Pregnancy and perinatal outcome among hypothyroid mothers: a population based cohort study

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ABSTRACT

Background: Maternal hypothyroidism has been associated with adverse pregnancy outcomes. We established a large nationwide register-based cohort with data on medication purchases to study the associations between maternal hypothyroidism, levothyroxine use and pregnancy and perinatal complications.

Methods: Our data included all singleton births between 2004 and 2013 (N=571,785) in Finland. Hypothyroid mothers (N=16,364) were identified in the Finnish Medical Birth Register. Of these women 95.8% used levothyroxine medication and 37.5% had consistent levothyroxine use during pregnancy. Hypothyroid mothers were compared with mothers without thyroid disease (N=550,860) using logistic regression. Main outcome measures were pregnancy and perinatal complications.

Results: Maternal hypothyroidism associated with several pregnancy and perinatal complications including gestational diabetes mellitus (GDM) (OR 1.19, 95% CI 1.13−1.25), gestational hypertension (OR 1.20, 95% CI 1.10−1.30), severe preeclampsia (OR 1.38, 95% CI 1.15−1.65), caesarean sections (CS) (OR 1.22, 95% CI 1.17−1.27), preterm births (OR 1.25, 95% CI 1.16−1.34), large-for-gestational age newborns (LGA) (OR 1.30, 95% CI 1.19−1.42), major congenital anomalies (OR 1.14, 95% CI 1.06−1.22) and neonatal intensive care unit (NICU) admission (OR 1.23, 95% CI 1.17−1.29). However, among mothers with consistent levothyroxine purchases, only the associations between GDM (OR 1.12, 95% CI 1.03−1.22), CS (OR 1.13, 95% CI 1.06−1.21), NICU admission (OR 1.09, 95% CI 1.01−1.29) and LGA newborns (OR 1.26, 95% CI 1.10−1.45) and maternal hypothyroidism remained.

Conclusions: Maternal hypothyroidism is associated with several pregnancy and perinatal complications but consistent levothyroxine use may reduce many of the risks.

INTRODUCTION

Overt or subclinical hypothyroidism affects up to 2-3% of all pregnancies (1, 2), but the prevalence of undiagnosed subclinical hypothyroidism in pregnant women varies widely from 3% to 15% in the literature (3). Untreated hypothyroidism is a threat to fertility (1), pregnancy (4) and fetal development (5). Pregnancy increases thyroid hormone requirements and the need for levothyroxine substitution is known to increase during pregnancy in up to 85% of hypothyroid women (6). Therefore, women with diminished thyroid reserve are especially at risk for sub-optimal treatment (7).

Subclinical or inadequately treated maternal hypothyroidism has been associated with adverse pregnancy outcomes including spontaneous abortions (3, 8, 9), gestational hypertension or preeclampsia (3, 10-13), gestational diabetes mellitus (GDM) (3, 10, 11, 14-16), preterm delivery (2, 3, 11), low birth weight (15), placental abruption (2) and fetal death (14). Positive maternal thyroid autoantibodies in euthyroid women have been associated with miscarriage (8), preterm birth (8, 17), and perinatal mortality (18). Moreover, caesarean section (CS) (9-11, 16), induction of labor (10) and neonatal intensive care unit (NICU) admission (11) have been associated with maternal hypothyroidism. However, not all studies have found an increased risk of adverse outcomes associated with maternal subclinical hypothyroidism (1, 19, 20).

We established a large register- and population-based cohort with data on medication purchases during pregnancy to study if maternal hypothyroidism associates with pregnancy or perinatal complications and how consistent levothyroxine use impacts these associations.

MATERIALS AND METHODS

The data are based on the Finnish Medical Birth Register (MBR, established in 1987 and maintained by the National Institute for Health and Welfare) and included all births in Finland between 2004 and 2013

(N=589,459). After excluding multiple pregnancies (N=17,674), the data consisted of 357,293 women with 571,785 singleton pregnancies.

