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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.

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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 hyperthyroidism 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 prodrug 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 (ACT H03BA02) and levothyroxine (ACT H03AA01). Only 2 were registered with liothyronine sodium (ACT H03AA02) exposure and these are pooled with the levothyroxine group. 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 χ^2-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

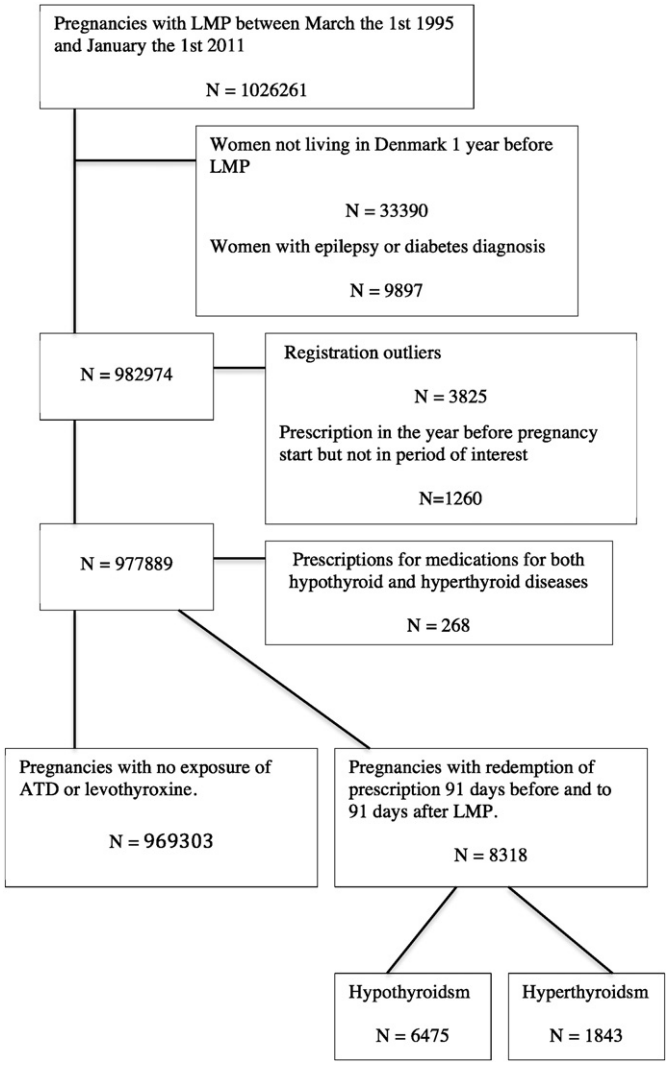

Fig. 1. Flowchart illustration of the selection of exposed pregnancies and the exclusions.

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