The Kempen study

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The Kempen study: Aspects of maternal well-being and obstectrical outcome in relation to gestational thyroid function

Hennie Wijnen

Stellingen behorende bij het proefschrift:
" The Kempen study: Aspects of maternal well-being and obstetrical outcome in relation to gestational thyroid function".

1. De basale verloskundige zorg biedt een uitstekende basis voor hoogwaardig wetenschappelijk onderzoek; de Kempen studies tonen dit aan.

2. Education is not the filling of a pail, but the lighting of a fire.
William B. Yeats

3. Aan ernstige klachten van zwangerschapsmisselijkheid liggen eerder psychologische dan biologische oorzaken ten grondslag. (dit proefschrift)

4. Keep away from people who try to belittle your ambitions. Small people always do that, but the really great ones make you feel that you too, can become great.
Mark Twain

5. Schildklierhormoon waardes in de laagste 30 percentiel zijn in het derde trimester van de zwangerschap gerelateerd aan een afwijkende ligging van de foetus.(dit proefschrift)

6. A small minority of medical interventions are supported by solid scientific evidence.
(vrij naar) Richard Smith, editor of the British Medical Journal

7. Vrouwen met veel angstklachten in het derde trimester van de zwangerschap hebben een verlengde ontsluitingstijd bij de bevalling. (dit proefschrift)

8. The best-laid schemes o' mice an 'men an 'bonny lasses
Gang aft agley,
An'lea'e us nought but grief an' pain,
For promis'd joy!
(vrij naar) Robert Burns

9. Het selecteren van laag risico zwangerschappen uitsluitend op basis van obstetrische gronden zonder het bepalen van een psychologisch risico profiel is geen optimale verloskundige zorg. (dit proefschrift)

10. " De bevalling thuis was zo mooi en natuurlijk, het leek bijna niet meer van deze tijd"

" Voor de eerste keer vader" 2001

11. Het nieuwe zorgstelsel per een januari 2006 is een zorgelijk stelsel.

12. " Beij maa insteij daat ge wiezer wert".

Oos Mo

H.A.A. Wijnen, 6 december 2005

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"The Kempen study: Aspects of maternal well-being and obstetrical outcome in relation to gestational thyroid function"

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit van Tilburg, op gezag van de rector magnificus, prof. dr. F.A. van den Duyn Schouten, in het openbaar te verdedigen ten overstaan van een door het college voor promoties aangewezen commissie in de aula van de Universiteit

op dinsdag 6 december 2005 om 14.15 uur

door

Henrica Anna Albertina Wijnen
geboren op 6 maart 1950
te Horst

Promotores: Prof. dr. V.J.M. Pop
Prof. dr. G.G.M. Essed

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Chapter I

GENERAL INTRODUCTION

I. The physiological process of labour

The mechanics of labour are influenced by three factors: "the power, the passenger and the passage". In labour the power has two major functions: to dilate the cervix and to push the foetus through the birth canal. Usually it is said that the delivery contains the occurrences and activities, which lead to the shift of the "passenger" (foetus, membranes and placenta) from the uterus to the outside world. Strictly speaking one could argue that with this definition labour actually starts around the 16^{th} to 20^{th} week of the gestation. At that time weak uterine contractions can start which cause the formation of the lower uterine segment, which can be seen as the first start of the activities necessary for the foetus to be born. It is obvious that such a definition cannot be used in every day practise. On the other hand it clearly shows that from a scientific as well as a practical point of view it is very difficult to pinpoint a distinct onset of labour: during the actual delivery nothing else happens but an acceleration and intensifying of activities (" the power") which have been going on for a long time. The definition, which is mostly used, is: the delivery has started when the uterine (myometrial) contractility pattern switches from contractures (long-lasting, low-frequency activity) to regular contractions (frequent, high-intensity, high-frequency activity) resulting in effacement and dilatation of the uterine cervix. Usually the onset of labour (in practise) is characterized by one or three of the following occurrences:

1. The appearance of rhythmic uterine contractions every five minutes for at least one hour, which during that time appear to become stronger, longer in duration and (sometimes) come more frequently.
2. Bloody show: a small amount of blood with mucous discharge from the cervix. This bloody show may precede the onset of labour by a few days.
3. Rupture of the foetal membranes with egress of amniotic fluid. In around 10% this will happen before the start of the uterine contractions.

During history many people have thought and theorized about the onset of labour. Hippocrates (460-377 BC) thought that the unborn child started labour. Like a chick picking its way to the outside world through the eggshell he believed that the baby at the end of the pregnancy, driven by hunger, would push itself off against the top of

the uterus. In the 11th century Avicenna wrote that labour starts by "the grace of God" a belief, which held for many centuries. Ferguson (1941) thought that labour started by a feedback mechanism in which by pressure on the uterine cervix, caused by the foetus, the maternal posterior pituitary releases oxytocin (=quick birth), which then causes contractions.

Nowadays there are several hypotheses about this process. It is likely that there is a cascade of events regulated and controlled by the foetal-placental unit. During pregnancy, uterine activity is present, but is minimal. At the end of gestation, there is a gradual down regulation of those factors that keep the uterus and cervix quiescent (progesterone suppresses uterine activity and oestradiol increases it) and an up regulation of pro-contractile influences. At term the foetus increases its production of cortisol and this cortisol reduces the production of placental progesterone and increases the production of oestrone and oestradiol. These changes also result in increased production of prostaglandins by the placenta and thus a further increase in myometrial activity and stimulate oxytocin release, which also enhances myometrial activity.

The cervix contains myocytes and fibroblasts and serves to contain the "passenger". Towards term the cervix becomes softened, as there is an increase in proteolytic enzyme activity. Once labour has started traditionally three stages can be discriminated, with the first stage further subdivided into two major phases. The first stage of labour is the interval between the onset of labour and full cervical dilatation, subdivided into the latent and the active phase, according to the rate of cervical dilatation. The second stage is the interval between full cervical dilatation (10 cm) and expulsion of the foetus. Indications that the second stage has started are an increase in bloody show, maternal desire to bear down with each contraction, a feeling of pressure on the rectum accompanied by the desire to defecate, and onset of nausea and vomiting. The third stage is the interval between the delivery of the baby and the expulsion of the placenta and the membranes. In time this stage is the most accurate because we know the start and finish.

The foetus, as a passenger, plays an active role in the whole birthing process. Foetal presentation at term is crucial for normal delivery. Up to 93% present in the cephalic position of whom 90% in vertex occipito-anterior, the most physiological presentation. Up to 4% present in breech often resulting in obstetrical interventions. During labour

the foetus uses flexion and deflexion of the head onto the chest (nodding yes) and rotation of the presenting part (shaking no) to pass through the pelvis.
The birth canal, the passage, consists of the bony pelvis and soft tissues. These joints always have a degree of mobility, which increases during pregnancy, particularly in multiparas. This movement of the pelvis is necessary to accommodate the foetal head and body through labour. Amongst the soft tissues the pelvic floor muscles (p.e. levator ani) are the most important. The soft tissues also become more distensible than in the non-pregnant state and substantial distension of the pelvic floor and vaginal orifice occurs during the descent of the head. This can result in tearing of the perineum and of the vaginal walls and sometimes in tearing and disruption of the external anal sphincter[1,2,3].

It is obvious that factors that negatively affect 'the power, the passenger and the passage', alone, or in combination will contribute to obstetrical complications during labour.
There is substantial literature concerning the effects on both biochemical and psychological factors on premature delivery. However, studies that investigated obstetrical complications during physiological labour in healthy pregnant women at term gestation have been reported much less frequently.

The main scope of this thesis is that in healthy low (obstetrical) risk women with term gestation (> 37 weeks') the effect of several independent factors on physiological labour will be investigated.

II. The role of the midwife in the Dutch obstetrical system

At the start of this millennium there were over 1700 (locum included) midwives working in the Netherlands. Most of those midwives (68%) were working independently in their own practise, and 17% were working in a hospital[4]. In the last decade about 40% of all deliveries in the Netherlands (ca. 220.000 per year) are supervised by an independent midwife and 75% of these are home births[5]. But not only during labour,

also during pregnancy most women will see a midwife for antenatal check-ups. Moreover, almost every woman, whether she gave birth at home or in the hospital, will spend most of her confinement week at home in the care of a midwife. During these eight days the women can receive help from a maternity home-care nurse. This maternity nurse also assists the midwife during homebirth. Maternity nurses are specially trained for assisting and teaching (bathing, feeding the baby) the "new parents" the first week after delivery. Her job is doing light household chores and taking care of the mother (and possibly other children) and the newborn. For the latter she works under supervision of a midwife.

Through the history of the obstetrical care in the Netherlands midwives have always played an important role. For the longest time there was no formal training to become a midwife. Women who felt attracted towards the profession learned in practise from other lay-midwives. This training then could be supplemented with reading manuals. One of the widespread midwifery manuals was, (freely) translated from German, "The rose garden of the fertilized women", written by Eucharius Roeslin, which had 28 editions between 1516 to 1742. Hendrik van Deventer (1651-1724) started a new era of midwifery literature with the publication of "Dageraet der Vroet-Vrouwen" (Daybreak of the midwives) in 1696, followed by his "Nieuw Ligt voor Vroedmeesters en Vroed-vrouwen" (New light for midwife-physicians and midwives) in 1701. In his book he defended that obstetrical actions had to be based on knowledge of the physiology and pathology of the female organism and of the reproductive process. In this way the medical doctors and surgeons would practise obstetrics following the correct method and would be able to raise the level of knowledge of midwives. Another historic document is the "Memory Boeck van de Vrouwens" (Memory book of the women) of the Frisian midwife Catharina Schraders (1656-1746). In this diary she kept record of 2980 deliveries including obstetrical actions such as version and extraction of a baby in breech presentation and manual placenta removal. Nowadays both those incidences would be a medical reason for referral from the primary level to the secondary level of obstetric care.

Obstetric care in the Netherlands is based on the principal of risk selection. Low-risk pregnant women receive primary level obstetric care provided by (independent) midwives or general practitioners. Women with a high-risk obstetric profile receive secondary level care, provided by obstetricians. Low obstetrical-risk women

may choose to give birth at home or in hospital with their primary care provider. Women evaluated as having an increased obstetrical risk deliver in hospital with a secondary level caregiver. If obstetric problems occur during pregnancy or birth, the primary level caregiver can consult with the secondary level caregiver and refer when appropriate. The secondary level care-provider can also refer the women back to primary care at any time if the condition, which prompted referral, is no longer a risk factor. This system is based upon the principal of close mutual co-operation between primary and secondary level obstetric caregivers (Table 1).

Table 1. Explanation of the codes used for the care providers in the "Kloosterman list".

Code	*Description*	*Care provider*
A Primary obstetric care	The responsibility for obstetric care in the situation described is with the primary obstetric care provider.	Midwife/G.P.
B Consultation situation	This is a case of evaluation involving both primary and secondary care. Under the item concerned, the individual situation of the pregnant woman will be evaluated and agreements will be made about the responsibility for obstetric care.	depending on agreements
C Secondary obstetric care	This is a situation requiring obstetric care by an obstetrician at secondary level for as long as the disorder continues to exist.	Obstetrician
D Transferred primary obstetric care	Obstetric responsibility remains with the primary care provider, but in this situation it is necessary that birth takes place in a hospital in order to avoid possible transport risk during birth.	Midwife/G.P.

The first List of Obstetric Indications appeared in 1959, the so-called "Kloosterman list" followed by a second one in 1987. The Obstetric Manual, made by and for obstetric professionals, was published in the spring of 1999, and updated in 2003. The main aim of the Manual is to provide the necessary tools to ensure that risk-selection within the field of obstetrics is carried out appropriately. The primary care provider (the independent midwife or general practitioner) is primarily responsible for this process of risk-selection. The main basic assumption is that pregnancy,

birth and puerperium are physiological processes that can take place at home. Another basic assumption is that optimal use must be made of the expertise of the various obstetric care-providers. Based upon this assumption, a normal pregnancy, birth and puerperium belong to the primary level care-provider's field of work. Pregnancy, birth and puerperium selected by the primary level care-provider as being 'at risk' belong to the secondary level care-provider's field of work. Guidelines for advice giving and consultation have been formulated to ensure that selection and referral take place optimally. In order to make this manual work, good working conditions between obstetricians, midwives and G.P.'s are necessary. In many places in the Netherlands, efficient co-operation already exists between primary and secondary obstetric care-providers, whether or not formally recognised[6].