For each delivery in Finland, personnel at the delivery hospital complete a structured form for the MBR completed at hospital discharge or at seven days after delivery, whichever occurs first. In Finland practically all women give birth in delivery hospitals led by obstetricians and planned home births are very rare with 13 per year during the study period. The MBR includes data on all live births and stillbirths with birth weight ≥500 g or gestational age at birth ≥22 weeks with key perinatal and newborn data up to the age of seven days. Maternal data from the MBR include age, occupation, place of residence, marital status, pregnancy history, smoking status, diseases and hospitalization during pregnancy and mode of delivery. Data on the newborn include sex, gestational age at birth, birth weight and height, head circumference, umbilical artery and vein pH, diagnosis, treatment, and hospitalization during the perinatal period. The data quality of the MBR is good or satisfactory when compared with hospital record data (21) and the usefulness of MBR increases when data from other registers are used (22).

Information on major congenital anomalies was obtained from the Finnish Malformation Register, which includes information on all newborns in Finland with at least one detected major congenital anomaly classified and coded according to the extended International Classification of Diseases version 9 (ICD-9). Minor anomalies are excluded from the register according to the practices of the European Surveillance of Congenital Anomalies (23).

The data on levothyroxine purchases three months prior and during the current pregnancy were obtained from the Statistics on Reimbursements for Medical Expenses (Prescription Register and Special Refund Entitlement Register) maintained by the Social Insurance Institution. The register collects information from all pharmacies in Finland on all reimbursed prescription-only medication purchases such as levothyroxine. Medications given in hospitals or over-the-counter drugs are not included in the register. The register data include information related to the medicine: the International Anatomic Therapeutic

Chemical classification code (codes H03A01−05 for levothyroxine) and the time and number of purchases. Any levothyroxine purchases indicated levothyroxine use in this study. Levothyroxine use was deemed consistent if a mother had purchased levothyroxine during each trimester of pregnancy with or without pre-pregnancy purchases. For pregnant women levothyroxine is the treatment of choice for hypothyroidism in Finland.

We collected information on maternal chronic diseases from the MBR, the Special Refund Entitlement Register maintained by Social Insurance Institution, and the Hospital Discharge Register. The Special Refund Entitlement Register comprises information on diagnosed chronic diseases with medication and reimbursement of medical expenses. The Hospital Discharge Register includes information on diagnoses at discharge from all hospital wards using the ICD-codes. The register has an accuracy of 83%−95% (24). Data linkage between MBR and the other registers was possible using the unique personal identification numbers assigned to all Finnish citizens and permanent residents. Personnel uninvolved with this study performed the data linkage and data encryption before statistical analyses.

Identification of women with hypothyroidism and exposure to levothyroxine during pregnancy in 2004−2013

In our study, women had hypothyroidism if they were listed as having the ICD-10 code E03 (with all digits), ICD-9 or ICD-8 code 244 for hypothyroidism in any of the registers or if they performed levothyroxine purchases three months prior or during the current pregnancy (N=16,364). Women diagnosed with ICD-10 code O99.2 (endocrine, nutritional and metabolic diseases complicating pregnancy, childbirth, and puerperium) who had documented levothyroxine purchases were also deemed hypothyroid. Women with other thyroid diseases (hyperthyroidism, thyroiditis, goiter, iodine-deficiency-related disorders, benign and malignant neoplasms of thyroid gland) (N=4544) were identified through the registers and excluded from the current study.

Pregnancy, perinatal and infant health outcomes

The main pregnancy-related outcome measures obtained from the MBR were as follows: gestational hypertension, mild/moderate or severe preeclampsia/HELLP (hemolysis, elevated liver enzymes, low platelet count syndrome), eclampsia, GDM, delivery mode (vaginal, breech, instrumental, or elective CS and acute CS), placenta previa and placental abruption. The main perinatal outcomes were early (< 34 completed gestational weeks) and late (34+0−36+6 gestational weeks) preterm births, number of small-for-gestational age (SGA, birth weight less than 2 standard deviations from the gestational age adjusted mean) and large-for-gestational age (LGA, birth weight more than 2 standard deviations from the gestational age adjusted mean) infants, low Apgar score (<7 points at 5 min), major congenital anomalies, admission to NICU, need for respiratory treatment, stillbirth, and early neonatal death.

Ethical issues

The study was approved by the ethical board of Northern Ostrobothnia Hospital District. The National Institute of Health and Welfare gave permission to use data obtained from the national health registers. Data collection was conducted with permission from the register administrators. The study was funded in part by the Northern Ostrobothnia Hospital District.

