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# High thyrotrophin levels at end term increase the risk of breech presentation.

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**Abstract**

*Objective.* To study the relationship between maternal TSH and breech presentation at term.

*Design.* Combined data sets of two prospective studies to obtain adequate epidemiological power.

*Patients:* 1058 healthy pregnant women (58 breech, 1000 cephalic) and 131 women who presented in breech at an obstetrical outpatient clinic.

*Measurements:* Maternal thyroid parameters (TSH, FT4, TPO-Ab) and fetal presentation were assessed in both groups between 35–38 weeks gestation. Power calculations suggested that at least 148 breech cases were required.

*Results.* The characteristics of the women in breech in both samples were similar. Women in breech (n=58+131) had significantly higher TSH (but not FT4) than those (n=1000) with cephalic presentation (Mann-Whitney U,  $p = 0.003$ ). Different cut-offs were used to define high TSH in the 916 TPO-Ab negative women with cephalic presentation: the 90<sup>th</sup>, 95<sup>th</sup> and 97.5<sup>th</sup> percentiles were 2.4mIU/l (n=149), 2.7 mIU/l (n=77) and 3.2 mIU/l (n=37). The prevalence rates of breech presentation in these women were all higher compared to the prevalence of breech in women below these cut-offs ( $df=1$ ,  $p < 0.01$ ). The R.R. of the 149 women with a TSH > 90<sup>th</sup> percentile (> 2.4 mIU/l) to present in breech was 1.82 (95% CI: 1.30 - 2.56).

*Conclusions.* Women with high TSH at end term are at risk for breech presentation.

Substantial evidence for a relation between breech presentation and neurodevelopmental delay exists. Since high TSH during gestation has also been linked to poor neurodevelopment, the relation between breech presentation and poor neurodevelopment might be thyroid-related.

Key words: thyrotrophin, breech presentation, neurodevelopment

## Introduction

Breech presentation occurs in 3-5 % of term women and is associated with neonatal as well as maternal morbidity and mortality. Breech is often an indication for elective caesarean section (CS)<sup>1</sup>, which, in itself, constitutes a prominent risk factor for decreased reproductive health.<sup>2</sup> According to a recent review, the currently known risk factors associated with breech presentation only account for up to 15 % of the variance.<sup>3</sup>

We previously reported that women who presented in breech had higher TSH levels than those who presented in cephalic position.<sup>4</sup> This study, however, was limited by small sample size. To overcome this limitation, the current study expanded on our previous findings by combining the breech cases (n=58) from our initial study<sup>4</sup> with a newly obtained larger sample of breech cases (n=131). Moreover, we reviewed the literature on possible consequences of breech presentation and long term infant development.

## Methods

### *Subjects*

The current study combines two samples of pregnant women from the same area in the South-East of the Netherlands. The first sample comprises 1058 pregnant women who were recruited between 2002 - 2004 for a follow-up study in which maternal thyroid status was assessed at 12, 24 and 36 weeks gestation.<sup>4</sup> Fetal position was assessed by ultrasound between 35 - 38 weeks gestation. The second sample comprises 161 pregnant women who, between 2007-2009, presented in breech at an obstetric clinic for an External Cephalic Version (ECV) attempt. Of these women, 151 were eligible and ultimately 141 women consented to participate. Prior to the ECV attempt, obstetrical parameters were assessed and blood samples were taken. While term of gestation in this sample varied between 35 - 39 weeks, for the purpose of the current study only women with a term between 35 - 38 weeks (n = 131, 93%) were included.