During the last decades midwives in the Netherlands also have started to participate in research. Because of their rigorous risk selection tasks, which can only be achieved by following the above-mentioned protocols, there is an excellent base for prospective research. From the first antenatal check-up at 10-12 weeks' gestation till the 6 weeks' postpartum assessment, a pregnant woman will be in personal contact with a midwife for a minimum of 6 hours. After the intake consultation at least ten antenatal check-ups of 10-15 minutes during gestation are followed by a home delivery that lasts with an average of 2-4 hours. During the first postpartum week women are visited by the midwife four to six times for consultations of 10-15 minutes. Finally, after six weeks' postpartum there is a final consultation of at least 15 minutes. These patient-midwife contacts during a period of eight months offer an excellent opportunity for prospective research.

The rate of home deliveries in The Netherlands has decreased from more than 50% after the war to less than 35% in the 90ties to remain stable for the last five to seven years. One of the consequences of increased hospital deliveries is an increase of technical interventions with all its short-term (increased risk of bleedings, neonatal complication and psychological problems such as posttraumatic stress symptoms) and long-term effects (uterus scars due to Caesarean section). The question whether spontaneous delivery at home is the most optimal way of delivery in low-risk women from an emotional point of view has hardly been investigated. Perhaps

this might be explained by the fact that The Netherlands is one of the very few countries in the Western world where home deliveries take place as a standard option in regular obstetrical health care. However, also in our country there are no appropriate scales to evaluate differences in the way delivery is perceived in home versus hospital delivery.

One topic of this thesis therefore was to develop an instrument that can be used to evaluate the emotional perception of delivery and confinement days. (Chapter VII). Moreover, the studies in this thesis were used to validate this instrument and to look at the effect of technical interventions on woman's emotional perception of delivery and confinement days taking into account mood changes and anxiety (Chapter VIII).

III. Maternal thyroid function during pregnancy

Thyroid function in general

Thyroid hormone is a very important factor for bone growth and development of the central nervous system in the foetus, the neonates and children. In adults it facilitates most metabolic processes, as such regulating the function of basically every organ system. To keep up its availability there are large stores of thyroid hormones, which are peptides containing iodine, in the circulation and in the thyroid gland. Thyroid hormone function is dependent in large part on the supply of iodine, which is derived solely from dietary sources and actively transported into the thyroid gland. The functional unit of the thyroid gland is the thyroid follicle. Colloid consists primarily of thyroglobulin, which provides tyrosine residues for serial iodination that results, through a complex series of biochemical and biophysical alterations, in the production of the thyroid hormones T4 and T3. The thyroid gland is responsible for the production of all circulating T4, while T3 is a product of the thyroid (20%) and of many other tissues where it is made by deiodination of T4. The thyroid hormones T4 and T3 circulate in a mostly bound form to thyroid-binding globulin (TBG), such that less than 1% circulates as free hormone, free T4 (FT4) and free T3 (FT3). As in most endocrine sys-

tems, it is the free fraction of these hormones, not the total concentration that is physiologically important[7].

Regulation of Thyroid Hormone Secretion.

Under normal circumstances, the circulating concentration of T4 is maintained within a narrow range that varies little from day to day. The thyroid is under the direct control of the hypothalamic-pituitary-thyroid axis. When the pituitary and the hypothalamus detect low levels of thyroid hormones, the hypothalamus produces the thyroid-releasing hormone (TRH), which stimulates specific cells (thyrotropes) to produce thyroid-stimulating hormone (TSH). TSH secretion varies during the day, with a peak secretion occurring between 23.00 and 04.00 hours. TSH enters the systemic circulation and interacts with specific receptors on the surface of thyroid follicular cells, which trigger the synthesis and release of thyroid hormones, thereby returning the level of thyroid hormone in the blood back to normal. This mechanism is controlled by a negative feedback loop, which will slow down TRH release[7].

Effect of pregnancy on thyroid function.

In pregnancy, renal clearance of iodine increases (because of an increase in the glomerular filtration rate) and substantial amounts of iodine and iodothyronines are transferred to the foetus. As pregnancy progresses and foetal thyroid hormone production increases, the foetus needs increasing amounts of iodine. To meet this demand, the placenta is able to rapidly and efficiently transport available iodine from the maternal to the foetal circulation. The placenta is also capable of mono-deiodination of iodothyronines, thereby making more iodine available for transport. The net result of these pregnancy-related physiological alterations is a decrease in the circulating concentration of inorganic iodine during pregnancy and a resultant increase in volume of the thyroid gland by 10-20% during pregnancy. Other changes in thyroid function are an increase in serum thyroxine-binding globulin (TBG) concentrations and stimulation of the thyrotropin (TSH) receptor by chorionic gonadotropin (hCG). The pregnancy-specific hormone hCG is structurally similar to TSH and has some weak thyrotropic activity, which is estimated at approximately 0.025% that of TSH.

The production of hCG begins during the first week after fertilization and is highest near the end of the first trimester, after which it declines. This increase causes a transient increase in serum freeT4 concentrations, which in turn decreases serum TSH concentrations during the first trimester. This cross-reactivity only becomes clinically significant if circulating levels of hCG are markedly elevated, such as that seen in complete molar pregnancies. Sometimes, high concentrations of hCG can be responsible for the syndrome hyperemesis gravidarum in which a pregnant woman looses up to 5% of her weight during early gestation.
The negative-feedback control system of the hypothalamic-pituitary-thyroid axis functions normally in pregnant women[7].

Thyroid function in the foetus.

The foetal thyroid gland and pituitary-thyroid axis only become functional late in the first trimester. Before that time, any thyroid hormone in the foetus must come from the maternal circulation. By the 10^{th} to 12^{th} week of gestation foetal TSH appears and the foetal thyroid is capable of concentrating iodine and synthesizing iodothyronines. However, little hormone synthesis occurs until the 18^{th} to 20^{th} week of pregnancy. From then on foetal thyroid secretion increases gradually. At term, foetal serum T4, T3 and TSH concentrations differ considerably from those in the mothers. Soon after birth serum TSH concentrations rapidly increase to 50 to 80 mU/L (TSH surge) and then drop to 10 to 15 mU/L within 48 hours. Serum T3 and T4 concentrations rapidly increase to values slightly higher than those in normal adults[7].

IV. Maternal thyroid dysfunction during pregnancy

Changes in immune system during pregnancy

Many autoimmune diseases have been shown to be affected by pregnancy. In normal pregnancy, the maternal immune system undergoes major adjustments to allow the maintenance of what may be immunologically considered a foreign body (the developing foetus) with 50 % paternal genes. The alterations in maternal immune

system, which permit the successful implantation of the foetal allograft, seem likely to be partially responsible for the generalized improvement in autoimmune thyroid disease, which is so characteristic of the pregnant state. In normal pregnancy, along with the overall dampening of the immune system, maternal immune responses have been shown to shift dramatically as reflected by a suppression of thyroid (and other) antibodies. Presumably, the rapid reduction in immune suppressor functions following delivery leads to the reestablishment and exacerbation of these conditions resulting in exacerbation of autoimmune thyroid disease (rebound). This pattern is especially well illustrated in patients with Hashimoto's disease, in euthyroid patients with positive thyroid antibodies who develop postpartum thyroid dysfunction, and in those with Graves' disease who frequently present exacerbations or recurrences of thyrotoxicosis following parturition[7].

Thyroid autoimmunity (TAI) and miscarriage

Despite these immune changes, up to 10% of the fertile women have antibodies against the thyroid (TPO-Ab, TSHrAb) at conception. During the last decades it has become increasingly clear that these antibodies are associated with increased risk of miscarriage. In a recent review and meta analysis including 5500 women it was found that TAI was significantly associated with an increased rate of miscarriage (O.R. 2.7) although this association does not imply a causal relationship. Several hypotheses have been proposed. Pregnancy loss is not directly related to the presence of circulating thyroid antibodies. In this view, TAI only constitutes a marker of an underlying (yet to be defined) more generalized autoimmune imbalance that, in turn, could explain a greater rejection rate of the foetal graft. Another explanation could be that despite apparent euthyroidism, the presence of TAI is associated with a subtle deficiency in thyroid hormone concentrations or with a lesser ability of the thyroid gland to adapt adequately to the necessary changes associated with the pregnant state. Finally, it might be argued that TAI could act by delaying the occurrence of pregnancies, because of its association with subfertility. In this view, TAI positive women would tend to become pregnant at an older age (on average 3-4 years later), and older women are more prone to pregnancy loss[7].

Hypothyroidism during gestation

Between 1 and 2% of women who become pregnant already receive thyroxin therapy for hypothyroidism. Two population-based studies of women without known hypothyroidism showed that 2 to 4% of women entering pregnancy might present hypothyroidism to various degrees, from subclinical to overt disease. Several studies have shown that when hypothyroid women become pregnant and maintain the pregnancy, they carry an increased risk for obstetric and foetal complications. Increased rates of anaemia, pre-eclamspia and cardiac problems have been described as well as placental loss and postpartum haemorrhage. Increased rates of foetal loss, premature delivery, foetal distress during labour, congenital malformations and perinatal loss have also been described. These complications urgently warranted that pregnant women with known hypothyroidism should be carefully monitored by an experienced endocrinologist who is familiar with pregnancy related changes of thyroid hormone suppletion. Inadequate substitution has resulted in an increased rate of abortion and miscarriage while adequate treatment of hypothyroid patients shows a similar obstetrical outcome as the general population[7].

Hyperthyroidism during gestation

The most common cause of hyperthyroidism in women of childbearing age is Graves' disease. Another important cause - resulting directly from the stimulatory effects of hCG on the thyroid is "gestational transient thyrotoxicosis" (GTT).
Overt Graves' disease during gestation is rare (1 to 2 / 1000 pregnancies) but an important concept is that both the maternal and foetal outcomes are directly related to adequate control of thyrotoxicosis. The most common maternal complication is gestational hypertension, which is five times higher in women with uncontrolled hyperthyroidism. Other obstetrical complications include low birth weight, preterm deliveries, foetal malformations, placenta abruptio and miscarriages. Congestive heart failure may occur in women untreated or treated only for a short period of time in the presence of gestational hypertension or operative delivery. In a recent study of over 200 pregnancies, no adverse impact on pregnancy of adequately treated Graves' disease was reported.

Gestational transient thyrotoxicosis (GTT) is defined as a transient increase in thyroid hormone secretion, of non-autoimmune origin, leading to thyrotoxicosis with variable degrees of severity, and occurring in women with an otherwise normal pregnancy, frequently in association with hyperemesis. GTT is not always clinically apparent, since it is most often transient. Its etiology is directly related to the thyrotropic stimulation of the thyroid gland associated with hCG. Its prevalence in Europe reaches 2-3 % of all pregnancies (that is 10-fold more prevalent than Graves' disease) while in other regions it appears to be highly variable, as low as 0.3% in Japan and as high as 11% in Hong Kong.

Owing to its transient nature, the clinical manifestations of the disorder are not always apparent or routinely detected. Symptoms compatible with thyrotoxicosis, including weight loss or the absence of weight increase, tachycardia and unexplained fatigue, are found in only one half of the women with GTT. In most cases, no specific treatment is required[7].

Maternal hypothyroxinemia

Maternal hypothyroxinemia is defined by a free T4 (FT4) within the lower range of reference (often set arbitrarily below 5th or 10th percent) with normal TSH. Hypothyroxinemia is frequently seen in iodine deficient areas, both during and outside pregnancy. In iodine sufficient areas hypothyroxinemia during gestation - sometimes even with dramatically low FT4 levels - for many decades has been regarded as being without consequences for the mother (and foetus) as long as TSH levels were not increased. However, during the last ten years it has become increasingly apparent that it is associated with impaired neurodevelopmental outcome of the offspring. As an explanation it is hypothesized that maternal hypothyroxinemia increases the risk of insufficient passage of maternal T4 to the foetus, which might impair normal development of the foetal central nervous system especially during the first half of gestation. A consisting finding of several studies was a delay of motor development in children of mothers with hypothyroxinemia during gestation[7].

Thyroid function and normal labour

The finding of impaired motor development of the offspring in relation to maternal hypothyroxinemia during gestation has led to the hypothesis that maternal thyroid hormone levels during gestation in the lower range also might interfere with normal labour. As described above, the 'passenger' (the foetus) is an important factor of normal labour. When entering the birth canal, flexion, deflexion and rotation of the head is crucial for normal expulsion. In adults, adequate thyroid hormone levels are needed for normal muscle tonus. When the foetus during delivery does not have appropriate amounts of thyroid hormone it might be argued that expulsion will become more problematic.

Recently, it was shown that hypothyroxinemia during gestation was related to an increased rate of breech position. Although significant correlations were found the sample size was rather small.

In literature, no publications are found on the possible role of thyroid hormone causing protraction of labour in healthy (e.g.: not suffering from thyroid disease) pregnant women. Even more surprising is the finding that in animal studies also the role of thyroid hormone on physiological labour has hardly been investigated[7].

