Spontaneous Abortion, Stillbirth and Hyperthyroidism: A Danish Population-Based Study

Stine Linding Andersen\textsuperscript{a, b} Jørn Olsen\textsuperscript{c} Chun Sen Wu\textsuperscript{c} Peter Laurberg\textsuperscript{a, b}

\textsuperscript{a}Department of Endocrinology, Aalborg University Hospital, and \textsuperscript{b}Department of Clinical Medicine, Aalborg University, Aalborg, and \textsuperscript{c}Section for Epidemiology, Department of Public Health, Aarhus University, Aarhus, Denmark

Abstract

Objectives: Pregnancy loss in women suffering from hyperthyroidism has been described in case reports, but the risk of pregnancy loss caused by maternal hyperthyroidism in a population is unknown. We aimed to evaluate the association between maternal hyperthyroidism and pregnancy loss in a population-based cohort study. Study Design: All pregnancies in Denmark from 1997 to 2008 leading to hospital visits (n = 1,062,862) were identified in nationwide registers together with information on maternal hyperthyroidism for up to 2 years after the pregnancy [hospital diagnosis/ prescription of antithyroid drug (ATD)]. The Cox proportional hazards model was used to estimate adjusted hazard ratio (aHR) with 95% confidence interval (CI) for spontaneous abortion (gestational age < 22 weeks) and stillbirth (≥ 22 weeks), reference: no maternal thyroid dysfunction. Results: When maternal hyperthyroidism was diagnosed before/during the pregnancy (n = 5,229), spontaneous abortion occurred more often both in women treated before the pregnancy alone [aHR 1.28 (95% CI 1.18–1.40)] and in women treated with ATD in early pregnancy [1.18 (1.07–1.31)]. When maternal hyperthyroidism was diagnosed and treated for the first time in the 2-year period after the pregnancy (n = 2,361), there was a high risk that the pregnancy under study had terminated with a stillbirth [2.12 (1.30–3.47)]. Conclusions: Both early (spontaneous abortion) and late (stillbirth) pregnancy loss were more common in women suffering from hyperthyroidism. Inadequately treated hyperthyroidism in early pregnancy may have been involved in spontaneous abortion, and undetected high maternal thyroid hormone levels present in late pregnancy may have attributed to an increased risk of stillbirth.

Introduction

Pregnancy loss is an adverse outcome of pregnancy in which conception does not result in a live-born child [1]. Early pregnancy loss (spontaneous abortion) is in Denmark defined as the spontaneous termination of pregnancy before gestational week 22 [2]. Of clinically recognized pregnancies, 10–15% terminate with spontaneous abortion [1]. Late pregnancy loss (stillbirth) is in Den-
Hyperthyroidism in women of reproductive age is most often caused by Graves’ disease with autoimmunity against the thyroid-stimulating hormone (TSH) receptor [3, 4]. About 1% of pregnant women have been treated before conception or are being treated during pregnancy for Graves’ hyperthyroidism [3, 4]. Untreated or inadequately treated hyperthyroidism in pregnancy may lead to both maternal and fetal complications [5–7], and it is generally agreed that the disease should be carefully controlled and adequately treated in pregnancy [8–10].

Hyperthyroidism and Pregnancy Loss

We a priori speculated on possible mechanisms which could cause an association between maternal hyperthyroidism and pregnancy loss including (a) inadequate treatment of known hyperthyroidism in pregnancy (an association with hyperthyroidism diagnosed before/during the pregnancy would be expected), (b) undetected and untreated hyperthyroidism in pregnancy (an association with hyperthyroidism diagnosed for the first time after the pregnancy would be expected), or (c) thyroid autoimmunity/genetics (an association with hyperthyroidism diagnosed before/during and also after the pregnancy would be expected).

The treatment of choice for hyperthyroidism in pregnancy is antithyroid drugs (ATDs) [8–10]. We recently reported that use of methimazole (MMI)/carbimazole (CMZ) and also propylthiouracil (PTU) in early pregnancy were associated with an increased risk of birth defects in live-born children [14, 15]. Considering this, it can be speculated whether ATD treatment in early pregnancy could be associated with an increased risk of pregnancy loss, e.g. severe birth defects not leading to the birth of a live-born child. Thus, in the group of pregnancies where maternal hyperthyroidism was diagnosed before/during the pregnancy, we subsequently identified pregnancies (a) exposed to ATD in early pregnancy and (b) pregnancies in which the mother had been treated for hyperthyroidism before the pregnancy alone, and we compared the risk of spontaneous abortion in these groups.

