Maternal Thyroid Hormone Parameters during Early Pregnancy and Birth Weight: The Generation R Study

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Context: Maternal hyperthyroidism during pregnancy is associated with an increased risk of low birth weight, predisposing to neonatal morbidity and mortality. However, the effects of variation in maternal serum thyroid parameters within the normal range on birth weight are largely unknown.

Objective: The aim was to study the effects of early pregnancy maternal serum thyroid parameters within the normal range on birth weight, as well as the relation between umbilical cord thyroid parameters and birth weight.

Design, Setting, and Participants: In early pregnancy, serum TSH, FT4 (free T_4), and thyroid peroxidase antibody levels were determined in 4464 pregnant women. Cord serum TSH and FT4 levels were determined in 2724 newborns. Small size for gestational age at birth (SGA) was defined as a gestational age-adjusted birth weight below the 2.5th percentile. The associations between normal-range maternal and cord thyroid parameters, birth weight, and SGA were studied using regression analyses.

Results: In mothers with normal-range FT4 and TSH levels, higher maternal FT4 levels were associated with lower birth weight [$\beta = -15.4$ (3.6) g/pmol · liter, mean (SE); $P = 1.6 \times 10^{-5}$], as well as with an increased risk of SGA newborns [odds ratio (95% confidence interval) = 1.09 (1.01–1.17); $P = 0.03$]. Birth weight was positively associated with both cord TSH [$\beta = 4.1$ (1.4) g/mU · liter; $P = 0.007$] and FT4 levels [$\beta = 23.0$ (3.2) g/pmol · liter; $P = 9.2 \times 10^{-13}$].

Conclusions: We show that maternal high-normal FT4 levels in early pregnancy are associated with lower birth weight and an increased risk of SGA newborns. Additionally, birth weight is positively associated with cord TSH and FT4 levels. These data demonstrate that even mild variation in thyroid function within the normal range can have important fetal consequences. (***J Clin Endocrinol Metab* 98: 59–66, 2013**)

Abnormal maternal thyroid function during pregnancy is associated with a wide range of adverse fetal and neonatal outcomes, including intrauterine fetal death, impaired neurodevelopment, and low birth weight (LBW) (1–3). LBW can be due either to intrauterine growth retardation [small size for gestational age (SGA) at birth] or

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Abbreviations: ANCOVA, Analysis of covariance; BMI, body mass index; FT4, free T_4; OR, odds ratio; SDS, SD score; SES, socioeconomic status; SGA, small size for gestational age; TPOAb, thyroid peroxidase antibody.

prematurity. SGA is associated with an increased risk of perinatal mortality and other complications such as low Apgar scores and seizures (4). For decades, it has been known that SGA is also associated with the occurrence of various diseases in later life, such as coronary heart disease, type 2 diabetes, and hypertension (5). SGA has also been associated with a wide range of other diseases, including renal failure, osteoporosis, male reproductive problems, and depression (6–10).

Various studies have investigated the effects of abnormal maternal thyroid function during pregnancy on birth weight (11–15). A few of these large studies have shown a substantially increased risk of LBW in children born to hyperthyroid mothers (11–13). However, little is known about the effects of variation in maternal serum thyroid parameters within the normal range on birth weight.

Various maternal autoimmune diseases such as systemic lupus erythematosus, antiphospholipid syndrome, and rheumatoid arthritis have been associated with a lower birth weight (16–19). Because thyroid peroxidase antibody (TPOAb) positivity is a common finding in pregnant women, it is remarkable that limited data are available on the relation between maternal TPOAb status and birth weight.

For these reasons, we investigated the effects of early pregnancy maternal serum thyroid parameters within the normal range on birth weight in 4464 mother-child pairs from a population-based cohort study, as well as the effects of maternal TPOAb status on birth weight. In addition, the associations between cord thyroid parameters and birth weight were studied. We hypothesized that, also in the normal range, higher free T_4 (FT4) and/or lower TSH levels would be associated with a lower birth weight. Because maternal autoimmune diseases have been associated with a lower birth weight (16–19), we additionally corrected the TPOAb status and birth weight analyses for maternal thyroid status to study the effects of the autoimmune status itself (independent of the effects on thyroid parameters).

