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Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy*

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Summary

BACKGROUND Maternal thyroid function during early pregnancy is an important determinant of early fetal brain development because the fetal thyroid is unable to produce any T4 before 12–14 weeks' gestation. Overt maternal hypothyroidism as seen in severe iodine-deficient areas is associated with severely impaired neurological development of the offspring. At present, it is not known whether low free T4 (fT4) levels during pregnancy in healthy women from iodine sufficient areas may affect fetal neurodevelopment.

METHODS Neurodevelopment was assessed at 10 months of age in a cohort of 220 healthy children, born after uncomplicated pregnancies and deliveries, using the Bayley Scales of Infant Development. Maternal TSH, fT4 and TPO antibody status were assessed at 12 and 32 weeks' gestation. Maternal gestational fT4 concentration was defined as an independent parameter for child development.

RESULTS Children of women with fT4 levels below the 5th (<9·8 pmol/l, n = 11) and 10th (<10·4 pmol/l, *n* = 22) percentiles at 12 weeks' gestation had significantly lower scores on the Bayley Psychomotor Developmental Index (PDI) scale at 10 months of age, compared to children of mothers with higher fT4 values (*t* test, mean difference: 14·1, 95% confidence interval (CI): 5·9–22 and 7·4, 95% CI: 1·1–13·9, respectively). At 32 weeks' gestation, no significant differences were found. In the group of women with the lowest 10th percentile fT4 concentrations at 12 weeks' gestation, a positive correlation was found between the mothers' fT4 concentration and children's PDI scores (linear regression, R: 0·46, *P* = 0·03). After correction for confounding variables, a fT4 concentration below the 10th percentile at 12 weeks' gestation was a significant risk factor for impaired psychomotor development (RR): 5·8, 95% CI: 1·3–12·6).

CONCLUSIONS Low maternal plasma fT4 concentrations during early pregnancy may be an important risk factor for impaired infant development.

In pregnant women suffering from thyroid dysfunction, decreased maternal fT4 levels play a critical role in the neurological development of the fetus, especially during the first trimester, since the fetus does not produce thyroid hormone itself until 16–20 weeks' gestation (Vulsma *et al*., 1989; Porterfield & Hendrich, 1993; Burrow *et al*., 1994; De Zegher *et al*., 1995; Emerson, 1996; Fisher, 1996). Similarly, animal and human studies have shown that impaired maternal thyroid function during early gestation is associated with impaired fetal neurological development, in contrast to maternal thyroid dysfunction in late gestation (Morreale de Escobar *et al*., 1990; Calvo *et al*., 1992; Contempre *et al*., 1993). To date, the relationship between the thyroid hormone status of healthy pregnant women and infant neurodevelopment has not been investigated in iodine sufficient areas. In a recent study, no relationship could be demonstrated between maternal plasma fT4 levels at 32 weeks' gestation and the infant's neurodevelopment at 5 years of age (Pop *et al*., 1995). However, it might be argued that it is the maternal plasma fT4 concentration earlier in gestation which is important for fetal maturation and,

* See commentary on page 147.

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consequently, for infant development (Calvo *et al*., 1992; Contempre *et al*., 1993). The present study overcomes these limitations. Firstly, the maternal thyroid hormone status was assessed in healthy women with no previous thyroid dysfunction, who experienced normal pregnancies and deliveries. Secondly, in order to avoid possible bias on child development from environmental factors (e.g. psycho-social aspects, diseases), child development was assessed at an early age (10 months). Finally, the outcome of maternal fT4 levels at 12 weeks' gestation on child development was compared with that of fT4 levels at 32 weeks' gestation.