Materials and Methods

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 the nationwide registers. All data were linked in Statistic Denmark and were made available only in encrypted form. The study was approved by the Danish Data Protection Agency.

We identified all clinically recognized pregnancies in Denmark from January 1, 1997 to December 31, 2008, leading to in- or outpatient hospital visit (n = 1,062,862) with a diagnosis of spontaneous or induced abortion, molar or ectopic pregnancy, stillbirth or live birth.

Definition of Pregnancy Outcomes

The Danish National Hospital Register (DNHR) [16] holds data on all inpatients since 1977 and all in- and outpatient visits since 1995. Diagnoses were coded according to the 8th revision of the International Classification of Disease (ICD-8) from 1977 to 1993 and ICD-10 from 1994 and onwards. We identified all hospital visits with a diagnosis of spontaneous abortion (O02.0–O03.9), induced abortion (O04.0–O05.2, O05.5–O06.9), induced abortion due to fetal disease (O05.3–O05.4), molar and ectopic pregnancy (O00.0–O01.9), and births (O080.0–O084.9) including information on whether it was a singleton (Z37.0–Z37.1) or multiple (Z37.2–Z37.7) stillbirth or live birth.

Information on gestational age (completed weeks plus days calculated from the first day of the last menstrual period) was obtained from the DNHR. Ultrasound verification of gestational age was increasingly used during the years of the study and was offered to all pregnant women in Denmark from the year 2004 [17, 18]. We included all pregnancies with a registered gestational age in the range from 2 to 45 completed weeks at the time of pregnancy termination. We used both the registered hospital diagnosis and the gestational age to define the outcomes under study. Spontaneous abortion was defined as a hospital diagnosis of spontaneous abortion with a registered gestational age <22 completed weeks [2]. Stillbirth was defined as a hospital diagnosis of stillbirth with a registered gestational age ≥22 completed weeks [2]. Live births were included when the hospital diagnosis was live birth and the registered gestational age was ≥22 completed weeks. Pregnancies with missing or inconsistent registration of gestational age were excluded from the main analyses (1.4%).

In Denmark, the definition of stillbirth was changed from ≥28 to ≥22 gestational weeks in the year 2004 [19]. Thus, the birth of a child with no signs of life in gestational weeks 22–27 would have been registered as a spontaneous abortion in the period from 1997 to 2003. These pregnancies were excluded from the main analyses because information on variables used for the analyses of stillbirth was not available. Information on the type of pregnancy (singleton/multiple) and maternal smoking status in pregnancy was only registered when the pregnancy terminated with a stillbirth or a live birth and not when the pregnancy was diagnosed as a spontaneous abortion.
Information on maternal hyperthyroidism was obtained from the DNHR [16]. In- and outpatient visits in the period from January 1, 1977, up to 2 years after the date of pregnancy termination were included. Hyperthyroidism was defined as ICD-8 (1977–1993): 242.00–242.29 and ICD-10 (1994–2010): E05.0–E05.9 (excluding thyrotoxicosis factitia (E05.4), overproduction of TSH (E05.8A) and thyrotoxic heart disease (E05.9A)).

The Danish National Prescription Register (DNPR) [20] holds data on all prescription drugs redeemed from Danish pharmacies since 1995 including the type of drug prescribed according to the Anatomical Therapeutic Chemical classification system (ATC) and the date of sale. Thyroid hormones (ATC H03A) and ATDs (ATC H03B) are sold solely as prescription drugs in Denmark, and we identified all prescriptions redeemed between January 1, 1995, and up to 2 years after the date of pregnancy termination.

Hyperthyroidism was defined by (1) a hospital diagnosis of hyperthyroidism and at least one prescription of ATD or (2) if no hospital diagnosis was registered, at least two prescriptions of ATD. Women with a hospital diagnosis before January 1, 1995, and no prescription of thyroid medication registered were included as treatment may have ended before the prescription registration was initiated (n = 549). Pregnancies with inconsistent registration of maternal hyperthyroidism (0.4%) were excluded from the main analyses.