Statistical analyses

Pregnancy was the unit of analysis for all statistical testing. Demographic data on mothers with hypothyroidism and mothers with hypothyroidism with consistent levothyroxine purchases were compared to mothers without thyroid disease using chi-squared test or Fisher's exact test. Logistic regression with generalized estimating equations (GEE) and a first-order autoregressive correlation matrix were used to estimate the odds ratios (ORs) with 95% confidence intervals (CIs) of adverse outcomes among women with hypothyroidism compared with mothers without thyroid disease. The GEE accounted

for the correlations among the repeated pregnancies of the same mother. All analyses were adjusted for maternal age at delivery, body mass index, parity, smoking status, socioeconomic status (i.e. upper white collar, lower white collar, blue collar worker, other, and unknown), year of delivery, and maternal residence within the five university hospital districts. As the unadjusted and adjusted odds were similar, only the adjusted odds are presented. Missing data on outcomes were rare and excluded on a case basis. Statistical analyses were performed using SAS version 9.3.

RESULTS

Demographic data

Overall 16,364 of all pregnancies (3%) were complicated by maternal hypothyroidism in years 2004-2013. Of these women, 95.8% had documented levothyroxine purchases at some state of pregnancy and 37.5% had consistent levothyroxine purchases during pregnancy. Altogether, 65.9% of mothers with consistent levothyroxine purchases had also pre-pregnancy purchases. The mothers with hypothyroidism were older, more often multiparous, more likely to be overweight or obese, smoked less and had had more miscarriages than women without thyroid disorders (Table 1).

Pregnancy complications

The odds of gestational hypertension (OR 1.20, 95% CI 1.10−1.30) and severe preeclampsia (OR 1.38, 95% CI 1.15−1.65) were associated with maternal hypothyroidism, but these odds were no longer statistically significant when restricting the data to hypothyroid mothers with consistent levothyroxine purchases (Figure 1). Moreover, an association between GDM (OR 1.19, 95% CI 1.13−1.25), placenta previa (OR 1.44, 95% CI 1.21−1.72), elective CS (OR 1.24, 95% CI 1.17−1.32) and acute CS (OR 1.15, 95% CI 1.09−1.21) with maternal hypothyroidism was observed. These associations persisted among

mothers with consistent levothyroxine purchases (Figure 1). We observed no association between breech presentation, instrumental delivery or placental abruption and maternal hypothyroidism.

Perinatal outcome

Maternal hypothyroidism was associated with both early and late preterm births (OR 1.35, 95% CI 1.19−1.53 and OR 1.20, 95% CI 1.10−1.31, respectively). Again, these odds were no longer statistically significant when restricting the data to mothers with consistent levothyroxine purchases (Figure 2). Moreover, we found an association between NICU admission (OR 1.23, 95% CI 1.17−1.29), need for respiratory treatment (OR 1.41, 95% CI 1.24−1.60) and lower Apgar scores at 5 min (OR 1.20, 95% CI 1.09−1.33) and maternal hypothyroidism, but none with umbilical artery pH. The newborns of hypothyroid mothers were more often LGA than those of mothers without thyroid disease (OR 1.30, 95% CI 1.19−1.42). Slightly increased odds of major congenital anomalies were found among children born to mothers with hypothyroidism (OR 1.14, 95% CI 1.06−1.22). Only the association between NICU admission (OR 1.09, 95% CI 1.01−1.18) and LGA newborns (OR 1.26, 95% CI 1.10−1.45) with maternal hypothyroidism remained among those with consistent levothyroxine purchases (Figure 2). The incidence of stillbirths and early neonatal deaths was low and did not differ between groups.

Additional analysis

The demographic data of mothers with consistent levothyroxine use was similar to those of mothers who had levothyroxine treatment started during the second and the third trimester. Including women with type I diabetes into analyses had no major effect on any of the results.

DISCUSSION

Our study is the only one that extensively evaluated pregnancy and perinatal complications with levothyroxine use established through medication purchases. We show that up to 3% of women giving birth were on levothyroxine medication during pregnancy. Maternal hypothyroidism increased the odds of GDM, CS, and LGA as well as the risk for NICU admission even if levothyroxine use was consistent during pregnancy. The odds of gestational hypertension, severe preeclampsia, preterm births and congenital anomalies seemed to be driven by non-consistent levothyroxine use, as we did not observe these increased odds for mothers with consistent levothyroxine use.