In both samples, women with twin pregnancies, on thyroid hormone replacement therapy, those with known auto-immune disorders (e.g., diabetes-I), or those who became pregnant after hormonal stimulation, were excluded, as well as women with preterm birth (study 1). To avoid potential language problems only women of Dutch Caucasian background

1  
2 were included. This resulted in a total of 121 women who were excluded from the first sample  
3  
4 and 20 women from the second sample.  
5

6 The study was approved by the Medical ethical Committee of the Catharina Hospital  
7  
8 Eindhoven.  
9

### 10 11 *Assessments*

12 Fetal presentation was assessed by ultrasound in study one by one researcher (HW) who was  
13  
14 blind to the thyroid hormone status, and in study two prior to the ECV attempt. Breech  
15  
16 position was categorized into complete, incomplete and frank breech. In all women a careful  
17  
18 obstetrical history was taken.  
19  
20  
21  
22

### 23 24 *Thyroid parameters*

25  
26 Thyroid parameters, free thyroid hormone (FT4), thyrotrophin (TSH) and thyroid peroxidase  
27  
28 antibody (TPO-Ab) were in the first sample assessed during the ultrasound visit at 35 - 38  
29  
30 weeks gestation, and in the second sample during the visit at the obstetrical outpatient clinic  
31  
32 just before the ECV attempt. Only the third trimester TSH/FT4 assessments at 35 - 38 weeks  
33  
34 in the first sample were taken into account and compared with the thyroid parameters of the  
35  
36 women with a similar term seen in the ECV outpatient clinic.  
37  
38

39 TSH was measured using a solid-phase, two site chemiluminescent enzyme  
40  
41 immunometric assay (IMMULITE Third generation TSH, Diagnostic Products Corporation, Los  
42  
43 Angeles USA). FT4 (concentration was also measured by means of a solid-phase  
44  
45 immunometric assay (IMMULITE Free T4). The IMMULITE Anti-TPO Ab kit was used for the  
46  
47 determination of antibodies against thyroid peroxidase (TPO). The anti-TPO assay was  
48  
49 standardized in terms of the International Reference Preparation for anti-TPO MRC 66/387.  
50  
51 TPO-Ab concentrations higher than 35 IU/ml were regarded as antibody positive.  
52  
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55

### 56 57 *Statistical analysis*

58 Statistical analysis was performed using the Statistical Package of Social Science  
59  
60 (SPSS 17.0). First, a power calculation was performed. The TSH numbers at 36  
weeks gestation of study one were log transformed and the difference (delta) in

1  
2 means between the women presenting in breech versus those presenting in cephalic  
3  
4 position was calculated. With an alpha of 0.05 and a power of 0.8, it was calculated  
5  
6 that the size of the breech group in the current study needed to be at least 148  
7  
8 women.

9  
10 Kolmogorov-Smirnov tests revealed a non-normal distribution of FT4 and TSH  
11  
12 in the current sample. Therefore, group comparisons on FT4 and TSH used Mann-  
13  
14 Whitney U tests. T-tests (two-tailed) and chi-square tests were used for other group  
15  
16 comparisons. Subsequently, we looked at different cut-offs for maternal TSH with  
17  
18 regard to breech position, and performed chi squares to test associations.  
19  
20

## 21 22 23 **Results**

24  
25 The characteristics of breech women in sample one (n = 58) and those in sample two (n =  
26  
27 131) were compared (Table 1). As can be seen, there were no significant differences between  
28  
29 the groups.  
30  
31

32  
33 Insert table 1 about here  
34  
35

36  
37 Table 2 shows the characteristics of the total group of breech women (58 + 131 = 189) versus  
38  
39 the women of sample one who presented in cephalic position (n = 1000). In the latter group,  
40  
41 TSH and FT4 reference ranges were calculated (between the 2.5<sup>th</sup> and 97.5<sup>th</sup> percentiles) at 36  
42  
43 weeks gestation for those women who were TPO-Ab negative at 12 weeks gestation (n = 916).  
44  
45 These ranges were: 0.42 – 3.2 mIU/l for TSH and 9.4 – 17.1 pmol/l for FT4. As can be seen in  
46  
47 Table 2, the women who presented in breech had significantly higher TSH levels compared to  
48  
49 those who presented in cephalic position (Mann-Whitney-U, p = 0.003), while no between  
50  
51 group differences were found for FT4 (Mann-Whitney-U, p = 0.62).  
52  
53

54  
55  
56 Insert table 2 about here  
57  
58

59  
60 Significantly more primiparous women were found among the breech-presenting women  
versus the cephalic-presenting women. Groups did not differ in terms of the prevalence of