**Exposure Groups**

The ‘onset’ of maternal hyperthyroidism was defined as the day the first prescription of ATD was redeemed. If a hospital diagnosis was registered before the year 1996, the day of first admission to hospital defined the onset of disease. The non-exposed group was defined as pregnancies with no registration of maternal thyroid dysfunction up to 2 years after the pregnancy. Thus, pregnancies with registration of maternal hypothyroidism were excluded from the study (1.0%).

In the main analyses, two exposure groups were defined: (1) maternal hyperthyroidism diagnosed and treated before the date of pregnancy termination (before/during the pregnancy) and (2) maternal hyperthyroidism diagnosed and treated for the first time in the 2-year period after the pregnancy.

To evaluate the possible association between ATD treatment in early pregnancy and spontaneous abortion, we subsequently focused on the group of pregnancies in which maternal hyperthyroidism was diagnosed before/during the pregnancy. In this group, we identified (a) pregnancies where the pregnant woman had only redeemed prescriptions more than 12 months prior to pregnancy start considered ‘previous ATD treatment’ and (b) pregnancies where the pregnant woman redeemed one or more prescriptions of ATD in the period from 6 months prior to pregnancy start to the end of gestational week 10 considered ‘exposure to ATD in early pregnancy’. If prescriptions of both MMI/CMZ and PTU were redeemed during the 6-month period prior to pregnancy start, the last prescription prior to pregnancy start defined the type of ATD exposure in early pregnancy.

**Covariates**

From Statistic Denmark we obtained information on maternal age, cohabitation, income, origin and geographical residence at the time of pregnancy termination. Pregnancies with missing values on these covariates were excluded from the main analyses (1.4%). Information on maternal diagnosis of hyperemesis gravidarum and preeclampsia/eclampsia as well as diagnosis and medical treatment of diabetes and psychiatric disease before, during and up to 2 years after the pregnancy was obtained from the DNHR, the Danish Psychiatric Central Register and the DNPR.

**Statistical Analyses**

Altogether 1,018,261 pregnancies (95.8%) were available for the main analyses. In the analyses of spontaneous abortion (follow-up from pregnancy start to the end of gestational week 21), pregnancies terminated with induced abortion, and molar or ectopic pregnancy were excluded. In the analyses of stillbirth (follow-up from pregnancy start to the day of birth) only pregnancies terminating with a singleton stillbirth or live birth were included, thus pregnancies terminated with induced or spontaneous abortion, molar or ectopic pregnancy were excluded as were multiple births.

The Cox proportional hazard model with gestational age as the underlying time scale was used to estimate crude and adjusted hazard ratio (aHR) with 95% confidence interval (95% CI) for spontaneous abortion and stillbirth in pregnancies exposed to maternal hyperthyroidism versus the reference group with no maternal thyroid dysfunction registered up to 2 years after the pregnancy. In all analyses, robust standard error was used to account for dependency between maternal multiple pregnancies. The adjusted model included: maternal age (<25, 25–29, 30–34, 35–39, and ≥40 years), parity (1, 2, 3, ≥4), income (1st, 2nd, 3rd, 4th quartile), cohabitation (married/not married), origin (born in Denmark/not born in Denmark), residence (East/West Denmark), and the year of pregnancy termination (3-year intervals). Information on maternal smoking in pregnancy (yes/no) was available for the analysis of stillbirth. Maternal diabetes, preeclampsia and psychiatric disease were a priori considered possible intermediates and included in the model in a subsequent analysis.

In a sensitivity analysis, the study population was restricted to first-time pregnancies in the study period. In other sensitivity analyses, pregnancies excluded from the main analyses due to missing or inconsistent registration were included (gestational age, maternal hyperthyroidism and maternal covariates).

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

**Results**

**Study Population**

Altogether 836,905 pregnancies terminated with spontaneous abortion, stillbirth or live birth (table 1) and in 0.9% of these pregnancies the pregnant woman had hyperthyroidism diagnosed and treated before/during (n = 5,229) or in the 2-year period after the pregnancy (n = 2,361). In pregnancies where maternal hyperthyroidism was diagnosed before/during the pregnancy, the pregnant women were older with a higher parity (table 1), whereas in pregnancies where maternal hyperthyroidism was diagnosed for the first time and treated in the 2-year
period after the pregnancy, characteristics of the pregnant women were more comparable with the large group of unexposed pregnancies.