Subjects and Methods

Design

This study was embedded in the Generation R Study, a population-based cohort from early fetal life onward in Rotterdam, The Netherlands, which has been described in detail previously (20–22). Mothers with a delivery date between April 2002 and January 2006 were enrolled. The Medical Ethics Committee of the Erasmus Medical Center, Rotterdam, approved the study. Written informed consent was obtained from all participants.

Population for analysis

Data on serum TSH and FT4 levels were complete for 5770 women with a live birth pregnancy without congenital anomalies or trisomies. Women with known thyroid disease or thyroid (interfering) medication usage (n = 88) were excluded. Women with known comorbidities (including diabetes, chronic hypertension, hypercholesterolemia, chronic heart disorder, and systemic lupus erythematosus; n = 227), twin pregnancies (n = 62), and pregnancies after fertility treatment (n = 69) were also excluded. From the resulting group of 5324 women, 4464 women had available data on birth weight and were included in one or more analyses. Cord serum TSH and FT4 levels were available in 2724 of their newborns.

Thyroid parameters

Maternal serum samples were obtained in early pregnancy (mean = 13.3 wk; SD = 1.7), and cord serum samples were obtained at birth (mean = 39.9 wk; SD = 1.9) (22). Maximally 3 h after sampling, plain tubes were centrifuged and serum was stored at −80 C (23). TSH and FT4 were determined in maternal and cord serum samples using chemiluminescence assays (Vitros ECI; Ortho Clinical Diagnostics, Rochester, NY). The intra- and interassay coefficients of variation were below 4.1% for TSH and below 5.4% for FT4. Maternal TPOAb was measured using the Phadia 250 immunoassay (Phadia AB, Uppsala, Sweden) and regarded as positive when above 60 IU/ml (22).

Outcome measurements

Information on birth weight was obtained from medical records completed by community midwives and obstetricians. SGA was defined as a gestational age-adjusted birth weight below the 2.5th percentile in the study cohort (less than −2.09 SD). Prematurity was defined as delivery at a gestational age of less than 37 wk. LBW was defined as a birth weight of less than 2500 g.

Ultrasound measurements were used to establish gestational age in early pregnancy (planned at gestational age 12 wk) and to estimate fetal weight in midpregnancy (planned at gestational age 20 wk) and late pregnancy (planned at gestational age 30 wk) using the formula of Hadlock *et al.* (24).

Covariates

Information on maternal age, parity, smoking habits, vomiting during first trimester, socioeconomic status (SES), ethnicity, and comorbidity (including diabetes, chronic hypertension, hypercholesterolemia, chronic heart disorder, and systemic lupus erythematosus) was obtained by questionnaires during pregnancy. Maternal prenatal smoking was classified as no smoking, smoking until pregnancy, and continued smoking during pregnancy (25). SES was defined by educational level, net household income, and employment status (20). At enrollment, maternal height and weight were measured to calculate body mass index (BMI) in kilograms per square meter. Information on fertility treatment and fetal gender was obtained from midwives and obstetricians.

Statistical analysis

Reference ranges for maternal TSH and FT4 were defined as the range between the 2.5th and 97.5th percentiles, after exclusion of women with positive TPOAbs, known thyroid disease,

thyroid (interfering) medication usage, comorbidities, twin pregnancies, and pregnancies after fertility treatment. In mothers with normal-range maternal TSH and FT4 levels (2.5th to 97.5th percentiles), reference ranges for cord TSH and FT4 were defined as the range between the 2.5th and 97.5th percentiles.

In women with normal-range TSH and FT4 levels, the association between FT4 and birth weight was studied using linear regression analyses. FT4 levels were additionally divided in quintiles and studied in relation to birth weight using analysis of covariance (ANCOVA). Linear regression was used to study the relation of FT4 with estimated fetal weight in mid-pregnancy and late pregnancy. We assessed the associations between maternal FT4 quintiles and longitudinally measured SD scores of weight (mid-pregnancy and late pregnancy estimated fetal weight and birth weight) using unbalanced repeated-measurement analysis, which enables optimal use of available data, taking into account correlations within subjects and assessing both time-dependent and -independent associations. Repeated measurement analyses were performed with the Proc Mixed module of the Statistical Analysis System (version 9.2; SAS Institute Inc., Cary, NC).

