Maternal hyperthyroidism and pregnancy outcomes: A population-based cohort study

Running title:

Pregnancy outcomes in hyperthyroid mothers

Suvi Turunen, MD[1]; Marja Vääräsmäki, MD, PhD[1]; Anna-Maria Lahesmaa-Korpinen, PhD[2]; Maarit K Leinonen, MD, PhD[2]; Mika Gissler, Professor[2,3]; Tuija Männistö, MD, PhD[4]; Eila Suvanto, MD, PhD[1]

Affiliations:

[1] Department of Obstetrics and Gynecology, PEDEGO Research Unit and Medical Research Center Oulu, University of Oulu and Oulu University Hospital, Oulu, Finland, [2] Finnish Institute for Health and Welfare, Information Services Department, Helsinki, Finland, [3] Karolinska Institute, Department of Neurobiology, Care Sciences and Society, Stockholm, Sweden, [4] Northern Finland Laboratory Centre Nordlab, Oulu University Hospital, Oulu, Finland

Correspondence:

Suvi Turunen
Oulu University Hospital, PO Box 10, 90029 OYS, Finland
Tel: +358503682033
E-mail: suvi.t.turunen@gmail.com

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ABSTRACT

Objective: Maternal hyperthyroidism and antithyroid medications have been associated with adverse pregnancy and perinatal outcomes. This nationwide register-based study investigated the association of maternal hyperthyroidism and antithyroid drug (ATD) use with pregnancy outcomes and included all singleton births in Finland between 2004 and 2013 (N = 571,785).

Design, patients, and measurements: Hyperthyroid mothers were identified in the Medical Birth Register, and data on ATD use before and/or during pregnancy were collected from the Prescription Register. The odds ratios, with 95% confidence intervals, for adverse outcomes among hyperthyroid mothers and mothers without thyroid disease were compared using logistic regression.

Results: In total, 2,144 (0.37%) of all the women had diagnoses of hyperthyroidism, and 580 (27%) of these women had used ATDs before and/or during pregnancy. Compared to the mothers without thyroid disease, maternal hyperthyroidism was associated with older age, multiparity, smoking, previous miscarriages, and overweight or obesity. The mothers diagnosed with hyperthyroidism also had increased odds of gestational hypertensive disorders, cesarean sections, placental abruptions, preterm births, small-for-gestational-age newborns, and neonatal intensive care unit treatment. The odds of pregnancy and/or perinatal complications were higher among those who had used ATDs (indicative of active disease), but those who had not received ATD treatment also had increased odds of such complications compared to the mothers without thyroid disease.

Conclusions: Women with active hyperthyroidism and those with histories of hyperthyroidism should be considered at risk of developing pregnancy and perinatal complications and should therefore be monitored during pregnancy.

Keywords: antithyroid drug, hyperthyroidism, pregnancy, perinatal, thyroid

INTRODUCTION

Hyperthyroidism is known to be associated with fetal and maternal complications.[1] Autoimmune Graves' disease is the most frequent cause of hyperthyroidism in women of childbearing age.[1,2] The reported prevalence of Graves' disease in pregnancy is approximately 0.5-1.0%, although the prevalence varies through the published literature.[3] In individuals with Graves' disease, circulating thyroid-stimulating hormone receptor antibodies stimulate the thyroid gland, causing hyperthyroidism with low or suppressed thyroid-stimulating hormone concentrations and elevated thyroid hormone concentrations.[4] In such cases, women are advised to postpone pregnancy until a euthyroid state is reached to ensure that the disease is adequately controlled before conception.[2] Gestational transient thyrotoxicosis/hyperthyroidism, which biochemically resembles Graves' disease, with an elevated free thyroxine and a suppressed thyroid-stimulating hormone, is diagnosed in approximately 1−3% of pregnancies.[2] It is a physical condition induced by elevated human chorionic gonadotropin concentrations and typically resolves during the first trimester in parallel with the decline in human chorionic gonadotropin.[5] It is important to differentiate this state from Graves' disease because antithyroid drug (ATD) treatment should be considered only for the latter.[5]

