Clinical Endocrinology (2011) **75**, 382–387 doi: 10.1111/j.1365-2265.2011.04083.x

ORIGINAL ARTICLE

Neonatal thyroid screening results are related to gestational maternal thyroid function

S.M.I. Kuppens*,†, L. Kooistra‡, H.A. Wijnen§, H.L.Vader¶, T.H.M. Hasaart*, S.G. Oei**,††, T. Vulsma‡‡ and V.J. Pop†

*Department of Obstetrics & Gynecology, Catharina Hospital, Eindhoven, †Department of Primary Care, University of Tilburg, Tilburg, the Netherlands, ‡Department of Pediatrics, Alberta Children's Hospital, University of Calgary, Calgary, AB, Canada, §Department of Midwifery Science, AVM University, Maastricht, ¶Department of Clinical Chemistry, Máxima Medical Centre, Eindhoven, **Department of Obstetrics & Gynecology, Máxima Medical Centre, Eindhoven, ††Department of Electrical Engineering, University of Technology, Eindhoven and ‡‡Department of Pediatrics, Emma Childrens's Hospital, Amsterdam, the Netherlands

Summary

Objective To study the relationship between maternal thyroid function at each pregnancy trimester and neonatal screening results.

Background Overt maternal thyroid dysfunction during gestation is associated with poor neonatal thyroid function. However, research on the relationship between suboptimal maternal thyroid function (assessed at three trimesters) and neonatal thyroid screening outcome is scarce.

Design/Patients Prospective follow-up study during three trimesters of gestation in 886 Dutch Caucasian healthy pregnant women followed from 12-week gestation until term delivery (>37 weeks) and their neonates.

Measurements The relation between neonatal data from the Congenital Hypothyroidism (CH) screening and maternal thyroid determinants [TSH, FT4 and thyroid peroxidase (TPO)-Ab] assessed at 12-, 24- and 36-week gestation.

Results Boys have lower screening TT4 levels and their mothers have higher TSH levels at 24- and 36-week gestation. Higher maternal TSH levels (>97·5th percentile, as defined in 810 women without TPO-Ab at 12 weeks) at one or more times during pregnancy (O.R: 2·26, 95% CI: 1·20–4·29) and lower gestational age (O.R: 1·22, 95% CI: 1·05–1·41) are independently related to lower screening TT4 levels.

Conclusions Maternal thyroid function during gestation is related to neonatal TT4 at screening. The finding of both lower neonatal TT4 levels in boys and higher TSH levels in mothers carrying boys is worthy of further investigation, as both observations may be meaningfully related.

(Received 22 March 2011; returned for revision 6 April 2011; finally revised 15 April 2011; accepted 19 April 2011)

Correspondence: Professor Victor J Pop, MD, PhD, Department of Clinical Health Psychology, University of Tilburg, P.O. Box: 90153, 5000 LE Tilburg, the Netherlands. Tel.: +31 40 2075836; Fax: +31 40 2075838; E-mail: v.j.m.pop@uvt.nl

Introduction

The foetus is totally dependent on maternal thyroid hormone supply during the first half of gestation. This dependency decreases during the second half of gestation when the ongoing maturation of the foetal hypothalamus-pituitary-thyroid axis (HPT axis) results in increased foetal T4 production.[1,2]

Evidence on whether poor neonatal thyroid screening results are dependent on (sub) clinical maternal thyroid dysfunction during gestation is limited. In iodine deficient areas, some studies found higher mean cord TSH levels compared with mean maternal TSH levels during different trimesters of gestation and at delivery.[3–5] Another study revealed a positive correlation between maternal FT4 and cord rT3 and between maternal rT3 and cord T3.[6] A recent study failed to demonstrate a relation between maternal thyroid function and neonatal screening results.[7] Conclusions based on these studies, however, cannot be definitive as they share a similar shortcoming; assessments of maternal thyroid function were performed at a single, variable time point, whilst the effect of maternal thyroid function on foetal thyroid development might be trimester-specific.[8,9]

This study reports on the neonatal thyroid screening outcome of a large group of healthy term-born (≥37 weeks) neonates (n = 886), whose healthy mothers were followed at each trimester until delivery. Primary outcome was the relation between maternal thyroid function at each trimester and neonatal total T4 (TT4) screening results, after adjustment for other determinants of screening results.