Subjects and methods

Sample

The study was carried out in an iodine-sufficient area in the south-east of the Netherlands, in and around the city of Veldhoven (Rees-Wortelboer *et al*., 1987). Between January and November 1994, 448 pregnant women (covering 80% of all pregnancies within the region) who checked in for antenatal assessment at four community midwife practices and at one obstetric centre (St Joseph Hospital, Veldhoven) at 12 weeks' gestation were invited to participate in a longitudinal study of postpartum thyroid dysfunction. Women receiving antithyroid drugs and/or thyroid hormones were excluded. The participants were examined at 12 and 32 weeks' gestation, four weeks' postpartum, and at eight-week intervals thereafter until 36 weeks' postpartum. The characteristics of the study group are shown in Table 1.

Maternal thyroid determinants (fT4, TSH and TPO-Ab) were assessed in early and late gestation and in the postpartum period. Neonatal thyroid function was assessed on the fifth to seventh postpartum days, as part of the Dutch national screening program for congenital hypothyroidism. 310 Women (69%) consented to participate, 291 of them (94%) completed the study. The women who did not participate did not differ as far as age, parity and educational level were concerned, 19 women were excluded, seven because of spontaneous miscarriage (of whom 1 TPO-Ab +), one women suffered from puerperal psychosis, nine had another pregnancy within 6 months after delivery (of whom 1 TPO-Ab +), and two had moved outside the area. At ten months' postpartum, 268 women were still eligible to be asked for informed consent to evaluate their child's neurodevelopment. Of the 23 women excluded (2 with TPO-Ab +), three had experienced neonatal deaths related to preterm birth, five had had children with congenital abnormalities, and 15 women had moved outside the area. Of the remaining 268 women, 244 (91%) consented to participate. Of these, a further 24 were excluded for reasons of prematurity (4, of whom 1 had TPO-Ab +), severe neonatal asphyxia (4), twins (3), severe eclampsia (2), intra-uterine growth retardation (2) and a birth weight of <2500 g (9, of whom 1 had TPO-Ab +). Data analysis is based on the remaining 220 women and their children, none of whom had serious complications during pregnancy or delivery and the details of whom are shown in Table 1. Permission for the study was obtained from the Medical Ethics Committee of St Joseph Hospital in Veldhoven.

Methods

Thyroid function. This was assessed by measuring the concentrations of thyroid stimulating hormone (TSH, Kodak Amerlite TSH-30, Ultrasensitive Assay, Kodak Clinical Diagnostics Ltd, Amersham, UK), free thyroxine (fT4, Kodak Amerlite MAB FT4 Assay), and thyroid peroxidase antibodies (TPO-Ab, Immunometric Enzyme, Combikit, Orgentec GMBH, Mainz, Germany). Evaluation of the assays throughout the study showed interassay coefficients of variation for TSH of 20%, 4·8%, 6·3% and 5·1% at concentrations of 0·04, 0·68, 8·2 and 29·2 mU/l, respectively, for fT4 of 11·1%, 11·3% and 12·2% at concentrations of 6·1, 19·3, and 27·7 pmol/l, respectively, and for a TPO-Ab of 18% and 8·5% at concentrations of 18 and 100 IU/ml, respectively.

Child neurodevelopment. This was assessed by means of the Dutch version of the Bayley Scales of Infant Development (Bayley, 1969). The Mental Development Index (MDI) scale of the Bayley test evaluates aspects of functioning such as eye-hand coordination, manipulation, understanding of object relations, imitation, and early language development. The Psychomotor Developmental Index (PDI) scale assesses gross motor development. The Dutch Bayley scales (Van der Meulen & Smrkovsky, 1983) have a mean of 100 and a standard deviation of 16 (these are still considered reliable). All children were visited at home by one developmental psychologist who was blind to the thyroid hormone and TPO-Ab status of the mother during pregnancy.

Several confounding variables which have been reported in the literature to be related to child neurodevelopment were assessed such as: maternal depression (using Research Diagnostic Criteria, RDC) (Spitzer *et al*., 1978), psycho-social factors, demographic features, life-style habits during pregnancy (smoking, alcohol), breastfeeding and the occurrence of stressful life events.

