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# Maternal Thyroid Function during Pregnancy and Mother and Infant Well-Being

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DISSERTATION

# Maternal thyroid function during pregnancy and mother and infant well-being

SOCIAL & BEHAVIORAL SCIENCES

Evelien Brouwers

# Maternal thyroid function during pregnancy and mother and infant well-being

# Maternal thyroid function during pregnancy and mother and infant well-being

PROEFSCHRIFT

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aan de Katholieke Universiteit Brabant,
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# Chapter 1

# General Introduction

Pregnancy is a time during which many changes occur in a woman's life. Apart from her visibly changing body, many more subtle physical changes occur, such as alterations in her hormone metabolism and dietary requirements. Changes in mood may also take place. The experience of anxiety and depression during gestation can be especially distressing because pregnancy is a time when women are usually expected to be happy about becoming a mother.

It is not always clear whether feelings of anxiety and depression during pregnancy are due to physical changes (e.g., hormonal fluctuations), or to psychological changes (e.g., worries about the changes ahead) or to a complex interplay between physical and psychological factors. Moreover, it is not known to what extent such changes affect child development either during or after pregnancy. Central to this thesis is the relationship between a biological determinant of well-being in the pregnant woman (thyroid function), a psychological determinant (depression and anxiety during and after pregnancy), and the effects of these factors on the development of the child.

In Chapter 1, a brief summary of the literature is presented. What is known about the following aspects will be discussed: maternal thyroid function during normal pregnancy and its impact on child development, thyroid function and anxiety and depression, maternal anxiety and depression during pregnancy, maternal anxiety and depression and child development, and co-morbidity between anxiety and depression. The methods are discussed in Chapter 2. Chapter 3 deals with the question of whether maternal hypothyroxinemia during early pregnancy affects subsequent infant development. This is the main question determining the design of this thesis. In Chapter 4, the impact of maternal anxiety during pregnancy on infant development is studied. Chapter 5 investigates whether the Edinburgh Postnatal Depression Scale contains an anxiety subscale, and Chapter 6 looks at the association between thyroid parameters and anxiety in pregnant women. Chapter 7 investigates whether the presence of a high thyroid antibody concentration during pregnancy can predict the occurrence of major depression during pregnancy and after delivery, and Chapter 8 studies the relationship between maternal thyroid hormone levels during pregnancy and obstetrical problems is studied. Finally, in Chapter 9, the general conclusion, the results of this thesis are briefly reviewed and summarised, and recommendations are made for future research.

## 1.1 Maternal thyroid function during normal pregnancy and its importance for child development

Pregnancy is associated with many physiological changes, among which profound alterations in the thyroid function of the pregnant woman. A full description of all the endocrine and biochemical changes that accompany the pregnant state is beyond the scope of this thesis. However, several changes in thyroid function that take place during pregnancy will be summarised below.

The rise in oestrogens that occurs during pregnancy results in an increase of serum thyroxine-binding globulin (TBG) levels. TBG is a thyroid hormone transport protein

that carries about 65% of the thyroid hormone T4 (known as *thyroxine*) in the serum of normal subjects. The rise in TBG reaches a maximum at 20-24 weeks' gestation and remains at this level until a few weeks after birth (Mestman et al., 1995). With the increase of TBG, the amount of T4 bound to transport proteins increases. By 20 weeks' gestation, T4 reaches a plateau value and is maintained until term. During pregnancy, there is increased renal clearance of iodide (iodide is a prerequisite for thyroid hormone synthesis), as well as increased turnover and production of thyroxine (Burrow et al., 1994). As the amount of T4 increases, concentrations of thyroxine that are not bound to transport proteins (known as *free T4* or *fT4*) decrease. However, in most pregnant women, free hormone levels are maintained within the non-pregnant reference range. Thyroid Stimulating Hormone (TSH, or *thyrotropin*) is a hormone from the pituitary gland that stimulates hormonal secretion from the thyroid gland. Due to a feedback mechanism, under normal circumstances TSH levels rise when fT4 levels decrease, and vice versa. After a transient fall near the end of the first trimester, TSH levels are thought to remain stable and to be comparable to pregestation levels (Glinoer 1997).

Elevated concentrations of antibodies against the enzyme thyroid peroxidase (TPO-Ab) are found in up to 10% of (euthyroid) women at 12-16 weeks' gestation (Pop et al., 1995; Lazarus et al., 1996). The concentration declines gradually throughout pregnancy until 30 weeks' gestation, and then remains stable until delivery (Fung et al., 1988), with a rebound in the postpartum period (Mestman et al., 1995) reflecting the immunological fluctuations during normal pregnancy and the postpartum.

After pregnancy, hormone levels in the Hypothalamus-Pituitary-Thyroid axis return to the normal range by approximately 6 weeks postpartum (Pedersen, 1993).

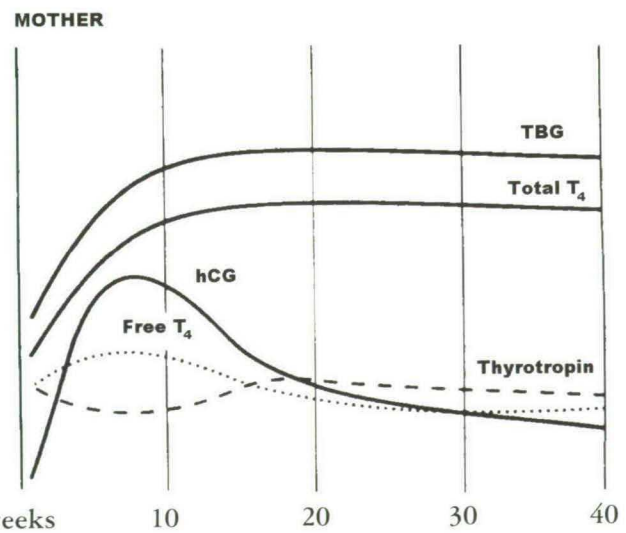


*Figure 1. Relative changes in maternal thyroid function during pregnancy.*
*Adapted from Burrow et al. (1994). Maternal and fetal thyroid function. The New England Journal of Medicine, 20, 1072-1078.*

Thyroid hormone is known to be essential for the development of different foetal tissues, especially the brain. It regulates normal neuronal growth and synaptogenesis and thyroid receptors are widely distributed throughout the central nervous system (Jackson 1998). The importance of thyroid hormone for adequate brain development is illustrated by different situations in which it is in short supply. For example, as iodine is indispensable for thyroid hormone synthesis, in iodine deficient areas the lack of thyroid hormone during gestation and after birth results in cretinism, a chronic condition in the newborn marked by arrested physical and mental development, dystrophy of the bones and soft parts, and lowered basal metabolism. Another example of the importance of thyroid hormone for adequate child development stems from research on congenital hypothyroidism (CHT). A child with CHT is born without a (functioning) thyroid of its own. In normal pregnancy, the foetus begins to produce substantial amounts of thyroxine (T4) by midgestation, but will receive maternal thyroid hormone until birth. Before the foetal thyroid starts to produce hormones, the foetus is entirely dependent on the thyroidal status of the mother. While, during pregnancy, the foetus receives maternal thyroid hormones by placental transfer (Vulsma et al., 1989), after birth it can no longer depend on the maternal supply. However, the need for thyroid hormones for adequate brain development continues during the first postnatal years and, if not substituted, the shortage will lead to irreparable brain damage and severe physical and mental retardation (Rovet, 1984). Although small amounts of maternal thyroid hormones have been shown to be present in the milk, these levels are not enough to protect the brain of an athyrotic baby from the damage it will sustain from a postnatal shortage of thyroid hormone (Porterfield & Hendrich, 1993). A third example of the importance of thyroid hormone for adequate child development can be seen when the mother is suffering from hypothyroidism or hypothyroxinemia in an iodine-sufficient area. *Hypothyroidism* is a disease characterised by lowered fT4 *and* increased TSH (both outside the reference range), often accompanied by symptoms such as fatigue and lethargy, sensitivity to cold, and a decrease in basal metabolic rate. *Hypothyroxinemia* is a condition characterised by normal TSH, but lowered fT4 levels (usually the lowest 5th or 10th percentile).

Although this condition is different from normal circumstances, in which TSH levels rise when fT4 levels decrease (and vice versa), due to the normal TSH levels, hypothyroxinemia is usually seen as not being harmful to the mother. However, the question of whether maternal hypothyroxinemia has no consequences for the development of the foetus still remains to be answered, and will be investigated as the main topic of research of this thesis.

Man & Serunian (1976) investigated the psychological development of three groups of seven-year-old children: (1) those whose mothers were euthyroid during pregnancy; (2) those whose mothers were hypothyroxinemic during pregnancy, but who had been treated adequately; and (3) those whose mothers were hypothyroxinemic during pregnancy but who had been treated inadequately. Results showed that the children of

inadequately-treated mothers performed worse than children of euthyroid mothers or of mothers who had received adequate treatment for their hypothyroxinemia. However, the authors found an incidence of maternal hypothyroidism that was about 20 times greater than current estimates, which was thought mainly to be explained by their assessment of serum T4 (Emerson 1991). This extremely high incidence might be the reason why relatively little interest was paid to this study and virtually no further research was conducted in this area in the ensuing 25 years.

As stated previously, in normal pregnancy, before midgestation the foetus is entirely dependent on the thyroid status of the mother. Therefore, if the mother is hypothyroid or hypothyroxinemic, the harmful effect is believed to occur during early gestation (Pharoah et al. 1981), when an important part of the CNS is developing and there is no foetal thyroid function yet to compensate for this.

Pop et al. (1995) found that the five-year-old children whose mothers had had high antibody concentrations (TPO-Ab) during late gestation, but normal thyroid function, had significantly lower scores on the McCarthy Scales of Children's abilities than the children of mothers who had been TPO-Ab negative. The reason for this finding was unclear, since TPO antibodies are thought to be an epiphenomenon of auto-immune disease rather than a direct harmful agent. In their study published in 1999, Pop et al. showed that the presence of elevated TPO antibody concentrations at 32 weeks' gestation formed a risk factor for low fT4 levels during early gestation, and that low-normal maternal fT4 levels were associated with impaired development in ten-months-old infants. This provided an explanation for the association between TPO antibodies and child development found in their study published in 1995, and emphasised the importance of maternal fT4 for the developing foetus. Haddow and colleagues investigated the effect of maternal hypothyroidism during the second trimester of pregnancy on child development. Specifically, they matched 62 children of mothers who had TSH levels within the highest 98 percentile during pregnancy with 124 children whose mothers had normal thyroid function during pregnancy. IQ scores of the cases on the Wechsler Intelligence Scale for Children were on average four points lower than those of the control group (Haddow et al. 1999). However, this study has received a considerable amount of criticism, for example, for having too few children with low scores in the control group, for concluding (prematurely) that screening for hypothyroidism and subsequent fT4 suppletion would benefit the child based on IQ differences of only 4 points, (Pop et al., 1999), for not taking into account other variables that play a role in the neuropsychological development of children (Herzman & Torrens, 1999), and for selecting subjects according to maternal TSH concentrations, not T4 or fT4 (Morreale de Escobar 1999).

The results of the above studies emphasise the importance of maternal thyroid function during pregnancy for the subsequent development of the child. In contrast to the study by Haddow, the studies of Pop et al. (1995, 1999) indicate that, not only hypothyroidism, but also maternal hypothyroxinemia during pregnancy may have adverse

consequences on the neurodevelopment of the infant. However, both studies used relatively small groups of subjects. Also, the association between maternal gestational fT4 levels and subsequent child development was not assessed longitudinally, and child development was assessed once only. Therefore, the main question in this thesis is: Is maternal hypothyroxinemia during early pregnancy related to infant development? Two related questions are: (a) do fluctuations in maternal fT4 concentrations throughout the trimesters affect infant development; and (b) since hypothyroidism has been associated with poor obstetrical outcome (Wasserstrum & Anania, 1995), is maternal hypothyroxinemia during pregnancy related to obstetric outcome?

### 1.2 Thyroid function and anxiety and depression

During the last 30 years, a large number of studies (in non-pregnant samples) have been conducted on the relationship between thyroid function and depression. Most patients with depression, although often biochemically euthyroid, show alterations in their thyroid function (Musselman & Nemeroff 1996). They have been reported to have alterations in their thyroid-stimulating hormone response to thyrotropin-releasing hormone (TRH), an abnormally high prevalence rate of antithyroid antibodies, and elevated cerebrospinal fluid TRH concentrations (Musselman & Nemeroff, 1996). In depressed individuals serum T4 levels (both T4 and fT4) are usually normal or elevated although often within the normal range (Jackson, 1998). Serum T3 levels are often found to be normal, although several studies have found reduced levels, especially in more depressed patients (Kirkegaard & Faber, 1998).

Conversely, patients with thyroid dysfunction often report mood problems. In both hyperthyroidism and hypothyroidism, cognition, mood, and behaviour are usually disturbed in varying degrees. In hyperthyroidism, fatigue, anxiety, tension, and emotional instability are most prominent, whereas hypothyroidism is often accompanied by depression, pronounced loss of interest, slowing of activity, memory loss, and apathy (Loosen, 1987). Since several authors have found thyroid dysfunction (or thyroid autoimmunity) and depression to be related (e.g. Harris et al. 1992; Pop et al., 1998), a relationship between thyroid parameters and anxiety can be expected, given the high comorbidity between depression and anxiety (Gorman 1997). However, the association between anxiety and thyroid function has not received as much attention as the relationship between depression and thyroid function.

Conflicting results have been found with regard to the association between elevated concentrations of antibodies against the enzyme thyroid peroxidase (TPO-Ab) and depression. For example, Oretti et al. (1997) found no difference in the prevalence of gestational depression in antibody-positive versus antibody-negative women. Moreover, they found that individual depressive symptom scores were not related to TPO-Ab titers. Haggerty et al. (1997) investigated the prevalence of thyroid antibodies in different subgroups of psychiatric inpatients and a non-psychiatric control group. They found no difference in the prevalence of elevated TPO-Ab between patients with unipo-

lar depression and the non-psychiatric control group. In a recent study by Kent et al. (1999), no relationship was found between thyroid antibody concentrations (TPO-Ab or MsAb) and depression at six months post partum. However, others have found high TPO-Ab levels to be associated with depression and anxiety. For example, Harris and colleagues found elevated antibody concentrations to be related to high depressive symptomatology in the postpartum, regardless of thyroid function (Harris et al., 1992). Similarly, Pop and associates found that women who had elevated TPO-Ab concentrations during late pregnancy had a slightly increased risk for postpartum depression (Pop et al., 1993) and Seeler et al. (1996) found that women with high TPO-Ab levels during the postpartum period had significantly higher state anxiety scores than women without antibodies. The association between elevated TPO-Ab and depression has also been confirmed in perimenopausal women (Pop et al., 1998). The presence of thyroid antibodies (TPO-Ab) has been shown to be of a highly persistent nature over a longer time span: in a study on the incidence of thyroid disorders in the community, 98% of the female subjects who had elevated antibody titers, still did at follow-up 20 years later (Vanderpump et al., 1995). Therefore, if an association between elevated TPO antibody concentrations and anxiety and depression does exist, would it be possible to predict maternal depression from TPO-Ab levels during early pregnancy? Considering the adverse consequences that maternal depression can have for the mother and child, it would seem worthwhile investigating the possibility of predicting its occurrence.

### 1.3 Maternal anxiety and depression during pregnancy

Maternal anxiety and depression during pregnancy may have a variety of adverse consequences for both mother and child. Anxiety and depression during pregnancy have been associated with somatic complaints (Lubin et al., 1975), obstetrical problems (Crandon, 1979a,b; Da Costa, 1998) and a heightened risk of maternal mood problems in the postpartum period (Pfost & Stevens, 1990; O'Hara, 1991; Kelly & Deakin, 1992; Tamaki et al., 1997). In addition, maternal anxiety and depression during gestation may affect foetal heart rate (Monk et al., 2000) and behaviour (Groome et al., 1995), neonatal behaviour (Ottinger & Simmons, 1964; Zuckerman et al., 1990) and infant development in the first year after birth (Davids et al., 1963; Lundy et al., 1999).

Studies investigating the question of whether pregnant women as a group experience anxiety and depression more often than non-pregnant women have found conflicting results. Several authors have reported more depressive and anxious symptoms in pregnant women compared to non-pregnant women (Kitamura et al., 1996; Keenan et al., 1998). In contrast, others found that pregnant and non-pregnant women do not differ significantly regarding the amount of anxiety and depression reported (e.g., Striegel-Moore et al., 1996; Behrenz, 1999). Similarly, mood has been described as being stable during pregnancy in some studies (Elliott et al., 1983; Paarlberg et al., 1996), whereas in others anxiety and depressive symptoms were found to fluctuate throughout pregnancy, usually with a considerable increase during the third trimester (Lubin et al.,

1975; DaCosta et al., 1999). It has been argued that pregnancy is a low-risk time for severe psychiatric disorders (Elliott et al., 1983), but that depressive disorders of a lesser severity may be common (O'Hara, 1986).

Several researchers have investigated the characteristics of women who do suffer from gestational anxiety or depression. For example, Kitamura et al. (1996) found that depression during pregnancy was associated with poor intimacy with the partner, having remarried, primiparae, higher public self-consciousness, and unwanted pregnancy. Similar factors have been associated with high gestational anxiety, such as being unmarried, experiencing more stressful life events, having a lower income, experiencing a greater frequency of daily problems, an unwanted pregnancy, having a lack of social support and / or a poor marital relationship (Kalil et al., 1993; Paarlberg et al., 1996; Da Costa et al., 1999).

One of the biological factors that possibly plays a role in anxiety and depression during pregnancy is thyroid function. Since in many studies using non-pregnant samples associations between anxiety and depression and thyroid parameters have been found (e.g. Loosen 1987; Musselman & Nemeroff 1996), such associations can also be expected during pregnancy. It may be especially relevant to investigate this relationship in pregnant women because gestational anxiety and depression have shown to be associated with obstetrical difficulties and impaired infant development. Therefore, an important question in this thesis is: are maternal thyroid parameters related to anxiety during pregnancy?

### 1.4 Maternal anxiety and depression and child development

The interaction between mother (or primary caregiver) and child constitutes an important part of the home environment of the infant. It determines to a great extent the amount and quality of stimulation the child receives, which in turn is essential for many different aspects of development. The quality of the home environment has shown to be related to the intellectual development of the child (Bradley & Caldwell, 1977; Widmayer et al., 1990; Johnson et al., 1993; Molfese et al., 1996).

Research has shown that maternal depression can adversely affect child development and behaviour. For example, Murray (1992) found that children of postnatally depressed mothers performed worse on object concept tasks, were more insecurely attached to their mothers, and showed more mild behavioural difficulties at the age of 18 months than children whose mothers were not depressed. Sharp et al. (1995) reported that, at the age of four years, boys of mothers who were depressed in the first year after birth were intellectually less well developed than boys whose mothers had not been depressed in that year. However, Murray et al. (1996) found no evidence of an adverse effect of postnatal depression in five-year-old children. In a meta-analysis on the effect of postpartum depression on the development of children older than the age of one year, postpartum depression was found to have a small but negative effect on children's cognitive and emotional development (Beck, 1998).

The mechanism through which maternal depression affects child development and behaviour is not clear. The developmental delay may partly be caused by an abnormal interaction between mother and child. Depressed mothers' interaction with their children has been described as being less active, less playful, decisive and responsive, with lower levels of warm acceptance of the child (Kumar & Hipwell, 1994). However, it has also been argued that depressed mothers' communication styles can be subdivided in three groups: (1) women whose interaction with their child is characterised by disengagement and apathy; (2) mothers who attempt to engage with their babies, but who are intrusive and angry; and (3) women who are able to relate positively to their infants (Kumar & Hipwell, 1994).

In addition to the interaction between depressed mothers and their children, several other pathways have been suggested by which maternal anxiety and depression might influence child development. Firstly, there may be indirect effects caused by the additional increased risk of some disorder in the child's father and of marital disharmony. Secondly, direct influences such as the physical or psychological abuse of the child, or separation from the parent(s), can affect child development (Kumar & Hipwell, 1994). Thirdly, it has been argued that, already during pregnancy, maternal anxiety and depression may affect later child development and behaviour (Davids et al., 1963; Lundy et al., 1999; Glover et al., 2000). The underlying mechanism of the relationship between antepartum maternal anxiety and depression and child development is not clear, although it has been hypothesised to be the result of the physical changes that accompany anxiety and depression (e.g., in norepinephrine and dopamine levels), or of life-style habits during pregnancy such as alcohol intake or smoking. So far, relatively few studies have investigated the association between maternal anxiety and depression during pregnancy and subsequent child development. Also, the long- term effects of prepartum maternal anxiety and depression on child development are unknown, since the few studies to have investigated this association have usually investigated infant development in the first year after birth (e.g., Davids et al., 1963; Van den Bergh, 1990; Zuckerman et al., 1990; Lundy et al., 1999). But does prenatal maternal anxiety and depression also affect infant development beyond the first year of life?

### 1.5 Co-morbidity between anxiety and depression

Depression and anxiety very often co-occur. For example, 50-65% of patients with panic disorders also have a major depressive disorder (APA, 1995), and approximately 85% of patients with depression also experience significant symptoms of anxiety (Gorman, 1997). Moreover, antidepressant drugs such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and the selective serotonin re-uptake inhibitors (SSRIs), have well-documented efficacy in a variety of anxiety disorders (Rouillon, 1999). In fact, the question of whether anxiety and depression are clearly separate entities continues to be a controversial issue (Gorman, 1997).

Clark & Watson (1991) introduced the tripartite model of anxiety and depression,

which is based on the assumption that anxiety and depression each have distinct features, (physiological hyperarousal and anhedonia, respectively) but also share a common dimension, known as general distress or negative affect. As was pointed out by Bieling et al. (1998), ideally, a measure of anxiety should assess both the general factor (negative affect) as well as physiological arousal, and should not measure anhedonia. Similarly, a measure of depression should assess negative affect and anhedonia, not physiological hyperarousal.

The Edinburgh Postnatal Depression Scale (EPDS; Cox et al. 1987), a frequently used screening instrument for depression (also used in this thesis), has been claimed to contain an anxiety subscale (Pop et al., 1992). This finding was confirmed by Green (1998), but the concurrent validity of this anxiety subscale has not been evaluated. In the present thesis, this leads to the following questions: (1) Can the existence of this anxiety subscale be confirmed; and (2) does this anxiety subscale measure anxiety more accurately than the total EPDS ?

### 1.6 Summary of the questions and hypotheses presented in this thesis:

*1a. Is maternal hypothyroxinemia during early pregnancy associated with impaired mental and motor development of the infant? (Chapter 3)*

It was hypothesised that children born to mothers with hypothyroxinemia during early pregnancy would have lower mental and motor developmental scores at the ages of one and two years than children whose mothers had had adequate fT4 levels during early pregnancy.

*1b. Is the pattern of fluctuations in maternal thyroid function throughout pregnancy related to the mental and motor development of the infant? (Chapter 3)*

It was hypothesised that fluctuations in maternal thyroid function throughout pregnancy were related to infant development; decreasing thyroid hormone levels, especially after maternal hypothyroxinemia during the first trimester were expected to be related to lower developmental scores in the infant.