Methods

Subjects

Over a 2 year period, 1190 of 1507 Dutch Caucasian pregnant women living in the Eindhoven city area consented to participate in a follow-up study at their first antenatal control visit at 12-week gestation. For various reasons (e.g. thyroid medication, overt hyperthyroidism/hypothyroidism at screening, severe congenital malformations, hormone induced pregnancy, diabetes-I, missing data), 56 women were excluded. The remaining 1134 women were

followed throughout pregnancy. Seventy-two of them delivered prior to 37-week gestation. Of the remaining 1062 women, 886 (83%) mothers gave written consent to access congenital hypothyroidism (CH) screening data.

The Eindhoven area has recently been shown to be iodine sufficient.[10] The Medical Ethical Committee of Máxima Medical Centre in Eindhoven/Veldhoven approved the study.

Assessments

Term was assessed in two ways: using the last menstrual period, and from an ultrasound assessment at the presumed 12-week gestation point. If there was a discrepancy of more than 7 days between these two measurements, another ultrasound assessment was performed within 2 weeks to assess the definite term. Gestational age was expressed in weeks and days.

Thyroid parameters, free thyroxine (FT4), thyrotropin (TSH) and auto-antibodies to thyroid peroxidase (TPO-Ab) were assessed at 12-, 24- and 36-week gestation. TSH was measured using a solid-phase, two site chemiluminescent enzyme immunometric assay (IMMULITE Third generation TSH; Diagnostic Products Corporation, Los Angeles, CA, USA). The inter-assay coefficients of variation were 5·0% and 4·4% at concentrations 0·22 and 2·9 mIU/l, respectively. FT4 concentration was also measured by means of a solid-phase immunometric assay (IMMULITE Free T4; Diagnostic Products Corporation). The inter-assay coefficients of variation for this technique were 6·7% and 4·4% at concentrations of 11·6 and 31·5 pmol/l, respectively. Reference ranges for TSH and FT4 were: 0·45–4·5 mIU/l and 10·3–25·7 pmol/l, respectively. The IMMULITE Anti-TPO Ab kit (Diagnostic Products Corporation) was used for the determination of antibodies against TPO. The inter-assay coefficients of variation for this analysis were 9% and 9·5% for concentrations of 40 and 526 kU/l, respectively. The TPO assay was standardised in terms of the International Reference Preparation for TPO MRC 66/387. Women with TPO-Ab concentrations higher than 35 IU/ml at 12-week gestation were regarded as antibody positive. Because TSH and FT4 reference ranges during gestation do not exist, TSH and FT4 were defined as low and high using the lowest 2·5th and upper 97·5th percentiles as cut-offs of women who were TPO-Ab negative at 12-week gestation.

In the Netherlands, neonatal screening on CH is performed by primarily assessing TT4 in heel-puncture blood samples collected on filter paper. In the current study (recruiting period: 2003–2005), TT4 was assessed between the 4th and 6th postpartum day using filter paper blood spots. The TT4 concentration was compared with the mean TT4 of all neonates assessed that day in the screening laboratory. Babies with a TT4 ≥ 0·8 SD below the daily mean receive a TSH assessment: by definition, this is around 20% of all neonates. The rationale and cost-effectiveness of this approach has been discussed elsewhere.[11]

Statistical analysis

Statistical analysis was performed using the Statistical Package of Social Science (SPSS). Kolmogorov–Smirnov tests revealed a normal distribution for neonatal TT4 values ($P = 0{\cdot}23$) but not for maternal TSH ($P < 0{\cdot}001$) and FT4 ($P < 0{\cdot}05$) at all trimesters during gestation. Therefore, mean (SD) of TT4 was calculated and median (range) of TSH and FT4. Means (SD) of TT4 of different subgroups of neonates were compared using *t*-tests, whilst Mann–Whitney-*U* tests were used to compare TSH and FT4 levels in different sub-groups. To evaluate whether neonatal TT4 was related to different maternal and neonatal parameters, we performed *t*-tests (two-tailed) and analysis of variance (ANOVA).

Subsequently, different cut-offs for maternal TSH and FT4 were calculated, and chi squares (χ^2) were used to test associations with neonatal TT4. Adjusted odds ratios (95% CI) of low neonatal screening TT4 (defined as ≥0·8 SD below the mean of the total study sample) were analysed using multiple logistic regression analysis. Confounders for which was adjusted for were: maternal BMI and age, term at birth, birth weight, neonatal sex, low FT4, high TSH and elevated TPO-Ab titers during gestation, smoking habits and alcohol use.