Untreated or undertreated overt hyperthyroidism is associated with pregnancy complications, including miscarriage, hypertensive disorders, preterm delivery, low birth weight, and maternal emergencies such as thyrotoxic crisis and maternal congestive heart failure.[5,6] Studies have also shown that neonates of hyperthyroid women are more likely to require respiratory or neonatal intensive care unit treatment.[7,8] In contrast, subclinical hyperthyroidism has not been associated pregnancy complications.[9] The thionamide antithyroid drugs (ATDs) propylthiouracil and methimazole, together with methimazole prodrug carbimazole, block the synthesis of thyroid hormones in the thyroid gland[10] and constitute the treatment of choice for hyperthyroidism during pregnancy.[11] ATDs can reduce or eliminate some pregnancy complications.[5,12,13] However, previous studies have demonstrated that there remains an increased risk of perinatal complications even if hyperthyroidism is treated with ATDs.[14-16] Both propylthiouracil and

methimazole cross the placenta and have been associated with congenital anomalies.[17,18] Birth defects associated with propylthiouracil use are reportedly less severe[4] or even absent compared to those linked to methimazole.[19,20]

The aim of this study was to investigate the association of maternal hyperthyroidism (with and without ATD use) with pregnancy and perinatal outcomes.

METHODS

The data used in this population-based study were collected from the Medical Birth Register (MBR) and supplemented with information from the Prescription Register, the Hospital Discharge Register, and the Register on Congenital Malformations. These data included all births in Finland between 2004 and 2013 (N = 589,489). After excluding multiple pregnancies (n = 17,674), the present study comprised 357,293 women with 571,785 singleton pregnancies. Data linkage between the aforementioned registers was possible due to the unique personal identification codes assigned to all Finnish citizens and permanent residents. In general, the registers employed in this study were of good quality, and their usefulness further increased when used together.[21-23]

The MBR, established in 1987, is maintained by the Finnish Institute for Health and Welfare (THL). Over the course of seven days after a delivery, personnel at the delivery hospital complete a structured form for submission to the MBR. This form includes maternal and newborn data concerning every live birth or stillbirth with a birth weight ≥ 500 g or a gestational age at birth ≥ 22 weeks. The maternal data include age, smoking status, pregnancy history, body mass index, socioeconomic status, marital status, place of residence, diagnoses and hospitalization during pregnancy, and mode of delivery, while the newborn data cover gestational age at birth, sex, birth weight, height and head circumference, and umbilical artery or vein pH, as well as diagnoses, treatment, and hospitalization during the perinatal period.

The Prescription Register and the Special Refund Entitlement Register are maintained by the Social Insurance Institution of Finland (Kela) and collect information from all the pharmacies in the country. This information includes the drug classification codes (according to the International Anatomic Therapeutic Chemical System) and the dates and number of purchases. We obtained data on ATD purchases during pregnancy and three months prior to pregnancy from these registries. Date of conception was defined on basis of date of birth and duration of pregnancy. In Finland, prescriptions are valid 1-2 years. However, pharmacies only provide three months' supply of prescription drugs to the customer at once. All the ATD purchases examined in the present study denoted either propylthiouracil (code H03BA02) or carbimazole (code H03BB01) use; methimazole was not used to treat pregnant women with hyperthyroidism during the study years.

The Hospital Discharge Register includes data on patient diagnosis codes at discharge based on the International Statistical Classification of Diseases and Related Health Problems (ICD) from all hospital wards. We collected information on maternal chronic diseases from this register and combined this information with data from the Special Refund Entitlement Register, which contains information on chronic diseases as well as medications and the reimbursement of medical expenses. The data from the Hospital Discharge Register spanned the years 1987-2013 while that from the Special Refund Entitlement Register ranged from 2004 to 2013. This data allowed us to capture diagnoses before and during pregnancy.