*2. Are high maternal anxiety levels during late pregnancy related to the impaired mental and motor development of the infant? (Chapter 4)*

It was hypothesised that high maternal anxiety levels during late pregnancy were associated with lower mental and motor developmental scores in the infant.

*3a. Does the Edinburgh Postnatal Depression Scale (EPDS) contain an anxiety subscale? (Chapter 5)*

It was hypothesised that the EPDS does contain an anxiety subscale

*3b. If the EPDS does contain an anxiety subscale, does this subscale measure anxiety more accurately than the total EPDS? (Chapter 5)*

It was hypothesised that the anxiety subscale of the EPDS measures anxiety more accu-

rately than the complete EPDS.

*4a. Are thyroid parameters and anxiety levels related during late pregnancy? (Chapter 6)*
It was hypothesised that thyroid parameters are related to anxiety levels during late pregnancy.

*4b. Are elevated maternal thyroid peroxidase (TPO) antibody concentrations during early gestation related to high anxiety levels during late gestation? (Chapter 6)*
It was hypothesised that elevated maternal TPO antibodies during early gestation are associated with high anxiety levels during late gestation.

*5a. Is the presence of elevated TPO antibody concentrations during early pregnancy a risk factor for the occurrence of an episode of major depression after childbirth? (Chapter 7)*
It was hypothesised that the presence of elevated TPO antibody concentrations during early pregnancy would be a risk factor for the occurrence of an episode of major depression after childbirth.

*5b. Is a high concentration of TPO antibodies during early pregnancy related to an increased depressive symptomatology during and after pregnancy? (Chapter 7)*
It was hypothesised that a high concentration of TPO antibodies during early pregnancy are related to an increased depressive symptomatology during and after pregnancy.

*6. Are lower maternal fT4 levels during pregnancy related to an increase in complications during labour? (Chapter 8)*
It was hypothesised that lower maternal fT4 levels during pregnancy are related to an increase in complications during labour.

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# Chapter 2

# Methods

## 2.1. Main variables and the instruments used for operationalisation

### 2.1.1 Maternal depression and anxiety

Before discussing the instruments used to measure depression and anxiety, a distinction needs to be made between (a) symptomatology, and (b) clinical diagnosis. The instruments selected for the assessment of depressive symptoms, the clinical diagnosis of depression and of anxious symptoms will now be discussed. With regard to anxiety, the main focus in this thesis was on symptomatology.

#### 2.1.1.1 Depressive symptoms

Depressive symptoms were measured by means of two instruments: the Edinburgh Postnatal Depression Scale (Cox et al., 1987; Dutch version: Pop et al., 1992) and the depression scale of the Symptom Check List-90 (Derogatis et al., 1973, Dutch version: Arrindell & Ettema, 1981).

##### 2.1.1.1.1 The Edinburgh Postnatal Depression Scale

The EPDS is a ten-item self-report scale designed as a screening instrument for postnatal depression. It has also been validated in non-postnatal women (Cox et al., 1996), and has often been used in pregnant samples. It measures the intensity of depressive symptoms but does not provide a syndromal diagnosis. In 1992, the EPDS was translated into Dutch and was found to have good psychometric properties (Pop et al., 1992). For example, Cox et al. (1987) reported a standardised Cronbach's alpha of 0.87 in the original EPDS, whereas the Dutch version had a Cronbach's alpha of 0.82 (Pop et al., 1992). While several other instruments designed to measure depression or depressive symptoms include items that relate to somatic complaints, the EPDS does not incorporate such items but measures the psychological aspects of depression. This makes it a very suitable instrument for the assessment of depressive symptoms in pregnancy or the postpartum, since these periods are characterised by physiological changes not necessarily related to depression. Another reason why the EPDS was chosen for this thesis is that, in addition to its good psychometric properties, it is also short, simple, and only takes a few minutes to complete.

##### 2.1.1.1.2 The Symptom Check List 90.

The SCL-90 (Arrindell & Ettema 1981), is the Dutch version of the original Symptom Check List-90 (Derogatis et al., 1973). The SCL-90 is a 90-item self-report scale measuring multidimensional psychopathology. Subjects are asked to indicate on a five-point scale to what extent they experienced the various items (e.g., difficulty in concentrating) over the preceding 7 days. Although the SCL-90 contains eight subscales, in this thesis only the depression subscale (16 items) and the general anxiety subscale (10 items) were used. The internal consistency of the Dutch version was found to be high, with Cronbach's alphas of 0.91 and 0.93 for the anxiety and depression sub-

scales, respectively (Meeuwesen et al., 1992). Moreover, the SCL-90 was found to be predictably associated with other measures of subjective well-being such as the General Health Questionnaire (Meeuwesen et al., 1992).

#### 2.1.1.2 Diagnosis of an episode of major depression

The diagnosis of major depression during pregnancy and early postpartum was made using the Research Diagnostic Criteria (Spitzer et al. 1978). The RDC diagnosis refers to the current state of the subject. After delivery subjects were visited once a year. Here, the 12 month version of the Composite International Diagnostic Instrument (CIDI; World Health Organisation, 1990a) was used to retrospectively investigate whether subjects had experienced an episode of major depression in the past year. This information was needed in order to control for the influence of maternal depression on infant development in the multivariate analyses.

##### 2.1.1.2.1 Research Diagnostic Criteria

The RDC were developed as a consistent set of criteria for the description or selection of samples of psychiatric patients. These diagnostic criteria were developed for research programs and were the precursors of the DSM-IV criteria. Briefly summarised, the RDC criteria for major depression are:

(a) The presence of one or more distinct and prominent periods with dysphoric mood or pervasive loss of interest or pleasure;
(b) at least four or five of the following symptoms should be present for, respectively, a probable or definite diagnosis: poor appetite or weight loss, difficulty in sleeping too much, loss of energy, psychomotor agitation or retardation, loss of interest or pleasure in usual activities including social contact and sex, feelings or self-reproach or inappropriate guilt, diminished ability to think or concentrate, recurrent thoughts of death or suicide;
(c) duration of dysphoric features of at least one week for a probable, and more than two weeks for a definite, diagnosis;
(d) the condition is causing impairment of functioning at home, at work, or socially, and help has been sought or medication taken;
(e) the diagnosis does not meet the criteria for schizophrenia.

During a short interview, the presence or absence of the above-mentioned symptoms is verified.

##### 2.1.1.2.2 Composite International Diagnostic Interview

The diagnosis of major depression was made by means of the Composite International Diagnostic Interview (CIDI; World Health Organisation 1990a). The CIDI is a fully-structured diagnostic interview developed to allow nonspecialist interviewers to obtain the data necessary to make a psychiatric diagnosis according to DSM-III-R (American Psychiatric Association, 1987) and ICD-10 (World Health Organization,

1990,b) criteria (Robins & Sartorius, 1993). For the study presented in this thesis, only the depressive disorder section of the 12-month version was used. The CIDI was conducted twice; at one and two years after delivery, in order to diagnose episodes of major depression in the mother. In this thesis, the CIDI was chosen because of its good psychometric properties: the inter-rater reliability has been demonstrated to be excellent, its test-retest reliability is good, and its validity has been demonstrated to be good (Andrews & Peters 1998). The CIDI was conducted by well-trained interviewers.

#### 2.1.1.3 Anxiety

Anxiety was operationalised in this thesis by means of two self-report instruments: the Dutch State-Trait Anxiety Inventory (Van der Ploeg et al. 1980) and the anxiety subscale of the Dutch SCL-90 (Arrindell & Ettema 1981). Since the latter has been described above, only the STAI will be discussed here.

##### 2.1.1.3.1 State-Trait Anxiety Inventory

The *State-Trait Anxiety Inventory* (STAI; Spielberger et al., 1970) was chosen for this thesis because it is one of the most widely used scales for measuring anxiety and has been used in over 3000 studies (Bieling et al., 1998). It consists of two subscales each containing 20 items. Another advantage of the STAI is that it makes a distinction between two types of anxiety: state and trait. The *state anxiety* subscale measures anxiety at the moment of scoring. State anxiety is conceptualized as a transient emotional condition of the individual, characterized by subjectively experienced feelings of tension, together with a heightened activity of the autonomous nervous system. *Trait anxiety* measures dispositional anxiety, or anxiety in general. Trait anxiety refers to proneness to anxiety, i.e., relatively stable individual differences in the tendency to react with a more intense state anxiety in situations that are perceived as threatening. Higher scores on the STAI indicate a higher intensity of anxiety.

The STAI has been criticised for not assessing pure anxiety, but to include items that reflect depression and negative affect (Bieling et al., 1998). According to the tripartite model of anxiety and depression (Clark & Watson, 1991), anxiety is characterised by physiological hyperarousal, depression by anhedonia, and the overlap between anxiety and depression by general affective distress. Therefore, Bieling and colleagues argue that ideally, a measure of anxiety should assess both negative affect as well as physiological arousal, and should not assess the presence of anhedonia. However, others have reported that the STAI has extremely good psychometric properties (Gunter, 1985). The Dutch version of the STAI has been validated previously (Dutch version: Zelfbeoordelings Vragenlijst STAI-DY; Van der Ploeg et al., 1980).

### 2.1.2 Infant development

In order to follow child development, repeated assessments were indicated. A neonatal test was performed because, at this age, the interference of (postnatal) environ-

mental influences would still be at a minimum. Because the individual pattern of progression over repeated assessments is thought to be an important aspect of child development, infant development was measured at the ages of one and two years. The age of two years is important since better predictions of future intellectual achievements can be made from this age onwards.

#### 2.1.2.1 Neonatal development

Newborn development was measured by means of the Neonatal Behavioral Assessment Scale (NBAS; Brazelton & Nugent, 1995). The NBAS was chosen in this thesis because it allows the systematic assessment of different aspects of newborn behaviour. The NBAS differs from other neonatal assessment scales in that it attributes an active role to the infant in its interaction with the environment. For example, whereas Prechtl considers states to be involuntary modes of neural activity, Brazelton appreciates the newborn's capacity to control levels of stimuli by using states of consciousness when adapting to the environment (Van Baar, 1998). Moreover, the NBAS includes many items that are related to behaviour and it was assumed that certain of these, such as being able to concentrate and pay attention to external stimuli, would be important determinants of later development.

The NBAS contains 28 behavioral items, 18 neurological reflex items, and seven supplementary items that measure the quality of responsiveness and the amount of input the baby needs from the examiner to show his or her best performance. The behavioral and supplementary items are scored on a nine-point scale, the reflexes on a four point scale.

A frequently-used method of data reduction, also used in the present thesis, is to reduce the scores on the NBAS to seven clusters: (1) *Habituation:* the ability to respond to and to inhibit discrete stimuli while asleep; (2) *Orientation:* includes the ability to attend to visual and auditory stimuli and the quality of overall alertness; (3) *Motor:* measures motor performance and the quality of movement and tone; (4) *Range of state:* a measure of infant arousal and state lability; (5) *Regulation of state:* measures the infant's ability to regulate its state in the face of increasing levels of stimulation; (6) *Autonomic stability:* records signs of stress related to homeostatic adjustments of the central nervous system; (7) *Reflexes.*

A practical problem when using the NBAS for quantitative research is the large number of missing values that can easily occur, as neonates have to be in the appropriate state for specific items to be observed. For example, in order to examine the infant's ability to attend to visual stimuli, the infant needs to be in an alert state with eyes open. Therefore, all NBAS examinations took place midway between feedings, in a quiet, semi-darkened environment. In the analyses, missing values were replaced by the individual mean cluster score. However, if more than two of the items in a cluster were missing, the child's cluster score was considered to be missing, and was not included in the analysis.

A number of studies have shown that it is hard to make predictions of cognitive development during infancy. It has been argued that, only after the age of two years old developmental assessments start to have a predictive value for later intellectual performance (Molfese et al., 1996). However, the predictive value of the NBAS for later infant development or behaviour measured with the Bayley Scales of Infant Development (BSID) has been confirmed by several researchers (e.g., Sostek & Anders 1977; Vaughn et al., 1980; Kalmar & Medgyes 2000), although most studies that reported a significant association between the NBAS and later developmental measures reported weak associations, and did not investigate child development beyond the first year of life. In a sample of preterm infants, Kalmar & Medgyes (2000) found that the NBAS did not have a predictive value for the Mental Developmental Scale of the BSID at the age of six to eight months. However, association was found between the NBAS and dimensions of emotion regulation, orientation, and engagement of the Infant Behaviour Record of the BSID, suggesting that the NBAS was able to measure individual characteristics of neonatal behavioral organisation, which had long-term implications.

#### 2.1.2.2 Infant development at the ages of one and two years

For the assessment of child development at one and two years, the Dutch version of the Bayley Scales of Infant Development (BSID) was chosen. The BSID provides information on three different aspects of infant development: mental, motor, and behavioural. Moreover, it is a frequently used instrument that provides norm scores for term infants. An additional advantage is that most children enjoy the test, which enhances cooperation and accuracy of test scores.

The BSID consists of three parts: a mental and a motor scale and the infant behaviour record. The mental scale is designed to assess sensory-perceptual skills, memory, learning, problem-solving ability, understanding of object constancy, vocalisations, and language development. The motor scale contains items that measure gross motor development (e.g., standing and walking), and fine motor development (e.g., grasping). The total of the positively scored items on the scales (i.e., the raw scores), is transformed into standardised scores that allow comparison with norm tables: the Mental Development Index (MDI) and Psychomotor Development Index (PDI). The Dutch version of the BSID was standardized in 1983 (Van der Meulen & Smrkovsky 1983) with mean scores on the MDI and PDI of 100 and a standard deviation of 16. Van Baar (1996) calculated that in practice, this means that a one year old infant with a mental or motor score of less than 68 (i.e., more than 2 SD under the mean) has the developmental quotient of an infant of eight months of age or younger. With a mental or motor score of between 1 and 2 SD under the mean, the developmental score of the 12-month-old infant is comparable to that of a child of nine to ten months of age. For two-year-olds, a score of less than 68 (i.e., more than 2 SD under the mean) indicates a delay in development of at least six months. A 24-month-old infant with a score of between 1 and 2 SD below

the mean, has a developmental score comparable to that of a child aged between 19 and 21 months.

The Infant Behaviour Record (IBR) of the BSID consists of 30 items that describe the behaviour of the infant during the examination. In the Dutch version, the IBR was reduced to six clusters: (1) task orientation; (2) test-affect extraversion; (3) activity; (4) auditory-visual awareness; (5) exploration; and (6) motor coordination.

Recently, the original 1969 version of the BSID was revised in the USA. The new version has not yet been translated into Dutch or standardised for the Netherlands, for which reason it was not used in this thesis.

### 2.1.3 The daily environment of the child

Important determinants of infant development are the amount of stimulation and attention received, and the interaction with others (especially the mother). In this thesis, the daily environment was operationalised as the total score on the Home Observation for Measurement of the Environment (HOME; Caldwell & Bradley 1978). The HOME consists of 45 items that are either observed by the researcher (e.g. "The mother praises the infant's behaviour twice or more during the interview") or asked during a structured interview (e.g., "Does the child get out of the house more than four times a week?").

Scores on the HOME are reduced to six clusters: (1) responsivity of the mother (or care-giver); (2) avoidance of restriction and punishment; (3) availability of appropriate play material; (4) organisation of the environment; (5) involvement of the mother with her infant; and (6) variety in daily stimulation. Hence, the separate clusters give information about specific areas of the home environment. The total HOME score is obtained by adding the positive scores of all items.

The quality of the home environment has been shown to have a considerable influence on child development. For example, scores on the HOME have been found to be associated with scores on both the Bayley Mental Development Index (e.g., Poresky & Henderson, 1982; Widmayer et al., 1990; Molfese et al., 1994;) and the Psychomotor Development Index (Poresky & Henderson, 1982). Moreover, Molfese et al. (1996) found the HOME to be related to children's scores on the Stanford-Binet Scales measured at three and four years.

### 2.1.4 Thyroid parameters

Thyrotropin (reference range: 0.15-2.0 mIU/l) was measured using a solid-phase, two-site chemiluminescent enzyme immunometric assay (IMMULITE Third generation TSH, Diagnostic Products Corporation, Los Angeles). The free T4 concentration (reference range: 8.7-19.6 pmol/l) was also measured with a solid-phase immunometric assay (Immulite Free T4). The IMMULITE Anti-TPO Ab kit was used to determine antibodies against Thyroid Peroxidase (TPO). The anti-TPO assay is standardised in accordance with the International Reference Preparation for anti-TPO MRC 66/387.

An antibody concentration of ≥35 IU/ml was regarded as elevated. A concentration of >100 IU/ml was regarded as clearly elevated.

**2.2 Operationalisation of the research questions:**

1a. Do children of mothers with hypothyroxinemia (defined as fT4 levels of <12.4 pmol/l and TSH levels between 0.15 and 2.0 mIU/l) at 10-14 weeks' gestation have lower scores on the Mental Developmental Index and the Psychomotor Developmental Index of the Bayley Scales of Infant Development at the ages of one and two years compared to children of mothers with adequate fT4 levels (defined as 15.6-19.1 pmol/l and TSH between 0.15 - 2.0 mIU/l)? (Chapter 3)

1b. Is the pattern of fluctuation of maternal fT4 levels measured at 12, 24 and 32 weeks' pregnancy related to infants' scores on the Mental Developmental Index and the Psychomotor Developmental Index of the Bayley Scales of Infant Development? (Chapter 3)

2. Are high scores on the State-Trait Anxiety Index during late pregnancy related to lower infant scores on the Mental Developmental Index and the Psychomotor Developmental Index of the Bayley Scales of Infant Development? (Chapter 4)

3a. Does the Edinburgh Postnatal Depression Scale contain an anxiety subscale? (Chapter 5)

3b. If the Edinburgh Postnatal Depression Scale does contain an anxiety subscale, does this subscale correlate higher with the anxiety subscale of the Symptom Check List-90, and the State-Trait Anxiety Index than the total EPDS? (Chapter 5)

4a. Are fT4 and TSH concentrations related to scores on the State and Trait Anxiety Index at 32 weeks' pregnancy? (Chapter 6)

4b. Are elevated TPO antibody concentrations at 12 weeks' gestation related to higher anxiety levels at 32 weeks? (Chapter 6)

5a. Is the presence of a TPO antibody concentration greater than 100 IU/ml during early pregnancy a risk factor for the occurrence of an episode of major depression after childbirth? (Chapter 7)

5b. Do women with a TPO antibody concentration greater than 100 IU/ml at 12 weeks' gestation have higher scores on the Edinburgh Postnatal Depression Scale at 24 weeks' gestation, and at one and two years after delivery? (Chapter 7)

6. Do women with maternal fT4 levels below 12.4 pmol/l at 12, 24 and 32 weeks' preg-

nancy more frequently experience breech presentations or non-spontaneous deliveries than women with higher fT4 levels? (Chapter 8)

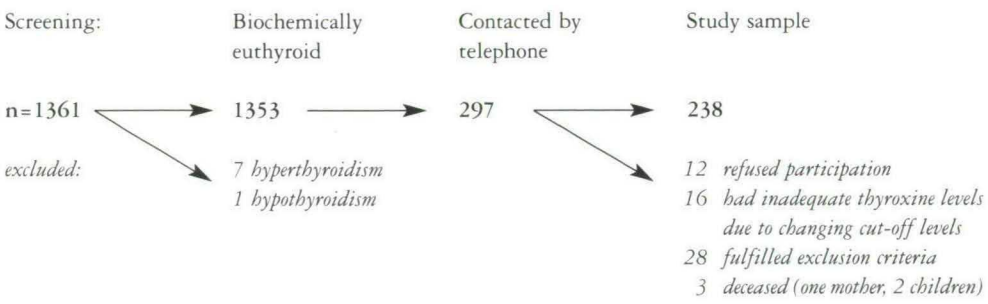
### 2.3 Procedure

Between January 1997 and April 1998, a large cohort of pregnant women from Eindhoven, the Netherlands, was screened for thyroid parameters. During their first antenatal visit to the midwife or gynaecologist at around 12 weeks' gestation, women were asked to participate in a study on maternal thyroid hormone during pregnancy and child development. In total, 1361 women participated in the study by donating a blood sample for the determination of thyroid parameters (fT4, TSH and TPO-Ab). Eight women were excluded because of biochemical thyroid disease, seven of whom having hyperthyroidism, and one hypothyroidism. In the remaining 1353 women, the tenth percentile, 50th, and 90th percentiles of fT4 were calculated. The aim of screening was to match women with low-normal fT4 (< 10th percentile) with women who had an fT4 concentration that was above average, but not high-normal (50-90th percentile) in order to investigate whether hypothyroxinemia during pregnancy adversely affected infant development (Chapter 3). Therefore, all women with fT4 levels within the lowest 10 percentile were invited to participate in the study, together with an equal amount of women with fT4 levels within the 50-90th percentile. Stratified random sampling was used and cases and controls were matched on parity and gravidity.

For the follow-up study, 297 women were contacted by telephone. Previously-set exclusion criteria were verified (gemelli, fertility problems, previous thyroid disease, rheumatism, diabetes mellitus, non-Caucasian and not fluent in Dutch), resulting in the exclusion of 17 (6%) women. A further 12 (4%) decided not to participate in the follow-up study. Because the number of women participating in the screening programme increased over time, the cut-off points of the tenth, 50th, and 90th percentiles were subject to small changes. As a result, 16 (5%) women initially included later had an fT4 within the tenth-50th percentile, or above the 90th percentile, and for this reason were excluded from the analysis. During the study period, an additional ten (3%) women were excluded because they delivered prematurely, or had severe psychiatric problems (n=1). One infant died of congenital heart disease, one of trisomy 18 syndrome and one mother died of cancer. The remaining 238 women originally contacted for the follow-up study participated in the studies presented in this thesis[1]. The selection procedure is illustrated in Figure 2.

[1] In some chapters sample sizes are smaller because of additional exclusion criteria or missing data.

*Figure 2. Selection of the study sample*




All subjects were visited at home at 24 and 32 weeks of pregnancy and at three weeks, and one and two years after birth. During the antenatal visits, a blood sample was taken for the determination of thyroid parameters (fT4 and TSH). Also, during structured interviews, a variety of health related issues were documented, such as gestational complications and medical history, life-style habits, and stressful life events. At 24 weeks' gestation the EPDS was implemented. Subjects completed the STAI at 32 weeks' gestation. At three weeks postpartum the NBAS was undertaken to assess newborn development, and a careful obstetric history was obtained. During the home visits at one and two years after birth, child development was measured by means of the BSID. Major depression in the mother during pregnancy and early postpartum was diagnosed by means of the RDC. At one and two years after delivery, an episode of major depression in the mother in the preceding 12 months was diagnosed by means of the CIDI. In addition, the general medical history for the preceding year in both mother and child was documented (e.g., period of breastfeeding, any serious diseases, chronic drug intake, life style habits).

**Table 1. Timetable for the instruments used.**

| | 12 weeks' gestation | 24 weeks' gestation | 32 weeks' gestation | 3 weeks' postpartum | 1 year postpartum | 2 years postpartum |
|---|---|---|---|---|---|---|
| Maternal fT4 & TSH | + | + | + | - | - | - |
| Maternal TPO-Ab | + | - | + | - | - | - |
| EPDS | - | + | - | - | + | + |
| SCL-90 Depression and anxiety subscale | - | + | - | - | - | - |
| RDC | - | + | + | + | - | - |
| STAI | - | - | + | - | - | - |
| CIDI | - | - | - | - | + | + |
| NBAS | - | - | - | + | - | - |
| BSID | - | - | - | - | + | + |

## 2.4 Subjects

The subjects in the follow-up study were all Caucasian, Dutch-speaking women, ranging in age from 20-39 years. In this group, 98 (41%) were nulliparous, and 140 (59%) multiparae. During pregnancy, 183 (77%) of the women were still employed. Women who were selected for the follow-up study (the subjects of this thesis) were very similar to the remainder of the screening sample with regard to demographic characteristics. The demographic variables of both groups are presented in Table 2.