Results

In Table 1, the characteristics of 886 pregnant women and their term-born neonates are shown. In Table 2, thyroid function at each trimester is shown according to neonatal sex. Women carrying male foetuses had significantly higher TSH levels at 24- and 36-week gestation (M-W-U, $P = 0{\cdot}03$) compared with mothers carrying girls, whilst FT4 did not differ. Heel punctures for CH screening were performed at a mean age of 5·2 days (SD = 0·56). As shown in Table 2, mean overall neonatal TT4 at screening was 179 nmol/l (SD = 38 nmol/l). Boys had significantly lower mean TT4 levels compared with girls ($t = 3{\cdot}1$, $P = 0{\cdot}002$).

The prevalence of elevated TPO-Ab concentrations decreased from 76 (8·6%) at 12 weeks to 65 (7·3%) at 24 weeks and to 55 (6·2%) at 36-week gestation. No differences in the prevalence of elevated TPO-Ab concentrations between mothers carrying boys *vs* mothers carrying girls were found (data not shown). Neonates who

Table 1. Sample characteristics of 886 pregnant women and term-born neonates

	Mean (SD)	*n* (%)
Pregnant women		
Demographic features		
Age (years)	30·5 (3·5)	
Life style habits		
Tobacco (mis)use		106 (12)
Alcohol (mis)use		115 (13)
Body mass index	25·3 (4·4)	
Obstetrical features		
Primiparity		340 (38)
Miscarriage earlier in life		117 (20)
Previous caesarean section		35 (4)
Term at birth in weeks	39·9 (1·24)	
Neonatal outcome		
Male sex		464 (52)
Birth weight in grams	3525 (486)	

Table 2. Thyroid function at three trimesters during gestation and heel TT4 values assessed between 3 and 5th postpartum day in 886 women and at term-born neonates (≥37 weeks)

	Total n = 886 Median (range)	Boys n = 464 Median (range)	Girls n = 422 median (range)	P M-W-U
Maternal thyroid function				
12-week gestation				
TSH (mIU/l)	1·10 (0·01–5·5)	1·10 (0·01–5·5)	1·0 (0·05–4·5)	0·12
FT4 (pmol/l)	16·0 (10·2–27·2)	16·1 (10·4–27·2)	15·9 (10·2–22·1)	0·44
24-week gestation				
TSH (mIU/l)	1·20 (0·03–5·7)	1·30 (0·03–5·7)	1·20 (0·18–4·1)	0·03
FT4 (pmol/l)	13·8 (8·4–31·3)	13·8 (8·4–31·3)	13·7 (8·8–18·8)	0·15
36-week gestation				
TSH (mIU/l)	1·40 (0·07–5·4)	1·50 (0·09–5·4)	1·40 (0·07–4·2)	0·03
FT4 (pmol/l)	13·3 (7·7–36)	13·3 (7·7–22·4)	13·2 (8·2–36)	
	Mean (SD)	Mean (SD)	Mean (SD)	*t*-test
Neonatal Heel results				
TT4 (nmol/l)	179 (38)	176 (36)	184 (39)	0·002

were born at 37- to 38-week gestation had significantly lower mean TT4 levels compared with those who were born after 38-week gestation (ANOVA, $F = 5{\cdot}6$, $P < 0{\cdot}001$). Low TT4 was defined as ≥0·8 SD below the mean of the overall group of 886 neonates: $179 - (0{\cdot}8 \times 38) = 149$ nmol/l. There were 189 neonates (21%) with a TT4 below this level. In Fig. 1, the percentages of children with low TT4 are shown in relation to gestational age. The percentage of children with low TT4 born at 37-week gestation was twice that of children born at 40 weeks or later (χ^2 (5): 22, $P < 0{\cdot}001$).