We obtained data on congenital anomalies from the Register on Congenital Malformations, which includes information about every newborn in Finland who has at least one detected major congenital anomaly. Congenital anomalies are reported to the Register on Congenital Malformations until the age of one year. From 2004 to 2013, these anomalies were classified and coded according to the extended ICD version 9 (ICD-9); however minor anomalies were not included according to the practices of the European Surveillance of Congenital Anomalies (EUROCAT).[24]

The ICD-10 code E05 (all digits) and the ICD-9/ICD-8 code both 242 denote a diagnosis of hyperthyroidism in the aforementioned registers (n = 2,144). Women with other thyroid diseases (hypothyroidism, thyroiditis without co-diagnosis for hyperthyroidism or thyrotoxicosis, iodine-deficiency-related disorders, goiter, and benign or malignant neoplasms of the thyroid gland; n = 19,267) were excluded.

Pregnancy and perinatal outcomes

The main pregnancy-related outcome measures obtained from the MBR were measures of gestational hypertensive disorders (ICD-codes O13-O15), gestational diabetes (ICD code O24.4 or O24.9) or reported abnormal oral glucose tolerance during pregnancy, delivery mode (vaginal, elective, or acute caesarean section, or instrumental/vacuum), placenta previa, and placental abruption. The main perinatal outcomes were preterm birth (early: < 34 completed gestational weeks; late: 34 + 0 to 36 + 6 gestational weeks), the number of small-for-gestational-age (SGA) and large-for-gestational-age (LGA) infants, major congenital anomalies, the need for neonatal intensive care unit treatment, the need for respiratory treatment at neonatal intensive care unit, stillbirth, and early neonatal death. SGA was defined as a birth weight less than two standard deviations from the gestational age-adjusted mean, and LGA was defined as a birth weight more than two standard deviations from the gestational age-adjusted mean.

Ethics and funding

The ethics board of the Northern Ostrobothnia Hospital District approved this study, and the THL and the Kela provided permission for the use of the data obtained from the aforementioned registers. The Northern Ostrobothnia Hospital District partially funded this study. The data were encrypted prior to statistical analysis.

Statistical analysis

Pregnancy was the unit of analysis in all the statistical tests. The demographic data of the mothers with hyperthyroidism were compared with those of the mothers without any thyroid disease (reference group) using a chi-squared test or a Fisher's exact test. The odds ratios (ORs), with 95% confidence intervals (CIs), for adverse outcomes among the hyperthyroid mothers were compared to those among the reference group using a logistic regression analysis with generalized estimating equations and a first-order autoregressive correlation matrix. The generalized estimating equations accounted for correlations between repeated pregnancies of the same woman. The analyses were adjusted for the following identified confounders: maternal age at delivery, body mass index, smoking during pregnancy, parity, socioeconomic status, year of delivery, pregestational type 1 or type 2 diabetes, and the catchment area of five tertiary hospitals in Finland. Only the adjusted ORs are presented as the unadjusted and adjusted ORs were similar. We also compared the hyperthyroid mothers (with and without ATD purchases) to those without thyroid diseases three months prior to or during pregnancy. There were no missing data for continuous variables. Missing outcome data were included as a category for categorical variables. Missing data were found only in our demographic characteristics and did not differ between exposed and unexposed. All analyses were performed using SAS version 9.3.

RESULTS

Demographic data

The mothers with diagnoses of hyperthyroidism (2,144; 0.37% of all mothers) were older, more often multiparous, overweight or obese, smoked more often, and had previously experienced miscarriages more often than the mothers without any thyroid disease (Table 1). ATD purchases were documented among 27% (n = 580) of the hyperthyroid mothers during and/or three months prior to pregnancy. Carbimazole was the most commonly purchased ATD (n = 559), and propylthiouracil was purchased by 30 women.

Nine mothers with hyperthyroidism purchased both of these ATDs. The majority of the mothers with diagnoses of hyperthyroidism (n = 1,564) did not purchase ATDs during pregnancy, but one-third of them (n = 503) purchased levothyroxine.

