancy associated changes in the immune system may influence the onset of disease, but population-based incidence rates in and around pregnancy have not been reported.

Objective: The objective of the study was to estimate the incidence of maternal hyperthyroidism (defined by redeemed prescription of antithyroid drugs) in and around pregnancy and to compare this with the incidence of other autoimmune diseases such as rheumatoid arthritis (RA) and inflammatory bowel disease (IBD).

Design: This was a population-based cohort study.

Setting: The study used the Danish nationwide registers.

Participants: The participants were women who gave birth to singleton liveborn children in Denmark from 1999 to 2008 (n = 403,958).

Main Outcome Measure(s): Incidence rates (IR) of maternal hyperthyroidism during a 4-year period beginning 2 years before and ending 2 years after the date when the mother was giving birth for the first time in the study period were measured.

Results: Altogether 3673 women (0.9%) were identified with an onset of hyperthyroidism from 1997 to 2010, and the overall IR of maternal hyperthyroidism was 65.0/100,000/year. The IR of hyperthyroidism in and around pregnancy varied widely and was high in the first 3 months of pregnancy (incidence rate ratio (IRR) vs the remaining study period: 1.50 (95% CI 1.09–2.06)), very low in the last 3 months of pregnancy (0.26 (0.15–0.44)), and reached the highest level 7–9 months postpartum [3.80 (2.88–5.02)]. The incidence variation in and around pregnancy was different for RA and IBD.

Conclusion: These are the first population-based data on the incidence of hyperthyroidism in and around pregnancy. The incidence of hyperthyroidism was high in early pregnancy and postpartum, whereas such particular pattern was not observed for other diseases of autoimmune origin. (J Clin Endocrinol Metab 100: 1164–1171, 2015)
against infections (2). The composition of immune cells is altered and both the number of T- and B-cells has been shown to decrease during pregnancy with a subsequent increase after birth (3). Moreover, the production of cytokines by T-helper cells is altered in pregnancy (4, 5), and there is usually a decline in the levels of circulating antibodies (6, 7).

The immunological adaptations in pregnancy and the rebound after birth may influence maternal development of autoimmune disease in and around pregnancy. Previous studies evaluating the risk of postpartum onset of Graves’ disease were based on the review of medical records in women referred to the hospital for the management of Graves’ disease (8–11). The postpartum period was considered a risk factor for onset of Graves’ disease in studies from Sweden (8), the United States (10), and Japan (9); whereas in a study from Italy (11) the authors concluded that the postpartum period was an overestimated risk factor. For onset of disease during pregnancy, no incidence data have been reported, but Amino et al (12) observed an aggravation of hyperthyroidism both in early pregnancy and postpartum in women with known Graves’ disease who were in remission prior to pregnancy.

The previous retrospective studies included a risk of selection bias, and population-based data are warranted. In Denmark, nationwide data on hospital diagnoses and redeemed prescriptions of drugs are registered, and the treatment of choice for newly diagnosed hyperthyroidism of Graves’ disease is antithyroid drugs (ATD). We used Danish nationwide data and identified incident cases of maternal hyperthyroidism from redeemed prescriptions of ATD in a 4-year period beginning 2 years before and ending 2 years after the birth of a liveborn child.

Autoimmune diseases tend to coexist in the same individuals (13). Rheumatoid arthritis (RA) is a chronic autoimmune disease (14). The incidence of RA peaks after the reproductive age (15), but it also affects younger age groups, and the postpartum period has been shown to be a risk factor for onset of the disease (16). Inflammatory bowel disease (IBD) is another autoimmune disease, which includes ulcerative colitis and Crohn’s disease (17). The incidence of IBD peaks in the reproductive age and how pregnancy influences IBD has mainly been investigated in women with known IBD prior to pregnancy (17). We included Danish nationwide data on the incidence of RA and IBD to evaluate if the observed perturbation in the incidence of hyperthyroidism in and around pregnancy is a potential general phenomenon for autoimmune diseases.

The etiology of an autoimmune disease is often considered a combination of both genetic and environmental factors and exposure to nongenetic factors may lead to the development of disease in susceptible individuals (18, 19). We observed that the postpartum period was a major risk factor for the onset of Graves’ disease and speculated whether the onset of disease would be influenced by maternal parity. If the postpartum period is a sufficient or strong factor for the development of disease in genetically disposed individuals, one may expect a tendency for disease onset to take place in the first postpartum period that the woman encounters.