Table 2 provides the distribution of pregnancy outcomes by exposure groups. The unadjusted data suggested that spontaneous abortion was more frequent when maternal hyperthyroidism was diagnosed before/during the pregnancy, and stillbirth was more frequent when maternal hyperthyroidism was diagnosed for the first time and treated in the 2-year period after the pregnancy.

**Spontaneous Abortion**

After adjustment for a number of possible confounders, an increased risk of spontaneous abortion in pregnancies with maternal hyperthyroidism before/during the pregnancy remained (fig. 1). On the other hand, no association was seen when maternal hyperthyroidism was diagnosed for the first time and treated after the pregnancy (fig. 1). Additional adjustment for maternal pre-eclampsia/eclampsia, diabetes and psychiatric disease did not change the results.

To evaluate the possible role of ATD treatment in early pregnancy, we subsequently focused on the group of pregnancies where maternal hyperthyroidism was diagnosed before/during the pregnancy. In this group, we were able to identify pregnancies where the pregnant woman had redeemed prescriptions of ATD before the pregnancy alone (n = 2,186) 'previous ATD treatment' and pregnancies where the pregnant woman redeemed prescriptions of ATD in early pregnancy (n = 1,899) 'early pregnancy ATD treatment'. As depicted in figure 2, the aHR for spontaneous abortion was similar in the two groups suggesting that the association observed was not predominantly explained by early pregnancy ATD treat-

---

Table 1. Maternal characteristics at the time of pregnancy by exposure groups

|                              | Hyperthyroidism before/during the pregnancy | Hyperthyroidism 0–2 years after the pregnancy | No hyper- or hypothyroidism up to 2 years after the pregnancy |
|------------------------------|--------------------------------------------|----------------------------------------------|-------------------------------------------------------------|
| n                            | %                                         | n                                           | %                                           |
| Pregnancies                  |                                            |                                              |                                              |
| Age                          |                                            |                                              |                                              |
| <25 years                    | 297                                        | 289                                          | 113,069                                      |
| 25–29 years                  | 1,373                                      | 745                                          | 281,633                                      |
| 30–34 years                  | 2,014                                      | 839                                          | 288,663                                      |
| 35–39 years                  | 1,265                                      | 408                                          | 121,622                                      |
| ≥40 years                    | 280                                        | 80                                           | 24,328                                       |
| Parity                       |                                            |                                              |                                              |
| 1                            | 2,211                                      | 1,373                                        | 449,232                                      |
| 2                            | 1,798                                      | 631                                          | 250,609                                      |
| 3                            | 796                                        | 243                                          | 91,043                                       |
| ≥4                           | 424                                        | 114                                          | 38,431                                       |
| Cohabitation                 |                                            |                                              |                                              |
| Married                      | 3,173                                      | 1,282                                        | 470,246                                      |
| Not married                  | 2,056                                      | 1,079                                        | 359,069                                      |
| Income, quartiles            |                                            |                                              |                                              |
| 1st (lowest)                 | 254                                        | 139                                          | 49,474                                       |
| 2nd                          | 1,760                                      | 810                                          | 267,525                                      |
| 3rd                          | 2,347                                      | 1,057                                        | 375,147                                      |
| 4th                          | 868                                        | 355                                          | 137,169                                      |
| Origin                       |                                            |                                              |                                              |
| Born in Denmark              | 4,544                                      | 1,998                                        | 732,396                                      |
| Not born in Denmark          | 685                                        | 363                                          | 96,919                                       |
| Residence                    |                                            |                                              |                                              |
| West Denmark                 | 2,800                                      | 1,297                                        | 448,465                                      |
| East Denmark                 | 2,429                                      | 1,064                                        | 380,850                                      |

* Previous pregnancies in the study period including index pregnancy.
Results were considerably the same when stratified by the type of ATD used in early pregnancy: MMI/CMZ alone (n = 1,169): aHR 1.22 (95% CI 1.06–1.41), PTU alone (n = 576): 1.12 (0.91–1.38), both MMI/CMZ and PTU (n = 154): 1.11 (0.73–1.68), and when the window of ATD exposure in early pregnancy was restricted to redeemed prescriptions 3 and 1 month prior to pregnancy start or to the weeks after pregnancy start alone (data not shown).