Pregnancy complications

Maternal hyperthyroidism was associated with a higher risk of gestational hypertensive disorders for women who used ATD (OR 1.67, 95% CI: 1.18, 2.36), but not for those without ATD use (OR 1.19, 95% CI: 0.93, 1.53) (Table 2). Maternal hyperthyroidism was also associated with elective and acute cesarean sections (OR 1.23, 95% CI: 1.04, 1.45 and OR 1.28, 95% CI: 1.10, 1.48, respectively), and placental abruptions (OR 1.98, 95% CI: 1.15, 3.41). However, these associations did not reach statistical significance in the group of mothers with ATD purchases. A maternal hyperthyroidism diagnosis was not associated with gestational diabetes, instrumental delivery, or placenta previa (Table 2).

Perinatal outcomes

Maternal hyperthyroidism was associated with preterm births (OR 1.34, 95% CI: 1.09, 1.64), early preterm births (OR 1.87, 95% CI: 1.39, 2.53), SGA (OR 1.30, 95% CI: 1.04, 1.63), and neonatal intensive care unit treatment (OR 1.65, 95% CI: 1.46, 1.86) (Table 3). Maternal hyperthyroidism was associated also with a higher risk of respiratory treatment of the newborn for women who used ATD (OR 1.95, 95% CI: 1.07, 3.56), but not for those without ATD use (OR 1.95, 95% CI: 1.07, 3.56). Maternal hyperthyroidism was not related to major congenital anomalies or LGA. The overall prevalence of stillbirth and early neonatal death was low and did not differ between the groups (Table 3).

Sensitivity analyses

Excluding levothyroxine-treated mothers with hyperthyroidism diagnoses had no substantial effect on any of the results (supplementary data, STable 1 and STable2). Maternal hyperthyroidism was associated with a higher risk of gestational hypertensive disorders (OR 1.39, 95% CI: 1.11, 1.76), caesarean sections (OR 1.27, 95% CI: 1.11, 1.47), instrumental delivery (OR 1.24, 95% CI: 1.02, 1.49), and placental abruptions (OR 2.39, 95% CI: 1.36, 4.21) when levothyroxine-treated mothers were excluded (STable 1). In this group, maternal hyperthyroidism was associated also with preterm births (OR 1.57, 95% CI: 1.27, 1.94), early preterm births (OR 2.13, 95% CI: 1.54, 2.95), SGA (OR 1.52, 95% CI: 1.20, 1.92), and neonatal intensive care unit treatment (OR 1.84, 95% CI: 1.60, 2.10) as in the main analyses (STable 2). In general, the effect estimates were slightly higher (range in differences -4% to +17%) when women with levothyroxine purchases were excluded.

DISCUSSION

In this large population-based register study, mothers diagnosed with hyperthyroidism had increased odds of pregnancy and/or perinatal complications such as gestational hypertensive disorders, preterm births, and neonatal intensive care unit treatment. The prevalence of diagnosed hyperthyroidism was 0.37%, which is consistent with the findings of previous reports.[1,2] This study also showed that 27% of hyperthyroid mothers had purchased ATDs during pregnancy, most likely indicating active hyperthyroidism during their pregnancies. Hyperthyroid mothers are assumed to be at high risk of developing pregnancy and/or perinatal complications due to active disease, and this was confirmed in the present study. In contrast, the majority of our study population (73%) did not use ATDs during pregnancy, and 23% used levothyroxine; both of these results suggest that these mothers had histories of hyperthyroidism rather than active disease that required treatment during pregnancy. Interestingly, we observed increased odds of adverse outcomes among these mothers as well, suggesting that a previous diagnosis of hyperthyroidism itself may pose a residual risk of developing pregnancy and/or perinatal complications. This supports the hypotheses that thyroid disorders can be considered expressions of