Table 2. Demographic variables of all women who participated in the screening (n=1361), divided into those who did not participate in the follow-up sample *(remainder of screening sample)* and those who did *(follow-up sample)*.

| Demographic variables | | Follow-up sample (n=238) | Remainder of screening sample (n=1123) | Number of Missing values (%) |
|---|---|---|---|---|
| Age of participant (mother) at start of pregnancy | Mean (SD) | 30.1 (3.3) | 29.8 (3.4) | 54 (4.0) |
| Parity | Mean (SD) | 0.9 (0.9) | 0.7 (0.8) | 19 (1.4) |
| Gravida | Mean (SD) | 2.1 (1.1) | 1.9 (1.0) | 23 (1.7) |
| Marital status | n (%) | | | |
| Married | | 206 (86.9) | 859 (87.4) | 141 (10.4) |
| Living with partner | | 30 (12.7) | 115 (11.7) | |
| No partner | | 1 ( 0.4 ) | 9 ( 0.9 ) | |
| Educational level of participant (mother) in years | Mean (SD) | 10.7 (3.1) | 11.0 (3.2) | 148 (10.9) |
| Educational level of partner of participant (father) in years | Mean (SD) | 11.1 (3.6) | 11.2 (3.5) | 152 (11.2) |

## 2.5 Statistical analysis

Statistical analyses were performed using SPSS. For differences between groups, t-tests, Mann-Whitney U tests and Chi-square tests were used, depending on the level of measurement of the variables. Pearson correlations were used to measure the strength of the linear relationship between two variables measured at interval level, and Principal Component Analysis for data reduction.

Multiple regression analysis was used to assess the relationship between one dependent variable and several independent variables, and logistic regression analysis to predict the dichotomous outcome from a set of independent variables. With the exception of the study presented in Chapter 7, all tests were two-tailed, since in most studies, the direction of the association was not evident. The statistical analyses performed throughout this thesis will be described in more detail in the relevant chapters.

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# Chapter 3

# Maternal hypothyroxinemia during early pregnancy and subsequent child development

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## Abstract

*Background*

Maternal hypothyroxinemia during early gestation (fT4 within the lower range with TSH within the reference range) even when followed by a further decline in fT4 during gestation is generally regarded to be without consequences for the mother. The impact on infant development is not known.

*Methods*

In a prospective follow-up study, child development was assessed by means of the Bayley Scales of Infant Development in children of mothers with hypothyroxinemia (an fT4 below the 10$^{th}$ percentile at 12 weeks' gestation, the cases) at 12 weeks' gestation and in children of mothers with an fT4 between the 50$^{th}$ - 90$^{th}$ percentile at 12 weeks' gestation (the controls), matched on parity and gravidity. Maternal thyroid function (fT4 and TSH) was assessed at 12, 24 and 32 weeks' gestation. At the age of one year scores on the mental and motor scale of 63 children of the cases were compared with that of 62 children of the controls, which was 57 and 58, respectively, at the age of two years.

*Results*

Children of mothers with hypothyroxinemia at 12 weeks' gestation had lower developmental scores compared to controls: 10 index points on the mental scale (95% CI: 4.5 - 15 points, P= 0.003) and 8 index points on the motor scale at one year of age (95% CI: 2.3 - 12.8 points, P=0.02) and 8 index points on the mental (95% CI: 4 - 12 points, P=0.02) and 10 index points on the motor scale (95%CI: 6 - 16 points, P=0.005) at the age of two years. At the age of one year the OR of children of mothers with hypothyroxinemia at 12 weeks' gestation to have a suspect score (> 1 SD below the mean) was 4.5 (95% CI: 1.7 - 8.9) for the mental scale and 3.9 (95% CI: 1.6 - 8.3) for the motor scale and at the age of 2 years 3.0 (95% CI: 1.6 - 16) and 4.5 (95% CI: 1.5 - 9.3), respectively. Children of hypothyroxinemic mothers in whom the fT4 concentration increased throughout 24 and 32 weeks' gestation had scores similar to controls, while in the controls developmental scores were not influenced by further maternal fT4 declines at 24 and 32 weeks' gestation.

*Conclusions*

Maternal hypothyroxinemia during early gestation is an independent determinant of infants' neurodevelopment. An increase of maternal fT4 levels in hypothyroxinemic mothers throughout pregnancy might benefit infant development. Whenever screening of pregnant women is advocated, fT4 measurement should be preferred as screening tool.

## Introduction

During the last decade, there has been renewed interest in the relation between maternal plasma thyroid hormone concentration during pregnancy and subsequent

infant neurodevelopment (Pop et al., 1995; Pop et al. 1999; Haddow et al., 1999; Lazarus 1999; Smit et al. 2000). It is well established that either maternal thyroid dysfunction during pregnancy (especially hypothyroidism) or severe iodine deficiency adversely affects child neurodevelopmental outcome (Delange 1994; Glinoer 1997; Mestman 1999). Even in iodine suppleted areas pregnant women often have fT4 plasma levels in the lower range without elevated TSH, defined as hypothyroxinemia, which is generally regarded as a normal condition. However, there is growing concern that hypothyroxinemia during early gestation may be harmful for the offspring (Pop et al., 1999; Utiger 1999). Besides, little is known about the course of maternal fT4 levels during normal pregnancy and its relation to the development of the children.

This paper describes the results of a longitudinal prospective study investigating whether maternal thyroid hormone levels assessed in women without (sub)clinical thyroid function at three trimesters during pregnancy are adversely related to child development at one and two years of age.

## Material and Methods

*Subjects*

Between January 1997 and April 1998, thyroid parameters (TSH, fT4 and TPO-Ab) were assessed at 12 weeks' gestation in a randomly selected cohort of 1361 Dutch Caucasian women who booked in for antenatal controls in an area around the city of Eindhoven, the Netherlands. Women with overt hyperthyroidism (n=7) and hypothyroidism (n=1) were excluded. Of the remaining 1353 women, the lowest 10$^{th}$ and the 50$^{th}$ - 90$^{th}$ fT4 percentiles were calculated: 12.4 and 15.6-19.1 pmol/l, respectively. The 135 women in the lowest fT4 percentile (cases) were matched on parity and gravidity with an equal number of women whose fT4 value was between the 50$^{th}$ - 90$^{th}$ fT4 percentiles (controls). All these women (n=270) were invited for a follow-up study. Twelve refused participation (4%) and 20 (6%) were excluded according to previously set exclusion criteria (fertility problems, the presence of autoimmune diseases such as rheumatoid arthritis, insulin dependent diabetes mellitus). The remaining 238 women were visited at home at 24 and 32 weeks' gestation for repeated assessments of thyroid function and assessment of gestational complications. Subsequently, a careful obstetrical history was obtained at 3 weeks' postpartum. At one and two years after giving birth a general medical history (period of breastfeeding, serious diseases, chronic drug intake, life style habits) was assessed during a home interview in which the occurrence of an episode of major depression was also assessed. One woman and two children died during the study period (unrelated to thyroid function). Infant neurodevelopment was assessed at one and two years of age.

Of the remaining 235 mothers and their children thyroid parameters of 24 and/or 32 weeks gestation were not obtained in 21 women. 44 Women with subclinical thyroid dysfunction (fT4 within reference range and TSH outside reference range) were excluded. Furthermore, data of mother-infant dyads suffering from potentially con-

founding circumstances were excluded: 18 women with obstetrical complications such as abortion, gestational diabetes, gemelli and pre / post-term delivery (<37 or >42 weeks' gestation); 19 women reporting at least one episode of major depression during pregnancy or the first postpartum year. Three children were excluded because of low birth weight (< 2500 gram) and 5 because of their enduring hospitalization. Consequently, at the age of 1 year, data-analysis refers to 125 children and their mothers, 63 cases (with hypothyroxinemia at 12 weeks' gestation: fT4 below the 10th percentile and TSH within reference range) and 62 controls (with fT4 at 12 weeks' gestation between 50-90th percentile and TSH within reference range). All these children had normal Apgar scores at birth and had normal screening results for congenital hypothyroidism on the seventh postpartum day. None of these children was on chronic medication known to interfere with neurodevelopment. The characteristics of these two groups are shown in Table 1.

**Table 1 Characteristics of the cases children (of women with hypothyroxinemia at 12 weeks' gestation: n=63, fT4 < 10th percentile and TSH within reference range: 0.15-2mIU/l) and the control children (n=62, fT4 between 50-90th percentile and TSH within reference range)**

| | cases N (%) | controls N (%) |
|---|---|---|
| Socio-economic status | | |
| educational level of mother | | |
| low | 8 (12) | 8 (12) |
| middle | 36 (58) | 32 (51) |
| high | 19 (30) | 22 (37) |
| educational level of father | | |
| low | 10 (16) | 14 (23) |
| middle | 30 (48) | 24 (38) |
| high | 23 (36) | 24 (39) |
| income of parents / year | | |
| low (< 25,000 US$) | 11 (17) | 8 (13) |
| middle (< 40,000 US$) | 23 (37) | 19 (31) |
| high(> 40,000 US$) | 24 (38) | 31 (49) |
| un-known | 5 (8) | 4 (7) |
| marital status | | |
| married / partner | 63 (100) | 61 (98) |
| divorced / single | - | 1 (2) |
| Breastfeeding (at least 4 times /day) | | |
| No | 24 (38) | 24 (38) |
| 1- 4 weeks | 10 (15) | 7 (12) |
| 5-12 weeks | 16 (26) | 19 (30) |
| > 12 weeks | 13 (21) | 12 (20) |
| Life style habits during pregnancy | | |
| Smoking | 14 (22) | 14 (23) |
| Alcohol intake | 9 (14) | 7 (12) |
| Caffeine | 49 (78) | 48 (77) |
| Sexe of the child | | |
| Boy | 26 (41) | 30 (53) |
| Girl | 37 (59) | 32 (47) |
| Mean birth weight, grams, / SD | 3410, 448 | 3425, 512 |
| Mean gestational age, weeks / SD | 39.4, 1.2 | 39.5, 1.3 |

With regard to the analysis at two years postpartum another 9 mothers who developed an episode of major depression were also excluded. One child was excluded because of repeated enduring hospitalizations. There was no change in marital status of the parents of all children between these two assessments. Therefore, data analysis of the infant development at 2 years refers to 115 children, 57 cases and 58 controls.

This study was approved by the Medical Ethical Committee of the St Joseph Hospital (Veldhoven, The Netherlands).

*Thyroid parameters*

TSH (reference range for women between 20-40 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 USA). The inter-assay coefficients of variation were 9.8%, 6.9% and 4.6% at concentrations 0.02 mIU/l, 0.15 mIU/l and 11mIU/l, respectively. The fT4 concentration (reference range for women between 20-40 years: 8.7–19.6 pmol/l) was also measured with 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 pmol/l, 19.8 pmol/l and 55 pmol/l, respectively. The IMMULITE Anti-TPO Ab kit was used for the determination of 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 IU/ml, 69 IU/ml and 114 IU/ml, respectively. The anti-TPO assay is standardized in terms of the International Reference Preparation for anti-TPO MRC 66/387. A concentration between 35 and 100 IU/ml was regarded as moderately elevated, whereas a concentration of > 100 IU/ml was regarded as clearly elevated.

*Infant Development*

Infant development was assessed at one and two years of age by means of the Dutch version of Bayley Scales of Infant Development (Van der Meulen & Smrkovsky 1983). The Mental 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 scale assesses motor development. The Dutch Bayley results in a Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) with a mean of 100 and a standard deviation of 16. A group difference between $^1/_2$ and 1 SD (8-16 index points) is regarded as clinically relevant, between 1 and 2 SD (reflecting a developmental delay of 2-4 months and of 3-5 months at one and two year, respectively) as suspect, and a difference of more than 2 SD as deviant. The investigators who were blinded for maternal thyroid function during pregnancy visited all children at home.

*Statistical analysis*

Statistical analysis was performed using the Statistical Package of Social Science

and Problems Solutions (SPSS). Differences in characteristics between the cases and controls were analyzed with chi-square tests. The differences in scores between the children of cases and controls were compared using the t-test (two-tailed). Odds Ratio's were calculated using logistic regression analysis.

## Results

In the women with hypothyroxinemia, at 24 weeks' gestation the prevalence of a TSH > 2mIU/l or > 4 mIU/l was 15% and 2% and at 32 weeks' gestation 16% and 2%, respectively. In the controls this was 11% and 0% and 7% and 0%, respectively. The prevalence of a TPO-Ab concentration above 35 IU/ml and >= 100 IU/ml at 12 weeks' gestation in mothers with hypothyroxinemia compared to controls was 7% and 5% versus 4% and 1%, respectively.

At one year of age, the mean Bayley mental and motor scores (SD) of the cases were 95 (15) and 91 (15), respectively, and of the controls 105 (14) and 99 (14). The group differences were statistically significant with a mean difference of 10 index points for the mental scale (p=0.003, 95% CI: 4-14) and 8 index points for the motor scale (p=0.02, 95% CI: 2 - 11). There were 19 children with a suspect score (> 1 SD below the mean) on the mental scale, 15 of whom (79%) had hypothyroxinemic mothers. Similarly, 21 children had a suspect score on the motor scale, 16 of whom (76%) had hypothyroxinemic mothers. The OR to have a suspect score with regard to maternal hypothyroxinemia at 12 weeks' gestation was 4.5 (95% CI: 1.7 - 8.9) for the mental scale and 3.9 (95% CI: 1.6 - 8.3) for the motor scale.

Figure 1 shows the distribution of Bayley scores in cases and controls at one year of age by patterns of maternal fT4 concentrations at 3 assessments during gestation. In the children of the hypothyroxinemic women, an increase of mean maternal fT4 between 12 and 24 weeks' followed by a further increase of fT4 between 24 and 32 weeks' gestation (n=16) resulted in similar mental and motor scores compared to the 50-90$^{th}$ percentile group (cases). Lower mental and motor scores were found in those cases in which the maternal fT4 levels decreased between 12 and 24 weeks or 24 and 32 weeks' gestation. The largest differences were observed in those cases (n=9) in which the maternal fT4 decreased both between 12 and 24 and 24 and 32 weeks' gestation. In the children of women with fT4 between 50-90$^{th}$ percentile a decrease of mean fT4 in 59 of the 62 women between 12 and 24 weeks' gestation followed by a further decline in 21 women between 24 and 32 weeks' gestation was not associated with lower Bayley scores at one year of age (Figure 1).

At the *age of 2 years*, the mean Bayley mental and motor scores (SD) of all cases were 98 (15) and 92 (16), respectively, and of the controls 106 (14) and 102 (16). The 57 cases children showed an 8 points index lower mean mental score (p=0.02, 95% CI of the difference: 4 - 12) and a 10 points index lower motor score (p=0.005, 95% CI of the difference: 6 - 16) compared to 58 controls. There were 11 children with a suspect score (> 1 SD below the mean) on the mental scale, 8 of whom (73%) had mothers with

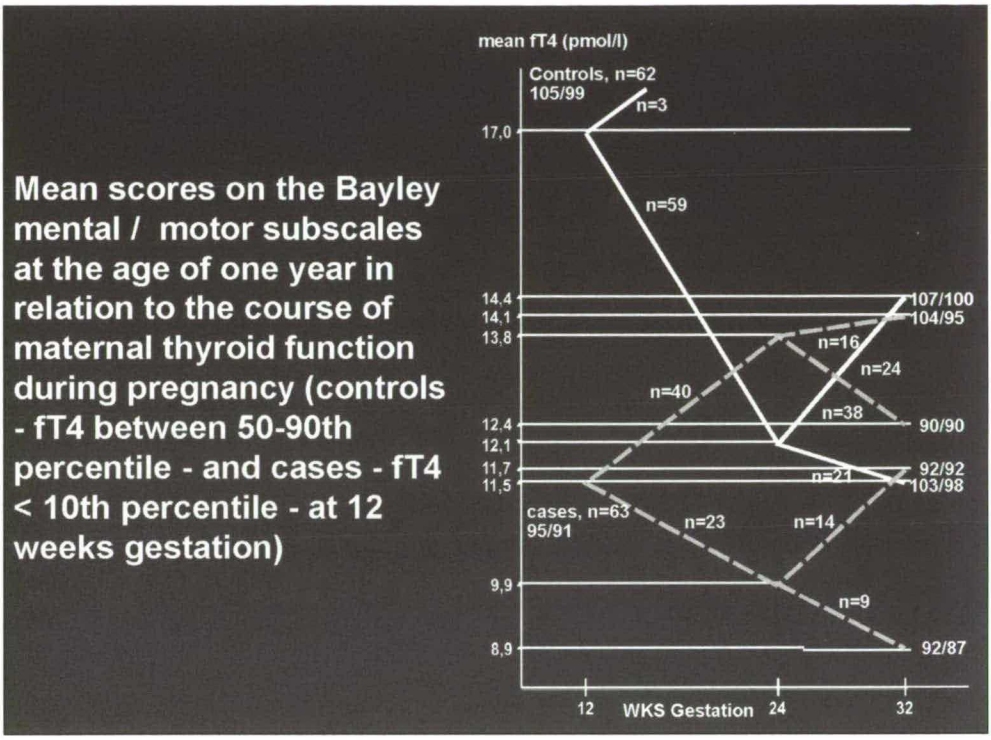


*Figure 1.Fluctuations in maternal fT4 levels and subsequent scores on the Bayley Scales of Infant Development at the age of one year*

hypothyroxinemia. Similarly, 22 children had a suspect score on the motor scale, 17 of whom (77%) belonged to the hypothyroxinemic group. The OR to have a suspect score at two years of age with regard to maternal hypothyroxinemia at 12 weeks gestation was 3.0 (95% CI: 1.2 - 16) for the mental and 4.5 (95% CI: 1.5 - 9.3) for the motor scale.

Of the 29 children with a suspect score (mental or/and motor < 84) at two years of age, 14 (48%) already had suspect scores at the age of one year.

## Discussion

This is the first study published investigating the relationship between repeatedly assessed fT4 concentrations in hypothyroxinemic women during gestation and neurodevelopment of the offspring.

Our findings show that the children of women with hypothyroxinemia (fT4 levels below the 10$^{th}$ percentile with TSH levels within reference range) during the first trimester of pregnancy are at risk for a delay in both mental as well as motor development at the age of one and still at two years. In addition, this study shows that the course of maternal fT4 concentrations during pregnancy is also important for development of the offspring. This is mainly observed in children of those women who had hypothyroxinemia during early gestation and who exhibited a further decline of fT4

during gestation: their children had the lowest scores. In contrast, those children whose mothers showed early hypothyroxinemia but whose fT4 levels increased during further gestation did not show developmental delay. Children of mothers who had higher levels of fT4 (50-90$^{th}$ percentile) during early pregnancy showed normal neurodevelopment that was not affected by maternal declines of fT4 levels throughout further pregnancy.

Hypothyroxinemia, by definition, refers to a condition with an fT4 within the lower range with TSH values within reference range. The reference range for TSH in our study is rather strict but similar to that which has been suggested in the longitudinal Whickham Survey data (Vanderpump et al., 1995). There was only one woman (2%) in the hypothyroxinemic group who during late gestation showed a TSH of 4.3 mIU/l, suggesting that the TSH - contrarily the study of Haddow et al. - may be inadequate as a risk marker for impaired neurodevelopment (Haddow et al., 1999). Besides, hypothyroxinemic mothers, at 12 weeks' gestation, had rather similar prevalence rates of elevated TPO-Ab concentrations suggesting that the TPO-Ab concentration also seems to be of little value to detect women at risk for an impaired development of the offspring.

The association between maternal fT4 during pregnancy and infant development might be mediated by other independent factors. Several precautions were taken to prevent known confounding variables to affect results. Maternal depression - both during pregnancy as well as during the first postpartum years - is associated with poor infant outcome (Murray et al. 1996; Weinberg & Tronick 1998). Therefore, data of women who suffered from at least one episode of major depression during the period of follow-up were excluded. Several pregnancy and infant related factors, which may interfere with child outcome, were also reasons for exclusion as described in the method section. Other factors (Olds et al., 1994; Frydman 1996; Seagull et al., 1996; Lucas et al., 1992), such as demographic features of the parents (educational level, marital status) and life style habits of the mother (alcohol intake and smoking habits during pregnancy) were rather equally distributed between the cases and the controls.

Several limitations of this study need to be mentioned. The subgroups defined according to maternal fT4 patterns during pregnancy turned out to be small after exclusion of cases with potentially confounding data. Although time-consuming and expensive, therefore even larger epidemiological studies are needed for accurate investigation of the relation between the course of maternal fT4 levels during pregnancy and neurodevelopment of the offspring. It should be remembered that different abilities might be affected by different (critical) periods of gestation during which the maternal fT4 is low and as a consequence they may be differentially sensible to a low maternal thyroid supply at different times during gestation (Mirabella et al., 2000).

Another limitation is that no careful daily food intake assessment has been carried out, taken into account for instance the intake of maternal flavonoids. In animals such flavonoids were shown to cross the placenta and were also found in the fetal brain, as such interfering with the availability of thyroid hormone in the fetal compartment (Schroder-van der Elst et al, 1998). However, there is no reason to believe that the daily

intake of flavonoids during pregnancy between the cases and the controls would be significantly different. Although 24 hours iodine intake was also not assessed, previous population studies in this area reported sufficient iodine intake in the general population within this area while other simulation studies questioned whether this daily intake is sufficient for pregnant women with regard to the fetus (Utiger 1999; Rees-Wortelboer et al., 1987; Brussaard et al., 1997; Morreale de Escobar & Escobar del Rey 1999). The finding of (highly) elevated TSH concentrations during late gestation in several studies (Haddow et al., 1999; Glinoer 1997) has lead to the suggestion of an inadequate iodine intake during pregnancy (Brussaard 1997; Utiger 1999). In the present study there was hardly any woman with elevated TSH at 32 weeks' gestation.

Finally, it might be questioned whether in the view of secular trend of norms of developmental or intelligence tests, the number of children showing developmental delay may even have been underestimated (Fuggle et al., 1992). With this regard it is interesting to note that in a previous study in 1998 in the same area as the current study the mean scores of the mental and motor scale of a group of 225 children of the general population at 10-12 months of age were 106 and 100, respectively, (Pop et al., 1999) suggesting that the mean scores of the control group in the current study seem to be representative of the general population.

The results of this study suggest - contrarily to what has been questioned recently (Pop et al., 1999)- that screening with fT4 at 12 weeks' gestation might indicate a subgroup of hypothyroxinemic women whose infant could benefit of an increase of maternal fT4 (for example by suppletion with thyroxin), even after the first trimester which is generally conceived as the most critical part of gestation because the lack of fetal own fT4 production (Burrow et al. 1994). However, with the exception of Man and colleagues' study several decades ago (before the fT4 and sensitive TSH assays were available) (Man & Serunian 1976), there are neither longitudinal follow-up studies published of children repeatedly assessed throughout infancy and school age showing a relationship between maternal thyroid functioning during pregnancy and neurodevelopment nor any study showing a benefit of maternal thyroxin substitution during early pregnancy and subsequent infant development.

