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Published in:
BJOG: An International Journal of Obstetrics and Gynaecology

Publication date:
2004

Document Version
Publisher's PDF, also known as Version of record

BJOG: an International Journal of Obstetrics and Gynaecology
September 2004, Vol. 111, pp. 925–930
DOI: 10.1111/j.1471-0528.2004.00213.x

Low concentrations of maternal thyroxin during early gestation: a risk factor of breech presentation?

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Objective To evaluate the relation between breech position at term (>37 weeks of gestation) and low maternal fT4 levels during gestation in women not suffering from overt thyroid dysfunction.

Design A prospective cohort study of pregnant women.

Setting Community-based study.

Population/Sample At random selected pregnant women of the general population.

Methods At antenatal booking, based on thyroid function assessed at 12 weeks of gestation in a large cohort of pregnant women, two groups of participants were defined: women with low fT4 levels—below the 10th centile ($n = 135$) and women with fT4—between the 50th and 90th centiles at 12 weeks of gestation ($n = 135$). Women with clinical thyroid dysfunction (fT4 and TSH outside reference range) at 12 weeks of gestation were excluded. Maternal thyroid function (fT4 and TSH) was subsequently assessed at 24 and 32 weeks of gestation. Analysis refers to 204 women who met the inclusion and exclusion criteria and in whom all thyroid parameters were assessed.

Main outcome measures Fetal presentation (cephalic–breech) at delivery in women with term gestation (>37 weeks of gestation) in relation to maternal thyroid function at 12, 24 and 34 weeks of gestation.

Results Breech presentation at term delivery was independently related to fT4 levels <10th centile at 12 weeks of gestation (OR = 4.7, 95% CI 1.1–19 [but not to an fT4 level below the 10th centile at 24 and 32 weeks of gestation]) as well as primiparity (OR = 4.7, 95% CI 1.3–15).

Conclusions Women with hypothyroxinaemia (fT4 level at the lowest 10th centile) during early gestation but without overt thyroid function are at risk for fetal breech presentation at term (>37 weeks of gestation).

INTRODUCTION

Approximately 3–5% of all pregnancies reach term with the fetus in the breech position.[1] In general, it is believed that breech deliveries are associated with higher morbidity and mortality, especially after vaginal delivery. Recently, a large, randomised, controlled multicentre trial showed an odds ratio (OR) of 0.33, with regard to perinatal mortality, neonatal mortality and serious neonatal morbidity, in fetus who presented in the breech position and who were delivered by caesarean section, compared with those who had a planned vaginal delivery.[2] It was questioned whether there is still a place for planned vaginal breech birth, and primary caesarean section was advocated for all breech term presentations, which was however criticised by others.[3] In general, caesarean section still has an increased maternal mortality rate compared with non-operative delivery[4] and has been estimated to double the costs for health care during the first two postpartum months.[5] External version to cephalic position substantially reduces breech presentations although serious fetal and obstetric complications have been described. It has been calculated that six attempted external cephalic version are needed to avoid one caesarean section because of breech position.[6]

The negative impact of maternal hypothyroxinaemia (low free thyroid hormone concentration [fT4] with thyrotrophin hormone [TSH] concentration within the reference range) during early gestation on subsequent infant development at one and two years of age has recently been demonstrated.[7] At one and two years of age, children of women with hypothyroxinaemia showed an 8- to 10-point index delay on the motor scale compared with children of women with fT4 between the 50th and 90th centiles. Because the fetus does not produce its own thyroxin up until 16–20 weeks of gestation, it is totally dependent on the maternal supply of fT4 during the first trimester of pregnancy.[8] Thyroid hormone is extremely important for the development of the fetal central nervous system: overt

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maternal hypothyroidism during pregnancy or major iodine (a major keystone of thyroid hormone synthesis) deficiency has been associated with the poor obstetric and developmental outcome of the infant.[9]