Statistical analysis. Statistical analyses were performed using the Statistical Package of Social Science (SPSS). Statistical testing was by Student's *t* test, linear regression and logistic regression analysis. In the logistic regression analysis, and unadjusted model with low scores on the Bayley Scales (below

Table 1 Characteristics of the study group.

Group	A	B	C
Number of women	291	71	220
Educational level (%)			
Basic school	0·7	1·3	1·0
Low college degree	22·1	27·1	20·2
High college degree	53·0	45·4	55·4
Graduated/academic	24·2	26·2	23·4
Mean age of women, years (SD)	29·6 (3·2)	29·4 (3·2)	29·5 (3·1)
Parity			
Primipara	105 (36)	27 (38)	78 (35)
Multipara	186 (64)	40 (62)	142 (65)
Smoking habits:			
Never	165 (57)	38 (54)	127 (58)
No smoking in pregnancy	80 (28)	22 (31)	58 (26)
Smoked in pregnancy	46 (16)	11 (15)	35 (16)
Alcohol intake:			
Never	90 (31)	22 (31)	68 (31)
No intake in pregnancy	151 (51)	32 (46)	119 (54)
Intake in pregnancy	50 (17)	17 (23)	33 (15)
Mean birth weight, g (SD)	3441 (579)	3386 (624)	3471 (550)
Sex			
No of girls (%)	129 (44)	34 (47)	99 (45)
No of boys (%)	162 (56)	37 (53)	121 (55)
No. of women breastfeeding* (%)	200 (69)	40 (57)	160 (73)
Mean fT4 concentrations, pmol/l (SD)			
12 weeks' gestation	13·2 (2·5)	13·6 (2·7)	13·1 (2·6)
32 weeks' gestation	10·4 (1·9)	10·8 (2·0)	10·4 (1·8)
No. with TPO-Ab (%)			
12 weeks' gestation			
>50 U/ml	29 (10)	5 (7)	24 (11)
⩾ 100 U/ml	18 (6·2)	3 (4)	15 (7)
32 weeks' gestation			
>50 U/ml	15 (5)	2 (3)	13 (6)
⩾100 U/ml	8 (3)	2 (3)	6 (3)
No. with postpartum thyroid dysfunction (%)	15 (5)	2 (3)	13 (6)
No. with depression (%)			
during pregnancy	70 (24)	19 (26)	51 (23)
during postpartum	110 (38)	29 (40)	81 (37)

A, characteristics of the women in the original sample, (n = 291); B, characteristics of the women not included in the follow up (n = 71); C, characteristics of the women in the follow-up study (n = 220). *: breastfeeding: at least four weeks' of exclusive breastfeeding.

1 SD of the mean, <84) was used as the dependent variable. The independent variables were entered into the regression at a univariate level in order to assess significant independent associations with the Bayley scores and, subsequently, at a multivariate level, to control for confounding effects regarding the association between maternal fT4 and these scores.

Results

Figure 1 shows the childrens' scores on the two Bayley subscales in relation to the maternal plasma fT4 concentrations at 12 weeks' gestation. The scores on the Psychomotor Development Index (PDI) of children of mothers with