241 autoimmunity in general and that adverse pregnancy and perinatal outcomes may be associated with other
242 underlying autoimmune diseases.
243
244 Consistent with previous reports,[7,15,25] maternal hyperthyroidism was associated with increased odds of
245 gestational hypertensive disorders in the present study. These odds seemed to be slightly attenuated
246 among the mothers who did not use ATDs during pregnancy, suggesting that these odds may be higher
247 among mothers with active disease. The mothers with hyperthyroidism in the present study also had
248 increased odds of early preterm birth; this finding has been reported in many[6,7,16,25] but not all[12,13,26]
249 previous studies. In the present study, this association was somewhat stronger in the group of mothers
250 with ATD purchase, which was assumed to have had active hyperthyroidism during pregnancy. Maternal
251 hyperthyroidism was also associated with SGA, which is consistent with many previous studies reporting
252 an association between maternal hyperthyroidism and low birth weight.[8,15,25,27] Furthermore, infants of
253 hyperthyroid mothers were more likely to require respiratory or neonatal intensive care unit treatment, a
254 result that is also in line with the findings of previous research.[8] Once again, these odds were attenuated
255 in the mothers with hyperthyroidism who did not use ATDs during pregnancy, suggesting that these odds
256 are mainly driven by active, treated disease. In the present study, maternal hyperthyroidism was also
257 associated with cesarean sections, which supports the finding of previous studies.[12]
258
259 Recent reviews[28,29] and meta-analyses[19,20] found that the use of methimazole or carbimazole significantly
260 increased the incidence of congenital anomalies. Nonetheless, several reports have suggested that
261 propylthiouracil is safer than methimazole and carbimazole for the purpose of treating hyperthyroidism
262 during pregnancy.[30,31] Current international guidelines recommend the use of propylthiouracil in the first
263 trimester of pregnancy to reduce the risk of birth defects and the use of methimazole or carbimazole
264 thereafter to reduce maternal hepatotoxicity.[2] However, although some previous studies have found an
265 elevated risk of congenital anomalies associated with both drugs,[17,18] one study found no difference in the
266 rates of congenital anomalies between hyperthyroid mothers treated with propylthiouracil or
267 methimazole/carbimazole and those in the general population.[13] We found no association between

congenital anomalies and maternal hyperthyroidism, even among the ATD-treated mothers. In Finland, the prodrug carbimazole is typically used instead of methimazole; carbimazole was the treatment of choice in the majority of the pregnancies in the present study, whereas propylthiouracil use was very rare (5%). However, the sample size of the mothers with ATD purchases was relatively small, and the present study only examined data on pregnancies that resulted in delivery. Furthermore, no data were available on the duration of drug treatment. Additional data from the Register on Induced Abortions between 1996 and 2014 documented only five induced abortions resulting from fetal indications following carbimazole use (data not shown). Hence, it is unlikely that the significance of maternal treatment with carbimazole was underestimated in the present study.

Strengths and limitations

The present study had a number of strengths, including its use of high-quality data from large, nationwide health registers. In Finland, mothers typically give birth in hospitals and are supervised by obstetricians. Planned home births are extremely rare. Therefore, the MBR covers practically all births in Finland, and combining it with other registers increased this study's reliability. We were also able to adjust our estimates for identified confounders, and the large sample size made it possible to assess less frequently occurring outcomes. However, accounting for very rare outcomes such as stillbirths would require even larger cohorts. An additional strength of this study was that the data on ATD use were based on recorded medication purchases, thereby enabling us to extensively evaluate pregnancy and perinatal complications. As the presently examined data were extracted from national health registers collected and maintained by law, and thus prospectively collected, this study avoided recall bias.

In terms of limitations, treatment was defined as a drug purchase but did not include information on ATD treatment duration or dosage. Another limitation of our register study was the absence of laboratory findings to analyze the mothers' thyroid hormone or antibody statuses. However, in Finland, it is recommended that hyperthyroid mothers with positive thyroid antibodies are carefully managed and

followed up by obstetricians and endocrinologists in maternity care units. Therefore, the quality of care among hyperthyroid mothers in Finland is considered to be good. Additionally, we did not collect data regarding the exact dates on which the diagnoses of hyperthyroidism had been made. Nevertheless, we used ATD use as a proxy for active disease during pregnancy and assumed that non-treated women mostly had histories of hyperthyroidism.

CONCLUSIONS

Pregnant women with diagnoses of hyperthyroidism are at an increased risk of gestational hypertensive disorders, preterm birth, SGA, and neonatal intensive care unit admission. Women with active hyperthyroidism as well as women with histories of hyperthyroidism should be considered at risk of developing pregnancy and perinatal complications and should therefore be monitored during pregnancy.