In conclusion, maternal hypothyroxinemia during early gestation is found to be consistently related to a delay in infant development suggesting that maternal thyroid fT4 concentration even in women without (sub)clinical thyroid dysfunction during early gestation is an independent determinant of impaired infant development.

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# Chapter 4

# Maternal anxiety during pregnancy and subsequent infant development

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## Abstract

The association between maternal anxiety during pregnancy and child development was studied prospectively in a group of 105 healthy Caucasian women and their infants. Anxiety was measured with the State-Trait Anxiety Inventory at 32 weeks' gestation. Infant development was measured at three weeks postpartum by means of the Neonatal Behavioral Assessment Scale, and at one and two years by means of the Bayley Scales of Infant Development. Findings of the present study showed that, even when controlled for a variety of confounding variables, high maternal anxiety levels during late pregnancy were associated with lower mental developmental scores at the age of 2 years. It is suggested that especially attention related processes may be affected, and should be studied in future research. If these findings are confirmed by future research, identification of highly anxious women during gestation may provide an important opportunity to start a support program in order to optimize later infant stimulation and caretaking.

## Introduction

Maternal anxiety during pregnancy has a variety of adverse consequences. High anxiety levels during pregnancy have been associated with somatic complaints (Lubin et al. 1975) and a variety of gestational and obstetric complications (Crandon, 1979a,b; Da Costa 1998). There is evidence that maternal stress responses and anxiety affect fetal heart rate patterns (Lederman 1981; Monk et al. 2000) and fetal motility (Rossi et al.. 1989; Van den Bergh 1990; Groome et al.,1995). Moreover, high anxiety during pregnancy increases the risk of high depressive and anxious symptomatology in the mother during the postpartum period (Tamaki et al., 1997).

The consequences of maternal anxiety during pregnancy do not seem to be limited to gestational and obstetric problems. Neonates of mothers with high anxiety levels during pregnancy have been found to cry more and change more frequently from one behavioral state to another as compared to those of non-anxious mothers (Ottinger & Simmons, 1964; Van den Bergh 1990). Goldman and Owen (1994), found that prenatal reports of high anxiety predicted an increased incidence of unscheduled acute health care visits in the first year of life.

Although several researchers have investigated the impact of maternal prenatal anxiety on fetal behavior or newborn development, few researchers have looked at child development at later ages. Van den Bergh (1990) investigated the influence of prenatal anxiety during each trimester on infant development and found no effect on the Prechtl Neurological examination at 1 week post partum and the Bayley Scales of Infant Development (BSID) at 7 months. However, children of anxious pregnant women did have more gastro-intestinal problems, and were perceived by their mothers as having a more difficult temperament. Davids et al. (1963) found high anxiety in the third trimester of pregnancy to be related to lowered scores on the Mental Developmental Index (MDI) of the BSID at the age of 8 months.

Aim of the present prospective, longitudinal study was to investigate the relationship between maternal anxiety during late gestation and subsequent infant development.

## Methods

*Subjects*

During the first antenatal visit to the midwife or gynecologist, women were invited to participate in a screening on thyroid parameters and a follow-up study. A total of 1361 Caucasian women participated in the screening. Only women with an adequate concentration of free thyroxine (fT4, defined as between the 50-90th percentile of the normal range) at 12 weeks' gestation were included in the present study, as low-normal thyroid hormone levels may negatively affect child development, even in iodine sufficient areas in women without thyroid disease (Pop et al., 1995; 1999). Stratified random sampling was used and 131 women were selected. Subjects with gemelli (n=2), gestational diabetes (n=1), a history of fertility problems (n=7), who delivered prematurely (<37 weeks; n=4) or who had missing data (n=9) were excluded from the sample. One woman and one child died during the study period, and one woman was excluded because of repetitive suicidal behavior, resulting in a sample size of 105. Only one woman was single, all others were married or living together with their partner. Subjects ranged in age from 21-38 (mean 30.4, SD 3.4). The mean number of years of education the women and their partners had received was 10.8 (SD 3.0) and 10.8 years (SD 3.8), respectively.

*Instruments*

Prenatal anxiety was measured at 32 weeks' gestation by means of the *State-Trait Anxiety Inventory* (STAI; Spielberger et al., 1970). This self-report questionnaire consists of two subscales each containing 20 items. The *state anxiety* subscale measures anxiety at the moment of scoring. State anxiety is conceptualized as a transient emotional condition of the individual, characterized by subjectively experienced feelings of tension, together with a heightened activity of the autonomous nervous system. *Trait anxiety* measures dispositional anxiety, or anxiety in general. Trait anxiety refers to anxiety proneness, i.e. relatively stable individual differences in the tendency to react with a more intense state anxiety in situations that are perceived as threatening. Higher scores on the STAI indicate a higher intensity of anxiety. The Dutch version of the STAI has been validated previously (Dutch version: Zelfbeoordelings Vragenlijst STAI-DY ; Van der Ploeg et al., 1980). The focus of the present study was on the possible effect of prepartum anxiety on infant development in general. Therefore, the distinction between state and trait anxiety was regarded as less relevant and high anxiety at 32 weeks was defined as having a high score on either state or trait anxiety (defined as ≥1 SD above mean; i.e. ≥39 and ≥37, respectively) or on both..

Child development was measured at 3 weeks postpartum by means of the Neonatal Behavioral Assessment Scale (NBAS; Brazelton & Nugent 1995) and at 1 and 2 years

using the Dutch version of the Bayley Scales of Infant Development (Bayley Ontwikkelingsschalen; Van der Meulen & Smrkovsky, 1983).

Scores on the NBAS are reduced into 7 clusters: (1) *Habituation:* the ability to respond to and inhibit discrete stimuli while asleep; (2) *Orientation:* includes the ability to attend to visual and auditory stimuli and the quality of overall alertness; (3) *Motor:* measures motor performance and the quality of movement and tone; (4) *Range of state:* a measure of infant arousal and state lability; (5) *Regulation of state:* measures infant's ability to regulate her state in the face of increasing levels of stimulation; (6) *Autonomic stability:* records signs of stress related to homeostatic adjustments of the CNS; (7) *Reflexes.* In addition, the NBAS contains seven supplementary items that assess qualitative aspects of the child's performance.

The *Bayley Scales of Infant Development* (BSID) consists of a mental and a motor scale and the Infant Behavior Record (30 ratings of the child's behavior during the examination). The mental scale results in a Mental Developmental Index (MDI), and is designed to assess sensory-perceptual skills, memory, learning, problem-solving ability, understanding of object constancy, vocalizations, and language development. The motor scale results in a Psychomotor Developmental Index (PDI) and entails items that measure gross motor development (e.g. standing and walking), and fine motor development, such as grasping. The Dutch version of the BSID was standardized in 1983 (Van der Meulen & Smrkovsky 1983) with mean scores on the MDI and PDI of 100 and a standard deviation of 16. In the Dutch version, the Infant Behavior Record was reduced to six clusters: (1) task orientation; (2) test-affect extraversion; (3) activity; (4) auditory-visual awareness; (5) Exploration; and (6) motor co-ordination.

In addition to anxiety and child development, other variables known to be of influence on child development were also assessed. Maternal depression was measured at 1 and 2 years post partum, by means of the 12 months version of the depression section of the Composite International Diagnostic Interview (CIDI; World Health Organization, 1990a). The CIDI is a highly structured psychiatric interview assessing major types of DSM-III-R (American Psychiatric Association, 1987) and ICD-10 (World Health Organization, 1990,b) diagnoses. Maternal depressive symptoms were measured by means of the Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987) at 12 months postpartum. The EPDS is a ten-item self-report scale designed as a screening instrument for postnatal depression. It has also been validated in non-postnatal women (Cox et al., 1996) and was translated into Dutch in 1992 (Pop et al., 1992). It has been suggested that the EPDS also is a good screening instrument for anxiety (Stuart et al., 1998; Brouwers et al., in press), as high correlations have been found between scores on the STAI and the EPDS (e.g., Tamaki et al., 1997; Stuart et al., 1998; Green 1998). Furthermore, the home environment was measured by means of the *Home Observation and Measurement of the Environment inventory* (HOME; Bradley & Caldwell, 1977), at 12 months post partum. This is an observation of the home environment and interaction between caregiver and infant during a structured interview on daily routines. Informa-

tion is gathered on six dimensions: responsivity of mother (or caregiver); avoidance of restriction and punishment; availability of appropriate play materials; organization of the environment; involvement of mother with her infant; and variety in daily stimulation. Prenatal alcohol use and smoking, demographic variables, and maternal and infant well-being were measured by means of a questionnaire specifically designed for the study.

The investigators who examined the children were not aware of mothers' antenatal anxiety scores.

*Statistical analyses*

Differences between the anxious and non-anxious group on a number of maternal and child variables were assessed by means of Chi-square tests, t-tests and Mann-Whitney U tests. Missing values on the NBAS items were replaced by the individual mean cluster score. However, if more than two of the items on a cluster were missing, the child's cluster score was considered missing and was not included in the analysis. Differences in scores on the BSID between the infants of the anxious and non-anxious group were investigated by means of t-tests, differences on the IBR by means of Mann-Whitney U tests.

Multiple regression analyses were computed to test whether prenatal anxiety played an independent role in the prediction of child mental and motor development at the ages of one and two years.

## Results

*Prenatal anxiety scores*

Women with a state and / or trait anxiety score of ≥ 1 SD above the mean formed the high anxiety group. This group consisted of 20 women, 7 (35%) of whom had high scores on both state and trait anxiety. Six (30%) had high scores on state anxiety but not on trait anxiety, and 7 (35%) had high scores on trait anxiety, but not on state anxiety. There was a high correlation between state and trait anxiety ($r=.74$ ; $p<0.001$). Mean state and trait anxiety for the anxious group were 41 (SD 8) and 40 (7), respectively. For the non-anxious group these were 29 (SD 5) and 28 (SD 4), respectively.

*Differences between women with high anxiety and low anxiety scores*

As can be seen in Table 1, anxious and non-anxious women did not differ significantly in demographic and life style variables, or obstetrical factors. All newborns had 1-minute and 5 minutes Apgar scores of 6 and 8 or above, respectively. The anxious group had significantly lower scores on one subscale of the HOME measured at 12 months post partum: 'organization of the environment' ($t=2.4$; $p<0.05$, two-tailed). No significant differences were found for the other subscales of the HOME.

Table 1. Differences between women with and without high anxiety at 32 weeks' gestation. High anxiety was defined as ≥1 SD on state and/or trait anxiety. Differences were investigated by means of t-test, c2 tests and Mann-Whitney U tests.

| | | High anxiety (n = 20) | Without high anxiety (n =85) |
|---|---|---|---|
| *Maternal factors* | | | |
| Maternal education level in years | (mean, SD; n=105) | 10.2 (2.7) | 11.0 (3.0) |
| Maternal age | (mean, SD; n=105) | 30.9 (3.1) | 30.3 (3.5) |
| Parity | n (%) | | |
| 1. 0 | | 9 (45.0) | 34 (40.0) |
| 2. ≥1 | | 11 (55.0) | 51 (60.0) |
| Smoking during pregnancy | n (%) | | |
| 1. No | | 14 (73.7) | 70 (83.3) |
| 2. Yes | | 5 (26.3) | 14 (16.7) |
| Alcohol consumption during pregnancy | n (%) | | |
| 1. None | | 15 (83.3) | 75 (88.2) |
| 2. Yes (1-5 drinks per week) | | 3 (16.7) | 10 (11.8) |
| Delivery: | n (%) | | |
| 1. Spontaneous vaginal | | 12 (60.0) | 65 (76.5) |
| 2. Non-spontaneous delivery | | 8 (40.0) | 20 (23.5) |
| Breastfed (4 feedings per day) | n (%) | 12 (60.0) | 64 (75.3) |
| Duration of breastfeeding (4 times a day, in weeks) | (mean, SD) | 19 (13) | 14 (12) |
| HOME subscales | (mean, SD) | | |
| Responsivity of mother | (n=101) | 9.6 (1.2) | 9.9 (1.2) |
| Avoidance of restriction and punishment | (n=104) | 7.3 (0.9) | 7.3 (0.7) |
| Organization of the environment | (n=101) | 5.1 (0.9) | * 5.6 (0.5) |
| Availability of appropriate play materials | (n=104) | 7.8 (1.2) | 8.1 (1.2) |
| Involvement of mother with infant | (n=102) | 5.2 (0.6) | 5.1 (1.0) |
| Variety in daily stimulation | (n=102) | 4.1 (0.6) | 4.1 (0.8) |
| Total HOME score | (n= 94) | 38.9 (3.2) | 40.3 (3.2) |
| *Child factors* | | | |
| Female sex | n (%) | 10 (50.0) | 42 (49.4) |
| Birth weight boys | (mean, SD) | 3458 (473) | 3510 (537) |
| Birth weight girls | (mean, SD) | 3402 (496) | 3497 (604) |
| Gestational age at birth in weeks (n=102) | (mean, SD) | 39.4 (1.2) | 39.8 (1.4) |
| NBAS | (mean, SD) | | |
| Habituation cluster | (n= 39) | 7.2 (2.0) | 7.5 (1.7) |
| Orientation cluster | (n= 97) | 6.0 (1.1) | * 6.5 (0.9) |
| Motor cluster | (n=100) | 4.9 (0.6) | 5.0 (0.8) |
| Range of state cluster | (n=102) | 3.2 (0.8) | 3.3 (1.0) |
| Regulation of state | (n= 99) | 5.2 (1.0) | 5.2 (1.3) |
| Autonomic stability | (n=101) | 7.1 (0.9) | 6.9 (1.0) |
| Number of abnormal reflexes | (n= 68) | 1.1 (0.5) | 0.8 (1.0) |

* sign. at p<0.05 level (2-tailed)

*Differences in child development between the anxious and non-anxious group*

At the age of three weeks, infants of mothers of the prenatally anxious group scored significantly lower on the Orientation cluster ($t=2.15$; $p<0.05$, 2-tailed) of the NBAS than infants of mothers of the non-anxious group (Table 1). No significant differences were found on the other clusters of the NBAS, nor on the reflexes or supplementary items.

At the ages of 12 and 24 months, mean scores on the mental and motor scales were lower in the anxious group, which was statistically significant for the PDI score at 12 months ($t=2.35$; $p<0.05$) and the MDI score at 24 months ($t=3.0$; $p<0.01$). Results are presented in Table 2.

**Table 2. Differences in Mental Developmental Index (MDI) and Psychomotor Developmental Index (PDI) scores between children of mothers with high state and/or trait anxiety during late pregnancy and children whose mothers had low anxiety. Differences investigated by means of t-tests (2-tailed).**

| | High anxiety group (n=20) | Group without high anxiety (n=85) | t | p |
|---|---|---|---|---|
| Mean MDI score at 12 months | 97 (SD 14) | 103 (SD 14) | 1.85 | 0.07 |
| Mean PDI score at 12 months | 89 (SD 14) | 97 (SD 16) | 2.35 | 0.02 * |
| Mean MDI score at 24 months | 95 (SD 14) | 106 (SD 14) | 2.96 | 0.004** |
| Mean PDI score at 24 months | 98 (SD 14) | 100 (SD 19) | 0.47 | 0.64 |

* sign. at $p<0.05$ ** sign. at $p<0.01$

At the age of 1 year, 5 (25%) of the children from the anxious group had a score on the MDI that was ≤ 84 (i.e., 1 SD or more below mean), versus 7 (8%) from the non-anxious group. On the PDI, 6 (30%) of the children from the anxious group had a score of ≤ 84, versus 12 (14%) of the non-anxious group. At the age of 2 years, 4 (22%) of the children from the anxious group had a score on the MDI that was ≤ 84, versus 5 (6%) from the non-anxious group. On the PDI, 3 (16%) of the children from the anxious group had a score of ≤ 84, versus 14 (18%) of the non-anxious group.

The Infant Behavior Record (IBR), which measures child behavior during Bayley examinations, showed that infants of anxious mothers scored significantly lower on the clusters 'task orientation' ($p<0.01$) and 'motor co-ordination' ($p<0.05$) of the Infant Behavior Record at 12 months. At two years of age, no significant differences on the IBR were found between the two groups (data not shown).

*Prenatal anxiety as a predictor of child development at ages1 and 2 in multivariate analyses*

To investigate the relationship between prenatal maternal anxiety and child development on a multivariate level, four multiple regression analyses were computed with

MDI and PDI scores at 12 and 24 months as dependent variables. Independent variables were: high anxiety at 32 weeks' gestation, educational level of the mother in years, sex of the child, birth weight, type of feeding (breast- vs. bottle), parity, the score on the 'Organization of the environment' subscale of the HOME, alcohol use and smoking during pregnancy, an episode of maternal depression in the first (two) year(s) after delivery and maternal anxiety/depressive symptoms at 12 months postpartum.

Of the regression analyses at 12 months, the F-tests were not significant, indicating that the models failed to predict mental and motor development at the age of 1 year. In contrast, the regression analysis of which the MDI at 2 years of age was the dependent variable, yielded a multiple R of .55, ($F=3.1$, $p<0.01$; Adjusted $R^2=.21$), and revealed three significant predictors of lower mental developmental scores: high prenatal anxiety, low maternal educational level and male sex (see Table 3). The final multiple regression analysis was computed using motor development (PDI score) at age two as the dependent variable. The F test was not significant, indicating that this model did not significantly predict motor development at age 2.

**Table 3: Regression results predicting mental development (MDI score) on the Bayley Scales of Infant Development at age 2 (n=105). F=3.1 p<0.01; Overall $R$=.55; Adj. $R^2$=.21**

| Variable | β | p |
|---|---|---|
| Prenatal anxiety | -0.33 | 0.003 ** |
| Maternal educational level in years | 0.26 | 0.01 * |
| Sex of child | 0.22 | 0.03 * |
| Birth weight | 0.02 | 0.82 |
| Type of feeding | 0.10 | 0.32 |
| Parity | -0.20 | 0.06 |
| Organisation of the environment subscale (HOME) | -0.11 | 0.31 |
| Prenatal alcohol use | -0.07 | 0.51 |
| Prenatal smoking | 0.17 | 0.11 |
| Maternal depression in 2 years after birth | -0.07 | 0.53 |
| Maternal score on the EDS 12 months postpartum | 0.03 | 0.78 |

* sign. at p<0.05, 2-tailed ** sign. at p<0.01, 2-tailed

## Discussion

The present study shows that maternal anxiety measured during late pregnancy was an important independent predictor of mental development of two-year-old children, even when controlled for confounding variables such as an episode of major depression in the mother or depressive/ anxious symptomatology after birth.

Van Baar (1996) described that a 12-months-old infant with a mental or motor score of 84 or less (i.e., ≤ 1 SD under the mean) on the BSID has the developmental quotient of an infant of ten months of age or younger. For infants of 24 months old, a score of 84 or less (i.e., ≤1 SD under the mean) indicates a delay in development of at

least 3 months. This means that at the age of 2 years, 22% of the children from prenatally anxious mothers had a developmental delay of at least 3 months, versus 6% of children from mothers who had not been anxious during late gestation.

At the age of 12 months, children from the prenatally anxious had lower scores on the 'task orientation' cluster of the Infant Behavior Record, which is a measure of attention and reactivity. At the age of three weeks, neonates of prenatally anxious mothers had lower scores on the orientation cluster of the NBAS, which is a measure of the ability to attend to visual and auditory stimuli and the quality of overall alertness. These findings suggest that maternal anxiety may specifically affect attention related processes, although future studies need to confirm this hypothesis. The fact that prepartum anxiety scores were most strongly related to mental developmental scores at the age of two years may be due to the increasing diversity in functions with older age that allows a better differentiation. The findings of the present study agree with those of other researchers. For example, Davids et al. (1963) found high anxiety in the third trimester of pregnancy to be related to lowered scores on the Mental Developmental Index (MDI) of the BSID at the age of 8 months. Moreover, newborns of prenatally anxious mothers have been reported as less alert and responsive on the NBAS, although in a later study this was only found for girls (Farber et al. 1981). Glover and associates (2000) found that high anxiety at 32 weeks' gestation doubled the risk of inattention and hyperactivity in boys at the age of four years, independently of anxiety and depression at other times during or after pregnancy or obstetrical and psychosocial variables. However, this study used mothers' self-report as a measure of child development and behavior. As high trait anxiety during pregnancy has been associated with negative infant perceptions in the postpartum period (Gunter 1985), it is preferable to use objective measures of infant development.

The association between prenatal anxiety and the lower mental developmental scores found in the present study can be explained in several ways. First, a biological hypothesis has been proposed, suggesting that prenatal maternal anxiety may precipitate the release of catecholamines, resulting in vasoconstriction of maternal blood vessels, a diminished blood flow to the fetus, and consequent restriction of oxygen and nutrients (e.g. Lobel et al. 1992; Monk et al. 2000), which in turn might interfere with an adequate development of the CNS. Furthermore, maternal stress may cause hormones such as cortisol to be transmitted in high doses to the fetus (Glover 1997). It has been shown that when maternal levels of cortisol and catecholamines increase, fetal levels increase as well, whereas it is not clear at which point these levels become detrimental to the fetus (McCool et al. 1994). Lundy et al. (1999) demonstrated that maternal depression was associated with higher cortisol and norepinephrine levels and lower dopamine levels in both mothers and neonates. Moreover, they found that depressed mothers' prenatal norepinephrine levels independently predicted inferior scores on the Neonatal Behavioral Assessment Scale (NBAS). Alternatively, fetal development may be affected by poor maternal health behaviors associated with mood problems during

gestation (Lobel et al., 1992). However, those health behaviors measured in the present study (smoking, substance abuse -non-existent in the present sample-, and alcohol intake during pregnancy), were not related to mental development.

Second, a psychosocial explanation can be given for the relationship between prenatal anxiety and the cognitive development of the child: prenatal anxiety may have continued as postnatal anxiety. Several studies have shown that anxiety and depressive symptoms during pregnancy are significantly associated with postpartum mood (e.g. Pfost & Stevens 1990; Engle et al., 1990; Kelly & Deakin 1992, Tamaki et al 1997). Anxious women may provide different stimulation and interaction experiences to their children than non-anxious women. Indeed, in the present study prenatally anxious women differed from their non-anxious counterparts on one of the subscales of the HOME ('Organization of the environment'), which was measured one year post partum. A poor score on this subscale has previously been associated with low IQ (Bradley & Caldwell, 1977). Farber et al. (1981) found prenatally anxious women to interact less skillfully with their infants at three and six months, and to communicate less (both verbally and non-verbally) with their children. Although the lack of a syndromal diagnosis of anxiety in the two years after delivery is a limitation of this study, the multivariate analyses controlled for depressive and anxiety symptoms at one year postpartum, the occurrence of a major depression in the mother in the two years after delivery and for the only cluster of the HOME on which prenatally anxious and non-anxious mothers were found to be different at 1 year postpartum ('Organization of the environment'). Given the high co-morbidity between anxiety and depression and the fact that the study was controlled for the difference between prenatally anxious and non-anxious mothers in maternal infant stimulation reflected in the 'Organization of the environment' cluster of the HOME, it is unlikely that the differences in mental development between two-year-olds of prenatally anxious and non-anxious mothers are purely of postnatal origin.