Logistic regression and ANCOVA were used to assess the associations between FT4 (quintiles) and LBW. The associations between TSH levels, birth weight, and estimated fetal weight in mid-pregnancy and late pregnancy were studied using similar analyses. Maternal TPOAb status (TPOAb positives *vs.* negatives) was studied in relation to birth weight, LBW, and estimated fetal weight in mid-pregnancy and late pregnancy using logistic regression and ANCOVA. To additionally test whether effects could be due to the autoimmune disease itself (independent of the effects on thyroid parameters), analyses were adjusted for maternal TSH and FT4 levels.

When associations with birth weight were detected, we additionally studied the separate effects on SGA and duration of pregnancy (including prematurity) because LBW can be due to either intrauterine growth retardation (SGA) or prematurity.

In newborns with normal-range cord FT4 and TSH levels whose mothers had normal-range FT4 and TSH levels, the association between cord FT4 and birth weight was studied using linear regression. Cord FT4 levels were additionally divided in quintiles and studied in relation to birth weight using ANCOVA. The association between cord TSH and birth weight was studied using linear regression. Linear regression was also used to study the relation between cord TSH and FT4. Analyses were additionally corrected for maternal TSH and FT4 levels.

All analyses were repeated using multivariate analyses, correcting for maternal age, ethnicity, SES, parity, smoking during pregnancy, vomiting, newborn gender, as well as for gestational age at weight measurement. Analyses were additionally corrected for maternal BMI.

Because outcome measures were correlated (fetal and birth weight endpoints), no multiple testing corrections were performed. Therefore, a P value threshold of 0.05 was used to declare statistical significance.

Results

Baseline characteristics of the study population are shown in Table 1. The group of newborns in which cord thyroid parameters were available had a higher SES and consisted of more Dutch newborns, compared with the group of newborns in which thyroid parameters were not available (% high SES, 46.7 *vs.* 42.8%, $P = 0.014$; % Dutch, 56.5 *vs.* 49.8%, $P = 1.5 \times 10^{-5}$).

TABLE 1. Population characteristics

Characteristics	
n	4464
Maternal age (yr)	29.7 (5.1)
Maternal ethnicity (% Western)[a]	65.4%
SES (low/middle/high)	9.7/45.1/45.2%
Maternal smoking during pregnancy	17.4%
Maternal BMI (kg/m^2)	24.4 (4.3)
Maternal TSH (mU/liter), median (IQR)[b]	1.34 (0.85; 2.02)
Maternal FT4 (pmol/liter)[b]	15.1 (3.5)
Maternal TPOAb positivity[b]	5.6%
Fetal gender (% male)	50.7%
Estimated fetal weight mid-pregnancy (g)	376.8 (84.1)
Estimated fetal weight late pregnancy (g)	1612.4 (250.9)
Birth weight (g)	3416.4 (560.2)
LBW	4.8%
Gestational age at delivery (wk)	39.9 (1.9)
SGA	2.8%
Cord TSH (mU/liter), median (IQR)[c]	9.42 (6.45; 14.30)
Cord FT4 (pmol/liter)[c]	20.9 (3.4)

Data are expressed as mean (SD), unless otherwise specified. IQR, Interquartile range.

[a] 53.0% Dutch, 11.5% Surinam/Antillean, 7.8% Turkish, 6.0% Moroccan, 9.2% other Western, and 12.5% other non-Western.

[b] Determined at gestational age 13.5 (2.0) wk.

[c] Based on 2724 newborns.

Based on the 2.5th and 97.5th percentiles, maternal reference ranges were 0.03–4.04 mU/liter for TSH and 10.4–22.0 pmol/liter for FT4, as reported previously (22). Maternal normal-range FT4 quintiles were: 10.38–12.80, 12.81–14.20, 14.21–15.40, 15.41–17.00, and 17.01–22.00 pmol/liter. Cord reference ranges were 3.41–33.80 mU/liter for TSH and 15.3–28.1 pmol/liter for FT4 (22).

