Pregnancy outcomes after fetal exposure to antithyroid medications or levothyroxine

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Abstract

Aim: To investigate whether fetal exposure to antithyroid drugs (ATD) and levothyroxine affects gestational age (GA), birth weight, birth length, head circumference and prevalence of congenital anomalies.

Methods: Cohort of all pregnancies from GA 12 weeks recorded in Danish registries from 1995–2010. Exposure was having a prescription for ATD or levothyroxine from 91 days before to 91 days after pregnancy start (n = 8318). The reference group was pregnant women without exposure of ATD or levothyroxine (n = 969 303). A subpopulation was linked to the Danish EUROCAT congenital anomaly register.

Results: Overall 0.66% of the pregnant women had a prescription for levothyroxine and 0.19% had a prescription for ATD during the exposure period. There was no difference in proportion of live births compared to non-exposed pregnancies, but infants exposed to ATD were more often born very preterm (1.99% versus 0.94% Odds Ratio 2.04, 95% CI 1.46 – 2.86) and had higher infant mortality (Odds ratio 2.37, 95% CI 1.42 – 3.94). Infants exposed to ATD were more likely to have low birth weight and length for GA (Odds ratios 1.29 (1.12 – 1.50) and 1.40 (1.17 – 1.66). There was no difference in head circumference for the 3 exposure groups. Prevalence of congenital anomalies was the same for exposed and non-exposed pregnancies.

Conclusion: Fetal exposure to ATD resulted in lower GA, birth weight, length and higher infant mortality. Treatment for hypothyroidism had no significant impact on these variables. There was no difference in prevalence of congenital anomalies.

1. Introduction

Maternal hyper- and hypothyroidism are two common endocrine disorders in pregnancy. Hyperthyroidism has a prevalence of 0.1–0.4%, whereas hypothyroidism has a prevalence between 0.4 and 3% [1–4]. A recent study has found an increase in the number of first-time diagnoses of thyroid dysfunction during pregnancy in Danish women since 1995 [5].

Hypothyroidism is classified as overt or subclinical hypothyroidism. Overt hypothyroidism is defined as symptomatic thyroid deficiency because of low free thyroxine hormone and elevated thyroid stimulating hormone (TSH). Subclinical hypothyroidism has no or only few expressed symptoms. However there is biochemical evidence of thyroid hormone deficiency with a normal concentration of free thyroxine and elevated TSH. Symptoms of hypothyroidism are weight gain, constipation, fatigue, muscle cramps and weakness, cold intolerance and dry skin [2].

Graves’ disease is the most common cause of hyperthyroidism. It is an autoimmune disease with elevated T4 and low TSH, which is a result of an overstimulation of the thyroid by circulating thyrotrophin receptor stimulating antibodies (TRAb). The major symptoms are palpitations, tachycardia, heat intolerance, weight loss, hand tremor and eye symptoms [3].

Both disorders, if untreated during pregnancy, are associated with an increased risk of preterm birth [5]. Untreated hypothyroidism has further been associated with intrauterine growth restriction and fetal death [5]. Other studies have shown increased risk of miscarriage, stillbirth and intrauterine growth restriction in relation to hyperthyroidism [3]. Untreated hypothyroidism in pregnancy has been associated with increased risk of congenital anomalies, miscarriage, preterm birth, low birth weight and perinatal mortality [4].

Hypothyroidism has been associated with increased admission of the newborn to neonatal intensive care and increased perinatal morbidity and mortality [2]. Furthermore previous studies have shown effects on fetal neurodevelopment such as lower IQ levels and developmental delay such as cognitive impairment [2].

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Hyperthyroidism is treated with antithyroid drugs (ATD) which all cross the placenta [1]. The recommended medications for treatment of hyperthyroidism are methimazole (MMI), its prodarg carbimazole (CMZ) and propylthiouracil (PTU) [6]. Treatment for hypothyroidism is hormone replacement therapy with levothyroxine.