Because maternal TSH and FT4 reference ranges during gestation have not yet been agreed upon, TSH and FT4 in this study were defined as low and high using the lowest 2·5th and upper 97·5th percentiles as cut-offs (i.e. to denote the 5% extremes of the general population). The cut-offs for each TSH sub-category are shown in Table 3 with the corresponding mean TT4 and the numbers of neonates with low screening TT4 (≥0·8 SD below the mean). Mean TT4 was the lowest in the TSH >97·5th percentile at 12- and 36-week gestation. Moreover, the percentage of neonates with low TT4 was the highest in the group with a TSH >97·5th percentile, especially at 12 weeks ($P = 0{\cdot}01$), and to a lesser degree at 36-week gestation ($P = 0{\cdot}06$). No differences in neonatal TT4 level amongst the maternal FT4 percentile groups were found for any of the three trimesters.

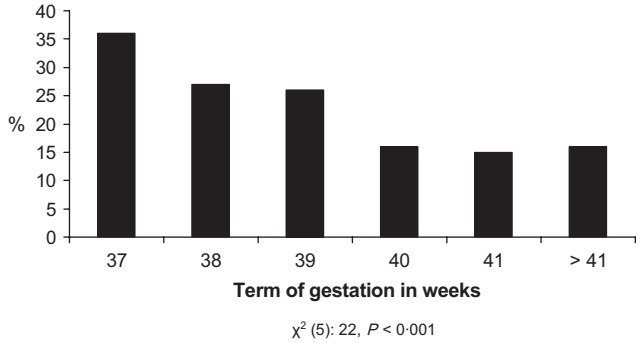

Fig. 1 Percentage of neonates with low TT4 (<0·08 SD below the mean, <149 nmol/l) at 3–5th postpartum day in relation to term of gestation.

Subsequently, women with a TSH >97·5th percentile at least once during gestation were designated as the high-normal TSH group (n = 46, 5%) and women with at least once a FT4 < 2·5th

Table 3. Mean screening TT4 (SD) and numbers (%) of neonates with low screening TT4 results (≥0·8 SD below the mean) according to maternal TSH cut-off's at three different trimesters

	Mean TT4 (SD) Total n = 886	n with low TT4 (<0·08 SD below Mean = below 149 nmol/l) Total n = 189
12 weeks		
TSH < 2·5th percentile, <0·14 mIU/l	177 (27)	3/23 = 13%
TSH between 2·5th – 97·5th percentile, 0·14–3·1 mIU/l	180 (38)	176/841 = 21%
TSH > 97·5th percentile, >3·1 mIU/l	166 (38)	10/22 = 45%*
24 weeks		
TSH < 2·5th percentile, <0·39 mIU/l	170 (42)	7/23 = 30%
TSH between 2·5th – 97·5th percentile, 0·39–2·98 mIU/l	180 (38)	175/841 = 21%
TSH > 97·5th percentile, >2·98 mIU/l	171 (35)	7/22 = 32%
36 weeks		
TSH < 2·5th percentile, <0·41 mIU/l	172 (35)	6/23 = 26%
TSH between 2·5th – 97·5th percentile, 0·41–3·28 mIU/l	180 (38)	174/841 = 21%
TSH > 97·5th percentile, >3·28 mIU/l	164 (39)	9/22 = 41%**

*χ^2(2): 8·6, $P = 0{\cdot}01$; **χ^2(2): 5·5, $P = 0{\cdot}06$.

percentile as low-normal FT4 group (n = 56, 6%). The prevalence of elevated TPO-Ab at 12-week gestation was substantially higher in the high TSH group (n = 17, 37%) compared with the remaining 840 women (n = 60, 7%), χ^2 = 48, df = 1, $P < 0{\cdot}001$, whilst this was not the case when comparing the low FT4 group with the remaining women (14% *vs* 9%). In the 46 women of the high TSH group, the prevalence of low FT4 was not significantly different from the remaining 840 women (9% *vs* 6%).

In Table 4, adjusted OR's (95% CI) are shown with low heel TT4 (≥0·8 SD below the mean) as the dependent and high-normal maternal TSH (>97·5th percentile) as the independent variable. Confounders that were entered into the regression were: maternal BMI and age, term at birth, birth weight, neonatal sex, low FT4, high TSH and elevated TPO-Ab titers during gestation, smoking habits and alcohol use. As can be seen, high-normal maternal TSH (>97·5th percentile) independently increased the risk of low screening TT4 (O.R.: 2·26, 95% CI: 1·20–4·29). Also lower term of gestation independently increased the risk of low screening TT4 (O.R.: 1·22, 95% CI: 1·05–1·41). Low FT4 (<2·5th percentile) was not related to neonatal TT4.