1 women with elevated TPO-Ab. Subsequently, for the overall group (n = 1189) different TSH  
2 cut-off values were defined in the TPO-Ab negative women with cephalic presentation: the  
3  
4 highest 90<sup>th</sup> (> 2.4 mIU/l, n =149), 95<sup>th</sup> (> 2.7 mIU/l, n = 77) and 97.5<sup>th</sup> (> 3.2 mIU/l, n =37)  
5  
6 percentiles. Comparing prevalence rates above and below these cut-offs of TSH categories,  
7  
8 breech-presenting women were significantly more prevalent than cephalic-presenting women  
9  
10 (25% versus 14%, 27% versus 15% and 35% versus 15%, p < 0.01, figure 1). The number of  
11  
12 women with elevated TPO-Ab bodies in the group with TSH > 90<sup>th</sup>, the 95<sup>th</sup> and the 97.5<sup>th</sup>  
13  
14 percentile was significantly higher compared to the number of women below these cut-offs: 14  
15  
16 versus 4.5%, 17% versus 5% and 18 versus 5.2%. The mean FT4 values between groups did  
17  
18 not differ: 13.2 pmol/l (in TSH > 3.2 mIU/l) versus 13.3 pmol/l (TSH <3.2mIU/l) or 13.4  
19  
20 pmol/l in women with a TSH < 50<sup>th</sup> percentile.  
21  
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Insert figure 1 about here

31 When high TSH (> 97.5<sup>th</sup> percentile) and parity were entered into a logistic regression  
32  
33 analysis, both were found to be significantly related to breech presentation (dependent  
34  
35 variable): O.R.: 2.3, 95% CI: 1.2 – 4.9 and O.R.: 5.1, 95% CI: 3.4 – 7.5, respectively. The 37  
36  
37 women with a TSH > upper reference limit (> 3.2 mIU/l) had a median TSH of 3.7 mIU/L with  
38  
39 a range between 3.3 – 10 mIU/L, and 13 presented in breech. Finally, women with a TSH >  
40  
41 90<sup>th</sup> percentile (>2.4 mIU/l) already had a 1.82 increased risk of breech presentation (R.R.:  
42  
43 1.82, 95% CI: 1.30 – 2.56).  
44  
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48

## 49 Discussion

50 The current study combined the data sets of two studies in which the relationship between  
51  
52 maternal thyroid status and fetal breech position was investigated. The present combined  
53  
54 results obtained in 189 breech versus 1000 cephalic cases were clear in showing that high  
55  
56 maternal TSH during pregnancy is related to increased rates of breech position. It is unlikely  
57  
58 that this relationship has arisen by chance, given the 189 breech cases in this study which was  
59  
60 substantially higher than the minimum group size of 148 suggested by the power calculations.



1  
2 In line with the literature, primiparity was significantly more prevalent in breech cases  
3  
4 compared to cephalic cases<sup>3</sup>.  
5

6 In a recent large retrospective study elevated maternal TSH levels in both the first and  
7  
8 second trimesters were not related to adverse obstetrical outcome.<sup>5</sup> In contrast, another large  
9  
10 retrospective study did report a relation between increased TSH and poor obstetrical outcome  
11  
12 (without detailed reports on fetal position), with TSH being assessed between 12 and 24 weeks  
13  
14 gestation.<sup>6</sup>  
15

16 How can the relation between high maternal TSH and breech position be explained? As  
17  
18 discussed in a previous paper, one might speculate that TSH directly acts to modulate uterine  
19  
20 contractility.<sup>4</sup> Another (more indirect) explanation might be that high maternal TSH reflects  
21  
22 suboptimal maternal thyroid function, which, in turn, would affect maternal-fetal T4 transfer,  
23  
24 with impaired fetal neuromotor outcome as a final consequence. The finding that women with  
25  
26 elevated TPO-Ab levels are especially at risk for high TSH levels does suggest that high  
27  
28 maternal TSH in these women is pathologic rather than physiologic (the latter, for example, to  
29  
30 compensate for high T4 turnover by deiodinase activity of the placenta).  
31  
32