Little is known about the aetiology of breech presentation. Together, factors such as prematurity, intrauterine growth retardation, gemelli, pelvic abnormalities, as well as uterus anomalies, placenta praevia, polyhydramnios, multiparity, umbilical cord problems and congenital fetal abnormalities only explain 15% of breech presentations.[10] However, there are several aetiological factors (umbilical cord problems, congenital akinesia syndrome) that might be related to fetal movements during pregnancy.[11,12] It is interesting to note that, in a few congenital endocrinological syndromes (Prader–Willi, pituitary agenesis) in which hypothalamic function is impaired (and, as a consequence, fetal thyroid function), the rate of breech presentations is very high: up to 20%.[13]

We hypothesised that motor development retardation in children at one and two years of age—if related to maternal hypothyroxinaemia during early gestation—should also be present during gestation. Because abnormal fetal movements could be related to breech presentation, we questioned whether breech presentation at term gestation was related to maternal hypothyroxinaemia during early gestation and the subsequent course of maternal thyroxin concentrations throughout pregnancy.

METHODS

Between January 1997 and April 1998, all pregnant women ($n = 1881$), living in and around the city of Eindhoven, the Netherlands, were invited to participate into the study at their first antenatal control with a community midwife (Fig. 1). Only Dutch Caucasian women ($n = 1722$) were eligible of whom 1361 (79%) consented to participate. Thyroid parameters (TSH, fT4 and TPO-Ab) were assessed at 12 weeks of gestation. Because of ethical reasons, women with overt hyperthyroidism ($n = 7$) and hypothyroidism ($n = 1$) were sent to their general practitioner with an advise for treatment and were excluded. In the first 220 of the remaining 1353 women, the lowest 10th and the 50th–90th fT4 centiles

			Total *n*
12 weeks of gestation	Invitation of all pregnant women at first antenatal control during 16 consecutive months		1881
	Eligible for participation (Dutch Caucasian)		1722
	Informed consent (79%): assessment of thyroid function		1361
	Exclusion of hyper- (n=7) and hypo- (n=1) thyroid women		1353
	Inclusion of 135 women with fT4 $\leq$ 10th centile and 135 women with fT4 between 50 and 90th centile, matched on parity and gravidity		**270**
	Refusals for follow up:	12	258
	Exclusion because of previously set criteria	20	238
24 – 32 weeks of gestation	Thyroid parameters not obtained	21	217
delivery	Exclusion because of:		
	pre-term delivery (< 37 weeks)	10	207
	gemelli	3	204
	number of women who completed the whole study		**204**

Data analysis refers to a group of 204 women of whom 108 with an fT4 < 10th and 96 with an fT4 between 50 and 90th centile at 12 weeks of gestation.

Fig. 1. Flowchart of inclusion and exclusion of women during follow up in pregnancy.

were calculated within the first 10 weeks of inclusion: 12.1 and 15.4–19.0 pmol/L, respectively. Thereafter, a further calculation was performed after every consecutive 150 women, which, after minor changes, resulted in the final cutoff scores for the total sample for the 10th (12.4 pmol/L) and 50th–90th (15.6–19.1 pmol/L) centiles. The 135 women in the lowest fT4 centile were matched for parity and gravidity with an equal number of women whose fT4 values were between the 50th and 90th centiles. All these women ($n = 270$) were invited to participate in a follow up study (Fig. 1). Twelve declined to participate, and 20 were excluded, based on previously determined exclusion criteria (fertility problems; presence of autoimmune diseases such as rheumatoid arthritis or insulin-dependent diabetes mellitus). The remaining 238 women were visited at home at 24 and 32 weeks of gestation for repeated assessments of thyroid function and gestational complications. No thyroid parameters were noted in 21 women at 24 and/or 32 weeks of gestation. Thirteen women with obstetric complications such as abortion, gemelli pregnancy and preterm delivery (<37 weeks of gestation) were excluded. Therefore, analysis of the data covers 204 women. The characteristics of these women (demographic features, lifestyle habits, obstetric and thyroid parameters) for the group as a whole are shown in Table 1.

This study was approved by the Medical Ethical Committee of Maxima Medical Centre Eindhoven (the Netherlands).