The purpose with this study was to investigate if fetal exposures to ATD or levothyroxine have impact on gestational age (GA), birth weight, birth length and head circumference. Furthermore, we wanted to investigate whether first trimester exposure to these medications increases the risk of congenital anomalies.

2. Methods and materials

2.1. Study population and design

We identified all pregnancies reaching a GA of at least 12 weeks, recorded as a live birth or stillbirth in the Danish Medical Birth Registry or as miscarriage or termination of pregnancy in the National Patient Register (DNPR). Included were pregnancies with date of start of last menstrual period (estimated based on GA) later than March 1st 1995 and pregnancy end date earlier than December 31st 2010. The unique personal identification number assigned to all Danish residents was used to link the pregnancy records to registry data on maternal education and residency history, as well as history of diabetes or epilepsy. Women not resident in Denmark for at least one year before last menstrual period (LMP) were excluded, as were women with a diagnosis of epilepsy or diabetes, or a record of prescription of medications for these diseases.

2.2. Exposure to ATD and hormone therapy

The DNPR contains data on all prescribed medication redeemed from Danish pharmacies since 1995. The data of prescriptions includes the patient’s personal identification number and the type of medication prescribed according to the Anatomical Therapeutic Chemical (ATC) classification system.

The exposure of interest in this study was redemption of at least one prescription in the time interval from 91 days before to 91 days after start of LMP. The medications of interest were MMI (ATC H03BB02), CMZ (ATC H03BB01), PTU (ATC H03BA02) and levothyroxine (ATC H03AA01). Only 2 were registered with liothyronine sodium (ACT H03AA02). Pregnancies were excluded if there was a prescription in the second or third trimester of pregnancy, but not in the exposure period. Two exposure groups were defined: Those exposed to medication for treatment of hyperthyroidism (MMI, CMZ, PTU) and those to medication for treatment of hypothyroidism (levothyroxine).

2.3. Outcomes

Pregnancy outcome was categorised as live birth, stillborn after 22 weeks, miscarriage earlier than 22 weeks and termination of pregnancy. Infant death was defined as the infant having a record in the registry of causes of death before 1 year of age. Birth weight, length and head circumference are recorded in the Birth Registry for live births (head circumference only from 1997). For very preterm births at less than GA 32 weeks, outliers (observations with > 1.5 IQR distance from the quartiles) for these variables were excluded. For births of GA 32 and older, extreme outliers were excluded (observations with > 3 IQR distance from the quartiles).

For the subpopulation resident in the county of Funen, we linked to information on congenital anomalies from the Danish EUROCAT congenital anomaly register [7].

2.4. Statistical analysis

The differences between the exposed and non-exposed pregnant women were tested with likelihood ratio χ²-tests. Adjusted odds ratios were estimated by logistic regression, adjusting for maternal age, education, parity and year of LMP.

The software used was SAS 9.3. The significance level was set to 5%.

3. Results

Among Danish pregnancies from 1995 to 2010, 1,026,261 were included from start. Exclusions are described in Fig. 1. Exclusion of outliers removed 3825 observations, 0.37% of the total. For 268 the mother redeemed prescriptions for medications for both hyperthyroidism and hypothyroidism; these observations were excluded. The final study population included 977,621 pregnancies: 969,303 unexposed to thyroid medications, 6475 pregnancies exposed to levothyroxine (0.66% of total) and 1843 pregnancies exposed to ATD (0.19%). Among the pregnancies exposed to ATD 64.4% were exposed to MMI/CMZ and 46.0% were exposed to PTU.

In total, 56.1% of the exposed women had a hospital diagnosis for thyroid disease of which 51.0% were diagnosed with hypothyroid disease and 9.3% with hyperthyroid disease.

Table 1 shows maternal characteristics and outcome of the pregnancies. Mothers with a prescription for thyroid medicines were older than...
non-exposed women \( (p < 0.0001) \), gave birth later in the study period \( (p < 0.0001) \) and had higher parity \( (p < 0.0001) \). Women with prescriptions for medications for hypothyroidism were more likely to have at least a bachelor’s degree than the control group, whereas women with prescriptions for hypothyroidism drugs were more likely to have only compulsory education. There was no statistically significant difference in birth outcome. Prescriptions exposed to ATD or levothyroxine resulted in a live birth in 95.5 and 95.8% of cases respectively, compared to 96.1% for the control group.