Maternal early pregnancy thyroid parameters and birth weight

In mothers with normal-range FT4 and TSH levels, maternal FT4 levels were negatively associated with birth weight [$\beta = -15.4$ (3.6) g/pmol · liter, mean (SE); $P = 1.6 \times 10^{-5}$]. This is illustrated in Fig. 1, which shows the birth weight for the maternal normal-range FT4 quintiles. Associations remained significant after additional correction for potential confounders, including maternal age, ethnicity, SES, parity, smoking during pregnancy, vomiting, child gender, and gestational age at birth [$\beta = -18.7$ (3.5) g/pmol · liter; $P = 1.0 \times 10^{-6}$].

Higher maternal normal-range FT4 levels were associated not only with a lower birth weight, but also with a lower estimated fetal weight at late pregnancy [$\beta = -3.3$ (1.6) g/pmol · liter; $P = 0.048$]. There was no association between maternal FT4 levels and estimated fetal weight at mid-pregnancy (data not shown).

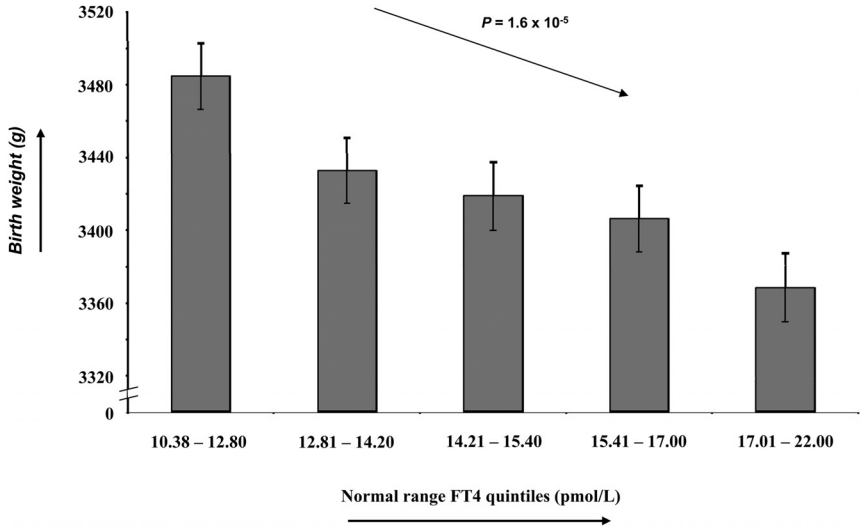

FIG. 1. Maternal early pregnancy normal-range FT4 quintiles and birth weight in 4464 mother-child pairs. Analyses were performed in mothers with normal-range FT4 and TSH levels, after exclusion of TPOAb positives, known thyroid disease or thyroid (interfering) medication usage, comorbidities, twin pregnancies, and pregnancies after fertility treatment. *Error bars* represent SE values.

Figure 2 presents the estimated differences in SD scores (SDS) for fetal and birth weight for the maternal early pregnancy normal-range FT4 quintiles, compared with the first (lowest) FT4 quintile (10.38–12.80 pmol/liter). Higher normal-range FT4 levels were associated with a lower weight, except for the second FT4 quintile (12.81–14.20 pmol/liter). Compared with the first quintile, differences in weight growth rates were 0.0038 ($P = 0.16$), −0.0011 ($P = 0.69$), and −0.0037 ($P = 0.19$) SDS/wk for the second, third, and fourth quintiles, respectively. For the fifth quintile, this was −0.0058 SDS/wk ($P = 0.038$), resulting in a 0.23 SD lower weight at birth, which corresponds to a 116 g lower birth weight.

When maternal FT4 levels were analyzed continuously, higher normal-range FT4 levels were associated with an increased risk of SGA newborns [odds ratio (OR) (95% confidence interval) = 1.09 (1.01–1.17); $P = 0.03$]. No associations with duration of pregnancy [$\beta = -0.002$ (0.012) wk; $P = 0.86$] or prematurity [OR = 1.03 (0.95–1.11); $P = 0.48$] were found.