TSH (reference range for women aged between 20 and 40 years: 0.15–2.0 mIU/L) was measured using a solid-phase, two-site, chemiluminescent enzyme immunometric assay (IMMULITE third generation TSH, Diagnostic Corporation, Los Angeles, California). The inter-assay coefficients of variation were 9.8%, 6.9% and 4.6%, at concentrations of 0.02, 0.15 and 11 mIU/L, respectively. The fT4 concentration (reference range for women aged between 20 and 40 years: 8.7–19.6 pmol/L) was also measured by means of a solid-phase immunometric assay (IMMULITE Free T4). The inter-assay coefficients of variation for this technique were 20%, 5.3% and 5.2% at concentrations of 3.1, 19.8, and 55 pmol/L, respectively. Subclinical thyroid dysfunction was defined by an fT4 within reference range with abnormal TSH, while clinical thyroid dysfunction was defined by both fT4 and TSH levels outside reference range. The IMMULITE anti-TPO Ab kit was used to determine antibodies against thyroid peroxidase (TPO). The inter-assay coefficients of variation for this analysis were 19.9%, 13.0% and 13.4% for concentrations of 36, 69 and 114 IU/mL, respectively. The anti-TPO assay was standardised according to the International Reference Preparation for anti-TPO MRC 66/387. A concentration of between 35 and 100 IU/mL was regarded as being moderately elevated, while one of >100 IU/mL as being clearly elevated. Because of the down-regulation of the immune system during pregnancy (as reflected by decreasing titers of antibodies), TPO-Ab was only assessed at 12 weeks of gestation.

During late gestation (>37 weeks of gestation) as well as at delivery, a careful assessment and registration of fetal position was carried out.

Statistical analysis was performed using the Statistical Package of Social Science and Problems Solutions (SPSS). Differences in characteristics between the various subgroups were analysed by means of the χ^2 test. ORs (with 95% CI) were calculated by means of multiple logistic regression analysis.

Table 1. Characteristics of the sample: 204 women with gestational age >37 weeks.

	n (%)
Socio-economic status	
Educational level	
low	26 (13)
middle	111 (54)
high	67 (33)
Educational level of father	
low	39 (19)
middle	90 (44)
high	75 (37)
Income of parents/year	
low (<US$25,000)	31 (15)
middle (<US$40,000)	69 (34)
high (>US$40,000)	88 (43)
unknown	16 (8)
Lifestyle habits during pregnancy	
Smoking	45 (22)
Alcohol intake	26 (13)
Caffeine	159 (78)
Obstetric parameters	
Parity	
Primiparity	84 (41)
Multiparity	120 (59)
Mean gestational age, weeks [SD]	39.8 [1.4]
Manner of delivery	
spontaneous at home	92 (45)
spontaneous in hospital	47 (23)
after induction vaginally	20 (10)
forceps/vacuum	26 (13)
caesarean section	19 (9)
Fetal position at term gestation (>37 weeks)	
Cephalic	192 (94)
Breech	12 (6)
Thyroid parameters	
Subclinical hypothyroidism during gestation at	
12 weeks	35 (17)
24 weeks	26 (13)
32 weeks	21 (10)
Subclinical hyperthyroidism during gestation at	
12 weeks	6 (3)
24 weeks	–
32 weeks	–
Elevated TPO-Ab titre at 12 weeks of gestation	
>35 IU/mL	22 (11)
≥100 IU/mL	14 (7)

RESULTS

At 12 weeks of gestation, there were 6 (3%) women with subclinical hyperthyroidism and 35 (17%) with subclinical hypothyroidism, 22 (11%) women had TPO-Ab titres >35 IU/mL and 14 (7%) >100 IU/mL (Table 1). At 24 and 32 weeks of gestation, there were 26 (13%) and 21 (10%) women with subclinical hypothyroidism, respectively. No women with subclinical hyperthyroidism were found at 24 and 32 weeks of gestation.