Table 2 shows distribution of GA for live born infants, risk of infant death and risk of having birth weight, length or head circumference below the 10th percentile for GA. The pregnancies exposed to MMI/CMZ and PTU had a higher proportion of very preterm born infants (GA < 32 weeks) \( (\text{Odds Ratio} 2.04, 95\% \text{ CI} 1.46–2.86) \) and similarly of preterm infants with GA 32–26 weeks \( (\text{Odds Ratio} 1.50, 95\% \text{ CI} 1.26–1.78) \). This group were also more likely to have birth weight and birth length below the 10th percentile for gestational age \( (\text{Odds Ratios} 1.29, 95\% \text{ CI} 1.12–1.50 \text{ and } 1.40, 95\% \text{ CI} 1.17–1.66 \text{ respectively}) \).

Women exposed to hypothyroidism medications were not more likely to give birth preterm or have infants with weight, length or head circumference below the 10th percentile for GA.

A sensitivity analysis excluding women without prescriptions for levothyroxine or ATD in the second or third trimester of pregnancy \( (5\% \text{ and } 31\% \text{ respectively}) \) did not change the overall results and conclusions regarding preterm birth, weight, length and head circumference.

First-year mortality was higher for infants of mothers treated for hyperthyroidism \( (\text{Odds Ratio} 2.37, 95\% \text{ CI} 1.42–3.94) \). No significant difference in mortality was found for infants of mothers with hypothyroidism \( (\text{Odds Ratio} 1.03, 95\% \text{ CI} 0.67–1.56) \).

For the women in the Funen subpopulation, 742 pregnancies were exposed to thyroid drugs. Of these 623 were exposed to levothyroxine and 138 to ATD. The Funen EUROCAT registry had records of major congenital anomaly for 14 of these pregnancies from mothers treated for hypothyroidism \( (\text{Fig. 2}) \). Three had records of ventricular septal defects.

There were two records each of clubfoot and cystic hygroma \( (\text{Table 3}) \). The proportion of major congenital anomalies was 2.50\% \( (95\% \text{ Clopper-Pearson CI} 1.35–3.79) \) for infants of mothers with hypothyroidism compared to the control population with a prevalence of 2.54\% \( (p = 0.64) \). Among the 138 pregnancies exposed to ATD there were two records of major congenital anomalies in the EUROCAT registry, one exposed for MMI and one exposed to PTU. One infant was multiple malformed (hydrocephalus and CHD) and one had an oral cleft.

### 4. Discussion

This population-based study defines exposure based on redemption of prescriptions of ATD and levothyroxine. To our knowledge, this is the first study based on prescriptions, which increases the size of the exposed group as only 56.1\% of the exposed had a hospital diagnosis. Only one other study was based on prescriptions, but this study examined only congenital anomalies and pregnancy complications \( [8] \). A Danish study included redeemed prescriptions, but only for pregnant women with a hospital diagnosis of thyroid disease and not those patients only seen by their general practitioner \( [9] \). Other studies of