33 In view of this latter explanation, several examples of delayed fetal neural maturation in  
34  
35 breech pregnancies are worth addressing. First, the fetus, from 24-35 weeks onwards changes  
36  
37 position through sudden leg extensions and active whole body movements (kicking).<sup>7</sup> These  
38  
39 changes are caused through excitation of antigravity muscles, i.e. extensors of the body axis.<sup>8</sup>  
40  
41 This excitation is a result of the interplay between inhibitory and stimulatory influences  
42  
43 generated in the reticular nuclei, cerebellum and motor cortex. One may speculate that sub-  
44  
45 optimal maternal thyroid function (reflected by high TSH) might affect the neural processes  
46  
47 involved in changes of fetal position. Secondly, neonates born in breech show different sensory  
48  
49 experiences compared to those presenting in cephalic position.<sup>9</sup> Although this was explained in  
50  
51 terms of more amniotic fluid surrounding the head in breech, also this effect might have been  
52  
53 due to suboptimal maternal-fetal thyroid hormone supply. In another study the development  
54  
55 of lateralized head-position preference was found to be less pronounced in breech fetuses than  
56  
57 in cephalic fetuses.<sup>10</sup> Although this may have been related to a smaller difference in  
58  
59 stimulation between the left and right otoliths, inadequate thyroid hormone supply for  
60  
development of the cochlear system might have been involved.<sup>11</sup>

1  
2 With regard to neonatal maturation, breech babies tend to be smaller<sup>12</sup>, have lower  
3 scores on neurological tests<sup>13,14,15</sup> and are balance-impaired until the age of 12-18 months.<sup>16</sup>  
4 Again, for all these findings inadequate maternal-fetal T4 supply may have been an underlying  
5 etiological factor with regard to optimal neurodevelopment. A large cohort study reported a  
6 significant IQ delay in 20 years old men born in breech compared to men born in cephalic  
7 presentation<sup>17</sup>. A similar IQ delay has been reported in children of women with high TSH  
8 during gestation<sup>18</sup>. Finally, autism spectrum disorder has been found to occur more frequently  
9 in children born in breech position<sup>19</sup>. Autism has also been linked to poor maternal thyroid  
10 function during gestation<sup>20,21</sup>.

11  
12 A limitation of the current study was that two different studies were combined. These  
13 studies, however, were performed in the same region, in women with similar characteristics,  
14 using identical thyroid assessments tests. Combining studies, however, also constituted a key  
15 strength, as it heightened the statistical power, thereby allowing a more accurate estimation of  
16 the relationship between high TSH and breech position. Other study strengths were its  
17 prospective design, and the fact that obstetric staff was blind to the thyroid status of the  
18 women.

19  
20 In conclusion, this study strongly suggests a relationship between high maternal TSH  
21 and fetal position at end term. It also suggests that neurodevelopmental delay, which has  
22 been related to breech presentation at term, might in fact reflect sub-optimal maternal thyroid  
23 function during gestation. Because breech presentation is associated with neonatal as well as  
24 maternal morbidity and mortality, future prospective studies are needed to further elucidate  
25 the relation between high maternal TSH and fetal presentation at term.  
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For Peer Review

Table 1 Characteristics (relevant to thyroid function) of a sample of 58 breech women of a general population sample of 1000 women, compared to 131 women in breech who visited an outpatient clinic for ECV. Term in both groups was between 35 – 38 weeks gestation.