Discussion

In the current study, high-normal maternal TSH at one or more times during pregnancy and lower term of gestation increased the risk of low screening TT4. Interestingly, not only had boys significantly lower screening TT4 levels than girls, mothers carrying boys were also found to have higher TSH levels at 24 and 36 weeks gestation compared with mothers carrying girls.

Our results showing a significant relationship between high-normal maternal TSH during pregnancy and low neonatal TT4 at screening contrast with those of a recent study in which no relationship between neonatal thyroid screening results and maternal thyroid function was found.[7] This discrepancy between studies may be attributed to the fact that (a) maternal thyroid function in the Oken study was assessed only once in the first half of pregnancy (<22 weeks), and (b) high TSH in the Oken study was defined as >2·5 mIU/l. Because a possible impact of sub-optimal maternal thyroid function on foetal thyroid function – and hence on neonatal thyroid function – could be trimester-specific, the current study opted for maternal thyroid function tests in each trimester of pregnancy.[8,9] Moreover, because maternal TSH and FT4 reference ranges during gestation have not yet been established, we used a reference range that is normally used to define the abnormal 5% of the normal population: <2·5th percentile for the low and >97·5th percentile for the upper TSH cut-off. Notably, if the upper TSH cut-off value used by Oken *et al.* was applied to the current data, TSH upper reference ranges would have been the 92nd percentile (trimester 1), 94th percentile (trimester 2) and 90th percentile (trimester 3), and no significant association between high-normal TSH and low neonatal TT4 would have been found.

Table 4. Adjusted OR (95% CI) for low screening TT4 (>0·8 SD below mean, <149 nmol/l) of 886 at term-born neonates (≥37 weeks gestation)

	O.R.	95% CI
Lower term of gestation (≥37-week gestation)	1·22	1·05–1·41
Female sex	0·89	0·59–1·16
Age of mother in years	1·01	0·96–1·08
Weight of baby in quartiles	0·87	0·73–1·02
Alcohol use in pregnancy	1·52	0·96–2·42
Smoking during gestation	1·15	0·69–1·91
Maternal FT4 < 2·5th percentile during gestation	1·75	0·88–3·25
Elevated titers of TPO-Ab during early gestation	1·95	0·74–4·02
Maternal TSH > 97·5th percentile during gestation	2·26	1·20–4·29
BMI of mother at 12 weeks'	0·98	0·94–1·02

Interestingly in a recent study from Japan (where neonatal screening is TSH-based), high maternal serum TSH in early pregnancy was significantly related to higher neonatal TSH levels at screening.[12] However, these findings are difficult to relate to the general population because the majority of mothers had excessive iodine intake during gestation and lactation. Similarly, the findings of other studies investigating the relationship between maternal thyroid function and neonatal thyroid function may be criticised for the potential confounding effects of iodine inadequacy, small sample size and limited thyroid assessment points during gestation.[3–5] As such, the inconclusive findings from the few available studies, intriguing as they are, underline the need for further replication research with greater methodological rigour.

How can the link between high-normal maternal TSH during gestation and low neonatal TT4 levels at screening be explained? During the first half of gestation, foetal thyroid function is totally dependent on maternal T4 supply. After the onset of foetal thyroid function, maternal transfer of T4 continues until term and represents an important proportion of thyroid hormones available to the foetus[2,8,9], although most of the maternal T4 supply is inactivated by deiodinase 3 (D3) into rT3. There is substantial evidence showing that inadequate supply of maternal thyroid hormone during gestation (as reflected by high maternal TSH) results in lower foetal T4 and T3 levels.[13] One third (37%) of the high-normal TSH women showed elevated TPO-Ab concentrations, reflecting thyroid auto-immunity. These women are known to be at risk for impaired maternal-foetal transfer of FT4.[14] In the current study, women in the high-normal TSH group had no lower FT4 levels, and no differences in neonatal TT4 level amongst the maternal FT4 percentile groups were found for any of the three trimesters. This may be because of the greater sensitivity of TSH to detect small changes in the set point of the HPT axis compared with FT4.[15] Besides, it has been reported that FT4 assessments during gestation are less reliable than non-pregnancy assessments.[16] An alternative hypothesis for the obtained association between high-normal maternal TSH during gestation and low neonatal TT4 levels at screening could be that a sub-sample of pregnant women in our study may have had increased placental deiodase activity. This would explain their increased TSH levels to preserve their euthyroid state. Increased placental deiodase as such would then be the likely cause of decreased foetal T4 availability, and hence lower screening neonatal TT4 levels.