### Table 1

<table>
<thead>
<tr>
<th>Description of the study population – pregnancies from GA 12 weeks 1995 to 2010.</th>
<th>Not exposed</th>
<th>Hyperthyroidism</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
</tr>
<tr>
<td>Total</td>
<td>969,303</td>
<td>100</td>
<td>1843</td>
</tr>
<tr>
<td>Maternal age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Older than 35 years</td>
<td>131,759</td>
<td>13.6</td>
<td>393</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>29.1 (4.9)</td>
<td>30.6 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Primiparous</td>
<td>416,826</td>
<td>43.0</td>
<td>631</td>
</tr>
<tr>
<td>Maternal education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compulsory education</td>
<td>174,760</td>
<td>18.0</td>
<td>386</td>
</tr>
<tr>
<td>Upper secondary or vocational training</td>
<td>392,651</td>
<td>40.5</td>
<td>688</td>
</tr>
<tr>
<td>Bachelor (BA) or more</td>
<td>387,977</td>
<td>40.0</td>
<td>744</td>
</tr>
<tr>
<td>Missing</td>
<td>13,915</td>
<td>1.4</td>
<td>15</td>
</tr>
<tr>
<td>Year of last menstrual period</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1995–2000</td>
<td>385,777</td>
<td>39.8</td>
<td>528</td>
</tr>
<tr>
<td>2001–2005</td>
<td>318,093</td>
<td>32.8</td>
<td>715</td>
</tr>
<tr>
<td>2006–2010</td>
<td>265,433</td>
<td>27.4</td>
<td>600</td>
</tr>
<tr>
<td>Pregnancy outcome</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Live birth</td>
<td>931,234</td>
<td>96.1</td>
<td>1760</td>
</tr>
<tr>
<td>Induced termination</td>
<td>9244</td>
<td>1.0</td>
<td>24</td>
</tr>
<tr>
<td>Miscarriage &lt; 22 weeks</td>
<td>24,137</td>
<td>2.5</td>
<td>46</td>
</tr>
<tr>
<td>Stillborn ≥ 22 weeks</td>
<td>4688</td>
<td>0.5</td>
<td>13</td>
</tr>
</tbody>
</table>

\(^a\) Likelihood ratio \( \chi^2 \)-test.

### Table 2

<table>
<thead>
<tr>
<th>Characteristics of live born infants from the three study groups.</th>
<th>Not exposed</th>
<th>Hyperthyroidism</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>OR (95% CI)(^a)</td>
</tr>
<tr>
<td>Total live births</td>
<td>931,234</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>Infant deaths within first year of life</td>
<td>3360</td>
<td>0.4</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Gestational age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 32 weeks</td>
<td>8798</td>
<td>0.9</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>32–36 weeks</td>
<td>50,355</td>
<td>5.4</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>≥ 36 weeks</td>
<td>872,081</td>
<td>93.7</td>
<td></td>
</tr>
<tr>
<td>Birth weight below 10th percentile for GA</td>
<td>91,071</td>
<td>9.8</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Birth length below 10th percentile for GA</td>
<td>56,314</td>
<td>6.0</td>
<td>1 (ref)</td>
</tr>
<tr>
<td>Head circumference below 10th percentile for GA</td>
<td>41,911</td>
<td>4.5</td>
<td>1 (ref)</td>
</tr>
</tbody>
</table>

\( \text{GA} \) = gestational age.

\(^a\) Adjusted for year of LMP, maternal age, parity and education.
maternal exposure of ATD and levothyroxine looked at women with a hospital diagnosis [5].

The mothers with prescriptions for ATC or levothyroxine were older and had higher parity, which can be explained by thyroid disease prevalence increasing with age [10].

No difference in infant mortality was found in this study after exposure with medication treatment for hypothyroidism. After exposure with ATD the infant mortality rate was significantly increased. This is likely to be explained by the increased proportion of preterm births. Other studies have shown increased infant mortality if untreated hyperthyroidism, which supports our data even though we assume our population are well treated [3].

Infants of mothers treated for hyperthyroidism were significantly more likely to be born preterm or very preterm, and to have low birth weight and length for GA. Lower median BW and GA at delivery was further found in a study after PTU exposure [10,11]. However, exposure to MMI had no impacts on BW [11]. The same study found that general ATD exposure resulted in low BW, increased risk of preterm birth and small for gestational age infants, which is supported by our data.

A recent Danish study found that both hypothyroidism and hyperthyroidism were associated with increased risk of preterm birth. These pregnant women, however, were not exposed to medication and the inclusion criterion was first-time diagnosis of a thyroid disease before, during or after pregnancy [5]. In the same population, maternal hypothyroidism was associated with high BW and hyperthyroidism with low BW of the infants [5].