A third explanation of the present findings could be that both prenatal anxiety and postnatal anxiety affect child development. Intra-uterine exposure to biological effects of maternal anxiety may be reinforced by subsequent environmental or interactive experiences.

Several limitations of the present study need to be pointed out. First, both prenatal anxiety and postnatal anxiety were measured only once. Moreover, a different instrument was used for these two measurements. Furthermore, the HOME was measured at 12 months post partum, and was also used as a predictor of child development at 24 months. However, there appears to be a moderate level of stability in the quality of stimulation available in the home environments of most children throughout infancy (Bradley et al. 1986) and the HOME has proven to be a very important predictor of cognitive outcome (e.g. Bradley & Caldwell 1977; Poresky et al. 1982; Widmayer et al., 1990; Molfese et al. 1994, 1996).

In conclusion, findings of the present study suggest that high maternal anxiety dur-

ing pregnancy is associated with a delay in mental developmental of the two-year-old child. Future studies will have to investigate the precise impact of antepartum and postpartum anxiety on infant development by means of repeated assessments, investigate whether the delay in cognitive development continues to exist at later ages, and should especially focus on attention related processes. If these findings are confirmed, identification of highly anxious women during gestation may provide an important opportunity to start a support program in order to optimize later infant stimulation and caretaking.

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# Chapter 5

# Does the Edinburgh Postnatal Depression Scale measure anxiety?

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## Abstract

*Objective*

The existence of a separate anxiety and depression dimension within the EPDS has been reported previously. However, the concurrent validity of this anxiety subscale was never evaluated. We investigated whether (1) this existence of an anxiety subscale could be confirmed; and (2) it more highly correlated with other measures of anxiety than the total EPDS.

*Methods*

The SCL-90-R, the EPDS and the STAI were filled out by 197 pregnant women. A principal component analysis was used for confirmation of the subscales and correlations were computed between the (subscales of the) EPDS and the other measures of anxiety.

*Results*

The existence of an anxiety scale within the EPDS was confirmed. However, this subscale did not yield higher correlations with other measures of anxiety than did the total EPDS.

*Conclusion*

Investigators using the EPDS to screen for depression should realise that the instrument does not exclusively measure depression. It seems that both anxiety symptoms and depressive symptoms are more accurately measured when using the total 10-item EPDS than when using the subscales.

## Introduction

The question whether anxiety and depressive disorders are clearly separate entities continues to be a controversial issue [1]. Clark & Watson [2] introduced the tripartite model of anxiety and depression, which is based on the assumption that anxiety and depression each have distinct features, (physiological hyperarousal and anhedonia, respectively) but also share a common dimension, called general distress or negative affect. As was pointed out by Bieling *et al.* [3], ideally, a measure of anxiety should assess both the general factor (negative affect) as well as physiological arousal and should not measure anhedonia. Similarly, a measure of depression should assess negative affect and anhedonia, not physiological hyperarousal.

It has been suggested that the Edinburgh Postnatal Depression Scale (EPDS, [4]) also is a good screening instrument for anxiety [5], as high correlations have been found between scores on the State-Trait Anxiety Inventory (STAI, Spielberger *et al.* [6]) and the EPDS [5, 7, 8]. Cox *et al.* [4] imply the EPDS is unidimensional. However, Pop *et al.* [9] found that there are separate anxiety and depression dimensions within the EPDS, a finding later confirmed in other work [8]. As they did not include any other instruments measuring anxiety, the concurrent validity of the anxiety subscale was not evaluated.

The aim of the present study is to investigate whether (1) the existence of the anxiety subscale within the EPDS could be confirmed; and (2) if confirmed, whether this anxiety subscale more highly correlated with other measures of anxiety than the entire (10-item) EPDS or the depressive symptoms subscale.

## Methods

*Subjects*

Subjects were derived from a larger study on the effect of maternal thyroid hormone during early gestation on child development currently being carried out. Here, 1361 women were screened on thyroid function. Of all subjects with normal thyroid function, women with a low-normal amount of thyroid hormone were matched with women with higher thyroid hormone concentrations and invited for the follow-up study. Of these 279 women, 12 (4 %) did not want to participate in the follow-up study, and 17 (6 %) were excluded according to exclusion criteria previously set for the larger study (fertility problems, gestational diabetes, gemelli, rheumatoid arthritis). Furthermore, 53 (19 %) women were excluded because of missing data on the EPDS, STAI or SCL-90 anxiety or depression subscales [10], resulting in a sample size of 197 women. Women in the follow-up study did not differ significantly from the 1361 women originally screened in educational level, marital status or age. Except for one woman who was divorced and one who was single, all women were married or living together with their partner. Sample characteristics of the subjects in the follow-up study are shown in Table 1.

**Table 1. Characteristics of the sample (n=197)**

| | | | |
|---|---|---|---|
| Age | mean (SD) | 30.8 | (3.2) |
| | range | 21-39 | |
| Parity | | n | % |
| 0 | | 82 | (41.6) |
| 1 | | 72 | (36.5) |
| ≥2 | | 43 | (21.9) |
| Educational level (highest qualification achieved) | | n | % |
| 1. | Lower education | 20 | (10.1) |
| 2. | Middle level | 122 | (61.9) |
| 3. | Higher education | 55 | (28.0) |
| Family income per year in Dutch guilders (1 Euro = 2.2 guilders) | | n | % |
| 1. | lower (<50.000) | 26 | (13.2) |
| 2. | Middle level (50.000-100.000) | 112 | (56.9) |
| 3. | Higher (>100.000) | 31 | (15.7) |
| 4. | Unknown | 28 | (14.2 ) |
| Subject has job outside the home (n %) | | 153 | (77.6) |

*Instruments*

Depressive symptoms were measured at 24 weeks' gestation by the EPDS and the depression subscale of the SCL-90. The EPDS (see appendix) is a 10-item self-report scale designed as a screening instrument for postnatal depression but has also been validated in non-postnatal women [11]. Each item is scored on a four-point scale (0-3) the minimum and maximum scores being 0 and 30, respectively. Scores are transformed so that higher scores indicate a higher intensity of depressive symptoms. The EPDS rates the intensity of depressive symptoms present within the previous seven days (see appendix for a description of the items). A cut-off score of 12/13 has been found to identify most seriously depressed women, although in case of a score of 9 or more, clinical assessment has been recommended [12]. In 1992 the EPDS was translated into Dutch and was found to have good psychometric properties [9].

The SCL-90 [13], the Dutch version of the SCL-90-R [10] is a 90 item self-report scale measuring multidimensional psychopathology. It was filled out at 24 weeks' gestation. The SCL-90 contains 8 subscales, of which only the anxiety subscale (10 items) and the depression subscale (16 items) were used in the present study. The (Dutch version of the) SCL-90 was found to have good psychometric qualities [14].

Finally, anxiety was also measured at 32 weeks of pregnancy, by means of the *State-Trait Anxiety Inventory* (STAI, [6]). This self-report questionnaire consists of two subscales each containing 20 items. The *state anxiety* subscale measures transient anxiety, or anxiety at the moment of scoring. State anxiety is conceptualised as a transient emotional condition of the individual, characterised by subjectively experienced feelings of tension, together with a heightened activity of the autonomous nervous system. *Trait anxiety* measures dispositional anxiety, or anxiety in general. It refers to relatively stable individual differences in the tendency to react with a more intense state anxiety in situations that are perceived as threatening. Trait anxiety measures reflect anxiety-proneness; differences between individuals in the probability that anxiety states will be manifested under circumstances involving varying degrees of stress. Higher scores on the STAI indicate a higher intensity of anxiety. The Dutch version of the STAI has been validated previously (Dutch version: Zelfbeoordelings Vragenlijst STAI-DY , [15].

*Statistical analysis*

Analyses were computed by means of SPSS. First, a principal component analysis was computed to investigate if in the present sample, an anxiety and a depressive subscale could be found. Cronbachs' alphas were computed to investigate the reliability of the subscales and the total EPDS. Subsequently, Pearson correlations were computed between the (subscales of the) EPDS and the other measures of anxiety. As Bieling *et al.* [3] have argued that the trait anxiety subscale contains a depression subscale, correlations were also computed between the (subscales of the) EPDS and the STAI-A subscale (i.e. the original trait anxiety subscale minus the items measuring depressive symptoms according to Bieling *et al.*).

## Results

Mean scores and standard deviations of the total group on the scales are presented in Table 2.

Table 2. Mean scores and standard deviations of the total group (n=197)

| | Mean (SD) |
|---|---|
| Depressive symptoms subscale (EPDS items 1, 2, 8*) | 0.7 (1.2) |
| Anxiety related symptoms subscale (EPDS items 3, 4, 5) | 2.8 (1.8) |
| Total EPDS score (10 items) | 4.9 (3.7) |
| Depression subscale of SCL-90 | 20.6 (4.5) |
| Anxiety subscale of SCL-90 | 11.8 (3.0) |
| State anxiety (STAI) | 31.6 (7.5) |
| Trait anxiety (STAI) | 30.0 (6.6) |

* See appendix

Principal component analysis (PCA) with varimax rotation revealed 3 components with eigenvalues of >1. Of the first component, items 1, 2, 6, 7, 8 and 9 had a factor loading higher than .40. Of the second and third these were items 3, 4, 5, 6 and 7, 8, 9, 10, respectively. Although item 8 loaded high on both the first and the third component, it loaded higher on the first, in which it was included. Items 6, 7 and 9 did not discriminate adequately between components and were omitted from the final subscales found: a depressive symptoms subscale (items 1, 2, and 8), and an anxiety symptoms subscale (items 3, 4, and 5). Item 10 ("The thought of harming myself has occurred to me") was the only item in the third component that discriminated well from the other components. The third component was not included in the correlational analysis. Because item 10 clearly was different from the other items it was verified if a PCA without this item would still yield an anxiety and a depressive symptoms subscale, which was confirmed. In the Principal Component Analysis with the 10 items, the 'depressive symptoms' and 'anxiety symptoms' subscales accounted for 39.9 and 12.2 percent of the total variance of the 10 items, respectively. Results are presented in Table 3. Cronbach's alpha for the total EPDS was found to be .80, for the depressive symptoms subscale 0.79 and for the anxiety subscale .60 (data not shown). Scores on the EPDS depressive and anxiety symptoms subscales were computed by summing scores on each item.

A Pearson correlation of .37 was found between the 'anxiety symptoms' subscale and the 'depressive symptoms' subscale ($p<0.001$, two tailed). Subsequently, Pearson correlations were computed between the following subscales: the anxiety symptoms and depressive symptoms subscales of the EPDS, the total EPDS, the SCL-90 depression and anxiety subscales, the state and trait subscales of the STAI and the STAI-A. All correlations were highly significant ($p<0.001$, two-tailed). As can be seen in Table 4, all correlations yielded similar results, although the highest correlations were found between the total EPDS and the SCL-90 and STAI measures.

Table 3. Principal component analysis computed for the 10 items of the EPDS* (n=197).

| Item no. | Component 1 Depressive symptoms | Component 2 Anxiety symptoms | Component 3 |
|---|---|---|---|
| 1 | .87 | | |
| 2 | .84 | | |
| 3 | | .68 | |
| 4 | | .73 | |
| 5 | | .71 | |
| 6 | .52 | .56 | |
| 7 | .49 | | .53 |
| 8 | .69 | | .43 |
| 9 | .46 | | .45 |
| 10 | | | .85 |

*See appendix for details of items. For reasons of clarity factor loadings under .40 are not presented.

Table 4. Pearson correlations between (subscales of) the EPDS, and subscales of the SCL-90 and the STAI (n=197).

| | Depression subscale of SCL-90 | Anxiety subscale of SCL-90 | State Anxiety (STAI) | Trait Anxiety (STAI) | STAI-A (Bieling et al '98) |
|---|---|---|---|---|---|
| Depressive symptoms (EPDS items 1,2,8*) | 0.65 | 0.46 | 0.49 | 0.42 | 0.36 |
| Anxiety related symptoms (EPDS items 3, 4, 5*) | 0.48 | 0.44 | 0.36 | 0.45 | 0.44 |
| Total EPDS (10 items) | 0.68 | 0.56 | 0.54 | 0.54 | 0.49 |

All correlations were significant on a $p<0.001$ level. *See appendix

## Discussion

In the present study the EPDS was found to contain an anxiety subscale and a depressive symptoms subscale. This finding corresponds with the work of others [8,9]. Items 6, 7 and 9 did not discriminate adequately between components and for this reason were left out of the subscales. With reference to the tripartite model of depression and anxiety, it may well be that these items measure general distress, a feature that depression and anxiety share. Principal component analysis also revealed a third component. However, the only item that discriminated well on this third component was item 10 ("The thought of harming myself has occurred to me"). This item has been criticised for not being suitable for antenatal use [16], as pregnant women may interpret this differently (e.g. "I am preoccupied by the thought of falling and hurting myself"). Moreover, in the present study 192 (97.5%) women indicated never to have had the

thought of harming themselves. For these reasons the third component was left out of further analyses.

Contrary to expectations, the anxiety symptoms subscale did not more highly correlate with other measures of anxiety than the depressive symptoms subscale or the total EPDS. In fact, it was found that using the total EPDS yielded slightly higher correlations than either subscale used separately. Several explanations can be given for the finding that the anxiety symptoms subscale did not more highly correlate with the other measures of anxiety than the total EPDS. First, based on the tripartite model of anxiety and depression, the ideal instrument for the assessment of anxiety should measure the feature that anxiety and depression share (i.e. negative affect) as well as physiological arousal, which is typical of anxiety. The 3-item anxiety scale that was found in the EPDS does not contain any items specifically on hyperarousal. A second explanation may relate to the fact that anxiety is not a unitary construct [17]. Anxiety may be generalised or focused upon particular situations. It may refer to fear, worries, feelings of insecurity and incompetence, increased arousal, a sense of respiratory constriction, muscular tension, tremor and restlessness and a variety of somatic discomforts based upon the overactivity of the autonomic nervous system. Keedwell and Snaith [17] argue that a problem with the attempted coverage of all aspects of anxiety in a single scale is that it is unusual for all aspects to be present to an equal degree in one individual. In addition, Kabacoff et al. [18] present the view that the diagnosis of a major depressive episode is a more discrete and circumscribed process than the diagnosis of an anxiety disorder. Hence, considering how difficult it is to measure anxiety accurately and reliably, a 3-item anxiety subscale is likely to be insufficient.

Furthermore, it should be pointed out that in contrast to the other items, all three items on the anxiety symptoms subscale contained a subjective, negative judgement about the feelings (I have blamed myself *unnecessarily* when things went wrong; I have been anxious or worried *for no good reason*; I have felt scared or panicky *for no very good reason).* This element may refer to a third factor, for example low self-esteem, which is not measured in the items of the 'depressive symptoms' subscale in a similar way. This could obscure an accurate measurement of anxiety.

In the present study, moderately high correlations were found between the total EPDS measured at 6 months' gestation and the anxiety measures assessed 2 months later. Stuart *et al.* [5] found similar correlations between the EPDS and state and trait anxiety measured 4 months later. However, when the EPDS and state and trait anxiety were measured at the same time, they found correlations ranging from r=.73 to r=.82. Similarly, Green [8] found correlations between trait anxiety measured at 16 weeks of pregnancy and the EPDS 5 and 8 months later that were similar to those of the present study, whereas correlations of state anxiety and the EPDS measured at the same time were higher. Although methodologically it would have been preferable to measure the EPDS and the STAI at the same point in time, it is unlikely that this has affected the correlational differences between the subscales. Hence, although the correlations be-

tween the EPDS and the STAI would have been higher had they been measured at the same time, there is no reason to assume the subscales of the EPDS would have had higher correlations with the other measures of anxiety and depression than the total EPDS.

An additional limitation of the study is that only self-report instruments were used and no syndromal diagnosis of anxiety was used as a golden standard to validate the anxiety symptoms scale. However, considering the STAI and SCL-90 have good psychometric properties, based on the present findings it is not to be expected that the use of a clinical assessment would yield markedly different results.

In conclusion, the existence of an anxiety subscale and a depressive symptoms subscale within the EPDS was confirmed. Investigators using the EPDS to screen for depression should realise that the instrument does not exclusively measure depression. It seems that both anxiety symptoms and depressive symptoms are more accurately measured when using the total 10-item EPDS than when using the subscales.

*Appendix*

The EPDS [4]

1. I have been able to laugh and see the funny side of things.
2. I have looked forward with enjoyment to things.
3. I have blamed myself unnecessarily when things went wrong.
4. I have been anxious or worried for no good reason.
5. I have felt scared or panicky for no very good reason.
6. Things have been getting on top of me.
7. I have been so unhappy that I have had difficulty sleeping.
8. I have felt sad or miserable.
9. I have been so unhappy that I have been crying.
10. The thought of harming myself has occurred to me.

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# Chapter 6

## Thyroid parameters and anxiety during pregnancy

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## Abstract

*Objective*

Thyroid dysfunction has often been associated with depression. Because there is a high comorbidity between depression and anxiety, a relationship between anxiety and thyroid dysfunction can be expected. Identifying new risk factors for high anxiety levels is especially relevant for pregnant women, as maternal anxiety during gestation has been associated with an increased risk for obstetrical complications during labour and adverse perinatal outcome, as well as post partum depression and anxiety.

*Methods*

In a group of 220 pregnant women, the presence of thyroid antibodies (TPO-Ab) was assessed at 12 weeks' gestation. At 24 weeks gestation, women filled out the Edinburgh Depression Scale and at 32 weeks, subjects were visited at home for an assessment of anxiety, several psycho-social determinants and thyroid parameters (fT4 and TSH). Anxiety was measured by means of the State-Trait Anxiety Inventory.

*Results*

A multiple regression analysis was conducted to investigate the independent relationships between anxiety and thyroid parameters. It was found that both elevated TPO-Ab levels and lower fT4 concentrations were associated with high trait anxiety, even when controlled for confounding variables such as high depressive symptomatology during pregnancy. TSH was related to neither state nor trait anxiety.

*Conclusions*

This study showed an independent relationship between thyroid parameters (fT4 and TPO-Ab) and trait anxiety in pregnant women. Further work is indicated to confirm this association, as it may in future add to a better identification of women at risk for mental health problems during pregnancy and the postpartum period.

## Introduction

Thyroid dysfunction has often been associated with depression (1, 2). For example, T4 suppletion has shown to diminish depressive symptoms in patients with hypothyroidism, (3). Moreover, the presence of thyroid antibodies is related to depression in postpartal as well as in postmenopausal women (4-7).

From a conceptual point of view, it might be hypothesised that if thyroid dysfunction (or thyroid auto-immunity) is related to depression, there should also be a relationship with anxiety, given the high comorbidity between depression and anxiety. Approximately 85% of patients with depression also experience significant symptoms of anxiety, and depressive symptoms are common in patients with anxiety disorders (8). Also, antidepressant drugs such as tricyclic antidepressants (TCA's), monoamine oxidase inhibitors (MAOI's) and the selective serotonin reuptake inhibitors (SSRI's), have a

well-documented efficacy in a variety of anxiety disorders (9).

Pregnancy is accompanied by changes in hormone concentrations such as thyroid hormones and estrogens, as well as by changes in mood (10). From a clinical point of view, it is worthwhile to identify pregnant women at risk for anxiety for two reasons. First, maternal anxiety during gestation has been associated with an increased risk for obstetrical complications during labour and adverse perinatal outcome (11-13). Second, high anxiety scores during late pregnancy have been found to be strongly correlated with depressive symptomatology and high anxiety scores in the postpartum period (14). As such, identifying women at risk for anxiety may help to prevent postpartum psychiatric illness if acted upon appropriately.

The origin of anxiety is multifactorial, indicating that studying the effect of a biological variable on anxiety, the influence of other (psycho-social) determinants of anxiety need to be taken into account. In this study, the relationship between thyroid function and anxiety was investigated in pregnant women in whom, besides thyroid function, several determinants were assessed that are related to anxiety.

## Methods

*Subjects*

In a randomly selected cohort of 1361 Dutch Caucasian women, thyroid parameters were assessed at 12 weeks' gestation, for a larger study on the influence of low-normal maternal thyroid hormone levels during early gestation on child development which is currently being carried out. The screening took place in the area of Eindhoven (The Netherlands), between January 1997 and April 1998. Women with overt (clinical) hypothyroidism (n=1) and overt (clinical) hyperthyroidism (n=7) were excluded from the screening sample (n=1353). Subsequently, women with an fT4 concentration within the lowest 10 percentile (i.e. <12.4 pmol/l) were invited for the follow-up study together with an equal amount of subjects who had an fT4 concentration between the 50-90th percentile (i.e. 15.6-19.1 pmol/l). Of these 281 women, 12 (4%) did not want to participate in the follow-up study, and 49 (17 %) were excluded because of missing data or previously set exclusion criteria (e.g. gestational diabetes, gemelli, rheumatoid arthritis, overt hypothyroidism at 32 weeks' gestation). Women in the follow-up study did not differ significantly from the 1361 women originally screened, in educational level, marital status or age (data not shown). Data analysis refers to 220 subjects, 112 of whom had a low-normal plasma fT4 concentration at 12 weeks' gestation versus 108 with a higher fT4 concentration. Sample characteristics of the subjects are shown in Table 1.

The participants filled out the Edinburgh Postnatal Depression Scale (EPDS) (15) at 24 weeks' gestation and were visited at home at 32 weeks' (+/- 2 weeks), for an assessment of anxiety, several psycho-social determinants and thyroid parameters (TSH, fT4, TPO-Ab). The study was approved of by the Medical Ethical Committee of the Saint Joseph Hospital (Veldhoven, The Netherlands), and a written informed consent of the participants was obtained prior to participation.

**Table 1. Sample characteristics of the 220 pregnant subjects.**

| | n | (%) |
|---|---|---|
| Years of education | 10.8 | (3) |
| (mean, SD) | | |
| Family income per year in Dutch guilders | | |
| (1 Euro = 2.2 guilders) | | |
| 1. lower (<50.000) | 30 | (13.7) |
| 2. Middle level (50.000-100.000) | 124 | (56.4) |
| 3. Higher (>100.000) | 34 | (15.5) |
| 4. Unknown | 32 | (14.6) |
| Reports having financial worries | 9 | ( 4.1 ) |
| Reports stressful life event in past 12 months | 133 | (64.0) |
| Smoking during pregnancy | | |
| 1. Non-smoking | 178 | ( 80.9) |
| 2. Smoking | 37 | (16.8) |
| 3. Unknown | 5 | ( 2.3 ) |
| Previous depression ( self-reported) | 53 | (24.1) |
| Has parent with (previous) depression | 75 | (34.1) |
| Previous miscarriage | 38 | (17.3) |
| Parity | | |
| 1. 0 | 89 | (40.5) |
| 2. >=1 | 131 | (59.5) |

*Anxiety*

Anxiety was assessed at 32 weeks' gestation by means of the *State-Trait Anxiety Inventory* (STAI) (16). This self-report questionnaire consists of two subscales each containing 20 items. The *state anxiety* subscale measures transient anxiety, or anxiety at the moment of scoring. State anxiety is conceptualised as a transient emotional condition of the individual, characterised by subjectively experienced feelings of tension, together with a heightened activity of the autonomous nervous system. *Trait anxiety* measures

dispositional anxiety, or anxiety in general. It refers to relatively stable individual differences in the tendency to react with a more intense state anxiety in situations that are perceived as threatening. Trait anxiety measures reflect anxiety-proneness - differences between individuals in the probability that anxiety states will be manifested under circumstances involving varying degrees of stress. Higher scores on the STAI indicate a higher intensity of anxiety. The Dutch version of the STAI has been validated previously (Dutch version: Zelfbeoordelings Vragenlijst STAI-DY) (17).