Higher FT4 levels were also associated with an increased risk of LBW newborns [OR = 1.09 (1.03–1.15); $P = 0.005$], which is illustrated for the normal-range FT4 quintiles in Fig. 3. Mothers in the highest normal-range FT4 quintile (17.01–22.00 pmol/liter) had a 2.8 times increased risk of a LBW newborn compared with mothers in the lowest quintile (10.38–12.80 pmol/liter) [OR = 2.81 (1.65–4.80); $P = 1.5 \times 10^{-4}$]. In these mothers, the TSH range was 0.10–2.96 mU/liter (median, 1.45 mU/liter).

Similar significant associations with SGA, LBW, and late pregnancy fetal weight were found after additional

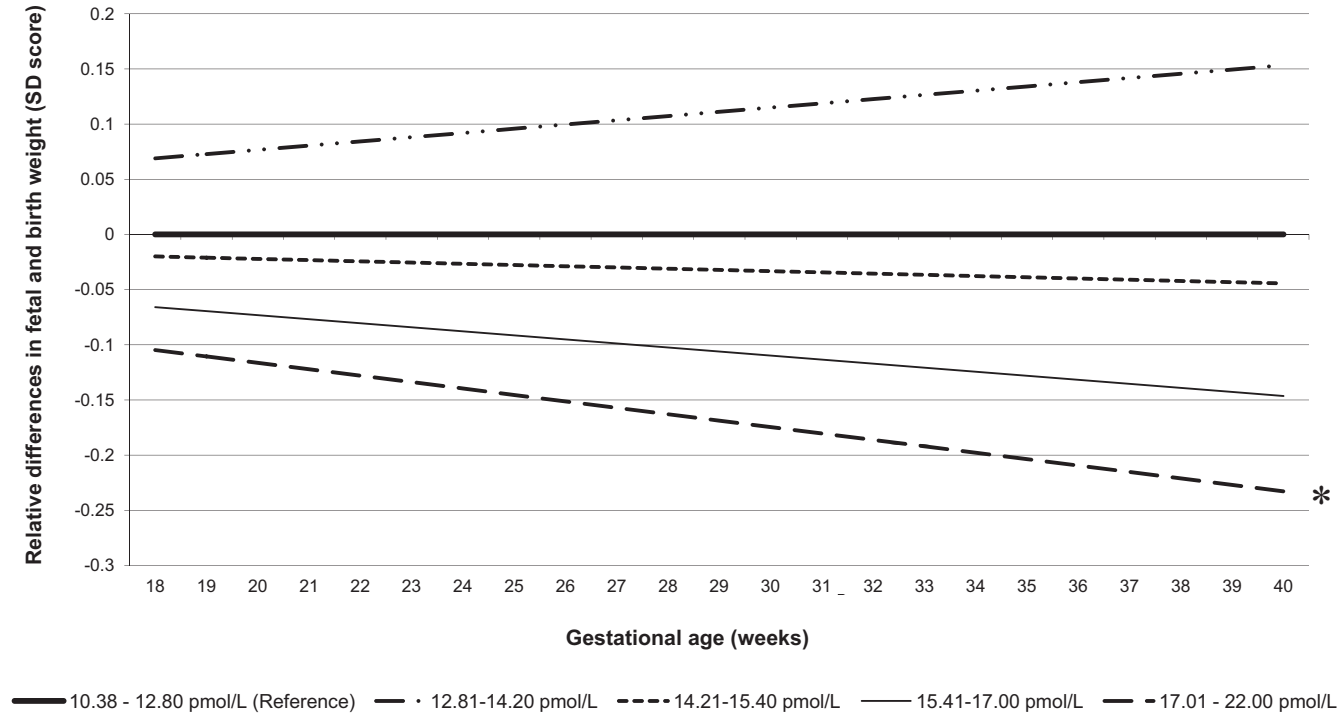

FIG. 2. SDSs for fetal and birth weight for maternal early pregnancy normal-range FT4 quintiles, as compared to the lowest quintile (10.38–12.80 pmol/liter). Values are based on repeated measurement regression models. *, $P < 0.05$.