Therefore another topic of this thesis was to look at the relation between maternal thyroid hormone levels and obstetrical outcome (Chapter VI).

V. Pregnancy, morning sickness, mood changes, anxiety and obstetrical outcome.

Morning sickness

Nausea and vomiting in the first trimester of pregnancy (NVP) is frequent, occurring in 50% to 90% of pregnancies[8]. It is commonly known as 'morning sickness' and may be used as a diagnostic symptom of pregnancy, both by the woman herself, the midwife or obstetrician. NVP generally starts by four to six weeks' gestation, peaking in incidence and severity at the eighth to twelfth week of pregnancy, and often resolves spontaneously by the 20th week[9]. NVP can produce symptoms with a gradation from

mild to moderate or severe symptoms. At the extreme top of the severe spectrum of NVP Hyperemesis Gravidarum (HG) can be distinguished. It is defined as persistent vomiting, weight loss greater than five percent of the pre-pregnancy weight and large ketonuria[10]. This may lead to dehydration and hospitalisation is often needed. Epidemiological data on HG are scarce but it is estimated that HG occurs in less than 1% of the pregnant women[11]. HG is beyond the scope of this thesis.

As far as *etiological factors* of NVP are concerned, in general two categories can be discriminated: psychological and biological. With regard to psychological mechanisms three different theories have been developed: (i) nausea as a conversion or somatisation disorder, (ii) nausea as the result of classical conditioning and, (iii) nausea caused by personality characteristics and disorders. Biological theories on NVP include endocrine, gastric neuromuscular dysfunctions, metabolic theories and nutritional deficiencies.

Although hormonal changes are the most studied theories on the aetiology of NVP, there is far from conclusive evidence for one of these hormones. Serum levels of beta human chorionic gonadotropin (β-hCG) peak early in gestation (10 weeks). Concurrently the oestradiol and progesterone levels increase. Several studies have shown that there is a direct relation between the severity of NVP and the degree of thyroid stimulation, as described above (suppressed TSH and elevated fT4 levels, gestational transient thyrotoxicosis).

So far, studies that investigate both psychological and biological factors of NVP within one design have not been published. Because NVP as a symptom - even in women suffering from thyroid dysfunction - might be largely influenced by the mental state of the woman (depression, anxiety) it is important to look at the effect of biological factors of NVP, taking into account psycho-social and psychological confounders such as depression, anxiety and somatisation.

Another topic of this thesis was to evaluate the relation between thyroid function and hCG levels and the severity of nausea and vomiting, taking into account several psychological confounders (Chapter 2).

Pregnancy and mood changes

Traditionally, pregnancy has been thought of as a period of well-being and happiness and even to protect women from mood disorders[12]. However, women of childbearing age frequently suffer from major depression[13,14]. Year prevalence rates of major depression for adults are 5.8 percent, but with a male/female ratio of 1 / 2, prevalence rates for women are around 8 to 10%[15]. A recent review of literature concerning depression during gestation using syndromal diagnosis methods showed a prevalence rate of major depression varying from 3.1 to 4.9% depending on the time of assessment[16]. This prevalence rate is lower compared to that of depression in the general female non-childbearing population of similar age, an explanation is still lacking but possible partly to be explained by methodological issues.

Symptoms of depression during pregnancy are essentially the same as symptoms of depression at any other time[17]. Major depression is classified under the mood disorders in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[18]. It is defined as the occurrence, during a two-week period, of depressed mood or loss of interest or pleasure in activities, along with at least four other symptoms during the same two-week period. Those other symptoms of depression might be: change in appetite, change in sleep patterns, fatigue or loss of energy, difficulty concentrating, excessive feeling of guilt or worthlessness, thoughts of suicide, extreme restlessness and irritability. Symptoms may be ignored or misdiagnosed because they are confused with symptoms of pregnancy. The more common ones include changes in appetite, sleep or loss of energy.

Consequences of unrecognised depression during pregnancy

Depression has been recognized now as a disease that not only interferes with the woman's general well-being but also affects foetal health[19]. Most researchers have found that untreated depression may have associated obstetric complications and puerperal pathologies [13,20,21,22]. Gestational hypertension and subsequent pre-eclampsia have been linked to mothers with unrecognised depression during pregnancy[23,24]. Furthermore, depression during pregnancy has been associated with adverse outcomes such as spontaneous abortion[25], bleeding during gestation[26],

increased uterine artery resistance[27], neonatal growth retardation[18,28,29], spontaneous early labour[30,31], foetal death[32], low birth weight in babies[33,34,35], low Apgar scores[32], admission to a neonatal care unit[18], perinatal and birth complications[24,26,36], and high cortisol levels in offspring at birth[37,38].

Depression has also been linked to an increased rate of Caesarean section or vaginal instrumental delivery[10] and to a subjective description of labour as more painful and therefore more commonly needing epidural analgesia[39,40]. Physiology aside, studies have found that mental illness can affect a mother's functional status, her ability to obtain prenatal care, and her ability to avoid unhealthy behaviour. Women suffering from depression are more likely to smoke or use alcohol or other substances, which may confound pregnancy outcome. Unrecognised antenatal depression is associated with a 50% to 62% risk of a postpartum depressive episode[41,42].

Aetiology of gestational depression

Both psychological and biological (hormonal) explanations have been proposed to explain why depression occurs. Depression has been associated with hypothalamo–pituitary–adrenal (HPA) axis hyperactivity. Maternal stress, anxiety, or depression, which are regulated by peptides derived from the activated HPA axis[33,38,43,44], are all thought to influence birth outcome. This increased HPA-axis activity may directly affect foetal growth. Maternal depression may not only activate the mother's HPA axis; it may in turn cause an increase in the release of corticotrophin-releasing hormone (CRH) from the placenta via the actions of catecholamines and cortisol. CRH may also influence the timing and onset of delivery, which could explain why women suffering from depression show higher rates of premature labour[33,43]. Animal studies have found that stress during pregnancy is associated with dysfunction of the HPA axis and subsequent abnormal development of foetal tissue[39,45,46].

Another hormone that has been related to depression in general and during gestation is thyroid hormone. Most patients with depression, although often biochemically euthyroid, show alterations in their thyroid function: abnormal TRH response, high prevalence of thyroid antibodies, T4 levels in the higher normal ranges[47]. Conversely, patients with thyroid dysfunction often report mood problems. Several authors have found thyroid dysfunction (or thyroid auto-immunity) and de-

pression in general to be related[48,49]. Conflicting results have been found with regard to the association between elevated concentrations of antibodies against the enzyme thyroid peroxidase (TPO-Ab) and depression. Some authors found no relationship[50,51,52] while others found elevated antibody concentrations to be related to high depressive symptomatology in the postpartum[48] or in women around menopause[49].

During gestation, the relation between thyroid function and depression is hardly investigated. There are only two reports showing conflicting data: Kuijpens et al.[53] found that women who had elevated TPO-Ab concentrations during late pregnancy were at increased risk for depression while Oretti et al.[50] found no difference in the prevalence of gestational depression in antibody-positive versus antibody-negative women. However, both studies suffered from methodological shortcomings and had relatively small sample sizes.

Although existing literature suggests various ways in which hormonal dysfunction may affect pregnant women, much remains unclear in regard to defining the mechanisms by which depression adversely affects pregnancy outcome.

In line with the statement that depression during gestation does not differ from depression in non-childbearing women, the 'classical' psycho-social determinants of depression in general also increase the risk of gestational depression: a personal or family history of depression, low socio-economic status, poor social support, the occurrence of major life events (recent or in the past) e.g. high vulnerability for gestational depression is found in unplanned pregnancies, single mothers and very young pregnant women (< 20 years)[18,45,54].

Another topic of the current study was to evaluate whether maternal thyroid hormone parameters had an independent effect on gestational depression taking into account several confounders (Chapter III).

Postpartum mood disorders

Mood changes that occur during the postpartum period can generally be classified into three categories[16]. The *baby blues* are a common experience amongst new mothers in the first days postpartum. They can include transient feelings of being

overly happy or sad and bouts of unexplainable crying. The 'baby blues' usually resolve within two weeks and require no formal treatment. At the other end of the spectrum is *postpartum psychosis*. This affects only about 1 in every 500-1000 new mothers. Postpartum psychosis is extremely serious and always requires immediate professional intervention. More severe than the 'blues', and more common than psychosis, is *postpartum depression*. It affects between 10-15% of women after childbirth. Although in general postpartum refers to the first year after childbearing, in the above mentioned DSM-IV-R, postpartum depression nowadays is defined to occur within the first month after parturition. Similar to gestational depression, signs and symptoms of depression during the postpartum period are essentially the same as symptoms of depression at any other time. One special aspect of postpartum depression is that it occurs during a period when the mother (and her environment) hardly expects mood disorders to occur. This is perhaps one of the main reasons why less than 20% of women who suffer from depression after childbearing do seek help[55]. Another specific aspect of postpartum depression is that many signs and symptoms of depression (fatigue, sleeping problems because of feeding at night, concentration problems) are often regarded as being typical for this period.

Giving birth may be considered as a major and sometimes extreme stressful event in the lives of many women as has been recently reviewed elsewhere[56]. The parturition may be experienced as traumatic by some women, even in normal spontaneous delivery in hospital, and may result in subsequent *posttraumatic stress (PTS)* or even posttraumatic stress disorder (PTSD); studies suggest that about 2% - 6% of the women will experience a PTSD reaction at some point in the early period after childbirth[57]. Both empirical and clinical literature describes several factors contributing to the experience of delivery as traumatic and to postpartum PTS or PTSD[56]. Identified risk factors are: (1) *prenatal factors*, e.g. previous traumatic deliveries, history of primary infertility and complicated pregnancies, delivery of an ill or stillborn baby, pre-existing depression, a history of childhood sexual abuse, nulliparity, and a history of psychiatric/psychological counselling; (2) *nature and circumstances of delivery*, e.g. long, hard and extremely painful labour, forceps delivery, emergency caesarean section, lack of control; and (3) *subjective factors during childbirth*, e.g. feelings of powerlessness, staff experienced as unsympathetic, lack of social support during the delivery and afterwards, feelings of fear about harming the baby, fear of harming one

self, and fear of dying oneself or dying of the baby during labour. In childbirth-related PTS studies, stressor severity is often defined in terms of intensity of the experience of pain[58]. However, another study did not find a relation between experienced pain and high levels of postpartum PTS[59]. In contrast, they established a relation between deliveries that are more technical (or intrusive) and high levels of postpartum PTS. As a more technical delivery often goes with more pain, these findings leave the question unanswered whether pain or type of delivery is the responsible factor for subsequent PTS. Trauma severity might be reinforced by complications during delivery or with the neonate, and there might be an interaction between pain and type of delivery. In a recent study in the same area as that of the current thesis studies, two pathways for postpartum PTS were confirmed: (1) delivery-related stressors predict postpartum PTS; and (2) previous depression predicts postpartum PTS[60]. However, a major limitation of this study was the 3-months postpartum retrospective report of PTS symptoms, which might have been affected by memory-bias and by the mental condition of the respondents at the time of assessment. In a study[61], which researched community violence, survivors showed that 3-months assessment of dissociation differed from assessment within days after the extreme event. Reports of severity of pain and intrusiveness of the delivery-procedure, as well the evaluation of perinatal support, may also be affected by the retrospective character of the assessment.

Another topic of the thesis was to assess posttraumatic stress symptoms within the first week after birth in relation to obstetrical outcome, taking into account ante-partum confounders,
(Chapter X).

Anxiety during gestation

In general depression and anxiety very often co-occur. For example, 50-65% of patients with panic disorders also have a major depressive disorder[62] and approximately 85% of patients with depression also experience significant symptoms of anxiety[63]. Moreover, antidepressant drugs such as tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and the selective serotonin reuptake inhibi-

tors (SSRIs), have well-documented efficacy in a variety of anxiety disorders[64]. In fact, the question of whether anxiety and depression are clearly separate entities continues to be a controversial issue[63].

Maternal anxiety during pregnancy may have a variety of adverse consequences for both mother and foetus and child[65,66]. Anxiety during pregnancy has been associated with somatic complaints, obstetrical problems and a heightened risk of maternal mood problems in the postpartum period. In addition, maternal anxiety during gestation may affect foetal heart rate and behaviour, neonatal behaviour and infant development in the first year after birth.

Studies investigating the question of whether pregnant women as a group experience anxiety more often than non-pregnant women have found conflicting results. Several authors have reported more anxious symptoms in pregnant women compared to non-pregnant women[67,68] while others did not[69,70]. Similarly, mood has been described as being stable during pregnancy in some studies[24,71] whereas in others anxiety (and depressive symptoms) were found to fluctuate throughout pregnancy, usually with a considerable increase during the third trimester[72]. Several researchers have associated high gestational anxiety level with factors 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[24,73,74].