To our knowledge, no previous studies have looked at ATD exposure and the impact on head circumference. Only one study shows that levothyroxine exposure in early pregnancy decreases head circumference [12]. Other studies have pointed that hypothyroidism might be associated with lower IQ and neurodevelopmental problems [2,12,13]. We could not detect an effect of thyroid disease on head circumference, but this study does not include information about further cognitive development of the infants.

A rather high percentage of women with ATD prescriptions early in pregnancy did not have a prescription in the second or third trimester (31%). However, these women may have continued to take the medication throughout pregnancy. As it is generally recommended to reduce the dose of ATD medication during pregnancy, a prescription of 100 tablets may last for 200 days. Further 10% women with prescriptions for ATD had a preterm birth and therefore less days in pregnancy for exposure.

Our study did not find a higher proportion of major congenital anomalies in the Funen population for pregnancies with exposure to levothyroxine, including validated data from the EUROCAT congenital anomaly registry. The spectrum of congenital anomalies was comparable to the background population with congenital heart defects (CHD) as the most frequent group. The number of malformed cases was too small for statistical analyses of individual subgroups of anomalies and for pregnancies exposed to ATD. The most common congenital anomaly described after MMI/CMZ exposure, aplasia cutis [1], was not found in our study with pregnant women in Funen County exposed to ATD medications. Others have shown increased risk of CHD with untreated hyperthyroidism [3,14]. No direct link between ATD exposure and heart defects has been found [14].

The ATD MMI and CMZ have been shown to possibly have teratogenic effects and may result in MMI/CMZ embryopathy [1]. This was stated for the first time in 1972, but no exact evidence has been given [6]. Congenital anomalies after PTU exposure seem to be less severe than for MMI and CMZ [6]. Exposure to PTU in uterus has been reported with maternal liver failure and cases of aplasia cutis and choanal atresia [1]. Recent study has shown that PTU exposure is associated with a lower risk of congenital anomaly than MMI/CMZ [1]. Other studies have shown that the livebirth prevalence of congenital anomalies after in utero exposure to PTU is within the expected range and with no increased risk of mental retardation [11,15]. Similar studies showed no increased risk of congenital anomalies after MMI exposure [10].

Recent Danish studies found that PTU and MMI/CMZ exposure resulted in higher rates of congenital anomalies in the urinary system, and face and neck region after PTU exposure only [1]. These questions the current guidelines that recommend pregnant women should be switched from MMI/CMZ to PTU in early pregnancy because MMI might be teratogen [1,9,17]. However, the Danish study (and many other studies) were based on livebirths only, without the most severe congenital anomalies resulting in TOPPA. Further validity of the data on congenital renal anomalies in the discharge database was limited [18] and oral clefts were grouped together with respiratory anomalies. There is no clear evidence of the best drug of choice for treatment of hyperthyroidism in the first trimester of pregnancy [1,14–17].

### 4.1. Strength and limitations

The strength of our study is the population-based design and based on prescriptions and not hospital diagnosis, which enlarges the investigated study population. The information about redeemed prescriptions was obtained from Danish registers, eliminating recall bias. We did not have information on daily dose of medicine and we do not know whether the women actually took the medicine. But the recommended daily dose of medicine varies only for levothyroxine, and women with a chronic disease may be assumed to take the medication for it. Furthermore the compliance for Danish women has earlier been found high [1]. It is a limitation that the congenital anomaly data was from a rather small subpopulation.
5. Conclusion

Pregnant women with medical treatment for a thyroid disease are older and have higher parity compared to the background population. The infants of mothers treated for hyperthyroidism have lower GA, BW and birth length and higher infant mortality. The treatment of hypothyroidism had no significant impact on these outcomes, and the infants had no increased mortality compared to the control population with no exposure. Our small sub-study population gave no evidence of an increased risk of major congenital anomalies after exposure with levothyroxine.

Pregnant women with hyperthyroidism need optimal management from pre-pregnancy planning to close monitoring of their disease and pregnancy throughout the pregnancy period.

References