Stillbirth

Whereas the increased risk of early pregnancy loss (spontaneous abortion) was mainly seen in pregnancies with maternal hyperthyroidism diagnosed before/during the pregnancy (fig. 1), an increased risk of later pregnancy loss (stillbirth) was observed in pregnancies where maternal hyperthyroidism was diagnosed for the first time and treated in the 2-year period after the pregnancy (fig. 3). Additional adjustment for maternal smoking in the pregnancy (pregnancies with missing value (3%) excluded) revealed similar results (hyperthyroidism before/during: aHR 0.78 (95% CI 0.43–1.40), hyperthyroidism in the 2-year period after the pregnancy: 2.21 (1.35–3.61)). Adjustment for maternal preeclampsia/eclampsia, diabetes and psychiatric disease did not change the results.

Table 3 gives characteristics of the 16 exposed cases of stillbirth. The time of the first ATD treatment postpartum was fairly evenly distributed between the first and the second year after the pregnancy and an increased risk of still-

### Table 2. Pregnancy outcomes by exposure groups

|                              | All pregnancies | Hyperthyroidism before/during the pregnancy | Hyperthyroidism 0–2 years after the pregnancy | No hyper- or hypothyroidism up to 2 years after the pregnancy |
|------------------------------|-----------------|---------------------------------------------|-----------------------------------------------|-------------------------------------------------------------|
|                              | n               | %a                                         | n                                              | %a                                                          | n                                              | %a |
| Pregnancies Spontaneous abortion | 836,905         | 13.2                                       | 5,229                                         | 16.0                                                       | 2,361                                          | 12.7 |
| Stillbirth                   | 110,744         | 13.2                                       | 838                                           | 16.0                                                       | 300                                            | 12.7 |
| Singleton                    | 2,630           | 0.31                                       | 14                                            | 0.27                                                       | 17                                             | 0.72 |
| Multiple                     | 269             | 0.03                                       | 1                                             | 0.02                                                       | 1                                              | 0.04 |
| Live birth                   | 723,262         | 86.4                                       | 4,377                                         | 83.7                                                       | 2,044                                          | 86.6 |
| Singleton                    | 709,134         | 84.7                                       | 4,241                                         | 81.1                                                       | 2,006                                          | 85.0 |
| Multiple                     | 14,128          | 1.7                                        | 136                                           | 2.6                                                        | 38                                             | 1.6  |

a Percentages are the percentage of all within the column. b p values are results of the χ2 test or Fisher’s exact test as appropriate: hyperthyroidism before/during the pregnancy vs. hyperthyroidism the first time 0–2 years after the pregnancy vs. no hyper- or hypothyroidism up to 2 years after the pregnancy. c Minimum 1 stillbirth.

### Fig. 1. Crude and adjusted HR with 95% CI for spontaneous abortion in pregnancies with maternal hyperthyroidism diagnosed and treated before/during the pregnancy (top) and in pregnancies with maternal hyperthyroidism diagnosed for the first time and treated in the 2-year period after the pregnancy (bottom). The reference is pregnancies with no maternal thyroid dysfunction before, during and up to 2 years after the pregnancy. The adjusted model included the year of pregnancy termination and maternal age, parity, cohabitation, income, origin and residence (see text for details).
Hyperthyroidism and Pregnancy Loss

Sensitivity Analyses

When restricting analyses to first-time pregnancies in the study period (n = 452,816), an increased risk of spontaneous abortion (aHR 1.19 (95% CI 1.07–1.32)) in pregnancies with maternal hyperthyroidism diagnosed before/during the pregnancy and an increased risk of stillbirth in pregnancies with maternal hyperthyroidism diagnosed for the first time and treated after the pregnancy (2.77 (1.60–4.78)) were also observed in this group. A hospital diagnosis of hyperemesis gravidarum was more common in women identified with hyperthyroidism (2.1% vs. no thyroid dysfunction 0.9%, p < 0.001), but associations remained the same when these women were excluded (hyperthyroidism before/during the pregnancy and spontaneous abortion (aHR 1.15 (95% CI 1.07–1.23)), hyperthyroidism after the pregnancy and stillbirth (2.16 (1.32–3.53)). Moreover, an increased risk of spontaneous abortion was still observed when women were diagnosed for the first time with hyperthyroidism during the pregnancy were excluded (1.21 (1.12–1.30)). When pregnancies excluded from the main analyses due to missing or inconsistent registration of gestational age, maternal hyperthyroidism or maternal covariates were included, results were similar to the main analyses (data not shown).
Discussion