Research into the impact of depression on maternal well-being during gestation often show methodological shortcomings such as not taking into account co-morbid aspects of anxiety.

Another topic of the current thesis was to evaluate the impact of co-morbid anxiety in women suffering of gestational depression when looking at a psychobiological model of depression.(Chapter III)

Anxiety and obstetrical outcome

There is a growing literature showing a relation between maternal anxiety during gestation and pre-term labour[75,76] or the occurrence of stress-full life events and pre-term labour[77]. Some authors reported a relation between depression / anxiety and

operative deliveries[18,65] which was not confirmed by others[66,78]. Several (mostly methodological) arguments are used to explain the rather inconclusive data[79]: poor definition and measurements of obstetric outcomes; inappropriate measurements and different definitions of anxiety; not taking into account confounding variables and inadequate sample sizes.
Surprisingly, there are hardy any studies published investigating the impact of anxiety on the most common example of delivery: physiological labour.

Another topic of this thesis was to evaluate the impact of maternal anxiety during late gestation on physiological labour in women who delivered at term (after 37 weeks' gestation) taken into account possible confounders (Chapter V).

VI. The present study

(This thesis contains three papers in which topics mentioned in the introduction have been investigated in a sample of women collected in 1989 - 1991 (Chapter IX), another sample in 2000 (Chapter VII) and one in 2000 - 2003, Chapter IV). The collection of these samples has been described in these chapters. The remaining six papers refer to collection of a sample of women of the main - present - study which will be described in detail below).

The subjects

This thesis describes a longitudinal study in pregnant women until the first postpartum week, their well-being and obstetrical outcome in relation to maternal thyroid function. Between July 2002 and November 2004, twenty midwives working in seven community midwifery practices (Bladel, Bergeijk, Eindhoven 2x, Hapert, Valkenswaard and Veldhoven) in the Netherlands, invited 1507 healthy Dutch Caucasian pregnant women to participate in the study at their first antenatal check-up (10-12 weeks' gestation). The 1191 (79%) low risk women who signed informed consent to participate, did not have a history of thyroid disease or other autoimmune disease, of known uterus anomalies, or a history of fertility problems prior to the current preg-

nancy. Of these 1191 women thyroid parameters (TSH, fT4 and TPO-Ab, urine iodine excretion) were obtained at 12 weeks' gestation. For various reasons (late abortion, moving out of the area, multiple pregnancy, immature birth) 48 women were excluded before 24 weeks' gestation (table 1). Because of ethical reasons, women with overt hyperthyroidism (n = 8) and hypothyroidism (n = 2) at their first assessment were also excluded and sent to their general practitioner. At 24 weeks' gestation thyroid parameters were obtained in 1143 women. Another 50 women were excluded (moving out of the area, premature birth) before 36 weeks ' gestation. At 36 weeks 'gestation thyroid parameters were obtained in 1093 women. (See table 1.) Therefore all thyroid parameters were assessed in 1093 women.

Figure 1 Flow-chart of inclusion and exclusion of women during follow-up in pregnancy.

			total n
10-12 wks gestation	Invitation of pregnant women at first obstetric control visit during 24 consecutive months		1985
	Eligible for participation (Caucasian, no auto-immune disease, no fertility problems with hormonal stimulation)		1507
	Informed consent (79%): assessment of general, medical and obstetrical history		1191
	Exclusion (n=48) because of:		
	overt thyroid dysfunction	10	
	twin pregnancy	12	
	triplet pregnancy	1	
	uterus anomaly	2	
	late abortion	13	
	moving out of the area	10	1143
24 wks gestation	Assessment of general, medical and obstetrical history		
between 24-36 wks gestation	Exclusion (n=60) because of:		
	moving out of the area	4	
	pre-term delivery	46	
			1093
36 wks gestation	Assessment of general, medical and obstetrical history Assessment of anxiety and depressive symptoms Ultrasound assessment foetal condition and possible malformations		

At 12 weeks' gestation all women were assessed for their own medical history (smoking, alcohol intake, drug use, BMI-index, diabetes- type I, hypertension, medication at time of the assessment, depression), their obstetrical history and their family's history (depression, thyroid dysfunction). Furthermore a socio - economic history was obtained for demographic features. The obstetrical history was obtained at 12 (previous pregnancies and their outcome, state of this pregnancy), 24 and 36 weeks' gestation (complaints and complications of this pregnancy, referral to G.P. or secondary level care, use of medication). Shortly after delivery, the obstetrical outcome was carefully assessed (using standardized forms) for: -place of delivery, -mode of delivery, duration of dilatation time in hours, -duration of expulsion time in minutes, -foetal position at birth, -use of pain relief, -gender of the baby as well as its birth weight (grams), the Apgar score, amenorrhoea time and feeding (Table 2). The following possibilities of delivery can be discriminated in the Netherlands: at home spontaneously or in hospital: -spontaneously, -after induction, - assisted per vacuum or forceps, -primary or secondary Caesarean section.

Questionnaires were filled out at 12, 24 and 36 weeks' gestation and 1 week postpartum.

Table 2: Design of the study

	12 week's	24 week's	36 week's	1 week post-partum
Thyroid parameters	x	X	x	
Urine samples iodine	x	X	x	
Medical history	x			
Socio/economic history	x			
Obstetrical history	x	x	x	x
Questionnaires				
Cidi*	x	x	x	x
EDS*	x	x	x	x
SCL-90*	x	x	x	x
Pitt's criteria*				x
PDEQ*				x
PEL*				x
SDQ-P*				x
KCS*				x

* Cidi: Composite International Diagnostic Interview[80], * EDS: Edinburgh Depression Scale[81], *SCL-90:subscale: somatisation and anxiety [82], *Pitt's criteria of blues[83], * PDEQ: Peritraumatic Dissociative Experiences Questionnaires-Self-Reporting Version[84], *PEL: Peritraumatic Emotions List[85], *SDQ-P: Somatoform Dissociation Questionnaire-Peritraumatic[86], *KCS: Kempen Confinement Self-rating scale[87].

Apart from the subjects' signed informed consent this study was approved by the Medical Ethical Committee of Máxima Medical Centre Eindhoven / Veldhoven, the Netherlands.

References

1. Heineman MJ. Obstetrie en gynaecologie: De voortplanting van de mens. 5th Edition Elzevier gezondheidszorg. 2004

2. Gabbe SG, Niebyl JR, Simpson JL. Pocket companion to accompany Obstetrics; Normal and problem pregnancies. 4th Edition Churchill Livingstone 2002

3. Cunningham G, Leveno KJ, Bloom SL, Hauth JC, Gilstrap LC, Wenstrom KD. Williams Obstetrics. 22th Edition Rev ed Higher Education 1993

4. Hingstman L, Kenenes R. NIVEL (Nederlands instituut voor onderzoek van de gezondheidszorg): Cijfers uit de registratie van verloskundigen; peiling 2002

5. Bleker OP, van der Hulst AM, Eskes M, Bonsel GJ. Place of birth: evidence for best practice. Personal communication.

6. Verloskundig Vademecuum . Obstetrical Manual .Final report of the Obstetric Working Group of the National Health Insurance Board of the Netherlands 2003

7. Werner & Ingbar's The Thyroid, A fundamental and Clinical Text. 9th Edition. Editors: Braverman LE & Utiger RD. Lippincott Williams& Wilkins 2004

8. Buckwalter, J.G., & Simpson, S.W. Psychological factors in the etiology and treatment of severe nausea and vomiting in pregnancy. American Journal of Obstetrics and Gynecology. 2002;186, S210-214.

9. Deuchar N. Nausea and vomiting in pregnancy: review of the problem with particular regard to psychological and social aspects. Br Journal Obstetric Gynaecol. 1995;102, 6-8.

10. Goodwin, T.M. Hyperemesis gravidarum. Cinical Obsterics and Gynecology. 1998; 41(3): 597-605.

11. Koren, G., Bishai, R. Nausea and Vomiting of Pregnancy : State of the Art 2000, Motherisk ©, University of Toronto, Canada 2000

12. Buist A. Managing depression in pregnancy. Aust Fam Physician 2000;29:663–7.

13. D'Alfonso A, Iovenitti P, Casacchia M, Carta G. Disturbances of humour in postpartum: our experience. Clin Exp Obstet Gynecol 2002;29:207–11.

14. Stocky A, Lynch J. Acute psychiatric disturbance in pregnancy and the puerperium. Baillieres Best Pract Res Clin Obstet Gynaecol 2000;14(1):73–87.

15. Kessler, McGonagle KA, Swartz M. Sex and depression in the National Comorbidity Survey I: lifetime prevalence, chronicity and recurrence. J Affect Disord 1993;29:85–96.

16 Gaynes BH, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner S, Brody S, Miller WC. 2005 Perinatal depression: prevelance, screening accuraty and screening outcomes. Evid Rep Technol Assess **119**:1-8.

17.. Ross LE, Sellers EM, Gilbert Evans SE, Romach MK. Mood changes during pregnancy and the postpartum period: development of a biopsychosocial model. Acta Psychiatrica Scandinavica. 2004 ;109:457-466.

18. Zimmerman M, Sheeran T, Young D. The Diagnostic Inventory for Depression: a self-report scale to diagnose DSM-IV major depressive disorder. J Clin Psychol. 2004 Jan;60(1):87-110.

19. Chung TK, Lau TK, Yip AS, Chiu HF, Lee DT. Antepartum depressive symptomatology is associated with adverse obstetric and neonatal outcomes. Psychosom Med 2001;63:830–4.

20. Orr T, Miller CA. Maternal depressive symptoms and the risk of poor pregnancy outcome. Review of the literature and preliminary findings. Epidemiol Rev 1995;17:165–71

21. Kelly R, Zatzick D, Anders T. The detection and treatment of psychiatric disorders and substance use among pregnant women cared for in obstetrics. Am J Psychiatry 2001;158:213–9.

22. Lou HC, Hansen D, Nordentoft M, Pryds O, Jensen F, Nim J, et al. Prenatal stressors of human life affect fetal brain development. Dev Med Child Neurol 1994;36:826–32.

23. Kurki T, Hiilesmaa V, Raitasalo R, Mattila H, Ylikorkala O. Depression and anxiety in early pregnancy and risk for preeclampsia. Obstet Gynecol 2000;95:487–90.

24. Paarlberg KM, Vingerhoets AJ, Passchier J, Dekker GA, van Geijn HP. Psychosocial factors and pregnancy outcome: a review with emphasis on methodological issues. J Psychosom Res 1995;39:563–95.

25. Michel-Wolfromm H. The psychological factor in spontaneous abortion. J Psychosom Res 1968;12(1):67–71.

26. Preti A, Cardascia L, Zen T, Pellizzari P, Marchetti M, Favaretto G, et al. Obstetric complications in patients with depression—a population-based case-control study. J Affect Disord 2000;61:101–6.

27. Teixeira JM, Fisk NM, Glover V. Association between maternal anxiety in pregnancy and increased uterine artery resistance index: cohort based study. BMJ 1999;318:153–7.

28. Field T, Diego M, Hernandez-Reif M, Salman F, Schanberg S, Kuhn C, et al. Prenatal anger effects on the fetus and neonate. J Obstet Gynaecol 2002;22:260–6.

29. Hoffman S, Hatch MC. Depressive symptomatology during pregnancy: evidence for an association with decreased fetal growth in pregnancies of lower social class women. Health Psychol 2000;19:535–43.

30. Dayan J, Creveuil C, Herlicoviez M, Herbel C, Baranger E, Savoye C, et al. Role of anxiety and depression in the onset of spontaneous preterm labor. Am J Epidemiol 2002;155:293–301.

31. Orr ST, James SA, Blackmore PC. Maternal prenatal depressive symptoms and spontaneous preterm births among African-American women in Baltimore, Maryland. Am J Epidemiol 2002; 156:797–802.

32. Zax M, Sameroff AJ, Babigian HM. Birth outcomes in the offspring of mentally disordered women. Am J Orthopsychiatry. 1977;47:218–30.

33. Sandman CA, Wadhwa PD, Chicz-DeMet A, Dunkel-Schetter C, Porto M. Maternal stress, HPA activity, and fetal/infant outcome. Ann N Y Acad Sci 1997;814:266–75.

34. Steer RA, Scholl TO, Hediger ML, Fischer RL. Self-reported depression and negative pregnancy outcomes. J Clin Epidemiol 1992;45:1093–9.