*Depression*

Depression was measured at 24 weeks' gestation by the Edinburgh Postnatal Depression Scale (15). The EPDS is a 10-item self-report scale designed as a screening instrument for postnatal depression. It was also validated in non-postnatal women (18). In 1992 the EPDS was translated into Dutch and was found to have good psychometric properties (19).

*Thyroid parameters*

TSH (reference range:0.15-2.0 mIU/l) was measured using a solid-phase, two site chemiluminescent enzyme immunometric assay (IMMULITE Third generation TSH, Diagnostic Products Corporation, Los Angeles). The inter-assay coefficients of variation were 9.8%, 6.9% and 4.6% at concentrations 0.02 mIU/l, 0.15 mIU/l and 11 mIU/l, respectively. The free T4 concentration (reference range: 8.7-19.6 pmol/l) was also measured with a solid-phase immunometric assay (Immulite Free T4). The inter-assay coefficients of variation for this technique were 20%, 10.5%, 5.3% and 5.2% at concentrations of 3.1 pmol/l, 11.8 pmol/l, 19.8 pmol/l and 55 pmol/l, respectively. The IMMULITE Anti-TPO Ab kit was used for the determination of 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 IU/ml, 69 IU/ml and 114 IU/ml, respectively. The anti-TPO assay is standardised in terms of the International Reference Preparation for anti-TPO MRC 66/387.

*Statistical analysis*

Women were included in the follow-up study as based on their fT4 level at 12 weeks' gestation.

As during pregnancy thyroid hormone levels are subject to change, the distribution of fT4 at 32 weeks' gestation was evaluated using a Kolmogorov-Smirnov test. Scores on the STAI were obtained at 32 weeks of pregnancy and were compared to fT4 and TSH also measured at 32 weeks.

To investigate the relationship between anxiety and thyroid parameters, Pearson correlations were computed. Subsequently, two multiple regression analyses were performed to test whether thyroid parameters played an independent role in the prediction of anxiety during pregnancy. State and trait anxiety were used as the dependent variables.

## Results

*Thyroid parameters*

A Kolmogorov-Smirnov test showed that at 32 weeks, fT4 was normally distributed (p=0.71). Mean fT4 was 11.6 pmol/l (SD 2.3), mean TSH was 1.3 mIU/l (SD 0.6). Of the total group, 21 (10%) had a marginally elevated antibody concentration at 12 weeks (TPO-Ab>35 IU/ml). Thirteen (6%) subjects had a TPO-Ab concentration of above 100 IU/ml. At 12 and 32 weeks' gestation, mean fT4 of the women with a TPO-Ab concentration of above 100 IU/ml was 11.9 and 10.8 pmol/l, respectively. Mean fT4 of women with lower TPO-Ab levels were 14.2 (SD 3.0) and 11.7 (SD 2.3) pmol/l at 12 and 32 weeks, respectively. The difference between these groups was significant at 12 weeks (p<0.01, 2-tailed), but not at 32 weeks (data not shown). Thyroid parameters of the total group are presented in Table 2.

**Table 2. Thyroid parameters of the 220 subjects at 12 and 32 weeks (+/- 2 weeks) of pregnancy.**

| | 12 weeks' gestation | 32 weeks' gestation |
|---|---|---|
| **Mean values of total sample** | | |
| 1. Mean fT4 in pmol/l (SD) of total group (n=220) | n/a* | 11.6 (2.3) |
| a. group with fT4 <12.4 pmol/l at 12 weeks (n=112) | 11.4 (1.0) | 10.6 (2.1) |
| b. group with 15.6<fT4<19.1 pmol/l at 12 weeks (n=108) | 17.0 (0.9) | 12.7 (2.0) |
| 2. Mean TSH in mIU/l (SD) of total group (n=220) | n/a* | 1.3 (0.6) |
| a. TSH of group with fT4 <12.4 pmol/l at 12 weeks | 1.6 (0.9) | 1.5 (0.7) |
| b. TSH of group with 15.6<fT4<19.1 pmol/l at12 weeks | 1.1 (0.8) | 1.1 (0.6) |
| **Thyroid dysfunction**** | | |
| 1. Subclinical hypothyroidism n (%) (Defined as: TSH>2.0 and 8.7<fT4<19.6) | 33 (15.0) | 23 (10.5) |
| 2. Subclinical hyperthyroidism n (%) (Defined as: TSH<0.15 and 8.7<fT4<19.6) | 7 (3.2) | 0 (0.0) |
| **Thyroid antibodies** | | |
| 1. TPO-Ab≥35 IU/ml n (%) | 21 (9.5) | 14 *** |
| 2. TPO-Ab≥100 IU/ml n (%) | 13 (5.9) | 7 *** |

* FT4 and TSH were not normally distributed at 12 weeks' gestation

** Subjects with overt thyroid dysfunction at 12 or 32 weeks' gestation were excluded from the sample

*** TPO-Ab was only assessed in women with TPO-Ab>100 IU/ml at 12 weeks' gestation

*Anxiety scores*

At 32 weeks' gestation, mean scores on the state and trait subscales for the total group (n=220) were 32 (SD 7) and 30 (SD 6), respectively. Scores on the state anxiety subscale ranged from 20-58, on the trait anxiety subscale from 20-56. A high correlation between state and trait scores was found (Pearson r=0.73; p<0.001).

*Anxiety scores in relation to thyroid function*

Pearson correlations showed a low but significant inverse relationship between trait anxiety and fT4 (r=-.16; p<0.05). No significant relationship was found between trait anxiety and TSH or TPO-Ab. State anxiety was not related to any of the thyroid parameters.

In order to investigate the independent relationships of fT4, TSH and TPO-Ab with anxiety, two multiple regression analyses were performed, using state and trait anxiety as dependent variables. Independent variables included were: financial worries during pregnancy, depressive symptomatology at 24 weeks' gestation (EPDS score), educational level in years, parity, TPO-Ab concentration at 12 weeks, fT4 concentration at 32 weeks, TSH level at 32 weeks, the occurrence of stressful life events in the past year, depression in a parent, previous miscarriage and previous episode of depression. The first regression analysis yielded a multiple *R* of .54, (F=6.6, p<0.001, adjusted $R^2$ =.24), and revealed two significant predictors of high state anxiety: high depressive symptomatology at 24 weeks' gestation and low maternal educational level. No significant relationship was found between the thyroid parameters and state anxiety (data not shown). The second multiple regression analysis, in which trait anxiety was used as the dependent variable, yielded a multiple *R* of .62, (F=10.0; p<0.001, adjusted $R^2$ =.34). Here, four predictors were independently related to high trait anxiety: high depressive symptomatology at 24 weeks' gestation, a previous episode of depression, an elevated TPO-Ab concentration at 12 weeks and low fT4 at 32 weeks' gestation. Table 3 presents the standardised Beta weights for each predictor in the analysis.

## Discussion

In the present study, thyroid parameters (fT4 and TPO-Ab) were found to be independently related to high trait anxiety in pregnant women, even when controlled for confounding variables such as high depressive symptomatology during gestation.

The relationship between elevated TPO antibodies and anxiety has been described before, albeit in the postpartum period; Seeler et al. (20) found women with an elevated antibody concentration (TPO-Ab>100 IU/ml, *n=10*) to have significantly higher state anxiety scores than subjects with a lower concentration *(n=10)*. Trait anxiety scores were also higher in antibody positive women, but this difference did not reach significance. In contrast, Harris et al. (7) found that antibody positivity was only related to depressive symptoms, not to anxiety. However, these authors used a different instrument to measure anxiety (the Hospital Anxiety Scale) and used a definition of antibody positivity that was different from the one used in the present study. In a study

on the relationship between antenatal mood disturbance and the presence of gestational TPO-antibodies, no such association was found (21).

**Table 3. Multiple regression analysis. Method: enter. Dependent variable: trait (dispositional) anxiety (n=220). F=10.0 p<0.001; Overall R=.62; Adj. R2=.34**

| Variable | Standardised Beta Weight | p |
|---|---|---|
| Financial worries during pregnancy | 0.01 | 0.87 |
| Depressive symptoms at 24 weeks' gestation (EPDS score) | 0.46 | 0.00 ** |
| Educational level in years | -0.03 | 0.56 |
| Parity | 0.07 | 0.26 |
| TPO-Ab at 12 weeks' gestation | 0.17 | 0.01 * |
| FT4 at 32 weeks' gestation | -0.13 | 0.03 * |
| TSH at 32 weeks' gestation | -0.10 | 0.09 |
| Stressful life events in past year | -0.06 | 0.32 |
| Depression in parent | 0.05 | 0.41 |
| Previous miscarriage | -0.04 | 0.56 |
| Previous episode of depression | 0.20 | 0.00 ** |

* $p< 0.05$ ; ** $p<0.001$

Recently, low levels of fT4 during late gestation have been associated with high scores on the EPDS during the postpartum period (22). Considering the overlap between depression and anxiety, the EPDS partly also measures anxiety; high correlations between state anxiety and EPDS scores have been reported (23). Therefore, low fT4 levels during late gestation are likely to be related to elevated anxiety scores during the post partum period as well. Moreover, high anxiety during pregnancy is a strong predictor for postpartum anxiety and depression (14, 24, 25). Combining these results with those of the present study, it can be expected that women with elevated antibody concentrations during early gestation and / or with low fT4 levels during late gestation are also at risk for high anxiety levels during the postpartum period.

In the present study, high TPO-antibody concentrations at 12 weeks' gestation were found to be significantly related to trait anxiety at 32 weeks. During gestation, the concentration of thyroid antibodies decreases with the progression of pregnancy

with a rebound in the postpartum period (26), reflecting the immunological fluctuations during normal pregnancy and the post partum. In the present study TPO-Ab was measured at 12 weeks' gestation, when concentrations are still relatively unaffected by subjects' pregnant state. Like trait anxiety –by definition-, the presence of thyroid antibodies (TPO-Ab) has shown to be of a highly persistent nature on a larger time span; in a study on the incidence of thyroid disorders in the community, 98% of the female subjects who had elevated antibody titers, still did at follow-up 20 years later (27). Because of its persistent nature, the presence of TPO-Ab at 12 weeks can be related to anxiety scores at 32 weeks.

The finding that thyroid parameters were not related to state anxiety may be explained by the fact that it is more difficult to predict state anxiety, due to its fluctuating nature. An additional finding of the study was that both a previous episode of depression and high depressive symptomatology were independent predictors of anxiety two months later. This corresponds with two common findings: (a) that previous mood disturbance is one of the strongest predictors of later mood disturbance, and (b) that there is a considerable overlap between anxiety and depressive symptoms.

There may be a neurobiological explanation for the findings of the present study in view of the high co-morbidity between depression and anxiety. Several antidepressants (e.g. the Selective Serotonin Reuptake Inhibitors) are very effective in the treatment of both depression and a variety of anxiety disorders (9). Although the underlying mechanism is not clear, the association between thyroid parameters and anxiety may be explained by findings of recent studies on depression in which alterations in both hypothalamic-pituitary-thyroid (HPT) axis activity and serotonin (5-HT) function were found (28). T4 replacement has been shown to increase central 5-hydroxytryptamine activity and reduce depressive symptoms (3). No such association has been described for TSH, which might explain why no relationship between TSH and anxiety was found.

A limitation of the present study is that subjects were not randomly chosen, but selected on the amount of fT4 at 12 weeks' gestation. However, fT4 was normally distributed at 32 weeks, and subjects of the present study did not differ significantly from women in the screening sample (n=1361) on a number of variables. A second limitation is that no explanations about the direction of the association between the thyroid parameters and trait anxiety can be given: it remains unclear whether thyroid parameters affect anxiety levels, or vice versa. Third, the trait scale of the STAI has been criticized to assess not pure anxiety but rather includes items that reflect depression and negative affect (29). However, the fact that TPO-Ab was found to be significantly and independently related to trait anxiety even when controlled for depressive symptoms during gestation suggests this criticism does not pose a problem for the present study. A fourth limitation of the study is that no information was obtained about subjects' previous history of anxiety or history of first degree relatives with anxiety disorders.

The aim of the present study was to investigate if, similar to depression, there was

a relationship between anxiety and thyroid parameters. Whereas for state anxiety no significant relationship was found, for trait anxiety, this relationship was confirmed. Further work is indicated to examine the association between thyroid parameters and anxiety, as they may in future add to a better identification of women at risk for mental health problems during pregnancy and the postpartum period.

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# Chapter 7

# Are thyroid antibodies during gestation a risk factor for subsequent maternal depression?

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## Abstract

*Objective*

It is investigated whether an elevated concentration of thyroid peroxidase antibodies during early pregnancy is a risk factor for depression during later pregnancy or 2 years after delivery.

*Methods*

A group of 233 pregnant women, selected during a screening on thyroid parameters (n=1361) participated in this follow-up study. Twenty-three women (10%) had an elevated antibody concentration and were included as the cases together with 210 women without elevated antibody concentrations (controls). Subjects were visited at home at 24 and 32 weeks' gestation, 3 weeks postpartum and at 1 and 2 years after delivery.

*Results*

Multiple logistic regression analyses showed that thyroid antibody status during early pregnancy was neither related to depressive symptoms nor to major depression during pregnancy or after delivery.

*Conclusion*

If antenatal screening on thyroid antibodies is implemented, it will only be useful for the identification of women with a high risk of postpartum thyreoditis, not of depression.

## Introduction

Depressive illness is a common problem of the first year of delivery with a prevalence of around 10-15% (O'Hara et al 1986; Lane et al., 1997; Brockington 1998). Apart from its detrimental effects on personal well-being, it may affect family relationships and have adverse consequences for the behavioural, emotional and cognitive development of the infant (Murray, 1992; Murray & Cartwright 1993). Many researchers have tried to identify risk factors, as they could be useful in the early detection of individuals at risk and in the prevention of postpartum depression. Several psychosocial variables have been identified as risk factors for postpartum depression such as the occurrence of depressive symptoms during pregnancy, marital disharmony, inadequate social support, a history of depression in earlier life and an increased number of stressful life events in the previous 12 months (Kumar & Robson 1984, Murray & Cartwright 1993). A biological variable that has been associated with depression and depressive symptoms (both during pregnancy and postpartum as well as in non-childbearing women) is the presence of elevated concentrations of thyroid antibodies (Harris et al. 1992; Lazarus et al. 1996a, Pop et al., 1998).

During early gestation, about 10% of pregnant women have elevated concentrations of thyroid peroxidase antibodies (TPO-Ab), a prevalence comparable with that of

non-pregnant women (Ball 1996). Due to the downregulation of the immune system, the concentration gradually decreases during further pregnancy with a rebound phenomenon in the postpartum period. About half of the women with elevated TPO antibody levels will develop post partum thyroiditis (PPT) during the first postpartum year (Lazarus et al. 1997). PPT is a generally transient, destructive autoimmune disease that causes temporary hyper- and/or hypothyroidism. Moreover, thyroid antibodies during pregnancy have been associated with an increased risk of spontaneous miscarriage (Glinoer 1997). The presence of elevated TPO-Ab has shown to be of a highly persistent nature on a larger time span, with a marked increased risk of developing overt hypothyroidism during later life (Vanderpump et al. 1995).

Because of the reported relationship between thyroid antibodies and depression or depressive symptoms and the high risk in TPO-Ab positive women to develop PPT, several investigators have argued in favour of a screening of thyroid antibodies during early gestation (e.g. Hayslip et al., 1988; Lazarus et al 1996b; Weissel 1997). However, others find it too early for a screening or have argued against its usefulness (e.g. Ball, 1996; Kent et al., 1999).

Several (methodological) aspects may explain these rather inconclusive data such as small sample sizes, different definitions of depression (depressive symptoms versus syndromal diagnoses of depression) and differences in the periods of follow-up.

In the present study it is investigated whether women with elevated concentrations of thyroid peroxidase antibodies during early pregnancy have a higher risk of becoming depressed during the second and third trimester of pregnancy, or in the first 2 years postpartum.

## Methods

*Subjects*

In a screening program on thyroid parameters of 1361 pregnant women of the general population 270 pregnant women were selected on their free thyroxine (fT4) concentration: 135 women with an fT4 within the lowest 10 percentile as well as 135 women with an fT4 between the 50$^{th}$ and 90$^{th}$ percentile matched on gravidity and parity. The rationale for this study has been published in detail elsewhere (Pop et al., 1999). All participants were Caucasian women, without overt thyroid disease at the time of the screening. Women with gestational diabetes (n=2), a history of fertility problems (n=10), rheumatoid arthritis (n=1), gemelli (n=5), severe psychiatric disturbance (n=1) and women who delivered prematurely (n=10) were excluded. One child died of congenital heart disease, one of trisomy 18 syndrome and one mother died of cancer. Twelve women did not want to participate, resulting in a final sample size of 233 women. Twenty-three women (10%) had an elevated antibody concentration and were included as the cases together with 210 women without elevated antibody concentrations (controls).

The women were visited at home at 24 and 32 weeks' gestation, at 3 weeks postpartum and at 1 and 2 years after delivery, where they were interviewed about mental

and physical health, life style habits and the course of pregnancy and delivery. All subjects were married or living with their partner. Age ranged from 21-40 (mean age 30.9, SD 3.3). Sample characteristics are presented in Table 1.

**Table 1. Sample characteristics of the 233 pregnant subjects. Antibody positive and negative women did not differ significantly on any of the variables presented.**

| | | *TPO-Ab≥35* n=23 | *TPO-Ab<35* n=210 |
|---|---|---|---|
| **Demographic variables** | | | |
| Age | mean (SD) | 31.3 ( 3.2 ) | 30.9 ( 3.3 ) |
| Parity ≥1 | n (%) | 13 (56.5) | 124 (59.0) |
| Educational level in years | mean (SD) | 11.0 ( 3.4 ) | 10.7 ( 3.0 ) |
| **Life style variables during pregnancy** | | | |
| Has not smoked during pregnancy | n (%) | 20 (90.9) | 160 (80.8) |
| Has not consumed alcohol during pregnancy | n (%) | 18 (81.8) | 171 (86.4) |
| **Obstetrical factors** | | | |
| Spontaneous vaginal delivery | n (%) | 17 (73.9) | 145 (69.0) |
| Duration of pregnancy in weeks | mean (SD) | 39.8 ( 1.4 ) | 39.8 (1.4) |
| **Psychosocial / psychiatric factors** | | | |
| Previous depression | n (%) | 4 (17.4) | 51 (24.4) |
| Subject has parent with a history of depression | n (%) | 8 (34.8) | 73 (36.0) |
| Reports stressful life events during pregnancy | n (%) | 16 (76.2) | 127 (63.8) |
| Reports financial worries during pregnancy | n (%) | 2 ( 8.7 ) | 8 (3.9) |

*Assessment of depression*

Depressive symptoms were measured at 24 weeks' gestation, 1 and 2 years postpartum by means of the Edinburgh Postnatal Depression Scale (Cox et al 1987). The EPDS is a 10-item self-report scale designed as a screening instrument for postnatal depression. It was also validated in non-postnatal women (Cox et al 1996). In 1992 the EPDS was translated into Dutch and was found to have good psychometric properties (Pop et al., 1992).

Syndromal diagnosis of depression during pregnancy was made at 24 and 32

weeks' gestation and 3 weeks' postpartum by means of the Research Diagnostic Criteria of Spitzer (RDC, Spitzer 1978). The RDC discriminate between major and minor depression. At 1 and 2 years after delivery syndromal diagnoses were made by means of the 12 months version of the depression section of the Composite International Diagnostic Interview (CIDI; World Health Organisation, 1990a). The CIDI is a highly structured psychiatric interview assessing major types of DSM-III-R (American Psychiatric Association, 1987) and ICD-10 (World Health Organisation, 1990,b) diagnoses. The CIDI was carried out by well-trained interviewers.

*Thyroid parameters*

The following thyroid parameters were assessed: thyrotrophin (TSH), free thyroxine (fT4) and antibodies against the thyroid peroxidase (TPO-Ab). TSH (reference range:0.15-2.0 mIU/l) was measured using a solid-phase, two site chemiluminescent enzyme immunometric assay (IMMULITE Third generation TSH, Diagnostic Products Corporation, Los Angeles). The inter-assay coefficients of variation were 9.8%, 6.9% and 4.6% at concentrations 0.02 mIU/l, 0.15 mIU/l and 11 mIU/l, respectively. The free T4 concentration (reference range: 8.7-19.6 pmol/l) was also measured with a solid-phase immunometric assay (Immulite Free T4). The inter-assay coefficients of variation for this technique were 20%, 10.5%, 5.3% and 5.2% at concentrations of 3.1 pmol/l, 11.8 pmol/l, 19.8 pmol/l and 55 pmol/l, respectively. The IMMULITE Anti-TPO Ab kit was used for the determination of 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 IU/ml, 69 IU/ml and 114 IU/ml, respectively. The anti-TPO assay is standardised in terms of the International Reference Preparation for anti-TPO MRC 66/387. An antibody concentration of ≥35 IU/ml was regarded as elevated. A concentration of >100 IU/ml was regarded as highly elevated.

*Statistical analysis*

Differences in characteristics between the antibody positive and negative women were investigated using Chi-square tests and t-tests. Differences between the 2 groups in EPDS scores at 24 weeks' gestation, 1 and 2 years postpartum were investigated by means of Mann-Whitney U tests. Finally, two multiple logistic regression analyses were conducted. In the first analysis, the dependent variable was the occurrence of an episode of major depression during pregnancy or early postpartum (according to the RDC). In the second analysis the dependent variable was the occurrence of an episode of major depression in the first 2 years after delivery (according to the CIDI). Other independent variables than TPO-Ab concentrations were the following factors known from literature to be associated with depression: having experienced one or more previous episodes of depression, the occurrence of stressful life event(s) in the past 12 months, a family history of depression, parity, and the presence of high depressive symptomatology during gestation.

## Results

Twenty-three (9.9%) women had TPO-Ab concentrations above 35 IU/ml, 15 (6.5%) of whose antibody concentrations were above 100 IU/ml. The mean EPDS scores of the total group were 4.9 (SD 3.6), 3.4 (SD 3.7) and 3.2 (3.4) at 24 weeks' gestation, 1 year and 2 years after birth, respectively. At 24 weeks' gestation 13 (6%) women had a minor depression according to the RDC, and 9 (4%) major depression. At 32 weeks of pregnancy 22 (9%) women had a minor and 4 (2%) a major depression. At 3 weeks postpartum, according to the RDC 13 (6%) women classified for minor and 5 (2%) for major depression. In the first year following childbirth, 9 women (4%) reported an episode of major depression as measured by the CIDI. In the second year after birth the number of women with a positive diagnosis for major depression was higher: 17 subjects (7%). Between antibody positive and negative women no differences could be found in demographic features, life style habits, obstetrical complications, psychiatric and psychosocial variables (see Table 1). As shown in Table 2, no significant differences in mean EPDS scores were found between the cases and controls at any of the measurements.