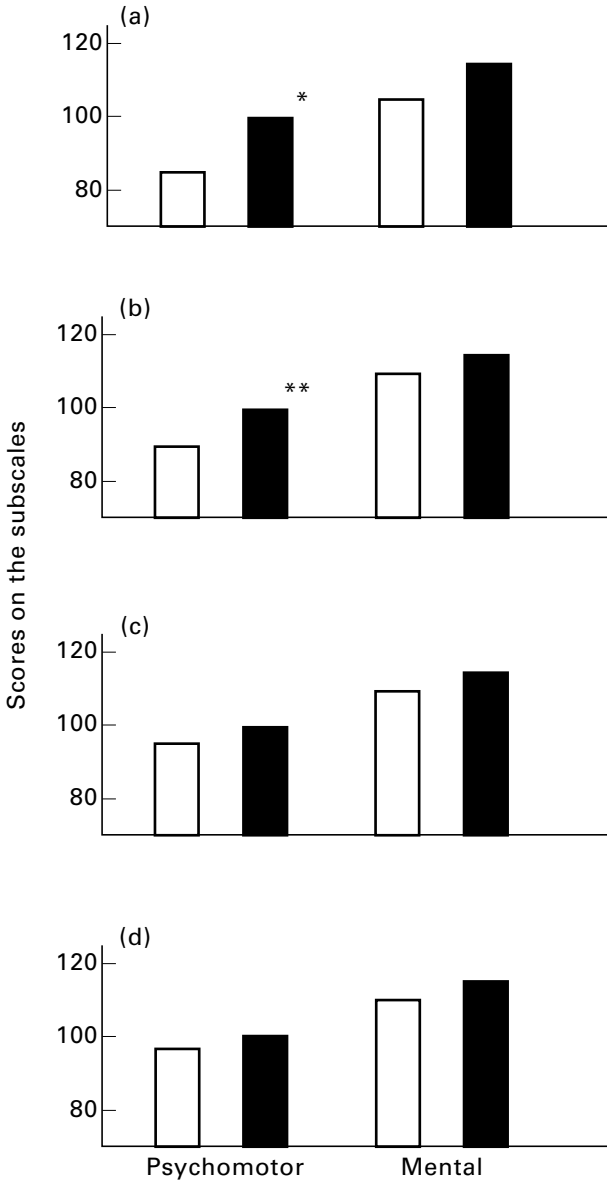

Fig. 1 Differences in mean scores on the two Bayley subscales comparing different percentiles of fT4 at 12 weeks' gestation (t test). a, Lowest 5th percentile (<9·8 pmol/l $n = 11$ □) versus remaining group ($n = 209$ ■). *mean difference: 14·1 (95% CI: 5·9– 22·3). b, Lowest 10th percentile (<10·4 pmol/l, $n = 22$ □) versus remaining group ($n = 198$ ■). **mean difference: 7·4 (95% CI: 1·1– 13·9). c, Lowest 15th percentile (<10·9 pmol/l, $n = 34$ □) versus remaining group ($n = 186$ ■). d, Lowest 20th percentile (<11·4 pmol/l, $n = 45$ □) versus remaining group ($n = 175$ ■).

fT4 concentrations in the lowest 5th and 10th percentiles at 12 weeks' gestation were significantly lower than the scores of the remainder of the group (mean difference: 14·1, 95% CI: 5·9–22·3, and 7·4, 95% CI: 1·1–13·9, respectively). At 32 weeks' gestation, no differences in scores could be demonstrated between any of the subgroups (data not shown). Similarly, children of mothers with fT4 concentrations in the lowest fT4 5th and 10th percentiles had lower scores on the Mental Development Index subscale (MDI), although these differences were not significant. Therefore, the PDI scores were studied more closely.

Figure 2 presents a scatter diagram of the group of women with the lowest 10th percentile plasma fT4 concentrations at 12 weeks' gestation and correlates maternal fT4 concentrations with their children's scores on the Psychomotor Developmental Index scale (PDI). From this, it can be seen that, the lower the mother's fT4 concentration, the lower the child's score (linear regression, R: 0·46, $P = 0·03$). All children who were assessed at 10 months of age had T4 and TSH values within the normal range by approximately one week after birth, as assessed by the national screening programme for congenital hypothyroidism (data not shown).