Methods and Materials

Incidence of maternal hyperthyroidism

We performed 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. By linkage of the Danish Civil Registration System (20) and the Medical Birth Registry (MBR) (21) we identified all women who gave birth to ≥1 singleton liveborn child in Denmark between January 1, 1999 and December 31, 2008 and in the same period had no registration of multiple births.

We studied incident hyperthyroidism from age 15 to 45 years. In this age group, the predominant cause of hyperthyroidism is Graves’ disease (1) and in Denmark, first choice therapy for hyperthyroidism caused by Graves’ disease is always ATD. The time of onset of hyperthyroidism was defined by the date the first prescription of the ATD was redeemed from a Danish pharmacy. The Danish National Prescription Register (DNPR) (22) holds nationwide data on all redeemed prescriptions of drugs from Danish pharmacies since 1995 classified according to the Anatomical Therapeutic Chemical classification system (ATC), and we identified all prescriptions of the ATD (H03B) and thyroid hormone (H03A) redeemed between January 1, 1995 and up to 2 years after birth of the child.

Incident cases of hyperthyroidism were defined as women who redeemed a minimum of two prescriptions of ATD in the period from January 1, 1997 to December 31, 2010 and who had redeemed a minimum of two prescriptions of ATD within 1 year with a minimum of 30 days between the first and subsequent redeemed prescription(s). In addition to this, women identified with incident hyperthyroidism had no previous redeemed prescription(s) of thyroid hormones or ATD, no previous hospital diagnosis of hyperthyroidism (except for in the 3-month period prior to the first redeemed prescription of ATD), no previous hospital diagnosis of hypothyroidism, and no previous registration of thyroid surgery. Information on previous hospital diagnoses of thyroid disease and thyroid surgery was obtained from the Danish National Hospital Register (DNHR) (23), which holds nationwide data on all inpatient visits to any Danish Hospital since 1977, and all hospital outpatient visits since 1995. The diagnoses were classified according to the eighth revision of the International Classification of Disease (ICD-8) from 1977 to 1993 and the 10th revision (ICD-10) from 1994. We included information on all in- and outpatient visits with a diagnosis of hyperthyroidism, hypothyroidism, or thyroid surgery from January 1, 1977 to December 31, 2010 using ICD-8/-10 codes of hyper- and hypothyroidism as previously described in detail (24). Thyroid surgery was defined by ICD-8: 08060-08220 and ICD-10: BAA20-BAA60.

The overall incidence rate (IR) of maternal hyperthyroidism from 1997 to 2010 was estimated as the number of women with...
new onset of hyperthyroidism from 1997 to 2010 divided by the total number of women observed in the 14-year observation period and expressed per 100 000 women per year. For every pregnancy, information was available on the date the child was born, and we subsequently studied the 4-year period beginning 2 years before and ending 2 years after the birth of the child. The estimated date of pregnancy start was 9 months prior to the date the child was born. The IR of maternal hyperthyroidism was calculated in each 3-month interval in and around the woman’s first pregnancy in the study period and incidence rate ratio (IRR) with 95% confidence interval (CI) (95% CI) was calculated by comparison to the IR in the rest of the period from 1997 to 2010. The first pregnancy in the study period was chosen to ensure that each woman was included only once and that there would be no overlap between study periods in women with more than one childbirth.

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

The study was approved by the Danish Data Protection Agency.

Incidence of RA and IBD

To evaluate if the observed hyperthyroidism incidence variation in and around pregnancy applied in more general to autoimmune diseases, we included information on RA and IBD. Information on a diagnosis of RA (ICD-8: 712.19, 712.39, 712.59 and ICD-10: M05.0-M06.9) and IBD (ICD-8: 563.00–563.02, 563.19, 569.04 and ICD-10: K50.0-K51.9) was obtained from the DNHR. From the DNPR we obtained information on redeemed prescriptions of drugs used in the treatment of the diseases (ATC A07EA, A07EC, L04AX01 and L04AX03). We studied incident RA and IBD from ages 15–45 years, and disease onset was defined by the date of the first hospital visit with a diagnosis of RA or IBD. Incident RA and IBD were defined as a hospital diagnosis of RA or IBD with no previous registration of redeemed prescription of the drugs used in the treatment of the diseases. Similar to the method described for hyperthyroidism, the overall IR of RA and IBD from 1997 to 2010 in and around the woman’s first pregnancy in the study period was estimated.