Table 2. Comparison of mean EPDS scores of women with elevated thyroid antibodies (TPO-Ab≥35) and those without, at 24 weeks' gestation, 1 year and 2 years postpartum.

| *EPDS score* | *TPO-Ab≥35* | | *TPO-Ab<35* | | *Mann-Whitney* |
|---|---|---|---|---|---|
| | Mean (SD) | n | Mean (SD) | n | |
| 24 weeks gestation | 4.4 (3.0) | 21 | 5.0 (3.6) | 187 | p =.63 |
| 1 year postpartum | 3.6 (3.2) | 23 | 3.9 (3.7) | 200 | p =.56 |
| 2 years postpartum | 4.2 (3.9) | 22 | 3.1 (3.4) | 192 | p =.17 |

Of the 40 (17%) of subjects who had a depression during pregnancy or early postpartum (according to the RDC), 35 (88 %) belonged to the control group. Similarly, of the 25 women who became depressed in the 2 years following delivery (according to the CIDI), 23 (92%) women did not have elevated antibody levels.

Table 3a shows that in the multiple logistic regression analysis only one variable was significantly associated with the occurrence of an episode of depression during pregnancy (2nd and 3rd trimester) or early postpartum, which was a history of depression (OR 2.7; 95% CI: 1.2 - 6.0). Table 3b shows that the only variable independently related to the occurrence of a major depressive episode during the two years after delivery was a high intensity of depressive symptomatology during pregnancy (OR 1.1; 95% CI: 1.0 -1.3). Hence, thyroid antibody status during early pregnancy was not related to depression during pregnancy nor to an episode of major depression after delivery. When the analyses were repeated using a higher concentration of elevated con-

centrations of TPO-Ab (TPO-Ab≥100 IU/ml) as cut-off point similar results were found (data not shown).

**Table 3a. Multiple logistic regression analysis. Method: Enter. Dependent variable: major depression (RDC) at one or more of the following measurements: 24 or 32 weeks' gestation or 3 weeks postpartum (RDC)**

| Variable | OR | 95% CI |
|---|---|---|
| TPO≥35 IU/ml | 1.53 | 0.5 – 4.9 |
| Previous depression | 2.70 * | 1.2 – 6.0 |
| Stressful life events in past 12 months | 1.69 | 0.7 – 4.0 |
| Financial worries during pregnancy | 2.5 | 0.6 – 10.7 |
| Subject has parent with history of depression | 0.99 | 0.5 – 2.2 |
| Parity | 1.26 | 0.9 – 1.8 |

* sign. at $p<0.05$

**Table 3b. Multiple logistic regression analysis. Method: Enter. Dependent variable: episode of major depression in the 2 years following childbirth (CIDI).**

| Variable | OR | 95% CI |
|---|---|---|
| TPO≥35 IU/ml | 0.37 | 0.0 – 3.7 |
| Previous depression | 1.92 | 0.7 – 5.1 |
| Stressful life events in past 12 months | 0.61 | 0.2 – 1.6 |
| Financial worries during pregnancy | 0.98 | 0.2 – 6.3 |
| Subject has parent with history of depression | 1.3 | 0.5 – 3.4 |
| Parity | 1.3 | 0.9 – 2.0 |
| Depressive symptoms at 24 weeks' gestation (EPDS) | 1.1* | 1.0 – 1.28 |

* sign. at $p<0.05$

## Discussion

The findings of the present study do not support the theory that women with elevated concentrations of TPO-Ab are specifically at risk to develop depression during pregnancy or after delivery. Moreover, no association was found between thyroid antibody status and depressive symptoms during pregnancy or 1 and 2 years after delivery.

The only variables that were significantly related to depression during pregnancy and the postpartum were a history of depression and a high intensity of depressive symptoms during pregnancy, respectively. Both relationships have consistently been reported by other researchers (e.g. O'Hara et al 1991, Kelly & Deakin 1992). The fact that the RDC criteria were used during pregnancy and not during the postpartum was related to the design of the study. During follow-up women were visited once a year which makes the RDC criteria not suitable for use since this instrument provides point prevalences.

Similar to the results of the present study, Harris et al. (1992) found microsomal (a previous nomenclature of TPO-Ab) antibody concentrations at 16 weeks' gestation not to be related to the occurrence of major depression after delivery. However, they found an excess of depressive symptoms in thyroid antibody positive women during the first eight months postpartum, as compared to women without antibodies. Antibody titers are known to decrease during pregnancy, then rise during the postpartum period with a peak at 5-7 months postpartum, after which they decline (Fung et al., 1988). Harris and colleagues (1992) measured depressive symptomatology repeatedly during the postpartum period, in which there are marked changes of TPO-Ab concentrations. High TPO-Ab levels frequently lead to postpartum thyroiditis (PPT), which in turn might cause hyper- and/or hypothyroidism. Since these two conditions are known to be associated with depressive symptomatology, this might explain the association between high TPO-Ab concentrations and increased risk of depressive symptoms when frequent assessments are performed as in the study of Harris et al. In the present study depressive symptoms were assessed during midgestation (when antibodies concentrations are decreased) and at 1 and 2 years postpartum when the increase of hyper- and/or hypothyroidism due to PPT does no longer exist.

Similar to the findings of the present study, several others also failed to find a relationship between the presence of elevated thyroid antibodies and depression or depressive symptoms. For example, Oretti et al. (1997) investigated the association between gestational thyroid antibodies and antenatal depression, but found no difference in the prevalence of antenatal depression in antibody positive versus antibody negative women. Moreover, they found individual depressive symptom scores not to be related to TPO-Ab titers. In a recent study by Kent et al. (1999) no relationship between thyroid antibody concentrations (TPO-Ab or MsAb) and depression was found at 6 months post partum. Haggerty et al. (1997) examined the prevalence of antimicrosomal and antithyroglobulin antibodies in various subgroups of psychiatric inpatients and a non-psychiatric control group. These authors found that when intervening influences of age and sex were taken into account, anti-thyroid antibodies were not more prevalent in patients with unipolar depression than in a psychiatric or non-psychiatric control group. Pop et al. (1993), who measured thyroid antibodies at 32 weeks' gestation and related them to postpartum depression, found that the sensitivity of antibodies as a marker for postpartum depression was low with almost no predictive value. The authors concluded that factors other than thyroid antibodies play a more important role in the

aetiology of postpartum depression.

A limitation of the present study concerns the fact that women were included in the study based on their fT4 levels at 12 weeks' gestation and therefore do not represent the general (pregnant) population. However, statistical analysis of the fT4 concentrations of the whole sample showed an equal normal distribution of fT4 during late gestation and controlling for fT4 levels in the multivariate analyses yielded similar results (data not shown). The 12 month prevalence of an episode of major depression in the present study during the first and second year is rather low compared to other studies which found higher prevalence rates of depression (Kumar and Robson, 1984, O'Hara 1991). However, these studies often had repeated assessments of depression during the postpartum period and used also RDC criteria for depression including minor depression. A recent large epidemiological survey in the Netherlands revealed a one year prevalence of 7% of major depression in women at similar age (childbearing and non-childbearing) which is comparable to that of the current study (Bijl et al., 1997).

Of those investigators who argue in favour of an antenatal screening for thyroid antibodies, some have argued that its relevance especially lies in the identification of women at risk for PPT, whereas others have emphasised the opportunity to identify women with an increased risk of postpartum depression (e.g. Weissel 1997). Results of the present study indicate that the presence of an elevated thyroid antibody concentration during early pregnancy does not discriminate between women who subsequently will develop an episode of major depression and those who do not. In conclusion, this means that the suggested association between TPO-Ab and major depression should not be used to promote screening strategies of all pregnant women.

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# Chapter 8

# Maternal hypothyroxinemia and breech delivery: an effect of impaired maternal-foetal thyroxin transfer?

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## Introduction

Recently, the negative impact of maternal hypothyroxinemia (low free thyroid hormone concentration (fT4) with a thyrotrophin hormone (TSH) concentration within reference range) during early gestation on subsequent infant development at the age of one and two years has been demonstrated (Pop et al., submitted) At the age of one and two years, children of women with hypothyroxinemia showed a 8 to10 point index delay on the motor scale compared to children of mothers with an fT4 between the 50-90$^{th}$ percentile (Pop et al., submitted). Because the foetus does not produce its own thyroxin up until 16-20 weeks' gestation, it is totally dependent on the maternal supply of fT4 during the first trimester of pregnancy (Burrow et al., 1994). Thyroid hormone is of major importance for the development of the foetal central nervous system: overt maternal hypothyroidism during pregnancy or major iodine deficiency has been associated with poor obstetrical and developmental outcome of the infant (Glinoer, 1997).

About 3-4% of all pregnancies reach term with a foetus in the breech presentation (Hickok et al., 1992). In general it is believed that breech delivery is associated with higher morbidity and mortality rate, especially after vaginal delivery. A recent large randomised controlled multi-centre trial showed and OR of 0.33 with regard to perinatal mortality, neonatal mortality and serious neonatal morbidity in foetuses who presented in breech and who were delivered by caesarean section compared to those who had a planned vaginal delivery (Hannah et al., 2000). It was questioned whether there is any place left for planned vaginal breech birth and a primary caesarean section was advocated for all breech term presentation (Hannah et al., 2000). However, Caesarean section in general still has an increased maternal mortality rate compared to non-operative delivery (Van Ham et al., 1997). Although external cephalic version substantially reduces breech presentation serious foetal and obstetrical complications have been described with high recidive to the breech position. It has been calculated that 6 attempted external cephalic version are needed to avoid one caesarean section (Healey et al., 1997).

Little is known about the aetiology of breech presentation. Factors as prematurity, intra-uterine growth retardation, gemelli, pelvic abnormalities as well as uterus-anomalies, placenta praevia, polyhydramnion, multiparity, umbilical cord problems and congenital foetal abnormalities all together only explain 15% of breech presentation (Rayl et al., 1996). However, there are several etiological factors (umbilical cord problems, congenital akinesy syndrome) that might be related to foetal movements during pregnancy (Soernes & Bakke, 1986; Adinma 1993).

We hypothesized that motor development retardation in children at the age of one and two years - if related to maternal hypothyroxinemia during early gestation - should also be present during gestation. Because abnormal foetal movements might be related to breech presentation we questioned whether maternal hypothyroxinemia during early gestation and subsequent course of maternal thyroxin concentrations was related to labour complications.

## Methods

*Subjects*

Although the study design has been described in detail elsewhere, it is briefly summarized here because different exclusion criteria resulted in different sample sizes.

Between January 1997 and April 1998, thyroid parameters (TSH, fT4 and TPO-Ab) were assessed at 12 weeks' gestation in a randomly selected cohort of 1361 Dutch Caucasian women who booked in for antenatal controls in an area around the city of Eindhoven, the Netherlands. Women with overt hyperthyroidism (n=7) and hypothyroidism (n=1) were excluded. From the remaining 1353 women, the lowest 10$^{th}$ and the 50$^{th}$ - 90$^{th}$ fT4 percentiles were calculated: 12.4 and 15.6-19.1 pmol/l, respectively. The 135 women in the lowest fT4 percentile (cases) were matched on parity and gravidity with an equal number of women whose fT4 value was between the 50$^{th}$ - 90$^{th}$ fT4 percentiles (controls). All these women (n=270) were invited for a follow-up study. Twelve refused participation (4%) and 20 (6%) were excluded according to previously set exclusion criteria (fertility problems, the presence of autoimmune diseases such as rheumatoid arthritis, insulin dependent diabetes mellitus). The remaining 238 women were visited at home at 24 and 32 weeks' gestation for repeated assessments of thyroid function and assessment of gestational complications. Subsequently, a careful obstetrical history was obtained at 3 weeks' postpartum.

Thyroid parameters of 24 and/or 32 weeks gestation were not obtained in 21 women. 44 Women with subclinical thyroid dysfunction (elevated / decreased TSH with normal fT4) were excluded, 23 and 21 with subclinical hypo- and hyperthyroidism, respectively. Furthermore, data of 18 women with obstetrical complications such as abortion, gestational diabetes, gemelli and pre / post-term delivery (<37 or >42 weeks' gestation) were excluded. Therefore, data-analysis refers to 155 women, 78 cases (with hypothyroxinemia at 12 weeks' gestation: fT4 below the 10$^{th}$ percentile and TSH within reference range) and 77 controls (with fT4 at 12 weeks' gestation between 50-90$^{th}$ percentile and TSH within reference range).

This study was approved by the Medical Ethical Committee of the St Joseph Hospital (Veldhoven, The Netherlands).

*Obstetrical outcome*

Generally speaking, in The Netherlands, there are three patterns of intra-partum care: birth at home with the aid of a community midwife (or occasionally a general practitioner), a '24-hour confinement' (parturition in hospital with the aid of the person who provided the antenatal care - community midwife, general practitioner or obstetrician - with the mother leaving the hospital within 24 hours); and a 'clinical' confinement (parturition in hospital with the mother remaining for more than one day (generally 5 to 7 days), when there is a medical indication, such as Caesarean section or postpartum haemorrhage). Both at home and in hospital similar standardized forms are used to complete (gynaecologist, midwife) the way of delivery. The following categories

can be discriminated: (1) spontaneous vaginal parturition at home; or in hospital as follows: (2) spontaneously; (3) vaginal parturition after stimulation with medication; (4) vaginal parturition with forceps / vacuum extraction; or (5) Caesarean section.

*Thyroid parameters*

TSH (reference range for women between 20-40 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 USA). The inter-assay coefficients of variation were 9.8%, 6.9% and 4.6% at concentrations 0.02 mIU/l, 0.15 mIU/l and 11mIU/l, respectively. The fT4 concentration (reference range for women between 20-40 years: 8.7–19.6 pmol/l) was also measured with 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 pmol/l, 19.8 pmol/l and 55 pmol/l, respectively. The IMMULITE Anti-TPO Ab kit was used for the determination of 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 IU/ml, 69 IU/ml and 114 IU/ml, respectively. The anti-TPO assay is standardized in terms of the International Reference Preparation for anti-TPO MRC 66/387. A concentration between 35 and 100 IU/ml was regarded as moderately elevated, whereas a concentration of > 100 IU/ml was regarded as clearly elevated.

*Statistical analysis*

Statistical analysis was performed using the Statistical Package of Social Science and Problems Solutions (SPSS). Differences in characteristics between the cases and controls were analysed with chi-square tests. Odds Ratio's were calculated using multiple logistic regression analysis.

## Results

The way of delivery of these two groups are shown in Table 1. Caesarean section occurred significantly more often (P=0.01, chi-square: 6.0, df=1) in the hypothyroxinemic women compared to those with an fT4 between 50-90$^{th}$ percentile at 12 weeks' gestation (controls). There was a significant difference in the occurrence of breech delivery between cases and controls: 9 versus 2, respectively (P= 0.03, chi-square: 4.9, df=1). In figure 1, different groups of women are shown according to their mean fT4 at 12 weeks' gestation and the subsequent course of mean fT4 concentration at 24 and 32 weeks' gestation. In the corresponding Table 2, the prevalence rate of breech delivery, spontaneous delivery and Caesarean section of the different groups are shown. The prevalence of breech delivery as well as Caesarean section increased in hypothyroxinemic women who subsequently showed a further decrease of mean fT4 throughout pregnancy (group I) while the occurrence of breech delivery in women who had adequate levels of fT4 at 12 weeks' gestation was not influenced by subsequent changes of mean

fT4 throughout pregnancy (group V and VI). Also, a further decline of maternal fT4 was associated with a lower rate of spontaneous delivery while the highest rate (90%) of spontaneous delivery was found in the group of control women who showed a further increase of mean fT4 from 24 to 32 weeks' gestation (group VI). In Table 3a, a multiple logistic regression showed that hypothyroxinemia at 12 weeks gestation was independently related to Caesarean section: O.R. 5.2, 95% CI: 1.3 - 20). Similarly, in Table 3b it is shown that breech delivery was also independently related to hypothyroxinemia at 12 weeks' gestation: O.R.: 5, 95% CI: 2.3 - 22.

**Table 1. Different ways of delivery in women with hypothyroxinemia at 12 weeks' gestation (cases, n = 78, fT4 below the 10th percentile and TSH within reference range) compared to these of women with a mean fT4 between 50 - 90th percentile (and TSH within reference range at 12 weeks' gestation (controls, n = 77).**

| way of delivery | cases n (%) | controls n (%) |
|---|---|---|
| spontaneous at home | 37 (46) | 36 (44) |
| spontaneous in hospital | 15 (18) | 25 (31) |
| after induction vaginally | 7 (9) | 7 (8) |
| forceps / vacuum | 10 (12) | 11 (13) |
| Caesarean section * | 12 (15) | 3 (4) |
| Breech delivery * | 9 (11) | 2 (2) |

* : $p < 0.05$ on chi-square, df = 1.

**Table 2. Way of delivery according to mean fT4 at 12 weeks' gestation and subsequent fT4 course during pregnancy**

| groups | spontaneous (%) | Caesarean section (%) | breech (%) |
|---|---|---|---|
| cases, n = 78 | 64 | 15 | 11 |
| controls, n = 77 | 74 | 5 | 3 |
| I, n = 14 | 64 | 21 | 15 |
| II, n = 20 | 54 | 9 | 5 |
| III, n = 29 | 67 | 17 | 17 |
| IV, n = 15 | 72 | 7 | 7 |
| V, n = 43 | 65 | 6 | 2 |
| VI, n = 31 | 90 | 0 | 3 |

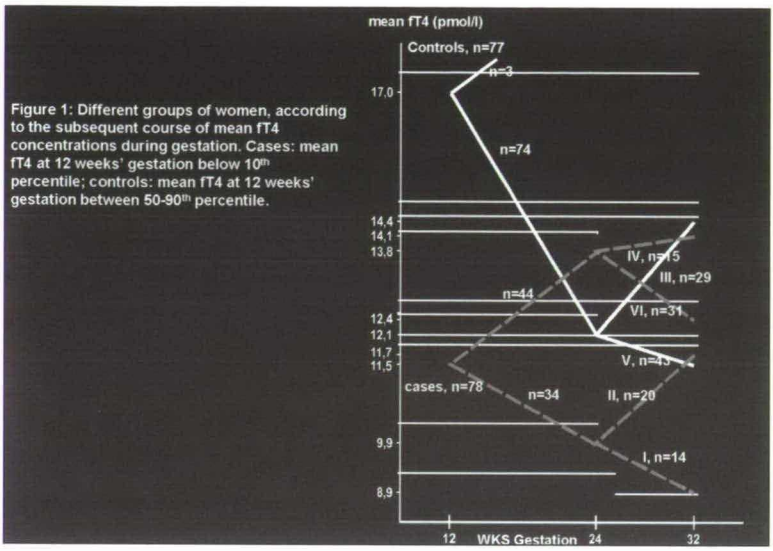


Figure 1: Different groups of women, according to the subsequent course of mean fT4 concentrations during gestation. Cases: mean fT4 at 12 weeks' gestation below 10th percentile; controls: mean fT4 at 12 weeks' gestation between 50-90th percentile.

*Figure 1: Different groups of women, according to their mean fT4 at 12 weeks' gestation (controls: mean fT4 below the 10th percentile; cases: mean fT4 between 50-90th percentile) and subsequent course during pregnancy.*

Table 3a. Multiple logistic regression analysis of 155 women with dependent variable: Caesarean section.

| | O.R. | 95% C.I. |
|---|---|---|
| Primiparity | 3.2 | 0.9 - 11.0 |
| Caffeine use | 2.8 | 0.6 - 14.4 |
| Alcohol use | 2.1 | 0.4 - 5.2 |
| Low income | 1.4 | 0.7 - 2.5 |
| Low education | 1.5 | 0.5 - 2.4 |
| Hypothyroxinemia | 5.2 | 1.3 - 20 |
| Smoking | 1.9 | 0.7 - 2.7 |

Table 3b. Multiple logistic regression analysis of 155 women with dependent variable: breech delivery.

| | O.R. | 95% C.I. |
|---|---|---|
| Primiparity | 3.8 | 0.8 - 17.2 |
| Caffeine use | 1.1 | 0.3 - 5.3 |
| Alcohol use | 1.8 | 0.4 - 8.6 |
| Low income | 1.1 | 0.5 - 1.9 |
| Low education | 1.1 | 0.5 - 1.7 |
| Hypothyroxinemia | 5.2 | 1.6 - 22 |
| Smoking | 1.9 | 0.8 - 8.9 |

## Discussion

As far as we know, this is the first publication of a study investigating the relation between maternal thyroid hormone levels in euthyroid women throughout pregnancy and subsequent obstetrical outcome. Maternal hypothyroxinemic pregnant women (defined as the lowest 10$^{th}$ percentile of fT4 at 12 weeks' gestation with TSH levels within reference range) were at high risk to reach term with a child in breech position O.R: 5, 95% CI: 2.3 - 22) and as a consequence to deliver by Caesarean section.

Overt maternal hypothyroidism has well been documented to be related to obstetrical complications (Glinoer, 1997). However, it is a rare condition in childbearing women. Moreover, because hypothyroidism often is associated with fertility problems (because of an-ovulation) most women with overt hypothyroidism only will be become pregnant after adequate substitution with thyroid hormone. Most of the women - at least in iodine suppleted areas - who show overt hypothyroidism during pregnancy are those who are inadequately treated (inadequate substitution with thyroid hormone in those with previous hypothyroidism or inadequate treatment with anti-thyroid drugs in those who suffered from hyperthyroidism).

The mechanism, which might explain the association between maternal hypothyroxinemia and an increased rate of breech position, remains to be explained. However, it might be hypothesized that adequate foetal movements are important to reach cephalic position. Moreover, it might be hypothesized that inadequate foetal movements interfere with the development of an adequate length of the umbilical cord, a shortage of which has been associated with an increased rate of breech position (Soernes & Bakke, 1986; Adinma 1993). As has been demonstrated recently hypothyroxinemic women during early pregnancy are at risk to have children with clear motor development retardation at one and two years of age. It is reasonable to accept that, if this were due to early (e.g. before the foetus produces its own thyroid hormone which is generally not until 16 weeks' gestation) shortage of thyroid hormone for the foetus during pregnancy, a possible detrimental effect on motor development would already be present during gestation. It is interesting to note that in a few congenital endocrinological syndromes (Prader Willy, pituitary agenesis) in which hypothalamic function is impaired (and by consequence foetal thyroid functioning) the rate of breech position is extremely high: up to 20% (Butler, 1990).

Direct echographic assessment of foetal movements has recently been developed (Kozuma et al., 1998; Ten Hof et al., 1999). However, the standard procedure is an assessment of foetal movements during a period of at least 40-60 minutes. Until now it is not clear whether echographic examinations of such a long duration is without negative consequences for the foetus which makes it difficult to use this instrument as a standard tool in research to assess foetal movement. It has been suggested that maternal hypothyroxinemia might be related to inadequate iodine intake during pregnancy (Delange 1994; Utiger 1999). However, the present study was carried in an area with adequate iodine intake of the general population although it is still a matter of specu-

lation whether adequate iodine intake in non-childbearing women also guarantees adequate iodine intake during pregnancy. Data of iodine intake of large samples of pregnant women are warranted.