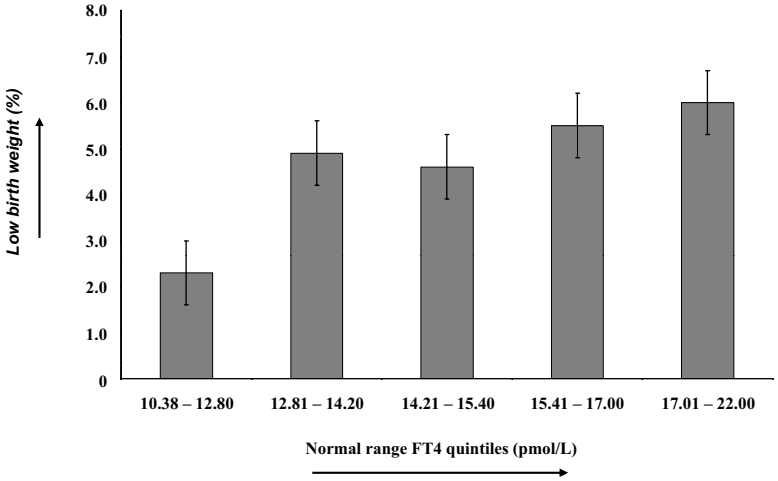

FIG. 3. Maternal early pregnancy normal-range FT4 quintiles and LBW (<2500 g) in 4464 mother-child pairs. Analyses were performed in mothers with normal-range FT4 and TSH levels, after exclusion of TPOAb positives, known thyroid disease or thyroid (interfering) medication usage, comorbidities, twin pregnancies, and pregnancies after fertility treatment. Logistic regression analysis over the entire normal FT4 range (10.38–22.00 pmol/liter) resulted in OR = 1.09 (1.03–1.15); $P = 0.005$. Logistic regression analysis over quintile 5 (17.01–22.00 pmol/liter) *vs.* quintile 1 (10.38–12.80 pmol/liter) resulted in OR = 2.81 (1.65–4.80); $P = 1.5 \times 10^{-4}$. *Error bars* represent SE values.

correction for maternal age, ethnicity, SES, parity, smoking during pregnancy, vomiting, newborn gender, and gestational age at weight measurement, as well as after additional correction for maternal BMI (data not shown).

Trends toward lower maternal TSH levels and lower birth weight and estimated fetal weights were observed but did not reach statistical significance (data not shown).

The percentage of women who were TPOAb-positive was 5.6. Maternal TPOAb status was not associated with birth weight, LBW, or fetal weight at mid- and late pregnancy or after correction for maternal TSH and FT4 levels (data not shown).

Cord thyroid parameters and birth weight

In newborns with normal-range cord FT4 and TSH levels, cord FT4 levels were positively associated with birth weight [β = 23.0 (3.2) g/pmol · liter; $P = 9.2 \times 10^{-13}$]. Figure 4 shows the birth weight for the cord normal-range FT4 quintiles. Cord TSH levels were also positively associated with birth weight [β = 4.1 (1.4) g/mU · liter; $P = 0.007$]. Similar significant associations were found after additional correction for maternal early pregnancy FT4 and TSH levels, maternal age, ethnicity, SES, parity, smoking during pregnancy, vomiting, and newborn gender, as well as after additional correction for maternal BMI (data not shown).

Finally, cord TSH levels were positively associated with cord FT4 levels [β = 0.03 (0.01) pmol/mU; $P = 0.001$], also after correction for maternal early pregnancy TSH and FT4 levels [β = 0.03 (0.01) pmol/mU; $P = 2.8 \times 10^{-4}$].

Similar significant associations were found after exclusion of SGA newborns (data not shown).

Discussion

In the present study, we investigated the effects of early pregnancy maternal thyroid parameters within the normal range and maternal TPOAb status on birth weight, as well as the relations between cord thyroid parameters and birth weight.