Parity as a predictor of onset of hyperthyroidism

To evaluate if maternal parity was a predictor of onset of hyperthyroidism we studied not only the first pregnancy in the study period, but all the pregnancies leading to birth of a live born child from 1999 to 2008. The risk of early pregnancy (first 3 months) and postpartum (4–15 months after birth) onset in subsequent vs first-time pregnancies was evaluated in multivariate logistic regression including birth year of the child (4-year intervals), maternal age (< or ≥30 years), income (quartiles), origin (born in Denmark/not born in Denmark), residence (East/West Denmark), and cohabitation (married/not married). Adjusted odds ratio (aOR) with 95% CI was estimated using robust standard error to account for dependency between maternal multiple pregnancies. Information on covariates was obtained at the time of the child’s birth from the MBR and Statistic Denmark. Pregnancies with missing value on covariates were not included in the study (0.8%). We used information on maternal residence as a proxy for iodine intake. Denmark was previously iodine deficient with regional differences (moderate iodine deficiency in West Denmark, mild iodine deficiency in East Denmark). The mandatory iodine fortification of salt was introduced in the year 2000 and had increased urinary iodine to a lower recommended level in 2005–2006 (25). From the DNHR we obtained information on maternal smoking in the pregnancy.

Results

Incidence of maternal hyperthyroidism

Altogether 403 958 women were included in this analysis and 3673 (0.9%) were identified with onset of hyperthyroidism from 1997 to 2010 at a median age of 31.9 years [interquartile range (IQR): 27.7–36.1 years]. Women with hyperthyroidism tended to be older with a higher parity, and they were more often smoking and not born in Denmark (Table 1). The overall IR of maternal hyperthyroidism from 1997 to 2010 (horizontal line in Figure 1) was 65.0/100 000/y (95% CI 57.1–72.9/100 000/y). Among cases of incident hyperthyroidism, altogether 1508 women had onset of disease in the 4-year period from 2 years before to 2 years after birth of the first child in the study period. In this group of women, the median age at onset of disease was 31.1 year (IQR: 27.6–34.9 years). The IR of hyperthyroidism in and around pregnancy varied widely (Figure 1) and was high in the first trimester of pregnancy [IRR vs the rest of the study period: 1.50 (95% CI 1.09–2.06)], very low in the third trimester [0.26 (0.15–0.44)], and reached the highest level at 7–9 months postpartum [3.80 (2.88–5.02)].

Incidence of maternal RA

To evaluate if the incidence of fluctuation in and around pregnancy was specific to hyperthyroidism or applied in more general to autoimmune diseases, we investigated and included data on some other autoimmune diseases (Figure 2). In the period from 1997 to 2010, altogether 1011 of the women studied were identified with onset of RA at a median age of 32.9 years (IQR: 28.0–37.1 years), and the overall IR of RA was 17.9/100 000/y (95% CI: 13.7–22.0/100 000/y). Among incident cases of RA, 264 women developed RA in and around the first pregnancy in the study period at median age 31.2 years (IQR: 27.5–35.0 years). The incidence of RA was low in pregnancy and increased in the postpartum period (Figure 2).

Incidence of maternal IBD

Altogether 2543 of the women studied were identified with an onset of IBD from 1997 to 2010 at a median age of 29.4 years (IQR: 24.9–34.3 years) and the overall IR of IBD from 1997 to 2010 was 45.0/100 000/y (95% CI: 38.6–51.7/100 000/y). Among incident cases of IBD, 723
women developed IBD in and around the first pregnancy in the study period at median age of 29.2 years (IQR: 26.3–34.3 years). Compared with hyperthyroidism, much less incidence variation of IBD in and around pregnancy was observed and there was no statistically significant early pregnancy or postpartum surge (Figure 2).

Parity as a predictor of hyperthyroidism onset in early pregnancy and postpartum

The 403,958 women included gave birth to 610,166 children from 1999 to 2008 (range 1–7 children). When analyses were extended to include not only the first pregnancy but all pregnancies leading to the birth of a liveborn child in the study period, altogether 1,056 women had onset of hyperthyroidism in a postpartum period corresponding to 28.8% of the women identified with incident hyperthyroidism from 1997 to 2010. In the adjusted analyses, postpartum onset of hyperthyroidism was influenced by maternal parity. Compared with first-time pregnancies, the risk of postpartum onset was lower after a subsequent pregnancy [aOR: 0.84 (0.74–0.96) with similar result when additionally adjusting for maternal smoking (aOR: 0.81 (0.71–0.93)]. Onset of hyperthyroidism in early pregnancy (n = 154) was less frequent than postpartum onset and results of the multivariate analysis were less certain. Results (model including maternal smoking) suggested a higher risk of early pregnancy onset in subsequent vs first-time pregnancies, but the estimates did not reach statistical significance; aOR: 1.31 (0.90–1.91).