A limitation of the present study is the rather low number of total women delivering in breech position. This is due to the fact, as mentioned earlier, that the design of the study was developed for another research question. Although within the present study statistically significant differences were found with rather small numbers, larger studies are needed with more epidemiological power to confirm the association between maternal hypothyroxinemia and breech position. It is only thereafter that intervention trials with thyroxin replacement should be considered.

During the last decade a debate has been generated questioning whether thyroid parameters (TSH, fT4 and thyroid peroxidase antibodies, TPO-Ab) should be screened in all pregnant women (Lazarus 1999; Pop et al., 1999). The association between elevated concentrations of TPO-Ab and increased rate of abortion, the high correlation between elevated TPO-Ab and the development of postpartum thyroiditis, the relation between maternal hypothyroxinemia and impaired infant development are all arguments in favour for screening. The possible role of maternal thyroid hormone (in euthyroid women) in obstetrical outcome would add another argument for screening. Practically, screening would be easy to implement in Western Societies: all pregnant women have already their blood samples taken between 12-16 weeks' gestation. However, as long as one of the main criteria to start screening has not been met (is there evidence that there is an effective treatment with realistic cost/benefits ratio) it is the opinion of the authors that screening should not be promoted.

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# Chapter 9

# Summary and discussion

Central to this thesis were maternal thyroid function during pregnancy and maternal and infant well-being. Thyroid function was seen as a biological determinant of maternal well-being, anxiety and depression as psychological determinants. Infant behaviour and development were seen as important aspects of child well-being. Satisfactory obstetrical progress was regarded as important for both maternal and child well-being.

The answers to the questions posed in paragraph 2.1 will be briefly summarised below, followed by a discussion of the implications and recommendations for future research in section 9.2.

## Summary of the findings

*1a. Is maternal hypothyroxinemia during early pregnancy associated with impaired infant psychomotor development? (Chapter 3)*
*1b. Is the pattern of fluctuations of maternal fT4 levels throughout pregnancy related to subsequent infant psychomotor development? (Chapter 3)*

Chapter 3 investigated to what extent maternal hypothyroxinemia during early pregnancy, although a biochemically euthyroid and clinically often symptom-free condition, may affect subsequent infant development. It was shown that children of women with hypothyroxinemia during the first trimester of pregnancy were at risk for a delay in both mental and motor development at the ages of one and two years. Specifically, at the age of 12 months, 24% and 25% of children of the cases had a delay in their mental and motor development of at least 2 months, respectively. At the age of two years, 14% and 29% of the children of the cases had a delay in mental and / or motor development of at least 3 months, respectively. A second important finding was that the time period in which hypothyroxinemia occurred was important for the development for the child. Most at risk for delayed development at the age of two years were children whose mothers were hypothyroxinemic during early gestation and in whom (maternal) fT4 concentrations showed a further decline by midgestation and during late pregnancy. In contrast, women who were hypothyroxinemic during early pregnancy, but whose fT4 levels *increased* during further pregnancy, had children whose developmental scores were comparable to those of children of mothers with adequate fT4 levels during early pregnancy.

*2. Are high maternal anxiety levels during late pregnancy related to an impaired infant psychomotor development? (Chapter 4)*

Since low-normal thyroid hormone levels were expected to be associated with a delay in infant development, when investigating the association between maternal prenatal anxiety and subsequent child development, only those women with adequate thyroid hormone levels during early pregnancy (the control group in Chapter 3) were

included. High maternal prenatal anxiety scores were found to be associated with lower mental developmental scores in two-year-old children. By the ages of three weeks and one year, differences could already be seen in the ability to concentrate of infants of mothers who had had high anxiety scores during late pregnancy versus those of mothers with low anxiety scores. This study is one of the first to assess the impact of maternal anxiety during pregnancy longitudinally on infant development after the age of one year.

*3a. Does the Edinburgh Postnatal Depression Scale (EPDS) contain an anxiety subscale? (Chapter 5)*
*3b. If the EPDS does contain an anxiety subscale, does its validity improve when this subscale is excluded? (Chapter 5)*

The study findings presented in Chapter 5 demonstrate that the EPDS does indeed include an anxiety subscale and, therefore, measures anxiety as well as depressive symptoms. However, in practice, exclusion of this anxiety subscale did not increase the validity of the EPDS as an instrument for measuring depressive symptoms. Conversely, the anxiety subscale did not correlate higher with the other measures of anxiety than did the complete EPDS. Therefore it would appear that both anxiety and depressive symptoms can be measured more accurately using the complete ten-item EPDS. Researchers using the EPDS as a screening instrument for depression should be aware that they are also measuring aspects of anxiety.

*4a. Are thyroid parameters and anxiety levels related during late pregnancy? (Chapter 6)*
*4b. Are elevated maternal thyroid peroxidase antibody (TPO-Ab) concentrations during early gestation related to high anxiety levels during late gestation? (Chapter 6)*

A multiple regression analysis was conducted to investigate the independent relationships between anxiety and thyroid parameters. It was found that both elevated TPO-Ab levels and lower fT4 concentrations were associated with high trait anxiety, even when controlled for confounding variables such as high depressive symptomatology during pregnancy. TSH was related to neither state nor trait anxiety.

The study showed an independent relationship between thyroid parameters (fT4 and TPO-Ab) and trait anxiety in pregnant women. Further work is indicated to confirm this association, as it may in future add to a better identification of women at risk for mental health problems during pregnancy and the postpartum period.

*5a. Is the presence of elevated TPO antibodies during early pregnancy a risk factor for the occurrence of an episode of major depression in during later pregnancy or after childbirth? (Chapter 7)*
*5b. Is a high concentration of TPO antibodies during early pregnancy related to increased depressive symptomatology during and after pregnancy? (Chapter 7)*

The presence of elevated TPO antibody titers appeared to have no predictive value for the occurrence of an episode of major depression in the mother in the two years following childbirth. Moreover, the number of depressive symptoms reported at 24 weeks' gestation, and one and two years postpartum, did not differ between women with or without elevated TPO antibodies.

*6. Are lower maternal fT4 levels during pregnancy related to increased complications during labour? (Chapter 8)*

The results presented in Chapter 8 show a relationship between maternal fT4 levels at 12, 24, and 32 weeks' gestation and subsequent obstetrical problems. In particular, women with hypothyroxinemia at 12 weeks' gestation, whose mean fT4 levels decreased during pregnancy, had a higher prevalence of breech deliveries and Caesarian sections than women with higher fT4 levels. In women with adequate fT4 levels at 12 weeks' gestation, subsequent changes in mean fT4 did not affect the risk of having a breech delivery.

## Discussion

When interpreting the results of this thesis, several issues should be addressed. One of the strengths of this study, when investigating the main question posed in Chapter 3, is the fact that, due to the large screening population, the effect of maternal hypothyroxinemia on subsequent child development could be studied in a large sample of hypothyroxinemic women and in a control group. Moreover, it is the first study to investigate the effects on infant development of fluctuation in maternal fT4 throughout the trimesters. Previously, it was assumed that, in healthy pregnant women, fT4 levels decreased with the progression of pregnancy (see, for example, the figure by Burrow et al., 1994; Figure 1 in this thesis). Data from the present study show that there are subgroups of women whose fT4 levels *increase* with the progression of pregnancy. Moreover, the results suggest that the pattern of increase or decrease in maternal fT4 during pregnancy has considerable consequences on the psychomotor development of the infant.

The study presented in Chapter 3 has important implications for the debate on whether or not screening should be carried out for thyroid parameters during pregnancy. Recently, Pop and colleagues argued that, before screening is implemented, some important questions need to be answered (Pop et al., 1999). First, they raised the question as to which variable should be used for screening. While Haddow et al. (1999) used TSH as an index of maternal thyroid (dys-)function in their study, the findings from this thesis suggest that it is fT4 rather than TSH that is related to the delay in infant development, since hypothyroxinemia is a condition characterised by low fT4 but normal TSH concentrations. A second issue addressed by Pop and colleagues was the question what cut-off value should be used to define a state in which thyroid hormone levels are sufficient for the mother, but perhaps not for the foetus. The results of this the-

sis suggest that maternal fT4 levels within the lowest tenth percentile of the normal range during early pregnancy with normal TSH are a risk factor for impaired infant development. This means that, of the 1353 women (without thyroid disease) who participated in the screening, 135 (10%) had low-normal fT4 levels. Of this group, 104 (7.7%) women had normal TSH, and were therefore considered hypothyroxinemic. In the Netherlands, about 200,000 women give birth each year. This could indicate that, each year, 7.7% (14,000 women) of the general population of pregnant women in the Netherlands could be at risk for giving birth to a child whose development will be delayed until at least the age of two years. Although in some, fT4 concentrations will rise protecting the offspring from developmental delays, it still poses a considerable problem for the community. A third issue addressed by Pop et al. was that, before starting out on a screening, first the best time for screening pregnant women should be clarified. In this thesis it was found that the developmental scores of children whose mothers were hypothyroxinemic during the first trimester, but whose fT4 levels had increased during the second and third trimesters, were comparable to those of children in the control group. This suggests that an assessment of thyroid function during the first antenatal visit to the gynaecologist or midwife may not be too late for screening. Perhaps maternal hypothyroxinemia during early pregnancy can still be compensated for by increased levels of maternal fT4 during later pregnancy. However, the results of the study do not all argue in favour of screening. The finding that children of mothers whose fT4 levels increased in the second and third trimesters had comparable scores to the control group, even when they had been hypothyroxinemic during early pregnancy, does not imply that fT4 substitution is necessarily the solution to this problem, since fT4 suppletion might suppress maternal or foetal fT4 production.

Another issue to address is the way in which these developmental differences need to be interpreted. A number of studies have presented results supporting the view that predictions of mental development are hard to make during early childhood (Risholm Mothander, 1989). In addition, most infants (mostly newborns) diagnosed as 'normal' indeed turn out to be 'normal' in later developmental assessments, while many infants diagnosed as 'abnormal' also turn out to be normal in later assessments (Van Baar 1998). It has been argued that, only after the age of two years old developmental assessments start to have a predictive value for later intellectual performance (Molfese et al., 1996). However, even though the predictive value of early developmental tests usually is low, for example the predictive value of the NBAS for later infant development or behaviour measured with the Bayley Scales of Infant Development (BSID) has been confirmed by several researchers (e.g., Sostek & Anders 1977; Vaughn et al., 1980; Kalmar & Medgyes 2000).

In this thesis, a longitudinal design was used in which not only thyroid parameters, but also child development was assessed repeatedly until the age of two years. Therefore, no conclusions can be drawn regarding the effects after the age of two years. It has been suggested that biomedical factors are more strongly related to cognitive and

language development in the first two years, and that environmental factors influence outcomes more strongly at an older age (Molfese et al., 1994). In contrast however, the often irreversible brain damage resulting from a shortage of fT4 such as in iodine-deficient areas or from undetected CHT suggests that environmental influences cannot overcome this deficit.

Another consideration when discussing the results of this thesis concerns the accuracy of the norm scores of the Dutch BSID. Several authors (e.g., Fuggle et al., 1992) have found IQ scores to be increased in both children and adults in the past 50 years. Therefore, the norm scores of the Dutch BSID (validated in 1983) may be too low. A study conducted in the Eindhoven area in 1998, in an unselected population (n=225) of children aged from ten to twelve months, found mean standardised scores on the mental and motor scales of 106 (SD 16) and 100 (SD 15), respectively (Pop et al., 1999). In the study sample in Chapter 3, the mean scores of the control group were 105 (SD 14) and 106 (SD 14) for the mental scale at the ages of 12 and 24 months, and 99 (SD 14) and 102 (SD 16) for the motor scale at 12 and 24 months, respectively. This suggests that, over the past 17 years, scores on the mental developmental index of the Dutch BSID have indeed increased, reflecting a normal population. This conclusion is also important for the study presented in Chapter 4, in which an association was found between maternal anxiety levels during pregnancy and delayed developmental scores.

Although the results of the study seem promising, in practice they do not justify a change in the current (treatment) procedures regarding maternal thyroid function during pregnancy. It is the first study published investigating the association between gestational fT4 levels of hypothyroxinemic women and infant development, and the results of a single study should not yet lead to such important changes. Earlier, it was suggested that fT4 substitution not necessarily is the solution, as fT4 suppletion might suppress maternal or foetal fT4 production. Therefore, future research should study this toppic in greater detail. It is the author's opinion that before a placebo-controlled trial is carried out, more long-term observational research is necessary.

One of the strengths of the studies presented in Chapters 3 and 4 is that infant development was examined repeatedly in an objective, standardised, double-blind manner. It is an important finding that women whose infants are at risk for developmental delay are identifiable during pregnancy. The ability to identify women at risk at such an early point in time provides an opportunity to start a support program in order to optimise later infant stimulation and caretaking. Regarding Chapter 4, future studies should focus on the question of whether the relationship between maternal anxiety during pregnancy and infant development is due to pre- or postnatal factors. These studies should repeatedly measure both pre- and postnatal anxiety and should follow child development preferably up to adolescence. Findings in this thesis suggest that cognitive, attention-related processes are of particular interest, and should be evaluated.

The relationship between high anxiety levels during pregnancy and subsequent infant development was only studied in the control group from Chapter 3 (subjects

with adequate fT4 levels during the first trimester). The results of this study raise the question of whether women with hypothyroxinemia during early pregnancy (the cases) are doubly at risk for giving birth to a child whose development will be delayed until at least the age of two years, considering the possible association between low fT4 levels and high anxiety in the third trimester. Although this question was not answered in this thesis, gestational hypothyroxinemia was found to be related to an additional adverse event, causing a higher incidence of obstetrical problems, especially breech deliveries. One of the limitations of this thesis is the small number of women in the subgroups when investigating the fluctuation in maternal fT4. This problem is made worse in the study on obstetrical problems (Chapter 8) because of the fact that only 3-4% of all pregnancies reach term with the foetus in the breech position (Hannah et al., 2000). Because breech delivery is associated with a higher morbidity and mortality rate (Klufio & Amoa, 1991), the findings in this study could be very important. Future studies investigating the effect of maternal hypothyroxinemia during pregnancy in large samples should, therefore, preferably investigate the association with both obstetrical problems and infant development.

An additional finding that needs to be addressed is that high TPO-Ab levels were found to be related to high trait anxiety near term, although no such association was found with depressive symptoms or maternal major depression during or after pregnancy. This may seem contradictory, since depression and anxiety often occur together. One explanation, with regard to the tripartite model of anxiety and depression, could be that elevated TPO-Ab levels may be related to those aspects of physiological hyperarousal associated with anxiety, rather than the anhedonia associated with depression. However, the fact that other studies did find elevated TPO antibody levels to be significantly related to depressive symptoms, makes this a less likely explanation. An alternative explanation could be the timing of the measurements. It has been argued that the third trimester, during which anxiety was measured, is characterised by the highest levels of general discomfort during pregnancy. The second trimester, however, during which depressive symptoms were measured, has been described as the trimester of stability and relative well-being. In addition to changes in well-being throughout the different trimesters, TPO-Ab concentrations also fluctuate during pregnancy and the postpartum. It has been suggested that, in particular the rapid increase in antibody concentrations during the postpartum period, may be associated with depressive symptoms (Harris et al., 1992). However, in the present thesis, neither anxiety nor depressive symptoms were measured during the course of the first postpartum year, and for this reason it may be that no association was found between TPO antibody titers and depressive symptoms after birth. Hence, although in Chapter 6 it was shown that TPO-Ab levels during early pregnancy have no predictive value for the onset of an episode of major depression in the two years following birth, the results of the present study do not indicate that highly elevated levels of TPO-Ab are necessarily unrelated to depressive symptomatology, for example, during the early postpartum period.

This thesis focussed on the relationship between one of the biological aspects of well-being of pregnant women (thyroid function) and a psychological aspect (mood disturbance during and after pregnancy), and the effects of these aspects on the development of the child. The findings presented suggest that these topics may all be related; the results showed that women with lower fT4 levels were not only at risk of having children with delayed development at the ages of one and two years, but also of having obstetrical complications and non-spontaneous deliveries. They might also have an increased risk for high trait anxiety which, in turn, is associated with both obstetrical problems and a delay in the cognitive development of their two-year-old infants. In conclusion, women with gestational hypothyroxinemia (and their children) could well form a vulnerable group in several respects. Therefore, the notion that hypothyroxinemia is a harmless condition due to normal TSH levels would seem to be inaccurate. Pop and Vulsma (2000) have already argued that, due to the sub-optimal supply of fT4, hypothyroxinemia may be harmful to the foetus, and this has been confirmed in the present study. Moreover, the findings in this thesis suggest that gestational hypothyroxinemia may also be harmful to the mother.

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# Chapter 10

# Samenvatting

In dit proefschrift stonden de maternale schildklierfunctie tijdens de zwangerschap en het welzijn van moeder en kind centraal. De schildklierfunctie werd beschouwd als een biologische determinant van het welzijn van de moeder, angst en depressie als psychologische determinanten. Het gedrag en de ontwikkeling van het jonge kind werden gezien als aspecten van diens welzijn. Een voorspoedige bevalling werd beschouwd als belangrijk voor het welzijn van zowel moeder als kind. De onderzoeksvragen en resultaten van dit proefschrift zullen hieronder kort samengevat worden.

In Hoofdstuk 3 werd onderzocht in hoeverre maternale hypothyroxinemie, een conditie gekenmerkt door een te laag gehalte schildklierhormoon (fT4) met een normale hoeveelheid Thyroid Stimulating Hormone (TSH), tijdens de vroege zwangerschap schadelijk kan zijn voor de ontwikkeling van het kind. Er werd aangetoond dat kinderen van vrouwen met hypothyroxinemie tijdens het eerste trimester van de zwangerschap een verhoogd risico hadden op een achterstand in mentale en motorische ontwikkeling op de leeftijden van 1 en 2 jaar. Een tweede bevinding van de studie was dat tevens het moment in de zwangerschap waarop de hypothyroxinemie plaatsvond van belang was voor de ontwikkeling van het kind.

De hoogste kans op een ontwikkelingsachterstand op de leeftijd van 2 jaar hadden kinderen van moeders met hypothyroxinemie tijdens de vroege zwangerschap en van wie de fT4 concentraties verder daalden gedurende de rest van de zwangerschap. Daarentegen hadden vrouwen met hypothyroxinemie in het eerste trimester van wie fT4 concentraties gedurende het tweede en derde trimester *omhoog* gingen kinderen met ontwikkelingsscores die vergelijkbaar waren met die van kinderen wiens moeders voldoende fT4 tijdens de vroege zwangerschap hadden.

In hoofdstuk 4 werd onderzocht of een hoge intensiteit van angstgevoelens tijdens de late zwangerschap gerelateerd is aan een achterstand in mentale en motorische ontwikkeling van het kind. Er werd inderdaad een verband gevonden tussen hoge maternale angstscores rond 32 weken zwangerschap en ontwikkelingsachterstanden in mentale ontwikkeling bij het 2 jarige kind. Reeds op de leeftijden van 3 weken en 1 jaar werden verschillen gevonden op het gebied van aandacht en concentratie tussen kinderen van moeders met lage versus hoge angstscores in de zwangerschap. De studie is een van de eerste die de impact van maternale angst in de zwangerschap op de ontwikkeling van het kind longitudinaal onderzoekt tot op de leeftijd van 2 jaar; het meeste onderzoek beperkt zich tot de eerste levensmaanden. Omdat verwacht werd dat maternale hypothyroxinemie tijdens de zwangerschap geassocieerd zou zijn met een vertraagde ontwikkeling van het kind en het design van de studie ook voor deze vraag ontworpen was, is het verband tussen maternale angst in de zwangerschap en de ontwikkeling van het kind onderzocht in de controlegroep, ofwel bij moeders die een adequate hoeveelheid schildklierhormoon hadden in de vroege zwangerschap.

In hoofdstuk 5 stond een meer psychometrische vraagstelling centraal, namelijk of de Edinburgh Postnatal Depression Scale (EPDS) een angstschaal bevat, en of deze angstschaal hoger correleert met andere instrumenten die angst meten dan de totale

EPDS. Het bestaan van een angstschaal werd inderdaad aangetoond, maar deze correleerde niet hoger met andere meetinstrumenten voor angstsymptomen dan de totale EPDS. Ook leidde exclusie van de angstschaal niet tot een hogere validiteit van de EPDS als meetinstrument voor depressieve symptomen. Het werd geconcludeerd dat de EPDS zowel symptomen van angst als depressie meet, en dat beiden het beste gemeten kunnen worden met de totale EPDS. Onderzoekers die het instrument gebruiken dienen zich te realiseren dat de EPDS meer meet dan depressieve symptomen alleen.

In hoofdstuk 6 werd het verband tussen schildklierparameters en angstsymptomen tijdens de zwangerschap onderzocht. In de studie werd een significante relatie gevonden tussen een hoge angstdispositie ('trait anxiety') en zowel hoge TPO antistofwaarden als lage fT4 concentraties, zelfs wanneer gecontroleerd werd voor variabelen als depressive sypmtomen tijdens de zwangerschap. Praktisch gezien betekenen de bevindingen dat vrouwen met een hoge kans op sterke angstgevoelens in het derde trimester wellicht al identificeerbaar zijn op 12 weken zwangerschap. Aangezien een hoge intensiteit van angstsymptomatologie aan het eind van de zwangerschap geassocieerd is met verscheidene nadelige gevolgen voor moeder en kind is een dergelijke identificatie wellicht de moeite waard. Echter, de richting van het verband en de aard van de relatie tussen schildklier parameters en angst zijn nog niet duidelijk.

In hoofdstuk 7 werd onderzocht of de aanwezigheid van een verhoogde TPO antistof concentratie tijdens de vroege zwangerschap een risicofactor was voor het ontstaan van depressie in engere zin in de 2 jaar na de bevalling. Dit bleek niet het geval te zijn; de aanwezigheid van een verhoogde concentratie TPO antistoffen had geen voorspellende waarde. Tevens werd onderzocht of zwangeren met een verhoogde TPO antistofconcentratie meer depressieve symptomen rapporteerden op 6 maanden zwangerschap en 1 en 2 jaar na de bevalling dan vrouwen met lagere antistof hoeveelheden. Ook dit bleek niet het geval.

In hoofdstuk 8 werd een verband aangetoond tussen maternale hypothyroxinemie en obstetrische problemen. Met name bij vrouwen met hypothyroxinemie op 12 weken zwangerschap van wie de fT4 concentraties verder daalden in het $2^e$ en $3^e$ trimester werd een hogere prevalentie stuitbevallingen en keizersneden geconstateerd dan bij vrouwen met hogere fT4 waarden. Bij zwangeren die op 12 weken een adequate hoeveelheid fT4 hadden waren verdere veranderingen in de hoeveelheid fT4 niet gerelateerd aan de manier van bevallen.

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Pregnancy is a time during which many changes occur in a woman's life. Apart from her visibly changing body, many more subtle physical changes occur, such as alterations in her hormone metabolism and dietary requirements. Changes in mood may also take place, and it is not always clear whether they are due to physical changes (e.g., hormonal fluctuations), or to psychological changes (e.g., worries about the changes ahead) or to a complex interplay between physical and psychological factors. Moreover, it is not known to what extent such changes affect child development either during or after pregnancy. Central to this thesis is the relationship between a biological determinant of well-being in the pregnant woman (thyroid function), a psychological determinant (depression and anxiety during and after pregnancy), and the effects of these factors on the development of the child.

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