Birth weight is often used as a proxy for fetal growth and development, as well as for fetal nutritional status. LBW is associated with neonatal mortality and morbidity, as well as with the occurrence of diseases in later life (4–10). Even mild variations in birth weight within the normal range are known to be associated with later life morbidity (5). A number of studies have investigated the effects of maternal thyroid dysfunction during pregnancy on birth weight (11–15). Most of these studies were performed in mothers with Graves' disease and showed a substantial increased risk of LBW newborns (11–13). A potential mechanism underlying this observed association is that hyperthyroid mothers have increased lipid and protein degradation, leading to a state of maternal chronic caloric deficiency, which has been shown to negatively affect birth weight (26, 27). Given the increased risk of LBW newborns in mothers with thyroid dysfunction during pregnancy, it is remarkable to note that limited data are available on the effects of variation in maternal thyroid parameters within the normal range on birth weight. Shields *et al.* (28) studied the relation between thyroid function during pregnancy and birth weight in 905 mother-child pairs and found a negative association between maternal FT4 levels at 28 wk gestation and birth weight. This is in line with the results from the current study, in which we show a negative association between early pregnancy maternal FT4 levels and birth weight in 4464 mother-child pairs. We additionally found an increased risk of LBW newborns with higher maternal FT4 levels, as well as a lower estimated fetal weight in late pregnancy. Similar patterns were observed in our repeated measurements regression analyses.

We did not find significant associations between maternal TSH levels and birth weight. This could be (partially) explained by an interfering role of human chorionic gonadotropin, which has important placental, uterine,

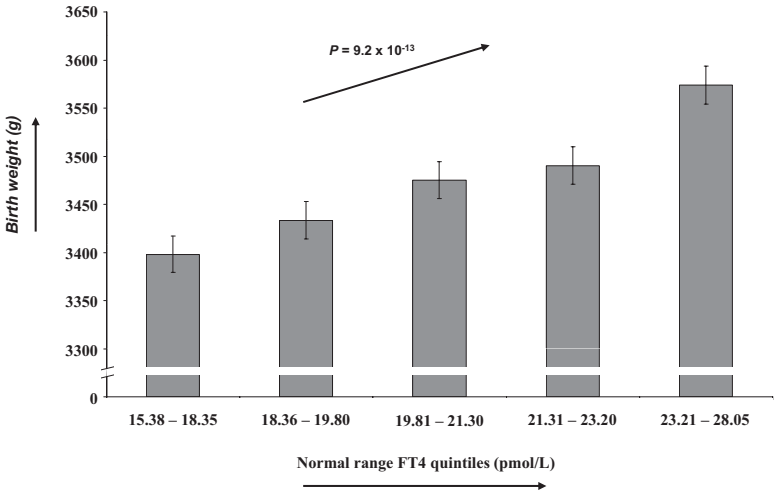

FIG. 4. Cord normal-range FT4 quintiles and birth weight in 2456 newborns. Analyses were performed in newborns with normal-range cord FT4 and TSH levels, whose mothers had normal-range early pregnancy FT4 and TSH levels, after exclusion of TPOAb-positive mothers, mothers with known thyroid disease or thyroid (interfering) medication usage, comorbidities, twin pregnancies, and pregnancies after fertility treatment. *Error bars* represent SE values.

and fetal functions and is an agonist of the TSH receptor leading to increased thyroid hormone production (2, 29).

LBW can be due to intrauterine growth retardation or a shorter duration of pregnancy. We therefore additionally studied the separate effects on SGA and prematurity and show that higher maternal normal-range FT4 levels are associated with an increased risk of SGA newborns, and not with a shorter duration of pregnancy or prematurity.

The effects of maternal early pregnancy FT4 levels on fetal weight, birth weight, and the risk of SGA and LBW newborns cannot be explained by a confounding role of maternal BMI because associations remained significant after additional correction for maternal BMI. Potential interfering roles of maternal age, ethnicity, SES, parity, smoking during pregnancy, vomiting, and newborn gender were excluded by correcting the analyses for these factors.

We also took a potentially interfering role of TPOAbs into account. TPOAb positivity is a common finding in the general population, as well as in pregnant women (30), with a prevalence of 5.6% in the current study. Although various maternal autoimmune diseases have been associated with lower birth weight (16–19), limited data are available on the effects of maternal TPOAb positivity on birth weight. In the current study, no associations were found between early pregnancy maternal TPOAb positivity and birth weight, LBW, or with fetal weight at mid- and late pregnancy. To study possible effects of autoimmunity itself (independent of the effects on thyroid parameters), analyses were additionally adjusted for maternal TSH and FT4 levels, but we did not find any associations. Shields *et al.* (28) studied the relation between maternal TPOAb positivity at 28 wk gestation and birth weight in 905 mother-child pairs and did not find any associations either. This is also in line with the results of Männistö *et al.* (31), who did not find associations between first trimester maternal TPOAb positivity and birth weight in 5763 mother-child-pairs. However, an increased risk of LBW newborns was found in this study. The origin of the discrepancy with the current study regarding the LBW risk is currently unknown and should be clarified in future studies taking the possible role of ethnicity and other concomitant autoimmune diseases into account.