The observed association between GDM and hypothyroidism was found in some (10, 14, 15, 17) but not all previous studies (25). Adequate thyroid function maintains normal energy and lipid metabolism (26). Therefore underlying changes in energy metabolism, insulin resistance and autoimmune diseases or shared risk factors (i.e. obesity, age, and parity) may explain the association between hypothyroidism and GDM. Moreover, women with hypothyroidism are at increased risk of subsequent diabetes, suggesting common risk factors (18). Like some previous studies, we also observed an association between hypothyroidism and LGA (27). The observed association between maternal hypothyroidism and GDM may at least partly explain this finding.

Mothers with hypothyroidism had increased odds of CS, a finding previously found in some (9-11, 17) but not all studies (20). In one previous work, hypothyroidism was an independent risk factor for CS (9), but the reason for increased risk could be due to the associated pregnancy complications, such as hypertension and diabetes. In previous studies, associations between maternal hypothyroidism and gestational hypertension, preeclampsia and preterm birth have been controversial (2, 8, 10-12, 15, 16, 20, 28). In our study, we also found these aforementioned associations but these odds were no longer statistically significant among mothers with consistent levothyroxine use, suggesting that adequate treatment throughout pregnancy may diminish the risk for these complications. Differences in the adequacy of treating hypothyroidism in different studies or lack of controlling for confounders may partly explain these controversial findings.

Newborns of hypothyroid mothers were more likely to need NICU admission or respiratory treatment, which is consistent with previous studies (11, 27). The odds of NICU admission and respiratory treatment persisted after restricting data to term births, thus suggesting that prematurity did not fully explain this association. A small but statistically significant association between congenital anomalies and maternal hypothyroidism was found. This finding was previously observed at least in two studies (10, 29). Our finding persisted after adjusting for covariates and the exclusion of women with type 1 diabetes who are known to have a higher risk of congenital anomalies (30).

Strengths and limitations

The strength of this study is its large sample size with comprehensive nation-wide data based on compulsory administrative health registers of high quality. The MBR covers practically all births in Finland. Combining medication data with the MBR data gave us a valuable database for research purposes. Data were derived from the population with minimal loss to follow-up of study subjects and therefore selection bias was not a concern. However, since our data are based on births, it contains only pregnancies that resulted in delivery. Therefore women with sub- or infertility, which possibly associate with thyroid dysfunction, may have not been included. The risk of recall bias was avoided, as the information was based on administrative register data and collected prospectively during routine visits to maternity welfare clinics. Practically all pregnant Finnish women attend this free-of-charge public maternity care with regular visits to a nurse/midwife and a physician near their local residence and they give birth at public hospitals led by obstetricians. The large dataset provided the opportunity to assess rare outcomes with the ability to evaluate and adjust for confounding factors. However, very rare outcomes like neonatal deaths might require even bigger cohort studies.

The compact study period (10 years) with a comprehensive data collection and uniform national recommendations to treat hypothyroidism gave us an outstanding database for our study. National

evidence-based guidelines, which include information on common pregnancy-related problems and their management, are available for maternity care personnel. Hypothyroid mothers without other pregnancy-related problems are mainly treated at the local maternity care during their pregnancies. In case of pregnancy complication they are sent to specialized maternity policlinics in the delivery hospital.

Laboratory data to confirm the thyroid hormone and thyroid antibody status would have been useful but were not feasible given the study size. Therefore, it is unknown whether women who were taking levothyroxine during pregnancy were adequately treated or if they had overt or subclinical hypothyroidism. In fact, in a recent study many levothyroxine-treated women had early gestational TSH levels above the recommended targets and even overt hypothyroidism (31). In our study, only 39% of hypothyroid women had levothyroxine purchases in each trimester. We considered that these hypothyroid women were most likely adequately treated during pregnancy and therefore had the lowest risk of adverse pregnancy and perinatal outcomes. Our study suggests that non-consistent levothyroxine use associates with adverse pregnancy and perinatal outcomes - regardless of whether the non-consistent use is due to inadequate treatment of a known thyroid disease or due to treating newly diagnosed hypothyroidism during pregnancy.

Conclusion

Hypothyroidism is common among women in child-bearing age, and it is associated with some adverse pregnancy and perinatal outcomes. In this large register- and population-based cohort study maternal hypothyroidism was associated with several pregnancy and perinatal complications, but among mothers with consistent levothyroxine use, the odds of some important complications (gestational hypertension, severe preeclampsia and preterm births) were no longer statistically significant. However, maternal hypothyroidism was associated with increased odds for GDM, CS, and LGA, as well as the risk for NICU admission, even if levothyroxine use was consistent during pregnancy.