In Table 2, the maternal fT4 and TSH status during pregnancy is shown in relation to the TPO-Ab titers. The three women with elevated TSH levels at 32 weeks' gestation had a TSH of 2·7, 3·2 and 7·1 mU/l with a fT4 of 8·3, 8·7 and 8·0 pmol/l respectively. At 12 weeks' gestation, 6/24 women (25%) with TPO-Ab >50 U/ml had fT4 levels < 10th percentile, compared to 16/196 (8%) of the TPO-Ab negative women. This means that the RR of women with TPO-Ab titers >50 mU/l at 12 weeks' gestation for fT4 >10th percentile at 12 weeks' gestation is 3·1 (95% CI: 1·3–7·1). Subsequently (maternal fT4 levels at 32 weeks' gestation not being related to child outcome), we looked at the relation between elevated TPO-Ab titres at 32 weeks' gestation and fT4 levels at 12 weeks'

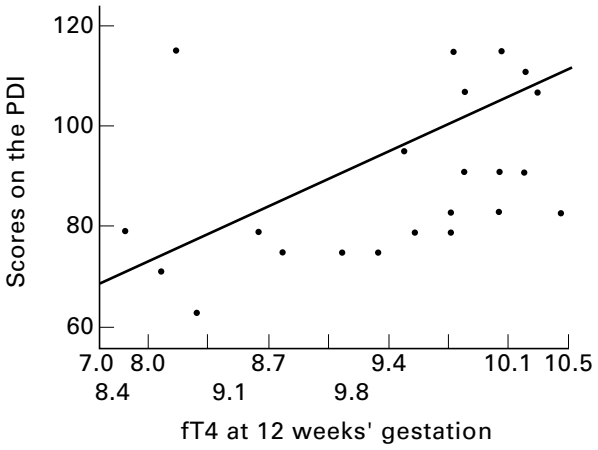

Fig. 2 Scatter diagram correlating the scores on the Psycho-Motor Developmental Index Scale of children of women with the lowest 10th percentile fT4 concentrations at 12 weeks' gestation (<10·4 pmol/l, $n = 22$).

Table 2 fT4 and TSH concentrations in relation to TPO-Ab titres of 220 women at 12 and 32 weeks' gestation.

	12 weeks gestation *N*	32 weeks gestation *N*
A. fT4 (10th percentile)	10·4 pmol/l	8·5 pmol/l
fT4 ⩽ 10th percentile	22	22
TPO-Ab > 50 U/ml	6	7
TPO-Ab ⩾ 100 U/ml	5	2
fT4 > 10th percentile	198	198
TPO-Ab > 50 U/ml	18	6
TPO-Ab ⩾ 100 U/ml	10	4
B. TSH		
TSH < 0·14 U/ml	10	4
TPO-Ab > 50 U/ml	2	0
TPO-Ab > 100 U/ml	1	0
TSH > 2·2 mU/l	4	3
TPO-Ab > 50 U/ml	2	0
TPO-Ab > 100 U/ml	2	0

Reference range for fT4: 8·8–18 pmol/l. Reference range for TSH: 0·14–2·2 mU/l.

gestation. Of the 13 women with TPO-Ab titres >50 mU/l at 32 weeks' gestation, 6 (46%) had fT4 levels <10th percentile at 12 weeks' gestation whereas of the 207 TPO-Ab negative women at 32 weeks' gestation only 16 (8%) had fT4 levels <10th percentile at 12 weeks' gestation. The RR therefore of women with elevated TPO-Ab titres at 32 weeks' gestation for low fT4 levels at 12 weeks' gestation is 6·0 (95% CI: 2·8–12·7).

Table 3a shows the results of the independent associations between several maternal variables and the low PDI scores of the children. Alcohol use, maternal TPO-Ab status during pregnancy, fT4 in the lowest 10th percentile (<10·4 pmol/l) at 12 weeks' gestation, gestational depression, low educational level of the mother, and the occurrence of a negative life event, were all significantly associated with a low PDI score. An fT4 concentration at 32 weeks' gestation in the range of the lowest 10th percentile (<8·5 pmol/l) was not related to a low PDI score. In order to correct the fT4 effect on the PDI scores for possible confounders of infant development, a multiple logistic regression analysis was carried out (Table 3b) with the PDI score as the dependent variable. An fT4 concentration in the range of the lowest 10th percentile (<10·4 pmol/l) at 12 weeks' gestation, alcohol intake by the mother during pregnancy, maternal depression during pregnancy, and the occurrence of negative life events (as rated by the mother), were all significantly related to a low score (below 1 SD of the mean) on the PDI scale. Again, fT4 concentrations in the range of the lowest 10th percentile (<8·4 pmol/l) at 32 weeks' gestation were not related to impaired psychomotor development, neither were high titres of TPO-Ab during pregnancy.