35. McAnarney ER, Stevens-Simon C. Maternal psychological stress/depression and low birth weight. Is there a relationship? Am J Dis Child 1990;144:789–92.

36. Cohler BJ, Gallant DH, Grunebaum HU, Weiss JL, Gamer E. Pregnancy and birth complications among mentally ill and well mothers and their children. Soc Biol 1975;22:269

37. Field T, Diego M, Hernandez-Reif M, Salman F, Schanberg S, Kuhn C, et al. Prenatal anger effects on the fetus and neonate. J Obstet Gynaecol 2002;22:260–6.

38. Ashman SB, Dawson G, Panagiotides H, Yamada E, Wilkins CW. Stress hormone levels of children of depressed mothers. Dev Psychopathol 2002;14:333–49.

39. Smith R, Cubis J, Brinsmead M, Lewin T, Singh B, Owens P, et al. Mood changes, obstetric experience and alterations in plasma cortisol, beta-endorphin and corticotrophin releasing hormone during pregnancy and the puerperium. J Psychosom Res 1990;34(1):53–69.

40. Mahomed K, Gulmezoglu AM, Nikodem VC, Wolman WL, Chalmers BE, Hofmeyr GJ. Labor experience, maternal mood and cortisol and catecholamine levels in low-risk primiparous women. J Psychosom Obstet Gynaecol 1995;16:181–6.

41. Josefsson A, Berg G, Nordin C, Sydsjo G. Prevalence of depressive symptoms in late pregnancy and postpartum. Acta Obstet Gynecol Scand 2001;80:251–5.

42. Evans J, Heron J, Francomb H, Oke S, Golding J. Cohort study of depressed mood during pregnancy and after childbirth. BMJ 2001;323:257–60.

43. Sandman CA, Wadhwa PD, Dunkel-Schetter C, Chicz-DeMet A, Belman J, Porto M, et al. Psychobiological influences of stress and HPA regulation on the human fetus and infant birth outcomes. Ann N Y Acad Sci 1994;739:198–210.

44. Wadhwa PD, Dunkel-Schetter C, Chicz-DeMet A, Porto M, Sandman CA. Prenatal psychosocial factors and the neuroendocrine axis in human pregnancy. Psychosom Med 1996;58:432–46.

45. Nonacs R, Viguera AC, Reminick A. Diagnosis and treatment of depression during pregnancy. CNS Spectr. 2004 Mar;9(3):209-16. Review.

46. Dorn LD, Susman EJ, Petersen AC. Cortisol reactivity and anxiety and depression in pregnant adolescents: a longitudinal perspective. Psychoneuroendocrinology 1993;18:219–39

47. Musselman DL & Nemeroff CB. Depression and endocrine disorders: focus on the thyroid and adrenal system. British Journal of Psychiatry. 1996;168:123-128.

48. Harris B, Lovett L, Newcombe RG, Read GF, Walker R, Riad-Fahmy D. Maternity blues and major endocrine changes: Cardiff puerperal mood and hormone study II. Br Med J 1994;308:949-953

49. Pop VJ, Maartens LH, Leusink G, van Son MJ, Knottnerus AA, Ward AM, Metcalfe R, Weetman AP. Are autoimmune thyroid dysfunction and depression related? J Clin Endocrinol Metab. 1998;83(9):3194-7.

50. Oretti RG, Hunter C, Lazarus JH, Parkes AB, Harris B. Antenatal depression and thyroid antibodies. Biological Psychiatry.1997;41:1143-1146.

51. Haggerty JJ, Silva SG, Marquardt M, Mason GA, Chang HY, Evans DL, Golden RN, Pedersen C. Prevalence of antithyroid antibodies in mood disorders. Depression and Anxiety.1997;5: 91-96.

52. Kent GN, Stuckey BGA, Allen JR, Lambert T, Gee V. Postpartum thyroid dysfunction: clinical assessment and relationship to psychiatric affective morbidity. Clinical Endocrinology.1999;54: 429-438.

53. Kuijpens JL, Vader HL, Drexhage HA, Wiersinga WM, van Son MJ, Pop VJ. Thyroid peroxidase antibodies during gestation are a marker for subsequent depression postpartum.Eur J Endocrinol. 2001;145(5):579-84.

54. Marcus SM, Flynn HA, Blow FC, Barry KL. Depressive symptoms among pregnant women screened in obstetrics settings. J Womens Health (Larchmont) 2003;12:373–80.

55. Scholle SH, Haskett RF, Hanusa BH, Pincus HA, Kupfer DJ. Addressing depression in obstetrics/gynecology practice. Gen Hosp Psychiatry 2003;25(2):83–90.

56. Bailham, D, Joseph S. Posttraumatic stress following childbirth: a review of the emerging literature and directions for research and practice. Psychology, Health & Medicine.2003;8:159-168.

57. Cohen, MM, Ansara, D, Schei B, Stuckless N, Steward DE. Posttraumatic Stress Disorder after Pregnancy, Labor and Delivery. Journal of Women's Health.2004;13: 315-324

58. Soet JE, Brack GA, Dilorio C. Prevalence and predictors of women's experience of psychological trauma during childbirth. Birth. 2003;30:36-46.

59. Söderquist J, Wijma K, Wijma B. Traumatic stress after childbirth: The role of obstetric variables. Journal of Psychosomatic Obstetrics & Gynecology. 2002;23: 31-39.

60. Van Son M, van der Hart O, Verkerk G, Pop V, Komproe I. Prenatal Depression, Mode of Delivery, and Perinatal Dissociation as Predictors of Postpartum Posttraumatic Stress: An Empirical Study. Clin. Psychol. Psychother. 2005;12:297–312.

61. Marshal GN, Schell TL. Reappraising the link between peritraumatic dissociation and PTSD symptom severity: Evidence from a longitudinal study of community violence survivors. Journal of Abnormal Psychology. 2002;111: 626-636.

62. American Psychiatric Association . Diagnostic and statistical manual of mental disorders (IV edition). Washington DC: American Psychiatric Association. 1995.

63. Gorman JM. Comorbid depression and anxiety spectrum disorders. Depression and Anxiety. 1997;4:160-168.

64. Rouillon F. Anxiety with depression: a treatment need. European Neuropsychopharmacology. 1999;9: 87-92.

65. Andersson L, Sundström-Poromaa I, Wulff M, Åström M, Bixo M. Implications of antenatal depression and anxiety for obstetric outcome. Obstet Gynecol. 2004;104(3):467-76.

66. Perkin MR, Bland JM, Peacock JL, Anderson HR. The effect of anxiety and depression during pregnancy on obstetric complications.Br J Obstet Gynaecol. 1993;100(7):629-34

67. Kitamura T, Sugawara M, Sugawara K, Toda MA & Shima S. Psychosocial study of depression in early pregnancy. British Journal of Psychiatry.1996;168: 732-738.

68. Keenan PA, Yaldoo DT, Stress ME, Fuerst DR, Ginsburg KA. Explicit memory in pregnant women. American Journal of Obstetrics and Gynecology. 1998;179: 731-737.

69. Striegel-Moore RH, Goldman SL, Garvin V, Rodin J. A prospective study of somatic and emotional symptoms in pregnancy. Psychology of Women Quarterly1996;20: 393-408.

70. Behrenz KM, Monga M. Fatigue during pregnancy: a comparative study. American Journal of Perinatology. 1999;16:185-188.

71. Elliott SA, Rugg AJ, Watson JP, Brough DI. Mood changes during pregnancy and after the birth of a child. British Journal of Clinical Psychology. 1983;22: 295-308.

72. Da Costa D, Larouche J, Dritsa M, Brender W. Variations in stress levels over the course of pregnancy: factors associated with elevated hassles, state anxiety and pregnancy-specific stress. Journal of Psychosomatic Research. 1999;47: 609-621.

73. Kalil KM, Gruber JE, Conley J, Sytniac M. Social and family pressures on anxiety and stress during pregnancy. Pre- and Perinatal Psychology Journal. 1993;8:113-118.

74. Da Costa D, Brender W, Larouche J. A prospective study of the impact of psychosocial and lifestyle variables on pregnancy complications. Journal of Psychosomatic and Obstetric Gynecology.1998;19:28-37.

75. Dayan J, Crevuil C, Herlicoviez M, Herbel C, Baranger E, Savoye C, Thouin A. Role of anxiety and depression in the onset of spontaneous preterm labor. Am J Epidemiol. 2002;155(4):293-301.

76. Copper RL, Goldenberg RL, Das A, Elder N, Swain M, Norman G, Ramsey R, Cotroneo P, Collins BA, Johnson F, Jones P, Meier A. The preterm prediction study: maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network.Am J Obstet Gynecol. 1996;175(5):1286-92.

77. Hedegaard M, Hendriksen TB, Secher NJ, Hatch MC, Sabroe S. Do stressful life events affect duration of gestation and risk of preterm delivery? Epidemiology. 1996 ;7(4):339-45

78. Wu J, Viguera A, Riley L, Cohen L, Ecker J. Mood disturbance in pregnancy and the mode of delivery. Am J Obstet Gynecol. 2002;187(4):864-7.

79. Johnson RC, Slade P. Obstetric complications and anxiety during pregnancy: is there a relationship? J Psychosom Obstet Gynaecol. 2003 Mar;24(1):1-14.

80. World Health Organization (1990a). Composite International Diagnostic Interview (CIDI). Geneva: World Health Organization.

81. Pop VJ, Komproe IH, van Son MJ. Characteristics of the Edinburgh Post Natal Depression Scale in The Netherlands. J Affect Disord. 1992;26(2):105-10.

82. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale--preliminary report. Psychopharmacol Bull. 1973;9(1):13-28.

83. Pitt B. 'Maternity blues'.Br J Psychiatry. 1973;122(569):431-3.

84. Marmar CR, Weiss DS, Metzler TJ. Peritraumatic dissociation and post-traumatic stress disorder. In JD Bremner & CR Marmar (Eds), Trauma, memory and dissociation (pp 229-52). Washington, DC: American Psychiatric Press

85. van der Velden PG, van den Burg S, Steinmetz CH, van den Bout J. Slachtoffers van bank-overvallen [Victims of bank robberies] . Houten: Bohn Stafleu van Loghum. 1992.

86. Douglass AB, Bornstein R, Nino-Murcia G, Keenan S, Miles L, Zarcona VP, Jr. Guilleminault C, Dement WC. The Sleep Disorders Questionnaire. I: Creation and multivariate structure of SDQ. Sleep. 1994 Mar;17(2):160-7.

87. Pop VJ, de Vries J, van Heck GL,Wijnen HA. Validation of the Kempen Confinement Self-rating scale (KCS).submitted.

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Chapter II

MORNING SICKNESS DURING GESTATION

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Introduction

Nausea and vomiting in the first trimester of pregnancy (NVP) is highly frequent, occurring in 50% to 90% of pregnancies[1]. It is commonly known as 'morning sickness' and may be used as a diagnostic symptom of pregnancy both by the woman herself and the midwife or obstetrician.. NVP generally starts by four to six weeks' gestation, peaking in incidence and severity at the eighth to twelfth week of pregnancy, and often resolves spontaneously by the 20th week. NVP can produce symptoms with a gradation from mild to moderate to severe symptoms. The extremely severe condition of NVP can be described as Hyperemesis Gravidarum (HG). It has been defined as persistent vomiting, weight loss greater than five percent of the pre-pregnancy weight and large ketonuria[2] . This may lead to dehydration and hospitalisation is often needed. Epidemiological data on HG are scarce but it is estimated that HG occurs in less than 1% of the pregnant women. Because HG refers to a collection of symptoms it is often considered as the syndrome of severe gestational nausea and vomiting while NVP refers more to nausea and vomiting as a symptom. HG is beyond the scope of this paper.

NVP has been associated with many *risk factors* which have been summarized elsewhere[1,] including younger maternal age, low socio-economic status, unplanned pregnancy, non-smoking status, passive smoking, increased body mass index, ethnicity, urban rather than rural areas. Women who have a history of oral conceptive sickness, travel sickness, or migraine headaches are twice as likely to develop symptoms of NVP than women without such a history[2]. Obstetric conditions associated with NVP are gastrointestinal tract dysfunction (possibly linked to infection with Helicobacter plyori), nulliparity, and previous pregnancy complicated by NVP[1] .