At term gestation (>37 weeks of gestation), 12 women showed fetal position in breech presentation (of whom in one of them cephalic position was reached after external version at 38 weeks of gestation). Of these 12 women, 10 (85%) belonged to the subjects with an fT4 <10th centile at 12 weeks of gestation and 2 (15%) to the controls with an fT4 between 50 and 90th centiles at 12 weeks of gestation ($P = 0.03$, $\chi^2 = 4.7$, $df = 1$). Three of the women with fetal breech presentation had a spontaneous vaginal delivery, one women (after external version in cephalic position at 38 weeks of gestation) delivered by vacuum extraction vaginally and the remaining eight delivered by elective caesarean section. In Table 2, the relation between breech presentation at term gestation (>37 weeks) and several independent variables is shown using univariate logistic regression analysis (OR, 95% CI). The risk of breech presentation at term gestation proved to be increased more than fourfold in those women with an fT4 <10th centile at 12 weeks of gestation (OR = 4.7, 95% CI 1.1–19) while low fT4 levels at 24 and 32 weeks of gestation were not related to fetal position at term (OR = 3.4, 95% CI 0.8–14 and OR = 1.9, 95% CI 0.4–9.5, respectively). Subclinical hypo- as well as hyperthyroidism was not related to breech position. Primiparity increased the risk for breech presentation threefold (OR = 3.0, 95% CI 1.1–10). Finally, in Table 3, multiple logistic regression showed that breech presentation at term gestation proved to be independently related to low fT4 levels at 12 weeks of gestation as well as to primiparity (OR = 5.1, 95% CI 1.2–22 and OR = 4.7, 95% CI 1.3–15, respectively).

Table 2. Factors associated with breech presentation at term analysis of 204 women. Dependent variable: breech presentation at term gestation (>37 weeks), method enter.

	OR	95% CI
Primiparity	3.0	1.1–10
Caffeine consumption	1.3	0.3–4.8
Smoking	1.9	0.8–4.9
Alcohol consumption	1.1	0.4–4.6
Low income	1.2	0.5–5.1
Low education	1.1	0.3–3.1
fT4 < 10th centile		
At 12 weeks	4.7	1.1–19
At 24 weeks	3.4	0.8–14
At 32 weeks	1.9	0.4–9.5
Subclinical hypothyroidism		
At 12 weeks	1.2	0.2–5.8
At 24 weeks	1.4	0.3–6.7
At 32 weeks	1.8	0.4–7.1
Subclinical hyperthyroidism		
At 12 weeks	1.1	0.4–1.9
TPO-Ab > 35 IU/mL at 12 weeks	1.4	0.2–6.1
TPO-Ab > 100 IU/mL at 12 weeks	1.1	0.1–4.7

Table 3. Factors affecting breech presentation at term analysis of 204 women. Dependent variable: breech presentation at term gestation (>37 weeks), method enter.

	OR	95% CI
Primiparity	4.7	1.3–15
Caffeine consumption	1.1	0.2–3.7
Smoking	1.9	0.4–3.6
Alcohol consumption	1.2	0.4–5.1
Low income	1.1	0.3–3.1
Low education	1.1	0.6–3.7
fT4 < 10th centile		
At 12 weeks	5.1	1.2–22
At 24 weeks	2.7	0.9–18
At 32 weeks	1.7	0.2–14
Subclinical hypothyroidism		
At 12 weeks	1.2	0.2–18
At 24 weeks	1.3	0.3–22
At 32 weeks	1.1	0.1–19
Subclinical hyperthyroidism		
At 12 weeks	1.2	0.2–22
TPO-Ab > 35 IU/mL at 12 weeks	1.1	0.1–16
TPO-Ab > 100 IU/mL at 12 weeks	1.2	0.2–19

DISCUSSION

As far as we know, this is the first study to be published that investigates the relationship between maternal thyroid hormone levels in women with no overt thyroid dysfunction during pregnancy and subsequent obstetric outcome. Women with low levels of fT4 (defined as the lowest 10th centile of fT4 at 12 weeks of gestation) were at high risk of being able to reach term with a child in the breech position, and consequently, of having to deliver by caesarean section.