Principal Findings

In a Danish population-based study, pregnancy loss was more common in women suffering from hyperthyroidism. Early pregnancy loss (spontaneous abortion) occurred more often in women diagnosed with hyperthyroidism before/during the pregnancy, and we speculate whether inadequate treatment of maternal hyperthyroidism in early pregnancy may have been involved. Late pregnancy loss (stillbirth) occurred more often in women diagnosed for the first time with hyperthyroidism in the 2-year period after the pregnancy, and we speculate whether undetected high maternal thyroid hormone levels in late pregnancy may have contributed to an increased risk of stillbirth.

Table 3. Characteristics of the 16 cases of singleton stillbirth in pregnancies where maternal hyperthyroidism was diagnosed the first time and treated with ATDs in the 2-year period after the pregnancy

| Birth year | Gestational week at birth | Maternal age, years | Maternal origin | Maternal smokinga | First ATD treatment (post-partum month)b |
|------------|---------------------------|---------------------|-----------------|-------------------|-----------------------------------------|
| 1998       | 39                        | 31 Denmark          | yes             | 6                 |
| 1998       | 28                        | 29 Denmark          | no              | 7                 |
| 1999       | 31                        | 25 Denmark          | no              | 5                 |
| 2001       | 34                        | 28 Denmark          | yes             | 9                 |
| 2003       | 36                        | 27 Denmark          | no              | 5                 |
| 2005       | 41                        | 26 Denmark          | no              | 7                 |
| 2006       | 22                        | 39 Yugoslavia       | no              | 12                |
| 2007       | 35                        | 23 Denmark          | no              | 3                 |
| 2007       | 37                        | 32 Denmark          | no              | 11                |
| 1998       | 31                        | 41 Denmark          | no              | 22                |
| 2001       | 38                        | 29 Thailand         | yes             | 13                |
| 2002       | 37                        | 36 Denmark          | no              | 22                |
| 2003       | 29                        | 29 Lebanon          | yes             | 24                |
| 2004       | 31                        | 37 Denmark          | no              | 15                |
| 2006       | 32                        | 33 Denmark          | no              | 23                |
| 2007       | 41                        | 27 Denmark          | no              | 22                |

Cases are grouped according to the time (first or second year postpartum) when maternal ATD treatment was initiated and ranged by birth year of the child in each group. a Smoking or smoking cessation during the pregnancy. b The month when the first prescription of ATD was dispensed from a Danish pharmacy.

Pregnancy Loss in Hyperthyroidism

In clinical reviews and guidelines on maternal hyperthyroidism in pregnancy it is rather consistently described that maternal hyperthyroidism in pregnancy is associated with adverse pregnancy outcomes including pregnancy loss [8–10, 21]. The evidence of pregnancy loss is mainly based on case series, and it appears that especially the untreated or inadequately treated hyperthyroidism may complicate pregnancy [5, 11–13]. In a study published in 1989, Davis et al. [5] described 60 pregnancies complicated by maternal hyperthyroidism (women diagnosed prior to pregnancy who were euthyroid throughout pregnancy were not included). Among the 60 women included, 8 women were untreated in pregnancy, whereas 36 women were treated with PTU to euthyroidism at delivery and 16 women were inadequately treated with PTU and were hyperthyroid at the time of delivery. In total, 1 case of abortion and 5 cases of stillbirth were observed and these adverse outcomes of pregnancy all occurred in pregnancies were the mother had untreated hyperthyroidism (abortion n = 1, stillbirth n = 4) or suffered from inadequately treated hyperthyroidism (stillbirth n = 2) at the time of delivery.

Early Pregnancy Loss

Spontaneous abortion is the most common adverse outcome of pregnancy [1]. Chromosomal abnormality is the single most common cause involved in approximately half of all cases of early spontaneous abortion, but several other risk factors have been examined [22]. In our study, an increased risk of spontaneous abortion was observed in pregnancies with maternal diagnosis of hyperthyroidism before/during the pregnancy. The lack of an association with maternal hyperthyroidism diagnosed after the pregnancy contradicts an inherited genetic association to some extent. Since we had no results of thyroid function tests, we were not able to distinguish between the possible role of inadequately treated hyperthyroidism in early pregnancy and ATD treatment in early pregnancy per se. However, the finding that women treated with ATD more than 1 year before the pregnancy alone had a similar high risk of spontaneous abortion may suggest that inadequately treated hyperthyroidism in early pregnancy was the main factor involved.