Discussion

Principle findings

This is the first population-based study on the incidence of maternal hyperthyroidism in and around pregnancy.
A wide incidence fluctuation was observed with a peak in early pregnancy followed by a sharp decrease in later pregnancy and the highest peak within the first year postpartum. Notably, this particular pattern was not seen, or was less prominent, for the two other autoimmune diseases studied.

Incidence of maternal hyperthyroidism in pregnancy

The two most common types of hyperthyroidism in pregnancy are gestational hyperthyroidism and Graves’ disease (26). Gestational hyperthyroidism is a nonautoimmune transient disorder in the first trimester of pregnancy caused by the early pregnancy peak in serum human chorionic gonadotropin (hCG). It is associated with hyperemesis gravidarum and the differential diagnosis from Graves’ hyperthyroidism may be difficult, but the presence of TRAb and the need for ATD favors a diagnosis of Graves’ disease (26).

Amino et al (12) studied women with Graves’ disease who were in remission prior to pregnancy and observed a transient increase in serum free T4 during 10–15 weeks of pregnancy in 18 of 41 pregnancies (12). A later study suggested that this phenomenon was caused by hCG (27). It can be speculated if the hCG mediated increase in thyroid hormone secretion in early pregnancy may increase the risk of developing Graves’ disease in susceptible women. It has been proposed that the state of thyrotoxicosis may by itself increase activity of Graves’ disease via the effect of thyroid hormone on the immune system (28). The lack of such early pregnancy peak for RA and IBD may favor this hypothesis.

Another possibility is that the increased incidence of Graves’ hyperthyroidism observed in early pregnancy was caused by a general tendency to generate TRAb. However, Tamaki et al (27, 29) found no early pregnancy increase in TRAb levels in women with known Graves’ disease who were in remission before the pregnancy. The possible role of parity and the mechanism behind the onset of hyperthyroidism in early pregnancy remains uncertain and needs to be addressed in further studies.

We aimed to study the incidence of Graves’ hyperthyroidism in pregnancy. We had no information on re-
sults of thyroid function tests or the presence of TRAb, but selection criteria were redeemed prescriptions of ATD. Among women with incident hyperthyroidism in the first trimester of pregnancy, 14 women also had a diagnosis of hyperemesis gravidarum. These women continued to redeem prescription(s) of ATD after the first trimester of pregnancy suggesting that they did not suffer from gestational hyperthyroidism. Graves’ disease is the predominant cause of hyperthyroidism in reproductive age (1), but we cannot exclude that some women suffered from nodular thyroid disease. In a Danish population-based study, thyrotoxicosis in women age 20–39 years was caused by nodular thyroid disease in 5.7% of the cases (1).

We defined the onset of hyperthyroidism by the day the first prescription of ATD was redeemed. We cannot exclude that the early pregnancy peak is partly explained by a lower threshold for the testing of thyroid function in early pregnancy and that the women suffered from undiagnosed hyperthyroidism prior to the pregnancy. We observed a significant decrease in the incidence of both hyperthyroidism, RA, and IBD in the period prior to pregnancy. This observation could possibly be confounding by treatment, that is, women with onset of the disease had low fertility or refrained from being pregnant.

**Incidence of maternal hyperthyroidism postpartum**

Thyrotoxicosis in the postpartum period is mainly caused by thyroiditis or Graves’ disease. We find it unlikely that the patients in our study suffered from thyroiditis. Thyrotoxicosis caused by thyroiditis should not be treated with ATD (26), and this transient disorder most often appears in the very early postpartum period (30, 31), where no increase in the initiation of ATD therapy was observed in our study. The high incidence of hyperthyroidism postpartum that we observed is in line with study conclusions from Sweden (8), Japan (9), and the United States (10), where 40–45% of new onset Graves’ disease in parous women occurred in the postpartum period. In the study from Italy (11), the frequency of postpartum onset in parous women of childbearing age was 20%, but the authors questioned the postpartum period as a risk factor for the onset of Graves’ disease. All previous studies were retrospective and clinic based with a risk of referral bias. Our study was population-based and included information on subsequent pregnancies after the onset of Graves’ disease. The referral rate to a specialized hospital unit for management and treatment of hyperthyroidism is high in young women in Denmark (32).