Overt maternal hypothyroidism is well documented as being related to obstetric complications.[9] However, it is a rare condition in childbearing women. Moreover, because hypothyroidism often is associated with fertility problems (due to anovulation), most women with overt hypothyroidism only become pregnant after adequate substitution with thyroid hormone. Most women—at least in iodine-supplemented areas—who present with overt hypothyroidism during pregnancy have been inadequately treated

(inadequate substitution of thyroid hormone in those with previous hypothyroidism, or inadequate treatment with anti-thyroid drugs in those who were suffering from hyperthyroidism).

The mechanism that could explain the association between maternal hypothyroxinaemia and an increased rate of breech deliveries still remains to be explained. However, it could be hypothesised that adequate fetal movement is important for reaching a cephalic position. Moreover, it could also be hypothesised that adequate fetal movement interferes with the development of a long enough umbilical cord, which, when it is too short, has been associated with an increased rate of the breech position.[11,12] As has been demonstrated recently, during early pregnancy, hypothyroxinaemic women are at risk of conceiving children with clear motor development retardation at one and two years of age.[7] It is reasonable to suppose that, if this is due to the fetus's early (i.e. before the fetus produces its own thyroid hormone, which is generally not until 16 weeks of gestation) shortage of thyroid hormone during pregnancy, a possible detrimental effect on motor development is already present during gestation. It is interesting to note that, in a number of congenital endocrinological syndromes (Prader–Willi, pituitary agenesis) in which hypothalamic function is impaired (and, as a consequence, fetal thyroid function), the rate of breech presentations is extremely high: up to 20%.[13]

The direct echo graphical assessment of fetal movements has recently been developed.[14,15] However, the standard procedure is to assess fetal movements for a period of at least 40–60 minutes. Up until now, it has not been ascertained whether such long-duration echo graphical examinations have any negative effects on the fetus, which makes it difficult to use this instrument as a standard research tool for assessing fetal movement. It has been suggested that maternal hypothyroxinaemia might be related to inadequate iodine intake during pregnancy.[16,17] However, the present study was carried out in an area in which the general population has an adequate intake of iodine, although it is still a matter of speculation whether adequate iodine intake in non-childbearing women also guarantees adequate intake of iodine during pregnancy. In this regard, data on iodine intake in large samples of pregnant women are certainly warranted.

Several limitations of the present study need to be mentioned. Firstly, the rather low number of women undergoing breech deliveries. Because statistically significant differences were found in rather small numbers in the present study, larger studies with more epidemiological power are needed in order to confirm the association between maternal hypothyroxinaemia and the breech position. Only then can interventional trials with thyroxin replacement possibly be considered. Secondly, after screening of a large sample, only women with two well-defined ranges of thyroid hormone concentration (<10th *vs* 50–90th centile) were included for reasons that have been published elsewhere.[7] Preferentially, the relation between thyroid hormone and breech position should be investigated in a large open pregnant population in which fT4 is equally distributed and thyroid function is assessed at different times during gestation.

During the last decade, a debate has generated which questions whether thyroid parameters (TSH, fT4 and thyroid peroxidase antibodies, TPO-Ab) should be screened in all pregnant women.[18,19] The association between elevated concentrations of TPO-Ab and an increased rate of abortion, the high correlation between elevated TPO-Ab and the development of postpartum thyroiditis and the relationship between maternal hypothyroxinaemia and impaired infant development are all arguments in favour of screening. The possible role of—what is up until now conceived as physiologically—low concentrations of maternal thyroid hormone (in euthyroid women) in obstetric outcome may be another argument in favour of screening, especially when one realises that true hypothyroxinaemia (fT4 below the 10th centile with normal TSH levels) refers to 5–7% of the general pregnant population. Practically, screening would be easy to implement in Western societies: all pregnant women have blood samples taken between 12 and 16 weeks of gestation. However, until one of the main criteria for screening is met (i.e. is there any evidence of an effective treatment with a realistic cost/benefit ratio?), we feel that screening should not yet be endorsed.

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Accepted 2 March 2004