As far as *etiological factors* are concerned, in general two categories of determinants of NVP can be distinguished: psychological and biological. With regard to psychological mechanisms three different theories have been developed: (i) nausea as a conversion or somatisation disorder, (ii) nausea as the result of classical conditioning and, (iii) nausea caused by personality characteristics and disorders.
Biological theories on NVP include endocrine, gastric neuromuscular dysfunctions, metabolic theories and nutritional deficiencies. Abnormalities of the gastrointestinal

tract such as gastric myoelectrical activity, gastric tone and contractility [3] have been reported in women with NVP. During pregnancy, the increased levels of progesterone lead to muscle relaxation by which oesophageal gastric and small bowel motility is impaired. This might contribute to nausea and vomiting because of lower oesophageal sphincter pressure [1]. Metabolic theories concerning NVP are mainly based on the physiological burden on the liver because of increased steroid production but are nowadays regarded as secondary phenomena due to hormonal changes. Although hormonal changes are the most studied theories on the aetiology of NVP, there is far from conclusive evidence for one of these hormones. Along with serum levels of beta human chorionic gonadotropin (β-hCG) peaks early in gestation (10 weeks) oestradiol and progesterone levels increase. Several studies [2,5,6] have shown that there is a direct relation between the severity of NVP and the degree of thyroid stimulation, as manifested by suppressed TSH while others did not. Although the exact role of thyroid function in the aetiology of NVP remains to be resolved there is substantial evidence that transient thyroid stimulation during early gestation (suppressed TSH and elevated fT4 levels, gestational transient thyrotoxicosis) is important in the aetiology of NVP and due to high peaks of HCG during the first trimester[1]. The individual serum levels of HCG correlated directly with free T4 levels and inversely with those of TSH.

So far, studies that investigated psychological in combination with biological risk factors of NVP within one design have not been published. It might be argued that when looking at biological explanations of NVP as a symptom it is also important to evaluate the woman's mental state: depression and anxiety will largely influence the perception of severity of NVP. The current study investigated the possible relation between thyroid function, HCG and psychological aspects of NVP.

Methods

Subjects

Between August 2002 and October 2004 all women (n=1507) who booked for antenatal control at 12 weeks' gestation in five community midwife practices were invited

to participate into screening of maternal thyroid function. Because the study used several questionnaires, only Caucasian women with appropriate knowledge of the Dutch language were eligible. The 1191 (79%) low risk women who signed informed consent to participate, did not have a history of thyroid disease or other autoimmune disease, of known uterus anomalies, or a history of fertility problems prior to the current pregnancy. Of these 1191 women thyroid parameters (TSH, fT4 and TPO-Ab, urine iodine excretion) were obtained at 12 weeks' gestation. Out of these 1191 women, an at random selected sample of 600 women was used to assess human chorionic gonadotropin (hCG) at 12 weeks' gestation.
Apart from the written informed consent of the participants, this study was approved by the Medical Ethical Committee of Máxima Medical Centre in Eindhoven / Veldhoven.

Assessments

Dependent variable:
Nausea and vomiting (NVP).

The dependent variable, nausea and vomiting, was assessed as follows. At 12 weeks' gestation the women were asked: 'during the previous three months of pregnancy did you suffer from nausea and / or vomiting?'. The women were able to answer on a five-point scale (varying from not at all to very severe).

Independent variables:
Thyroid hormones, thyroid autoimmunity and human chorionic gonadotropin.

Thyroid function

TSH (thyrotropin) was measured using a solid-phase, two site chemiluminescent enzyme immunometric assay (IMMULITE Third generation TSH, Diagnostic Products Corporation, Los Angeles USA). The inter-assay coefficients of variation were 5.0% and 4.4% at concentrations 0.22 mIU/l and 2.9mIU/l, respectively.

The fT4 (free-thyroid hormone, thyroxin) concentration was measured with a solid-phase immunometric assay (IMMULITE Free T4). The inter-assay coefficients of variation for this technique were 6.7% and 4.4% at concentrations of 11.6 pmol/l and 31.5 pmol/l, respectively. For both parameters, the above-mentioned non-pregnant reference ranges were used: 0.45 – 4.5 mIU/l and 10.3 - 25.7 pmol/l, 0.45 – 4.5 mIU/l and 10.3 - 25.7 pmol/l, respectively.

The following categories of thyroid dysfunction were defined.

Clinical (overt) thyroid dysfunction: TSH and fT4 outside reference ranges referring to hyperthyroidism (decreased TSH and increased fT4) and hypothyroidism (increased TSH and decreased fT4). Similarly, sub-clinical thyroid dysfunction was defined by an abnormal TSH with fT4 level within reference range. Hypo- and hyperthyroxinemia were defined by an FT4 concentration at or below the 10^{th} percentile and at or below the 90^{th} percentile, respectively, with a TSH concentration within reference range.

Finally, 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 9% and 9.5% for concentrations of 40 kU/l and 526 kU/l, respectively. The anti-TPO assay is standardized in terms of the International Reference Preparation for anti-TPO MRC 66/387. A woman with an TPO-Ab titers > 35 IU/ml at 12 weeks' gestation was defined as immunologically compromised irrespective of a possible decrease of the titer throughout pregnancy resulting in low titers at 24 or 34 weeks' gestation. Women were defined as TPO-Ab negatives when the titer was below 35 IU/ ml at 12 weeks' gestation.

Human Chorionic Gonadotropin

Human chorionic gonadotropin (hCG) was assessed also using immulite technique(IMMULITE HCG, Diagnostic Corporation, Los Angeles USA). The coefficient of variation was 5.8% at a concentration of 370 IU/l. High levels of hCG were defined by a cut-off of the highest 90^{th} percentile.

Psychological parameters

Depressive symptoms were assessed using the Edinburgh Depression Scale[7], which was originally developed for use during the postpartum period and was called the Edinburgh Postnatal Depression Scale[8]. The Dutch version of the E(P)DS has been validated among postpartum women in The Netherlands by Pop et al.[9], and revealed appropriate psychometric characteristics. Recently, the EPDS was validated in a group of non-childbearing mothers [7,10], resulting in new nomenclature: Edinburgh Depression Scale (EDS). It consists of ten items, to be completed within five minutes. The total score ranges between 0 and 30, with cut-off scores between 11 and 13 [11,12]. In the present study, women with a score above 11 were defined as suffering from depression.

Anxiety was measured using the 10-items anxiety subscale (range 10 – 50) of the SCL-90 scale of Derogatis[13]. The SCL-90 is a self-rating scale consisting of six sub-scales measuring all kind of psychopathology. The item score ranges from one to five. The SCL-90 has been validated before in The Netherlands and its use as well as the use of several subscales only has revealed appropriate psychometric properties[14] Normally, no cut-off levels are used but in the present study scores at and above the highest 90th percentile defined high levels of anxiety.

Somatisation was measured using the 12-items somatisation subscale (range 12 tot 60) of the SCL-90 scale of Derogatis. Scores at and above the highest 90th percentile defined a high level of somatisation.

Possible confounders

Several factors which are known from literature to interfere with NVP were also assessed: the occurrence of a recent major life event during the previous 12 weeks' of gestation, a previous history of depression, marital status, socio-economic status, education level, life style habits and obstetrical factors (parity, planned pregnancy, history of previous miscarriage or abortion provocatus). Finally, the occurrence of

major stressful life events earlier in life were also investigated: sexual, physical, and emotional abuse.

Statistical analysis

Statistical analysis was performed using the Statistical Package of Social Science and Problems Solutions (SPSS). Differences in scores on NVP nausea item in relation to several independent variables were compared by Mann-Whitney-U test. Subsequently, a multivariate regression analysis was performed with scores on the NVP item as the dependent variable, bringing into the regression all independent variables that showed significant differences at a uni-variate level.

Fifty-five of the 600 women did not complete all questionnaires. Therefore, data analysis refers to 545 women.

Results

The characteristics of the participants are shown in Table 1.

In Table 2, hCG levels are shown in four different quartiles with the corresponding mean levels of FT4 and TSH.

The correlations between hCG and FT4 and TSH levels were 0.26 ($p < 0.001$) and – 0.19 ($p < 0.001$), respectively and between FT4 and TSH – 0.29 ($p < 0.001$).

Correlations between the sub-scale anxiety and somatisation, between anxiety and depression on the EDS, and between depression and somatisation were 0.51, 0.62 and 0.48, respectively. (two-tailed, $P < 0.001$). Correlation between the scores on NVP and sub-scale somatisation, between NVP and sub-scale anxiety and between NVP and depression were: 0.48, 0.24 and 0.28, respectively (two-tailed, $p < 0.001$).

In Table 3, differences in NVP scores between several groups are shown (Mann-Whitney-U-test). As can be seen, several obstetrical factors (non-planned pregnancy, abortion provocatus earlier in life), demographic features (not working outside home), thyroid hormone (hyperthyroxinemia (FT4 > 90^{th} percentile) and several psychological factors (high somatisation and anxiety scores and depression, the occurrence of

Table 1 Characteristics of a sample of 545 women at 12 weeks' gestation with no history of previous thyroid dysfunction

	n	(%)
Demographic features		
age (mean, SD)	28.7	(0.4)
marital status		
with partner	534	(98)
single	11	(2)
educational level		
low	54	(9)
middle	251	(46)
high	202	(38)
academic	38	(7)
working outside home		
yes	458	(84)
no	87	(16)
life style habits		
smoking	71	(13)
alcohol intake	45	(10)
body mass index		
<20	54	(8)
between 20 and 25	417	(42)
between 26 and 30	299	(36)
>30	136	(14)
Obstetrical features		
parity		
primiparity	417	(47)
multiparity	491	(53)
pregnancy not planned	49	(8)
previous miscarriage	114	(20)
previous abortion provocatus	17	(3)
Biological parameters		
thyroid parameters		
TSH (mn, SD)	1.2	(0.8)
fT4 (mn,SD)	16.1	(2.5)
Sub-clinical hypothyroidism	32	(3.1)
Sub-clinical hyperthyroidism	29	(2.8)
Hypothyroxinemia (fT4 < 13 pmol/l with normal TSH)	77	(7.3)
Hyperthyroxinemia (fT4 >18 pmol/l with normal TSH)	74	(7.4)
TPO-Ab titers > 35 IU/ml	83	(8.1)
Human Chorionic Gonadotropin		
hCG IU/L (mean, SD)	571	(309)
Psychological parameters		
Previous history of depression	120	(11)
Occurrence of a stressful life event during 12 weeks' gestation	234	(21)
Mean scores (SD) of EDS	5.0	(4.2)
Mean scores (SD) of anxiety subscale	12.2	(3.5)

Table 2 Mean FT4 and TSH LEVELS according to four different quartiles of hCG (n = 545).

hCG percentiles	n	FT4 Mn (SD)	TSH Mn (SD)
< 25th	136	14.8 (2.1)	1.37 (0.78)
between 25 – 50th	137	15.4 (2.2)	1.25 (0.69)
between 50th – 75th	137	15.9 (2.3)	1.14 (0.75)
> 75th	135	16.5 (2.5)	1.01 (0.74)

Table 3 Difference in NVP scores between several groups (Mann-Whitney-U, two tailed) in 545 pregnant women at 12 weeks' gestation

	n yes	n no	Z	p
Socio-economic status & life style habits				
Smoking	59	486	-0.65	0.51
Alcohol drinking	69	476	-0.68	0.61
BMI > 30	81	464	-0.23	0.82
Low education	47	498	0.45	0.67
Not-working outside home	**63**	**482**	**-2.90**	**0.003**
Obstetrical factors				
Not planned pregnancy	**38**	**507**	**-3.16**	**0.002**
Multi-parity	324	221	-1.93	0.34
Miscarriage earlier in life	114	431	-0.29	0.76
Abortion provocatus earlier in life	**18**	**527**	**-2.10**	**0.04**
Thyroid parameters				
Hypothyroidism	1	544	-0.15	0.9
Hyperthyroidism	6	539	-0.82	0.4
Sub-clinical hypothyroidism	7	538	0.24	0.8
Sub-clinical hyperthyroidism	17	528	-0.84	0.35
Hyperthyroxinemia (FT4 > 90th percentile)	**32**	**513**	**-2.41**	**0.016**
Hypothyroxinemia (FT4 < 10th percentile)	64	481	1.23	0.25
TPO concentration > 35	46	499	-0.05	0.95
High HCG levels (> 90th percentile)	53	492	-0.32	0.74
Psychological parameters				
Depressed (EDS > 11)	**47**	**498**	**-4.50**	**0.0001**
Anxious (anxiety scores > 90th percentile)	**49**	**496**	**-3.60**	**0.0001**
High somatisation (> 90th percentile)	**54**	**501**	**-7.40**	**0.0001**
Previous episode of depression	64	481	-1.75	0.08
Occurrence of major life event in pregnancy	82	463	-0.73	0.46
Major stressors earlier in life (< 16 years of age)				
Sexual abuse	**18**	**527**	**-2,70**	**0.006**
Physical abuse by parents	**22**	**523**	**-4.90**	**0.0001**
Emotional abuse by parents	**23**	**522**	**-2.80**	**0.006**

- Z means that the mean ranking of the yes-group > than the no-group

a major life event before the age of 16 years) were associated with significantly higher scores on NVP. Variables which did not show significant differences in NVP scores included high HCG levels (> 90th percentiles) nor did high levels of TSH.. Other sub-divisions of HCG and TSH did not result in significant differences either (data not shown). Subsequently, the variables, which differed significantly at a univariate level, were entered into a multiple linear regression analysis (method stepwise) with NVP score as the dependent variable (Table 4).