Discussion

This is the first study to show that low material fT4 concentrations in apparently healthy women during early gestation implicate a significantly increased risk (RR 5·8) of impaired neurodevelopment in the infant.

Animal studies have shown that thyroid hormone is a major importance to early fetal cerebral development, possibly due to its direct effect on the development of the cerebral T3 nuclear receptor (Brent, 1994). Moreover, animal studies have shown that during early pregnancy, the fetus is totally dependent on maternal fT4 concentration, since it is unable to produce thyroid hormone (Calvo *et al*., 1992). In humans, clinical studies have shown that fetal and/or neonatal thyroid hormone deficiency, due to congenital hypothyroidism or iodine deficiency, has a dramatic negative impact on cerebral development (Contempre *et al*., 1993; Delange, 1996; Foley, 1996; de Vijlder & Vulsma, 1996). Moreover, premature neonates show psychomotor retardation associated with low postnatal thyroxine concentrations (Den Ouden *et al*., 1996; Reus *et al*., 1996; Vulsma & Kok, 1996). These are all examples of mothers and infants with serious health problems.

In contrast, this study questioned whether low normal plasma fT4 concentrations during pregnancy in healthy women with no previous thyroid dysfunction guarantees an adequate thyroid hormone status for the fetus, and we hypothesised that there might be differences in the individual thyroxine requirements of mother and child. During the first trimester of normal pregnancy there is an increase of fT3 and fT4 with a moderate suppression of TSH, both related to the increase in hCG levels (Burrow *et al*. 1994). Moreover, total T4 and T3 levels are increased throughout pregnancy, due to an increase in serum thyroxine binding globulin. The increase in fT4 and fT3 during early pregnancy seems to be highly relevant for the fetus which produces no thyroxine during this stage of gestation. It might be hypothesised that women with low levels of fT4 during early gestation, which seems to be without any consequences for a normal physiological pregnancy, are at risk of sub-optimal levels of fT4 for the fetus. Since fetal development is completely dependent on the maternal thyroid hormone supply, we measured fT4 at 12 weeks' gestation. The regression line in Figure 2 suggests (although the correlation is rather low) that, within the lower range (10th percentile) of maternal fT4 concentrations during early pregnancy, the young child's psychomotor development is directly related to the maternal thyroid hormone status. In contrast, after the first trimester of

Table 3 Logistic regression analysis, (method enter, $n = 220$) dependent variable: low score of the Psychomotor Scale (PDI) of the Bayley Scale of Infant Development. (SD = 16, Mean = 100). Low score: more than 1 SD below the mean.