CONFLICT OF INTEREST

Prof. Gissler and Dr. Leinonen report that they received grants from the Innovative Medicines Initiative (Building an ecosystem for better monitoring and communicating the safety of medicines' use in pregnancy and breastfeeding: validated and regulatory endorsed workflows for fast, optimised evidence generation, IMI ConcePTION, grant agreement number 821520) while conducting the study.
The other authors have explicitly stated that there are no conflicts of interest related to this article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are not publicly available. According to the national data protection legislation, permission to access the research data must be applied from the FinData.

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Table 1. Demographic Characteristics of the Mothers With Singleton Pregnancies With and Without Hyperthyroidism in Finland between 2004 and 2013.

Characteristics	Hyperthyroid mothers			Mothers without thyroid disease (reference group)
	All hyperthyroid mothers	Hyperthyroid mothers with thyreostatic medication	Hyperthyroid mothers without thyreostatic medication	
	n=2144	*n*=580	*n*=1564	*n*=550 860
Maternal age, years				
<20 years	10 (0.5)	3 (0.5)	7 (0.4)	13 669 (2.5)
20-34 years	1584 (73.9)	450 (77.6)	1134 (72.5)	436 181 (79.2)
≥35 years	550 (25.7)	127 (21.9)	423 (27.0)	101 010 (18.3)
Smoking				
No smoking	1757 (81.9)	456 (78.6)	1301 (83.2)	453 142 (82.3)
Quit smoking during 1st trimester	83 (3.9)	25 (4.3)	58 (3.7)	27 232 (4.9)
Smoked through pregnancy	256 (11.9)	80 (13.8)	176 (11.3)	57147 (10.4)
Data missing	48 (2.2)	19 (3.3)	29 (1.9)	13 339 (2.4)
Parity				
Nulliparous	594 (26.3)	160 (27.6)	434 (27.7)	231 523 (42.0)
Multiparous	1549 (72.2)	420 (72.4)	1129 (72.2)	318 858 (57.9)
Data missing	1 (0.0)	0 (0.0)	1 (0.1)	479 (0.1)
Previous miscarriages				
No previous miscarriages	1549 (72.2)	442 (76.2)	1107 (70.8)	435 207 (79.0)
One or more previous miscarriage	593 (27.7)	137 (23.6)	456 (29.2)	115 042 (20.9)
Data missing	2 (0.1)	1 (0.2)	1 (0.1)	611 (0,1)
Body mass index				
<18.5	86 (4.0)	29 (5.0)	57 (3.6)	19 943 (3.6)
18.5-24.9	1221 (56.9)	322 (55.5)	899 (57.5)	327 734 (59.5)
25-29.9	480 (22.4)	142 (24.5)	338 (21.6)	112 836 (20.5)
≥30	263 (12.3)	66 (11.4)	197 (12.6)	59 734 (10.8)
Data missing	94 (4.4)	21 (3.6)	73 (4.7)	30 613 (5.6)
Socioeconomic status				
Upper white-collar worker	343 (16.0)	77 (13.3)	266 (17.0)	92 011 (16.9)
Lower white-collar worker	674 (31.4)	171 (29.5)	503 (32.2)	174 948 (31.8)
Blue-collar worker	268 (12.5)	85 (14.7)	183 (11.7)	67 704 (12.3)
Student	187 (8.7)	49 (8.4)	138 (8.8)	55 107 (10.0)
Other	170 (7.9)	41 (7.1)	129 (8.2)	32 327 (5.9)
Data missing	502 (23.4)	157 (27.1)	345 (22.1)	127 878 (23.2)

The data are reported as number of mothers (%) unless stated otherwise.

Table 2. Prevalence and Odds of Pregnancy Complications Among Singleton Pregnancies of Mothers With and Without Hyperthyroidism in Finland Between 2004 and 2013.