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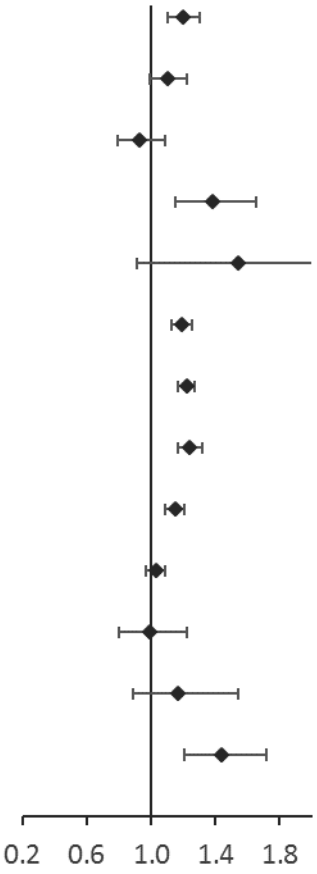
Table 1.
Demographic Characteristics of Mothers With Singleton Pregnancies (2004-2013) With and Without Hypothyroidism

Characteristics	Mothers with hypothyroidism (all)	Mothers with hypothyroidism with consistent levothyroxine purchases	Mothers without thyroid disease
	n=16 364	*n*=6132	*n*=550 860
Maternal age, years			
<20 years	111 (0.68)	22 (0.36)	13 669 (2.48)
20-34 years	11 597 (70.87)	4294 (70.03)	436 181 (79.18)
>35 years	4656 (28.45)	1816 (29.62)	101 010 (18.34)
Smoking			
No smoking	14 139 (86.40)	5446 (88.81)	453 142 (82.26)
Quit smoking during 1st trimester	712 (4.35)	232 (3.78)	27 232 (4.94)
Smoked through pregnancy	1179 (7.20)	344 (5.61)	57147 (10.37)
Data missing	334 (2.04)	110 (1.79)	13 339 (2.42)
Parity			
Nulliparous	6391 (39.06)	2522 (41.13)	231 523 (42.03)
Multiparous	9970 (60.93)	3609 (58.86)	318 858 (57.88)
Data missing	3 (0.02)	1 (0.02)	479 (0.09)
Previous miscarriages			
No previous miscarriages	11 954 (73.05)	4465 (72.81)	435 207 (79.01)
One or more previous miscarriage	4406 (26.92)	1666 (27.17)	115 042 (20.88)
Data missing	4 (0.02)	1 (0.02)	611 (0,11)
Body mass index			
<18.5	349 (2.13)	128 (2.09)	19 943 (3.62)
18.5-24.9	8236 (50.33)	3229 (52.66)	327 734 (59.49)
25-29.9	3946 (24.11)	1460 (23.81)	112 836 (20.48)
≥30	3210 (19.62)	1145 (18.67)	59 734 (10.84)
Data missing	623 (3.81)	170 (2.77)	30 613 (5.56)
Socioeconomic status			
Upper white-collar worker	2864 (17.50)	1174 (19.15)	92 011 (16.91)
Lower white-collar worker	5677 (34.69)	2084 (33.99)	174 948 (31.76)
Blue-collar worker	1811 (11.07)	691 (11.27)	67 704 (12.29)
Student	1273 (7.78)	426 (6.95)	55 107 (10.00)
Other	1027 (6.28)	323 (5.52)	32 327 (5.87)
Data missing	3712 (22.68)	1434 (23.39)	127 878 (23.21)
Marital status			
Married/cohabiting	14 803 (90.46)	5595 (91.24)	490 590 (89.06)
Single	750 (4.58)	224 (3.65)	31 435 (5.71)
Data missing	811 (4.96)	313 (5.10)	28 835 (5.23)

The data are reported as number of mothers (%) unless stated otherwise.
Data on mothers with hypothyroidism and mothers with hypothyroidism with consistent levothyroxine purchases were compared to mothers without thyroid disease using chi-squared test or Fisher's exact test. All comparisons were statistically significant with a p-value <0.0001.

Figure 1.