	R.R.	95% CI
A. Univariate regression		
Pregnancy-related factors		
Smoking during gestation	1·7	0·6–5·2
Obstetric factors	1·2	0·6–2·9
Alcohol use during pregnancy	3·0	1·4–6·6
TPO-Ab ⩾ 100 U/ml at 12 weeks' gestation	3·8	1·3–10·2
TPO-Ab ⩾ 100 U/ml at 32 weeks' gestation	2·9	0·6–13·8
fT4 of lowest 10th percentile at 12 wks gest	3·6	1·1–12·1
fT4 of lowest 10th percentile at 32 wks gest	1·1	0·4–3·2
Breastfeeding	1·2	0·6–2·5
Female	1·3	0·5–3·1
Maternal mood state		
Gestational depression	3·1	1·3–6·3
Postpartum depression	1·4	0·8–2·7
Postpartum major depression	1·3	0·4–4·0
Depression in parents	1·0	0·5–1·9
Demographic features		
Marital state	1·9	0·7–5·4
Low educational level	1·8	1·1–2·9
Previous episode of depression	1·5	0·7–3·2
Occurrence of negative life events	1·9	1·1–3·7
Work outside home	1·9	0·8–3·8
B. Multiple regression		
Pregnancy-related factors		
Smoking during gestation	1·2	0·5–2·8
Obstetric factors	1·2	0·6–2·9
Alcohol use during pregnancy	3·3	1·3–8·7
TPO-Ab ⩾ 100 U/ml at 12 weeks' gestation	3·4	0·3–14·0
TPO-Ab ⩾ 100 U/ml at 32 weeks' gestation	2·7	0·2–42·0
fT4 of lowest 10th percentile at 12 wks' gest	5·8	1·3–12·6
fT4 of lowest 10th percentile at 32 wks' gest	1·0	0·4–3·2
Breastfeeding	1·4	0·5–3·4
Female	1·5	0·4–4·1
Maternal mood state		
Gestational depression	3·3	1·1–10·3
Postpartum depression	1·9	0·8–4·6
Postpartum major depression	2·5	0·3–16·2
Depression in parents	2·3	0·9–5·7
Demographic features		
Marital state	1·1	0·4–6·2
Low educational level	2·0	1·1–4·8
Previous episode of depression	3·1	0·9–9·5
Occurrence of negative life events	2·6	1·1–6·1
Work outside home	1·9	0·6–4·6

pregnancy, if there is sufficient iodine intake, the increasing fetal thyroid hormone production gradually becomes responsible for fetal growth and development (Calvo *et al*., 1992; Contempre *et al*., 1993). Indeed, at 32 weeks' gestation, low maternal fT4 concentrations were not correlated with impaired development. In a previous study, a significant relation has been demonstrated between maternal TPO-Ab levels at 32 week's gestation and impaired child development at the age of 4·5 years: a reduction in IQ of 10 points (Pop *et al*., 1995). A reason for this finding was unclear: TPO-Ab are supposed to be an epiphenomenon of auto-immune disease rather than a direct 'harmful agent'. However, the present study might provide an explanation for the previous finding: women with elevated titres of TPO-Ab at 32 week's gestation are at particular risk (RR: 6, 95% CI: 2·8–12·7) of low fT4 levels during early gestation.

What is the clinical relevance of a statistically significant impaired score on the PDI scale in children of mothers with low fT4 during early gestation? A difference of 10 points on the psychomotor developmental index score reflects a delay of one month in the development of the retarded group (Bayley, 1969). Although the impact of this delay might be barely perceptible at the age of 10 months, the consequences will be important if the difference persists in later life. While it may be argued that child neurodevelopment on the Bayley Scales is more reliable if the child is assessed at 18–24 months of age, the literature on prematurity (33 weeks' gestation) and the outcome following prenatal complications show that results from assessments at as early as six months of age are able to predict the later outcome (Siegel, 1982; Van Baar & De Graaff, 1994; Van Wassenaer *et al*., 1997). The children in the present study were all born after pregnancies and deliveries with no serious complications, and were free of any explicit abnormalities during the first postpartum year. In order to evaluate whether there is an association between child development and a prenatal factor in a cohort of children in whom a barely perceptible difference could be expected, the investigation should be carried out as early as possible (for example, during a neonatal examination). The clinical implications of these findings could be impressive. If children of women from the general population in iodine-sufficient areas, with fT4 concentrations in the lowest 5th to 10th percentiles during early gestation, are more likely to have impaired neuro-development, the question arises as to whether this impairment could be prevented by the administration of thyroxine to pregnant women with low fT4 levels. The implications of this supplementation for the offspring of women from iodine-deficient areas could be even greater. From this study, one preliminary conclusion could be that maternal fT4 values in the low normal range during early pregnancy are associated with impaired child development and that women with high TPO-Ab titres are particular at risk. further research is needed to determine whether these borderline' concentrations of maternal fT4 can any longer be accepted as 'normal', with regard to infant development.

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