The mechanisms involved in the onset of Graves’ disease postpartum are thought to be related to the rebound of the immune system after pregnancy (33, 34). There is a gradual increase in the levels of TRAb postpartum, but other immunological mechanisms may also be involved (29). We observed that the risk of postpartum onset was higher after first-time pregnancies. This finding may suggest that in genetically disposed women, the first postpartum period that the woman encounters is a sufficient factor for the development of disease. However, further studies are needed to clarify the association with parity. We defined postpartum onset as the period ranging from 4 to 15 months postpartum to take into account a possible time span from onset of symptoms to redeemed prescription of ATD.

The incidence pattern for RA and IBD was different from what we observed for hyperthyroidism. Similar to hyperthyroidism, the incidence of RA was low during the pregnancy and increased postpartum. This finding is in line with previous studies showing that both onset of RA and known RA seem to ameliorate during pregnancy and aggravate after birth (16, 35). However, no early pregnancy peak was observed and the postpartum peak was lower than for hyperthyroidism. How pregnancy influences IBD has been evaluated in women with known IBD prior to pregnancy (17). In general, the rate of relapse has been considered similar in pregnant and nonpregnant women with no increased risk of relapse in the postpartum period (17), but a recent European study found an increased risk of relapse in ulcerative colitis during pregnancy and postpartum (36). An increased risk of coexisting RA and IBD in Graves’ disease has been reported (13) and the diseases are of autoimmune origin, but it appears from our observations that different autoimmune diseases may interact differently with pregnancy. Interestingly, a recent analysis of the sex differences observed in various autoimmune diseases also showed rather larger differences between female to male ratios and the female predominance in Graves’ disease was similarly found in RA, but not in IBD (37). The drugs used for the treatment of RA and IBD also have other indications and we had to define onset of disease from the first registered hospital diagnosis, but it is to be expected in Denmark that women of reproductive age are referred to a specialized hospital unit for definitive diagnosis, management, and treatment of the diseases. Adding to this, a diagnosis of RA and IBD registered in the DNHR has been found to be sufficient for epidemiologic studies (38, 39), and the overall incidence of RA and IBD that we observed in women of reproductive age were in line with previous reports in which medical records of individual cases were reviewed according to diagnostic classification systems (15, 40).

**Methodological comments**

The study was population-based, but selection of study participants was made from the birth of a liveborn child.
Women with multiple births were not included and the exclusion of women with intermediate pregnancies not leading to the birth of a liveborn child (pregnancy loss) did not change results.

We used the DNPR to obtain information on redeemed prescriptions of ATD and the validity of this register is considered high (22). Since the DNPR was initiated in 1995, we only had information on hospital diagnoses to ascertain previous thyroid dysfunction; however, we included a time period of 2 years from the start of prescription registration to exclude possible prevalent cases, and the number of women identified with incident hyperthyroidism from 1997 who had been treated with ATD before 1995 is expected to be low.

We calculated pregnancy start by subtracting 9 months from the day the child was born. Results were similar when we excluded pregnancies with a gestational age at birth <39 or >41 weeks. Loss to follow-up due to maternal emigration or death was expected to be low and the women were not censored in the main analyses. When maternal emigration and death during the observation period were taken into account, the overall IR was similar. To exclude a possible interference by previous or subsequent pregnancies, sensitivity analyses were restricted to women who were nulliparous prior to January 1, 1999 and to women who only gave birth once during the study period. After such restrictions, the incidence pattern in and around pregnancy remained similar.

In this register-based study we had no access to results of thyroid function testing or thyroid antibody measurements. As discussed in detail, the variations observed in the incidence of hyperthyroidism are likely to be caused by Graves’ disease. However, we cannot exclude that some cases had been inappropriately treated with ATD or suffered from other types of hyperthyroidism.

**Conclusion**

The incidence of maternal hyperthyroidism varied widely in and around pregnancy and both early pregnancy and the postpartum period were associated with an increased risk of onset of hyperthyroidism. More studies are needed to corroborate an early pregnancy incidence peak of Graves’ hyperthyroidism. Notably, the incidence pattern appeared specific for hyperthyroidism when compared to RA and IBD, but further studies of autoimmune thyroid disease and other autoimmune disorders are needed to clarify the interaction between pregnancy and onset of disease and the possible differential mechanisms involved.

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