Possible determinants related to normal TT4 (and TSH) in healthy term babies such as gestational age and foetal sex (boys) have been described earlier.[7,17–21] To our knowledge, this is the first report describing higher TSH levels in pregnant women carrying a male foetus. An explanation for this finding is lacking, but one might speculate that male foetuses have a more active deiodase activity than female foetuses, given consistent reports that boys have lower neonatal TT4 (and higher cord TSH) compared with girls. [7,19,21] However, in the current study, amniotic fluid data or newborn rT3 values to support this hypothesis were not available. It could also be hypothesised that boys, because of production of testosterone, have lower TBG levels and therefore have lower TT4 levels. Unfortunately, no TBG values are available. Moreover, the question whether this finding is clinically relevant remains unresolved. It would be interesting to study whether neonatal male TT4 levels are associated with any of the neuro-developmental problems, such as autism or ADHD, known to preferentially affect boys.[22–25]

Regarding gestational age, it is well known that foetal synthesis of both T4 and TSH increases as a function of gestational age, reflecting ongoing maturation of the HPT axis.[21]

Several limitations of the study need to be mentioned. First, iodine excretion data in mothers and neonates were not collected. It might be argued that increased maternal TSH and lower neonatal screening TT4 reflect the same underlying mechanism: sub-optimal iodine intake. Although all participants lived in an iodine-sufficient area, it is generally questioned whether adequate iodine intake outside pregnancy also guarantees sufficient iodine intake to meet the demands of pregnancy.[26] Second, the absence of thyroid cord blood data did not allow us to examine whether the obtained association between high maternal TSH and low neonatal screening TT4 was already present *in utero*. Finally, newborn TBG or rT3 analyses were not performed on neonatal heel-puncture blood samples. A major strength of the study includes the rather strict time frame of thyroid hormone assessments at each trimester during gestation.

There are two concluding points to emphasise. Firstly, maternal thyroid function during gestation is related to neonatal TT4 at screening. Future research should also link TSH-based neonatal screening results (besides TT4) to maternal thyroid function, assessed at fixed time points for each trimester of pregnancy. Secondly, finding both lower neonatal TT4 levels in boys and higher TSH levels in mothers carrying boys is worthy of further investigation, as both observations may be meaningfully related.

Acknowledgements

We acknowledge the kind support of the Dr De Grood Foundation for its funding that allowed us to purchase the reagents for the study.

Conflict of interest

Authors have no conflict of interest. All authors have been involved with data collection, analyses, writing, or combinations of these activities.

References

1 Vulsma, T., Gons, M.H. & De Vijlder, J.J. (1989) Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. *New England Journal of Medicine*, **321**, 13–16.

2 Obregon, M.J., Calvo, R.M., Del Rey, F.E. *et al.* (2007) Ontogenesis of thyroid function and interactions with maternal function. *Endocrine Development*, **10**, 86–98.

3 Glinoer, D., Delange, F., Laboureur, I. *et al.* (1992) Maternal and neonatal thyroid function at birth in an area of marginally low iodine intake. *Journal of Clinical Endocrinology and Metabolism*, **75**, 800–805.

4 Eltom, A., Eltom, M., Idris, M. *et al.* (2001) Thyroid function in the newborn in relation to maternal thyroid status during labour in a mild iodine deficiency endemic area in Sudan. *Clinical Endocrinology*, **55**, 485–490.

5 Elahi, S., Laeeq, F., Syed, Z. *et al.* (2005) Serum thyroxine and thyroid stimulating hormone levels in maternal circulation and cord blood at the time of delivery. *Pakistan Journal of Medical Sciences*, **21**, 325–330.

6 Hume, R., Simpson, J., Delahunty, C. *et al.* (2004) Human fetal and cord serum thyroid hormones: developmental trends and interrelationships. *Journal of Clinical Endocrinology and Metabolism*, **89**, 4097–4103.

7 Oken, E., Braverman, L.E., Platek, D. *et al.* (2009) Neonatal thyroxine, maternal thyroid function, and child cognition. *Journal of Clinical Endocrinology and Metabolism*, **94**, 497–503.