	Breech women of general population sample N = 58			Breech women of outpatient ECV clinic N = 131			P
	Mn (SD)	n (%)	median (range)	Mn (SD)	n (%)	median (range)	
Age	31.2 (3.7)			31.6 (4.1)			0.6
<b>Life style habits</b>							
smoking (yes/no)		6 (11)		8 (6)			0.3
any alcohol use		10 (18)		12 (9)			0.1
<b>Obstetrical features</b>							
Parity							
Primiparity		33 (57)		87 (66)			0.2
Multiparity		25 (43)		44 (34)			
one child		21 (37)		42 (32)			
two children		5 (9)		8 (6)			
>two children		1 (2)		4 (3)			0.7
Miscarriage earlier in life		11 (19)		31 (24)			0.5
<b>Fetal characteristics</b>							
Boy		34 (59)		62 (48)			0.2
Girl		24 (41)		68 (52)			
Birth weight (grams)	3190 (464)			3329 (438)			0.1
Placental weight (grams)	583 (128)			607 (132)			0.2
<b>Thyroid function parameters</b>							
Family history of thyroid dysfunction		5 (8)		13 (10)			0.8
TSH median (range)			1.60 (0.58 – 5.4)			1.59 (0.51 – 9.7)	0.6
FT4 median (range)			13.3 (9.8 – 17.5)			13.2 (9.6 – 18.2)	0.7
TPO-Ab > 35		5 (8)		10 (7.6)			0.8

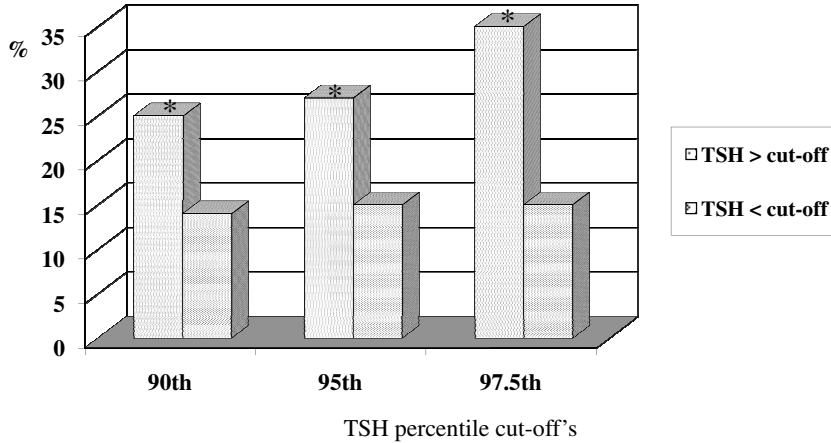
Table 2 Characteristics of a sample of 189 breech women and 1000 women who present in cephalic position. Term in both groups was between 35 – 38 weeks gestation.

	Breech women			Cephalic women			P		
	Mn (SD)	n (%)	median (range)	Mn (SD)	n (%)	median (range)	t-test	$\chi^2$	M-W-U
Age	31.7 (3.9)			32.3 (3.6)					
<b>Life style habits</b>									
smoking (yes/no)		13 (7)			120 (12)				
alcohol use		23 (12)			130 (13)				
<b>Obstetrical features</b>									
Parity									
Primiparity		<b>120 (64)</b>			<b>480 (48)</b>				
<b>Multiparity</b>		<b>69 (36)</b>			<b>520 (52)</b>			<b>0.003</b>	
Miscarriage earlier in life		51 (27)			190 (19)				
<b>Fetal characteristics</b>									
Boy		96 (51)			520 (52)				
Girl		93 (49)			480 (48)				
<b>Birth weight (grams)</b>		<b>3299 (440)</b>			<b>3530 (485)</b>			<b>&lt; 0.001</b>	
Placental weight (grams)		612 (109)			623 (113)				
<b>Thyroid function parameters</b>									
Family history thyroid dysfunction		23 (12)			170 (17)				
<b>TSH</b>		<b>1.61 (0.48 – 9.7)</b>			<b>1.30 (0.05 – 5.1)</b>			<b>0.003</b>	
FT4		13.3 (9.6 – 18.2)			13.2 (7.2 – 24.6)			0.58	
TPO-Ab > 35		15 (8)			60 (6)				

M-W-U: Mann-Whitney-U test

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Figure 1: Comparison of prevalence rate of breech presentation at 35 – 38 weeks between women above and below different percentile cut-off's of TSH. (n total group =1189, of which 189 breech and 1000 cephalic presentations)



\* : p < 0.01, chi-square, df=1.

Peer Review