As can be seen, there were five determinants that fitted the model: high somatisation, physical abuse before the age of 16, a non- planned pregnancy, hyperthyroxinemia and a history of sexual abuse before the age of 16 years. The total set of variables explained 25% of the variance of which somatisation contributed the most. Variables that did not fit the model: the occurrence of major life events earlier in life (emotional abuse), abortion provocatus earlier in life, not working outside home, depression at 12 week's gestation and high anxiety scores at 12 weeks' gestation.

Because the sub-scale somatisation of the SCL-90 (12 items) contains an item about nausea, a similar analysis was performed without this item (11-items sub-scale), which showed similar results (data not shown).

Table 4 Multiple regression analysis (method stepwise) at 12 weeks' gestation (N=545), dependent variable: severity of nausea and / or vomiting during previous 3 months

	R	R^2	p
high somatisation (> 90th percentile	0.40	0.16	0.0001
emotional abuse	0.47	0.22	0.0001
not-planned pregnancy	0.48	0.23	0.013
hyperthyroxinemia (FT4 > 90th percentile	0.49	0.24	0.031
physical abuse	0.50	0.25	0.039

variables that did not fit the model: the occurrence of major life events earlier in life (sexual abuse), abortion provocatus earlier in life, not working outside home, depression at 12 week's gestation, high anxiety scores at 12 weeks' gestation.

Discussion

As far as we know this is the first study that investigated within one model both biological (thyroid hormone and hCG) as well as psychological factors (anxiety, depres-

sion and somatisation) of gestational nausea and vomiting (NVP) taking into account possible confounders. Within this model, of the 25% explained variance on NVP scores, 24% (=96%) consisted of psychosocial variables (high somatisation, emotional and physical abuse in childhood), while high levels of FT4 (> 90th percentile) and a non-planned pregnancy only marginally contributed to the explained variance of NVP. Although different quartiles of HCG clearly show higher mean FT4 and lower mean TSH levels (Table 2), TSH and HCG did not contribute at all to differences in NVP scores, not even at an uni-variate level.

The fact that somatisation showed the highest contribution to high symptoms of NVP might be explained by the characteristics of this instrument. It should be remembered that the SCL-90 (and its sub-scales) measures all kinds of psychopathology and that the sum-score can be regarded as an index of psycho neuroticism[13] High somatisation scores actually reflect high neuroticism. As such, the results of the current study suggest NVP to be explained by personality characteristics and disorders. One study[17] identified several subgroups of patients with severe nausea and vomiting during pregnancy based on personality pathology, psychiatric symptoms and psychosocial stressors. They noted six categories including neuroticism and extraversion. Validation studies of the SCL-90 subscales have shown high correlation between all sub-scales including anxiety and somatisation (Derogatis 1977). Also in this study the correlations were high (0.51). This might explain why – bringing these variables into the regression – one of the variables show significant correlations by excluding other variables, which partly measures similar characteristics. Other researchers [16] showed that in a sample of 273 women the severity of NVP was correlated with GHQ subscales for anxiety/insomnia, severe depression and somatic symptoms, and social dysfunction. A study on psychosocial factors in nausea, vomiting and fatigue in pregnancy [17] found depression to be related to physical symptoms in a descriptive study among 113 women.

The fact that non-planned pregnancy was an independent determinant of NVP is in line with the research of Fitzgerald [18] who showed – using the Goldberg Standardized Psychiatric Interview in 86 pregnant women - that women with NVP reported more unplanned and undesired pregnancies.

In the present study, maternal FT4 levels in the upper normal level (> 90th percentile) in the absence of abnormal TSH showed to be an independent (albeit modest) de-

terminant of NVP. As such, hyperthyroxinemia should be discriminated from transient gestational thyrotoxicosis (GTT) in which there are suppressed TSH concentrations and supranormal FT4 concentrations [19]. There is substantial evidence that HG and GTT is linked to increased levels of hCG, resulting in lower TSH and higher FT4 levels. However, HG is a rare condition, in the current study no women met the criteria of severe NVP with more than five percent loss of body weight. It might be hypothesized that high (but within normal reference ranges) levels of FT4 - in combination with increased levels of estrogen and progesterone - might contribute to provoke NVP symptoms. It remains a matter of speculation whether the high levels of FT4 might actually reflect high levels of hCG: hCG has a TSH like activity resulting in low TSH and higher FT4 which are classically described in early pregnancy. The correlation between hCG and FT4 in the current study - although significant - was rather low: 0.26.

Several limitations of the study need to be mentioned. Firstly, the design of the study was cross-sectional. It is clear that to have more insight in the quantifications of NVP prospective studies are needed in which weekly reports are collected on NVP. Secondly, NVP was assessed using one single question referring to nausea and vomiting during the first 12 weeks 'of gestation. An instrument frequently used in NVP research is the 31-item aadapted Symptom Distress Scale-2 (ASDS-2), developed in cancer chemotherapy[20]. However, this instrument covers other dimensions, which are less specific for NVP. In recent studies Koren et al [21,22] found very high correlations between a 3 items self rating scale included the number of daily vomiting episodes, the length of nausea per day in hours, and the number of retching episodes (pregnancy-unique-quantification of emeses and nausea, PUQE) and the "gold standard" Rhodes' score (r= 0.90) and favoured this short type of assessment of NVP.

Thirdly, other biological factors such as estrogen and progesterone should be taken into account to complete a multifactorial psychobiological model of NVP. It might be that synergism of several different hormones (progesterone, oestradiol and thyroid hormone) might contribute more substantially to explain NVP symptoms rather than one single hormone. Finally, it is clear that using one (or several) questions in relation to NVP only gives information at a symptom level. This means that conclusions about possible related factors should be made at a symptom level rather than at a syndrome level.

What might be the clinical relevance of this study? Because psychological factors seem to be important risk factors to explain NVP to occur, midwifes and obstetricians should be aware that women with severe NVP actually suffer from psychological problems related to increased neuroticism such as anxiety, depression and somatisation rather than a biological syndrome. Women with severe NVP should be followed and further examined on the presence of depression and anxiety, both conditions, which are known to interfere with obstetrical and neonatal outcome.

In conclusion, this study using a psycho-biological model with several psychological determinants and two important hormones (HCG and thyroid hormone) susceptible to major changes during early pregnancy, shows that - after correction for risk factors known from literature to be related to NVP - the intensity of NVP symptoms should mainly be explained by psychological rather than biological factors.

References

1. Eliakim R, Abulafia O, Sherer DM Hyperemesis gravidarum: a current review.Am J Perinatol. 2000;17(4):207-18. Review

2. Goodwin, T.M. (1998). Hyperemesis gravidarum. Clin Obstet Gynecol. 1998;41(3):597-605. Review

3. Koch KL.Gastrointestinal factors in nausea and vomiting of pregnancy. Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S198-203.

4. Leylek OA, Cetin A, Toyaksi M, Erselcan T Hyperthyroidism in hyperemesis gravidarum. Int J Gynaecol Obstet. 1996;55(1):33-7.

5. Verberg MF, Gillott DJ, Al-Fardan N, Grudzinskar JG. Hyperemesis gravidarum, a literature review.Hum Reprod Update. 2005 Jul 8; [Epub ahead of print]

6. Herschman JM.Human chorionic gonadotropin and the thyroid: hyperemesis gravidarum and trophoblastic tumors.Thyroid. 1999;9(7):653-7. Review.

7. Cox JL, Chapman G, Murray D, Jones P Validation of the Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women. J Affect Disord. 1996;39(3):185-9.

8. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression: Development of the 10-item Edinburgh Postnatal Depression Scale. British Journal of Psychiatry. 1987;150: 782-786.

9. Pop VJ, Komproe IH, van Son MJ. Characteristics of the Edinburgh Post Natal Depression Scale in The Netherlands. J Affect Disord. 1992;26(2):105-10.

10. Becht MC, Van Erp CF, Teeuwisse TM, Van Heck GL, Van Son MJ, Pop VJ. Measuring depression in women around menopausal age: towards a validation of the Edinburgh Depression Scale.J Affect Disord. 2001;63(1-3):209-13.

11. Harris B, Huckle P, Thomas R, Johns S, Fung H. The use of rating scales to identify post-natal depression.Br J Psychiatry. 1989;154:813-7.

12. Murray L, Caroters AD. The validation of the Edinburgh Post-natal Depression Scale on a community sample. Br J Psychiatry. 1990;157:288-90.

13. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale--preliminary report. Psychopharmacol Bull. 1973;9(1):13-28.

14. Arrindell WA Ettema JH. SCL-90, a multidimensional Psychopathologie Indicator. Lisse; Swets & Zeitlinger.

15 Lub-Moss MM, Eurlings-Bontekoe EH. Clinical experience with patient suffering from hyperemisis gravidarum. Patient Education and Counselling 1997;31:65-75.

16. Swallow BL, Lindow SW, Masson EA, Hay DM. Psychological health in early pregnancy: relationship with nausea and vomiting. J Obstet Gynaecol. 2004;24(1):28-32.

17.Chou FH, Lin LL, Cooney AT, Walker LO, Riggs MW. Psychosocial factors related to nausea, vomiting, and fatigue in early pregnancy.J Nurs Scholarsh. 2003;35(2):119-25.

18. FitzGerald CM.Nausea and vomiting in pregnancy. Br J Med Psychol. 1984;57 (Pt 2):159-65.

19. Glinoer D: Thyroid hyperfunction during pregnancy. Thyroid 1998 ;8:859.

20. Rhodes VA, McDaniel RW. Cancer Nurs. 2000;23(1):49-54). The Index of Nausea, Vomiting, and Retching: a new format of the Index of Nausea and Vomiting. Oncol Nurs Forum. 1999;26(5):889-94.

21. Koren G, Boskovic R, Hard M, Maltepe C, Navioz Y, Einarson A. Motherisk-PUQE (pregnancy-unique quantification of emesis and nausea) scoring system for nausea and vomiting of pregnancy. Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S228-31.

22. Koren G, Piwko C, Ahn E, Boskovic R, Maltepe C, Einarson A, Navioz Y, Ungar WJ. Validation studies of the Pregnancy Unique-Quantification of Emesis (PUQE) scores. J Obstet Gynaecol. 2005 ;25(3):241-4.

Chapter III

THE RELATION BETWEEN GESTATIONAL THYROID PARAMETERS AND DEPRESSION: A REFLECTION OF THE DOWN REGULATION OF THE IMMUNE SYSTEM DURING PREGNANCY?

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Introduction.

Traditionally, pregnancy has been thought of as a period of well-being and happiness. But in addition to the physical challenges women face during their pregnancy, they also must cope with shifting hormones and lifestyle changes. Emotional difficulties, specifically mood changes, may be frequently encountered during pregnancy. In recent reviews, up to 10% of the women were shown to suffer from depressive symptomatology (minor depression) during gestation and up to 5% of a major depressive episode (1,2).

Depression during gestation has been recognized to affect fetal health and to interfere with obstetrical outcome: gestational hypertension and subsequent pre-eclampsia, spontaneous abortion, bleeding during gestation, neonatal growth retardation, spontaneous early labour, fetal death, low birth weight in babies, low Apgar scores, admission to a neonatal care unit, perinatal and birth complications, and high cortisol levels in offspring at birth (3-8). Moreover, women who suffer from a major depressive episode during gestation are at high risk to suffer from postpartum depression with all its possible negative consequences for the mother-infant relation (9).

The relation between thyroid dysfunction and depression in general has been well documented for many decades as reviewed elsewhere (10, 11, 12). Several symptoms of hypothyroidism are similar to those of depression (fatigue, cognitive problems, sleeping problems, low mood). Moreover, many patients with depression, although biochemically euthyroid, show alterations in their thyroid function: abnormal TRH response, high prevalence of thyroid antibodies, T4 levels in the higher normal ranges.

Several authors report an association between high titres of thyroid peroxidase antibodies (TPO-Ab) and depression in general, while others did not (13 – 20). These conflicting results are mainly to be explained by methodological issues such as: different use of definition of depression (depression at a symptom level versus at a syndrome level), small samples and use of biased population (psychiatric inpatient clinics versus the general population).