Late Pregnancy Loss

Stillbirth might also be caused by genetic factors although chromosomal abnormalities are less frequently involved than in spontaneous abortion [1]. In our study, an increased risk of stillbirth was only observed in the
Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss

Hyperthyroidism and Pregnancy Loss
Acknowledgements

Chun Sen Wu is supported by the individual postdoctoral grants from the Danish Medical Research Council (FSS: 12-132232).

Disclosure Statement

The authors have no conflicts of interest to disclose.

References

1. Simpson JL, Jauniaux ER: Pregnancy loss; in Gabbe SG, Niebyl JR, Simpson JL, Landon MB, Galan HL, Jauniaux ER, Driscoll DA (eds): Obstetrics: Normal and Problem Pregnan-
cies, ed 6. Philadelphia, Saunders/Elsevier 2012, pp 592–608.
2. Statens Serum Institut: Fællesindhold for ba-
sisregistrering af sygehuspatienter. Vejled-
tningsbog del 3, 1993.
3. Laurberg P, Bournaud C, Karmisholt J, Orgi-
azzi J: Management of Graves’ hyperthyroid-
ism in pregnancy: focus on both maternal and
foetal thyroid function, and caution against
surgical thyroidectomy in pregnancy. Eur J
Endocrinol 2009;160:1–8.
4. Carle A, Pedersen IB, Knudsen N, Perrild H,
Ovesen L, Rasmussen LB, Laurberg P: Epide-
miology of subtypes of hyperthyroidism in
Denmark: a population-based study. Eur J
Endocrinol 2011;164:801–809.
5. Davis LE, Lucas MJ, Hankins GD, Roark ML,
Cunningham FG: Thyrotoxicosis complicat-
ing pregnancy. Am J Obstet Gynecol 1989;
160:63–70.
6. Sheffield JS, Cunningham FG: Thyrotoxicosis
and heart failure that complicate pregnancy.
Am J Obstet Gynecol 2004;190:211–217.
7. Andersen SL, Olsen J, Wu CS, Laurberg P:
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 Na-
tional Hospital Register study. Eur J Thyroid
2013;2:135–144.
8. Stagnaro-Green A, Abalovich M, Alexander
E, Azizi F, Mestman J, Negro R, Nixon A,
Pearce EN, Soldin OP, Sullivan S, Wiersinga
W: American Thyroid Association Taskforce
on Thyroid Disease during Pregnancy and
Postpartum: Guidelines of the American
Thyroid Association for the diagnosis and
management of thyroid disease during preg-
nancy and postpartum. J Clin Endocrinol
Metab 2013;98:4373–4381.
9. Bahn RS, Burch HR, Cooper DS, Garber JR,
Greenlee MC, Klein I, Laurberg P, McDougall
JR, Montori VM, Rivkees SA, Ross DS, Sosa
JA, Stan MN: American Thyroid Association,
American Association of Clinical Endocri-
nologists: Hyperthyroidism and other causes
of thyrotoxicosis: management guidelines of
the American Thyroid Association and American
Association of Clinical Endocri-
nologists. Thyroid 2011;21:593–646.
10. De Groot L, Abalovich M, Alexander EK,
Amino N, Barbour L, Cobin RH, Eastman CJ,
Lazarus JH, Luton D, Mandel SJ, Mestman J,
Royer J, Sullivan S: Management of thyroid
dysfunction during pregnancy and postpar-
tum: an Endocrine Society Clinical Practice
Guideline. J Clin Endocrinol Metab 2012;97:
2543–2565.
11. Sugrue D, Drury ML: Hyperthyroidism compli-
cating pregnancy: results of treatment by
antithyroid drugs in 77 pregnancies. Br J Ob-
set Gynaecol 1980;87:970–975.
12. Momotani N, Ito K: Treatment of pregnant
patients with Basedow’s disease. Exp Clin En-
docrinol 1991;97:268–274.
13. Hamburger JI: Diagnosis and management of
Graves’ disease in pregnancy. Thyroid 1992;2:
219–224.
14. Andersen SL, Olsen J, Wu CS, Laurberg P:
Birth defects after early pregnancy use of an-
tithyroid drugs: a Danish nationwide study. J
Clin Endocrinol Metab 2013;98:4373–4381.
15. Laurberg P, Andersen SL: Antithyroid drug
use in early pregnancy and birth defects. Time
windows of relative safety and high risk? Eur
J Endocrinol 2014;171:R13–R20.
16. Andersen TF, Madsen M, Jorgensen J, Mel-
lemkjoer L, Olsen JH: The Danish National
Hospital Register. A valuable source of data
for modern health sciences. Dan Med Bull
1999;46:263–268.
17. Jorgensen FS: Organization of obstetric ultra-
sound in Denmark 2000. Description of the
development since 1990. Ugeskr Laeger 2003;
165:4404–4409.
18. Sundhedsstyrelsen. Retningslinjer for fostet-
diagnostik – prænatal information, risikovur-
delingsdøgn og diagnostik 2004;1.
19. Sundhedsstyrelsen. Anbefalinger for Svange-
rørsorg 2013;1. http://sundhedsstyrelsen.
dk/publ/Publ2013/100kt/Svangeromsorg
2013.pdf.
20. Kildemoes HW, Sorensen HT, Hallas J: The
Danish National Prescription Registry. Scand
J Public Health 2011;39:38–41.
21. Cooper DS, Laurberg P: Hyperthyroidism in
pregnancy. Lancet Diabetes Endocrinol 2013;
1:238–249.
22. Fedor Nilsson S, Andersen P, Strandberg-
Larsen K, Nybo Andersen AM: Risk factors
for miscarriage from a prevention perspec-
tive: a nationwide follow-up study. BJOG
2014, Epub ahead of print.
23. Millar LK, Wing DA, Leung AS, Koonings PP,
Montoro MN, Mestman JH: Low birth weight
and preeclampsia in pregnancies complicated
by hyperthyroidism. Obstet Gynecol 1994;84:
946–949.
24. Morreale de Escobar G, Obregen MJ, Escobar
del Rey F: Role of thyroid hormone during
early brain development. Eur J Endocrinol
2004;151:U25–U37.
25. Evans RW, Farwell AP, Braverman LE: Nu-
clear thyroid hormone receptor in the rat
uterus. Endocrinology 1983;113:1459–1463.
26. Galton VA, Martin C, Freedom MB, Brody
EA, Bates JM, St Germain DL: Pregnant
rat uterus expresses high levels of the type 3
iodothyronine deiodinase. J Clin Invest 1999;
103:979–987.
27. Huang SA, Dorfman DM, Genest DR, Salvato-
tore D, Larsen PR: Type 3 iodothyronine de-
ioinase is highly expressed in the human
uteroplacental unit and in fetal epithelium. J
Clin Endocrinol Metab 2003;88:1384–1388.
28. Contempre B, Jauniaux E, Calvo R, Jurkovic
D, Campbell S, de Escobar GM: Detection of
thyroid hormones in human embryonic cavi-
ties during the first trimester of pregnancy. J
Clin Endocrinol Metab 1995;77:1719–1722.
29. Calvo RM, Jauniaux E, Gubris B, Assmion M,
Gery C, Contempre B, Morreale de Escobar
G: Fetal tissues are exposed to biologically rel-
levant free thyroxine concentrations during
early phases of development. J Clin Endocri-
nol Metab 2002;87:1768–1777.
30. Anselmo J, Cao D, Karrison T, Weiss RE,
Redefoff S: Fetal loss associated with excess
thyroid hormone exposure. JAMA 2004;292:
691–695.
31. Olsen J: Calculating risk ratios for spontane-
ous abortions: the problem of induced abor-
tions. Int J Epidemiol 1984;13:347–350.
32. Laurberg P, Andersen SL, Pedersen IB, An-
dersen S, Carle A: Screening for overt thyroid
disease in early pregnancy may be preferable
to searching for small aberrations in thyroid
function tests. Clin Endocrinol (Oxf) 2013;
79:297–304.
33. Casey BM, Dashe JS, Wells CE, McIntire DD,
Leveno KJ, Cunningham FG: Subclinical hy-
perthyroidism and pregnancy outcomes. Ob-
stet Gynecol 2006;107:337–341.