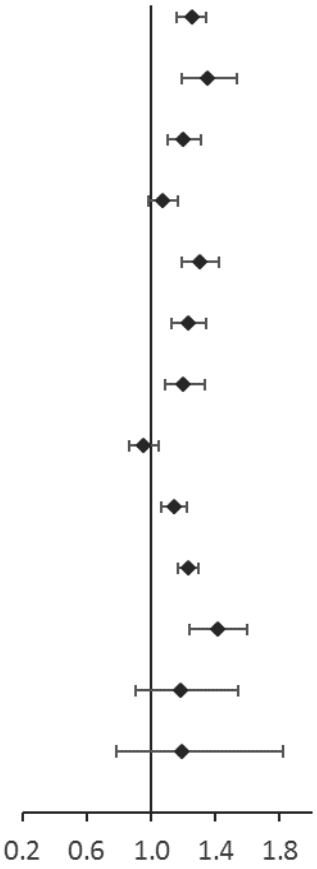
Pregnancy outcome	Ref. mothers 550 860 (97.12%) N (%)	Mothers with hypothyroidism (all), 16 364 (2.29%) N (%)	OR with 95% CI	OR (95% CI)	Mo
Gestational hypertension	15 950 (2.9)	676 (4.1)		1.2 (1.1–1.3)	237
Any preeclampsia	10 285 (1.9)	414 (2.5)		1.1 (1.0–1.2)	117
Mild preeclampsia	5136 (0.9)	164 (1.0)		0.9 (0.8–1.1)	60
Severe preeclampsia	2575 (0.5)	133 (0.8)		1.4 (1.2–1.7)	27
Eclampsia*	285 (0.05)	16 (0.1)		1.5 (0.9–2.6)	6
Gestational diabetes	49 041(8.9)	2620 (16.0)		1.2 (1.1–1.3)	898 (
Any cesarean section	86 450 (15.7)	3470 (21.2)		1.2 (1.2–1.3)	
Elective cesarean section	34 636 (6.3)	1495 (9.1)		1.2 (1.2–1.3)	517
Acute cesarean section	51 814 (9.4)	1975 (12.1)		1.2 (1.1–1.2)	719 (
Instumental delivery	45 121 (8.2)	1381 (8.4)		1.0 (1.0–1.1)	568
Breech presentation	3349 (0.6)	97 (0.6)		1.0 (0.8–1.2)	44
Placental abruption	1561 (0.3)	55 (0.3)		1.2 (0.9–1.5)	20
Placental previa	2693 (0.5)	130 (0.8)		1.4 (1.2–1.7)	48



*Please note that upper limits of confidence intervals for eclampsia lie outside the plot area
The data are reported as number of mothers (%) and odds ratios (ORs) with 95% confidence interval (95% CI)

Figure 2.

Perinatal outcome	Ref. mothers 550 860 (97.12%) N (%)	Mothers with hypothyroidism (all), 16 364 (2.29%) N (%)	OR with 95% CI	OR (95% CI)	Mo
All preterm births	21 629 (3.9)	882 (5.4)		1.3 (1.2–1.3)	219
Early (<34 gest.weeks)	6160 (1.1)	266 (1.6)		1.4 (1.2–1.5)	28
Late (34+0-36+6 weeks)	15 469 (2.8)	616 (3.8)		1.2 (1.1–1.3)	191
Small for gestational age	19 674 (3.6)	599 (3.7)		1.1 (1.0–1.2)	199
Large for gestational age	13 127 (2.4)	697 (4.3)		1.3 (1.2–1.4)	234
Low birth weight	12 364 (3.2)	639 (3.9)		1.2 (1.1–1.3)	147
Apgar scores <7 at 5min	10 610 (2.3)	424 (2.6)		1.2 (1.1–1.3)	154
Umbilical artery pH	12 688 (3.5)	432 (2.6)		1.0 (0.9–1.1)	174
Congenital anomalies	22 918 (4.2)	818 (5.0)		1.1 (1.1–1.2)	287
NICU treatment	55 072 (10.0)	2352 (14.4)		1.2 (1.2–1.3)	761 (
Respiratory treatment	5490 (1.0)	252 (1.5)		1.1 (1.2–1.6)	61
Stillbirths	1547 (0.3)	57 (0.3)		1.2 (0.9–1.5)	11
Early neonatal deaths	642 (0.1)	23 (0.1)		1.2 (0.8–1.8)	6



The data are reported as number of mothers (%) and odds ratios (ORs) with 95% confidence interval (95% CI)
NICU = neonatal intensive care unit