A potential mechanism underlying the observed association between high-normal maternal FT4 levels, fetal weight, birth weight, and SGA is the transplacental delivery of high-normal FT4 levels to the fetus. In a normal-functioning fetal hypothalamus-pituitary-thyroid axis, this will be compensated by a decreased production of T_4 by the fetal thyroid. However, various factors are known to influence the hypothalamus-pituitary-thyroid axis function, such as common polymorphisms in thyroid hormone pathway genes (32–34).

Limited data are available on the correlations between early pregnancy FT4 levels and FT4 levels later in pregnancy. Lambert-Messerlian *et al.* (35) found a weak positive correlation (r = 0.32) between FT4 levels in the first and second trimesters of pregnancy. Because there are no other large studies correlating FT4 levels throughout pregnancy, more large studies are needed that also take the third trimester into account. Because only early pregnancy (mean = 13.3 wk) FT4 levels were available in the current study, we do not know whether all women with high-normal FT4 levels had high-normal FT4 levels during the entire pregnancy. However, in this context it is important to note that Shields *et al.* (28) also found a lower birth weight in newborns of mothers with a higher FT4 level in midpregnancy (mean = 28 wk).

Taken together, we show that maternal high-normal FT4 levels in early pregnancy are associated with lower fetal weight, lower birth weight, and an increased risk of SGA and LBW newborns. These data demonstrate that even mild variation in thyroid function within the normal range can have important consequences for the fetus and newborn and underline the importance of tight regulation of FT4 levels during pregnancy. The exact mechanism underlying the observed associations should be clarified in future studies, taking the maternal metabolic profile and placental passage of T_4 into account.

Our results suggest that it could be beneficial to narrow down the maternal early pregnancy FT4 reference ranges. However, before taking such measures, the effects on the risk of other pregnancy complications need to be considered as well. Low thyroid function has, for example, been associated with miscarriage, preeclampsia, and delayed child cognitive function (1, 3, 36). However, little is known about the effects of variation in FT4 levels within the normal range on these endpoints. Because we show clear effects of variation in maternal FT4 levels within the normal range on birth weight, our results should prompt others to study the effects of variation in normal-range FT4 levels on these other endpoints as well.

Contrary to what might be expected based on the negative association between early pregnancy maternal FT4 levels and birth weight, a positive association between cord FT4 levels and birth weight was found. Recently, Shields *et al.* (28) studied birth weight in relation to cord FT4 levels in 616 mother-child pairs and found a similar positive association. Leptin is produced by adipocytes and is known to stimulate the hypothalamus-pituitary-thyroid axis by increasing TRH production (37). In this context, it is interesting to note that in the current study we additionally found a positive association between birth weight and cord TSH levels, as well as a positive association between cord TSH and FT4 levels. We have previously shown a positive association between maternal and cord TSH levels, as well as a positive association between maternal and cord FT4 levels (22). Given these interrelations between maternal and cord thyroid parameters and birth weight, we additionally corrected the cord thyroid parameter and birth weight analyses for maternal thyroid parameters, but no differences in effects were observed. Taken together, these findings suggest that increased leptin production in heavier newborns could play a role in these observed associations, which needs to be clarified in future studies. These studies should also take a possible role for insulin into account, given the complex relations between maternal and newborn thyroid parameters and weight.

In conclusion, we show that maternal high-normal FT4 levels at an early stage of pregnancy are associated with a lower fetal weight and birth weight, as well as with an increased risk of SGA and LBW newborns. We did not find any association between maternal TPOAb status and fetal or birth weight. Finally, positive associations between birth weight and cord TSH and FT4 levels were found, as well as a positive association between cord TSH and FT4 levels.

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