	Mothers without thyroid disease (reference group)	Hyperthyroid mothers								
		All hyperthyroid mothers			Hyperthyroid mothers with antithyroid medication			Hyperthyroid mothers without antithyroid medication		
	N (%) 550 860 (96.34)	N (%) 2144 (0.4)	Odds ratios	95% confidence interval	N (%) 580 (0.1)	Odds ratios	95% confidence interval	N (%) 1564 (0.3)	Odds ratios	95% confidence interval
Gestational hypertensive disorders	24 106 (4.4)	114 (5.3)	1.32	1.08, 1.63	77 (4.9)	1.67	1.18, 2.36	42 (2.6)	1.19	0.93, 1.53
Gestational diabetes	49 041(8.9)	211 (9.8)	0.91	0.77, 1.07	62 (10.7)	0.98	0.72, 1.34	149 (9.5)	0.89	0.73, 1.07
Any caesarean section	86 450 (15.7)	414 (19.3)	1.26	1.12, 1.42	93 (16.0)	1.05	0.84, 1.31	321 (20.5)	1.35	1.18, 1.55
Elective caesarean section	34 636 (6.3)	178 (8.3)	1.23	1.04, 1.45	41 (7.1)	1.08	0.79, 1.48	137 (8.8)	1.27	1.04, 1.54
Acute caesarean section	51 814 (9.4)	236 (11.0)	1.28	1.10, 1.48	52 (9.0)	1.03	0.77, 1.38	184 (11.8)	1.39	1.17, 1.65
Instrumental delivery	45 121 (8.2)	162 (7.6)	1.14	0.96, 1.35	44 (7.6)	1.14	0.82, 1.58	118 (7.5)	1.14	0.93, 1.38
Placental abruption	1561 (0.3)	13 (0.6)	1.98	1.15, 3.41	3 (0.5)	1.68	0.54, 5.23	10 (0.6)	2.11	1.13, 3.92
Placenta previa	2693 (0.5)	14 (0.7)	1.24	0.74, 2.10	4 (0.7)	1.35	0.51, 3.61	10 (0.6)	1.21	0.65, 2.25

The data are reported as number of mothers (%) unless stated otherwise.

401 Table 3. Prevalence and Odds of Perinatal Complications Among Singleton Pregnancies of Mothers With and Without
402 Hyperthyroidism in Finland Between 2004 and 2013.

	Mothers without thyroid disease (reference group)	Hyperthyroid mothers					
		All hyperthyroid mothers			Hyperthyroid mothers with antithyroid me		
	N (%) 550 860 (96.34)	N (%) 2144 (0.37)	Odds ratios	95% confidence interval	N (%) 580 (0.10)	Odds ratios	95% confid interva
All preterm births	21 629 (3.9)	111 (5.2)	1.34	1.09, 1.64	35 (6.0)	1.56	1
Early (<34 gestational weeks)	6160 (1.1)	44 (2.1)	1.87	1.39, 2.53	15 (2.6)	2.29	1
Late (34+0-36+6 gestational weeks)	15 469 (2.8)	67 (3.1)	1.11	0.85, 1.43	20 (3.4)	1.23	0
Small-for-gestational age	19 674 (3.6)	91 (4.2)	1.30	1.04, 1.63	34 (5.9)	1.76	1
Large-for-gestational age	13 127 (2.4)	67 (3.1)	1.11	0.85, 1.44	20 (3.4)	1.20	0
Major congenital anomalies	22 918 (4.3)	109 (5.1)	1.15	0.95, 1.40	33 (5.7)	1.27	0
Neonatal intensive care unit treatment	55 072 (10.0)	325 (15.2)	1.65	1.46, 1.86	108 (18.6)	2.10	1
Respiratory treatment	5490 (1.0)	30 (1.4)	1.40	0.98, 2.02	11 (1.9)	1.95	1
Stillbirths	1547 (0.3)	7 (0.3)	1.14	0.54, 2.40	2 (0.3)	1.11	0
Early neonatal deaths	642 (0.1)	4 (0.2)	1.63	0.60, 4.46	0 (0.0)	NA	

403 The data are reported as number of mothers (%) unless stated otherwise.
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