8 Morreale de Escobar, G., Obregon, M.J. & Escobar del Rey, F. (2004) Role of thyroid hormone during early brain development. *European Journal of Endocrinology*, **151**, U25–U37.

9 Williams, G.R. (2008) Neurodevelopmental and neurophysiological actions of thyroid hormone. *Journal of Neuroendocrinology*, **20**, 784–794.

10 Wiersinga, W.M., Podoba, J., Srbecky, M. *et al.* (2001) A survey of iodine intake and thyroid volume in Dutch schoolchildren: reference values in an iodine-sufficient area and the effect of puberty. *European Journal of Endocrinology*, **144**, 595–603.

11 Lanting, C.I., van Tijn, D.A., Loeber, J.G. *et al.* (2005) Clinical effectiveness and cost-effectiveness of the use of the thyroxine/thyroxine-binding globulin ratio to detect congenital hypothyroidism of thyroidal and central origin in a neonatal screening program. *Pediatrics*, **116**, 168–173.

12 Orito, Y., Oku, H., Kubota, S. *et al.* (2009) Thyroid function in early pregnancy in japanese healthy women: relation to urinary iodine excretion, emesis, and fetal and child development. *Journal of Clinical Endocrinology and Metabolism*, **94**, 1683–1688.

13 Krassas, G.E., Poppe, K. & Glinoer, D. (2010) Thyroid function and human reproductive health. *Endocrine Reviews*, **31**, 702–755.

14 Haddow, J.E., Palomaki, G.E., Allan, W.C. *et al.* (1999) Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *New England Journal of Medicine*, **341**, 549–555.

15 Benadi, N., Wiersinga, W., Reitsma, J.B. *et al.* (2009) Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death. *European Journal of Endocrinology*, **160**, 985–991.

16 Lee, R.H., Spencer, C.A., Mestman, J.H. *et al.* (2009) Free T4 immunoassays are flawed during pregnancy. *American Journal of Obstetrics and Gynecology*, **200**, 260. e1–e6.

17 Bernard, B., Oddie, T.H. & Fisher, D.A. (1977) Correlation between gestational age, weight, or ponderosity and serum thyroxine concentration at birth. *Journal of Pediatrics*, **91**, 199–203.
18 Franklin, R.C., Carpenter, L.M. & O' Grady, C.M. (1985) Neonatal thyroid function: influence of perinatal factors. *Archives of Disease in Childhood*, **60**, 141–144.
19 Chan, L.Y., Leung, T.N. & Lau, T.K. (2001) Influences of perinatal factors on cord blood thyroid-stimulating hormone level. *Acta Obstetricia et Gynecologica Scandinavica*, **80**, 1014–1018.
20 Williams, F.L., Mires, G.J., Barnett, C. *et al.* (2005) Transient hypothyroxinemia in preterm infants: the role of cord sera thyroid hormone levels adjusted for prenatal and intrapartum factors. *Journal of Clinical Endocrinology and Metabolism*, **90**, 4599–4606.
21 Herbstman, J., Apelberg, B.J., Witter, F.R. *et al.* (2008) Maternal, infant, and delivery factors associated with neonatal thyroid hormone status. *Thyroid*, **18**, 67–76.
22 Román, G.C. (2007) Autism: transient *in utero* hypothyroxinemia related to maternal flavonoid ingestion during pregnancy and to other environmental antithyroid agents. *Journal of the Neurological Sciences*, **262**, 15–26.
23 Sadamatsu, M., Kanai, H., Xu, X. *et al.* (2006) Review of animal models for autism: implication of thyroid hormone. *Congenital Anomalies*, **46**, 1–9.
24 Vermiglio, F., Lo Presti, V.P., Moleti, M. *et al.* (2004) Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. *Journal of Clinical Endocrinology and Metabolism*, **89**, 6054–6060.
25 Alvarez-Pedrerol, M., Ribas- Fitó, N., Torrent, M. *et al.* (2007) TSH concentration within the normal range is associated with cognitive function and ADHD symptoms in healthy preschoolers. *Clinical Endocrinology*, **66**, 890–898.
26 Utiger, R.D. (1999) Maternal hypothyroidism and foetal development. *New England Journal of Medicine*, **341**, 601–602.