Although up to 2- 4% of the pregnant women present with thyroid dysfunction (currently treated or in the past) and up to 8 - 10% show elevated TPO-Ab titres, the

relation between thyroid dysfunction and depression *during gestation* has hardly been investigated. This is the more surprising, while the immune system of a pregnant woman is susceptible to major alterations (due to the classical down regulation to keep the paternal allograft) as reflected by a substantial decrease of antibody titres during gestation, thyroid related as well to other organs. There are only two reports showing conflicting results: Kuijpens et al found that women with elevated TPO-Ab during early gestation were at increased risk for depression, while Oretti et al.found no differences in the prevalence of gestational depressive symptoms in relation to antibody status (17, 21). However, both studies suffered from methodological shortcomings and used relatively small samples.

The current study investigated the relation between depression and thyroid parameters during gestation taking into account important methodological aspects: a large sample of pregnant women of the general population, a diagnosis of depression at a syndrome level rather than a symptom level, repeated measurements at three different trimesters of gestation and inclusion of possible confounders of depression.

Materials and methods

Subjects

Between August 2002 and November 2004 all women (n=1507) who booked for antenatal control at 12 weeks' gestation in five community midwife practices were invited to participate into screening of maternal thyroid function. N=1191 (79%) women signed an informed consent for participation. Because the study used several questionnaires, only Caucasian women with appropriate knowledge of the Dutch language (n=1113) were eligible. Moreover, women on thyroid medication (n=10), those who became pregnant after hormonal stimulation (n=8), those with a multiple pregnancy (n=8) as well as women with Diabetes-1 (n=5) were excluded. Also excluded were all women (n=69) who did not participated into all assessments and did not complete all questionnaires. Therefore 1017 (91%) women were eligible for this study.

Apart from the own written informed consent of the participants, the Medical Ethical Committee of Máxima Medical Centre in Eindhoven/Veldhoven approved this study.

Assessments

Dependent variable: depression

A syndromal diagnosis of depression was assessed using the Composite International Diagnostic Interview, short version of the depression module (22). The CIDI is a fully structured diagnostic interview developed to allow lay interviewers to obtain the data necessary to make a psychiatric diagnosis according to DSM-IV-TR I (American Psychiatric Association, 2000) and ICD-10 (World Health Organization, 1992) criteria (22, 23). The women were seen by one midwife (2/3 of the assessments, HW) and a team of five psychology students (as a part of a graduating research program). They all received a CIDI-training and were blinded for biochemical results of the women. Only women suffering from major depression were diagnosed as a case, women who were not depressed at the time of assessment but who met the criteria of dysthymia according to the CIDI were not included as a case.

Independent variable: thyroid hormones and thyroid autoimmunity

TSH (thyrotropin) was measured using a solid-phase, two site chemiluminescent enzyme immunometric assay (IMMULITE Third generation TSH, Diagnostic Products Corporation, Los Angeles USA). The inter-assay coefficients of variation were 5.0% and 4.4% at concentrations 0.22 mIU/l and 2.9mIU/l, respectively.

The fT4 (free-thyroid hormone, thyroxin) concentration was measured with a solid-phase immunometric assay (IMMULITE Free T4). The inter-assay coefficients of variation for this technique were 6.7% and 4.4% at concentrations of 11.6 pmol/l and 31.5 pmol/l, respectively. For both parameters, the above-mentioned non-pregnant reference ranges were used: 0.45 – 4.5 mIU/l and 10.3 - 25.7 pmol/l, 0.45 – 4.5 mIU/l and 10.3 - 25.7 pmol/l, respectively.

The following categories of thyroid dysfunction were defined.

Clinical (overt) thyroid dysfunction: TSH and fT4 outside reference ranges referring to hyperthyroidism (decreased TSH and increased fT4) and hypothyroidism (increased TSH and decreased fT4). Similarly, sub-clinical thyroid dysfunction was defined by an abnormal TSH with fT4 level within reference range. Hypo- and hyperthyroxinemia

were defined by an FT4 concentration at or below the 10th percentile and at or below the 90th percentile, respectively, with a TSH concentration within reference range.
Finally, 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 9% and 9.5% for concentrations of 40 kU/l and 526 kU/l, respectively. The anti-TPO assay is standardized in terms of the International Reference Preparation for anti-TPO MRC 66/387. A woman with an TPO-Ab titers > 35 IU/ml at 12 weeks' gestation was defined as immunologically compromised irrespective of a possible decrease of the titer throughout pregnancy resulting in low titers at 24 or 34 weeks' gestation. Women were defined as TPO-Ab negatives when the titer was below 35 IU/ ml at 12 weeks' gestation.

Possible confounders

Because *anxiety* shows to be a highly co-morbid condition of depression anxiety symptoms were measured using the 10-items anxiety subscale (range 10 – 50) of the SCL-90 scale of Derogatis (24). The SCL-90 is a self-rating scale consisting of six subscales measuring all kind of psychopathology. The item score ranges from one to five. The SCL-90 has been validated before in The Netherlands and its use as well as the use of several subscales only has revealed appropriate psychometric properties (25). Normally, no cut-off levels are used but in the present study scores at and above the highest 90th percentile defined high levels of anxiety. Several other confounders as described in literature were assessed at one or more trimesters such as: demographic features, life style habits, an earlier episode of depression in the woman's life or her parents and the occurrence of major life events during pregnancy prior to the assessment. Finally, the effect of several obstetrical factors (parity, planning of pregnancy) was also investigated.

Statistical analysis

Statistical analysis was performed using the Statistical Package of Social Science (SPSS). Univariate logistic regression analysis was performed with depression according to the CIDI as the dependent variable (O.R., 95% CI). Subsequently, a multi-

ple logistic regression analysis was performed again with a syndromal diagnosis by the CIDI as the dependent variable.

Results

The characteristics of the participants are shown in Table 1.

Table 1 Characteristics of a sample of 1017 pregnant women of the general population assessed at 12 weeks' gestation

	n	(%)
Demographic features		
age (mean, SD)	29	(0.5)
marital status		
with partner	997	(98)
single	26	(2)
educational level		
low	91	(9)
middle	458	(45)
high	387	(38)
academic	81	(8)
Working outside home	874	(86)
life style habits		
smoking	113	(13)
alcohol intake	112	(13)
body mass index		
<20	61	(6)
between 20 and 25	467	(46)
between 26 and 30	336	(33)
>30	153	(15)
Obstetrical features		
Parity		
primiparity	468	(46)
multiparity	549	(54)
pregnancy not planned	76	(7.5)
previous miscarriage	195	(19.2)
Risk factors of depression		
Previous history of depression in woman herself	123	(12.1)
History of depression in first line relatives	185	(18.2)
The occurrence of a major life event:		
during first trimester	252	(25)
during second trimester	221	(22)
during third trimester	211	(20)

In Table 2, the prevalence rates of depression according to the CIDI are shown as well as mean scores on the sub-scale anxiety at three different trimesters. Moreover, thyroid parameters are shown. As can be seen in Table 2, the prevalence rate of depression according to CIDI remained at 5% until the second trimester and dropped below 3% toward end gestation. The mean scores of the anxiety subscale of the SCL-90 gradually increased during gestation. Thyroid parameters showed a decrease of mean concentrations of FT4 and an increase of mean TSH toward end gestation.

Table 2 Prevalence rates of depression and thyroid parameters at three different trimesters during gestation in 1017 women of the general population.

	12 weeks	24 weeks	36 weeks
Depression according to CIDI (N, %)	54 (5.3)	46 (4.5)	30 (2.9)
Anxiety (Mn, SD)	12.1 (3.3)	12.4 (3.4)	12.7 (3.6)
Thyroid parameters (N, %)			
TSH (Mn, SD)	1.2 (0.8)	1.3 (0.65)	1.5 (0.74)
FT4 (Mn, SD)	16.1 (2.5)	13.8 (2.0)	13.3 (2.1)
Sub-clinical hyperthyroidism	30 (2.9)	7 (0.7)	4 (0.4)
Sub-clinical hypothyroidism	33 (3.2)	17 (1.7)	25 (2.5)
Hyperthyroxinemia	78 (7.7)	72 (7.1)	72 (7.1)
Hypothyroxinemia	85 (8.4)	99 (9.7)	86 (8.5)
TPO-Ab > 35	85 (8.4)	74 (7.3)	66 (6.5)
Women who were TPO-Ab negative (< 35 IU/ml) at 12 weeks' gestation, n = 932:			
TPO Mean (SD)	10.3 (3.4)	10.1 (5.6)	10.4 (8.6)
Range IU/ml	9 - 35	9 - 130	9 - 180
Women who were TPO-Ab positive (> 35 IU/ml) at 12 weeks' gestation, n = 85			
TPO Mean (SD)	356) (322)	170) (146)	108) (92)
Range IU/ml	36 - 1900	9 - 1300	9 - 1100
FT4 10th percentile (pmol/l):	13.3	11.2	10.8
FT4 90th percentile (pmol/l):	18.9	16.4	15.9

The number of women with sub-clinical hyperthyroidism decreased toward end gestation, while the prevalence of sub-clinical hypothyroidism fluctuated with regard to different trimesters. Finally, the number of women with elevated titers of TPO-Ab

Table 3 Univariate logistic regression analysis in 1017 women at three different assessments during gestation. Dependent variable: depression according to CIDI. (O.R., 95% CI).

	O.R.	95%CI
12 weeks' gestation		
Low education	1.8	0.8-4.1
Working outside home	1.6	0.6-3.4
Obstetrical features		
Not-planned pregnancy	**4.5**	**2.2-8.7**
Nulliparity	1.2	0.7-2.1
Miscarriage earlier in life	1.4	0.6-1.9
Life style habits		
Smoking during gestation	**3.1**	**1.7-5.8**
Alcohol intake	1.2	0.4-1.9
High BMI (>25)	1.5	0.7-3.1
Risk factors of depression		
Previous history of depression in life	**2.7**	**1.4-5.2**
Depression in family	1.6	0.8-3.2
Occurrence of stress-full life event in first trimester	**2.6**	**1.8-6.3**
Anxiety: (scores > 90th percentile)	**7.9**	**4.1-14.2**
Thyroid parameters		
Sub-clinical hypothyroidism	1.1	0.6-4.9
Sub-clinical hyperthyroidism	**2.8**	**1.2-8.5**
Hypothyroxinemia (FT4 < 10th percentile)	1.2	0.8-2.3
Hyperthyroxinemia (FT4 > 90th percentile)	2.4	0.5-6.7
Increased TPO-Ab titers (> 35)	**1.6**	**1.2-3.8**
24 weeks' gestation		
Low education	1.6	0.6-3.6
Working outside home	1,4	0.5-3.7
Obstetrical features		
Not planned pregnancy	1.2	0.6-2.6
Nulliparity	1.3	0.6-2.4
Miscarriage earlier in life	1.2	0.8-1.8
Life style habits		
Smoking during gestation	1.8	0.8-3.8
Alcohol intake	1.9	0.5-2.7
High BMI (>25)	**2.1**	**1.2-3.9**
Risk factors of depression		
Previous history of depression in life	1,7	0.8-3.2
Depression in family	1.8	0.6-3.8
Occurrence of stress-full life event in second trimester	**4.6**	**2.8-8.3**
Anxiety: (scores > 90th percentile)	**8.9**	**5.2-15-8**
Thyroid parameters		
Sub-clinical hypothyroidism	1.6	0.9-5.2
Sub-clinical hyperthyroidism	--	--
Hypothyroxinemia (FT4 < 10th percentile)	1.4	0.6-4.1
Hyperthyroxinemia (FT4 > 90th percentile)	1.8	0.7-5.3
Increased TPO-Ab titers (> 35)	1.9	0.9-4.2

(Suite)		
36 weeks' gestation		
Low education	1.6	0.6-4.7
Working outside home	1.5	0.7-3.2
Obstetrical features		
Not planned pregnancy	1.9	0.7-5.7
Nulliparity	1.5	0.6-3.1
Miscarriage earlier in life	1.9	0.6-2.9
Life style habits		
Smoking during gestation	1.9	0.7-4.8
Alcohol intake	1.3	0.5-2.5
High BMI (>25)	1.1	0.6-3.3
Risk factors of depression		
Previous history of depression in life	**3.2**	**1.4-7.3**

O.R.= odds ratio; CI= confidence interval

decreased gradually toward end term. In the group of women with elevated titers at 12 weeks 'gestation (n =85), the mean concentration of TPO-Ab decreased toward end term as well as the upper range level: from 1900 to 1100 IU/ml.

In Table 3, a uni-variate logistic regression is shown at three trimesters with the dependent variable: a syndromal diagnosis of depression according to the CIDI and the independent variables: several thyroid parameters.

Moreover, the relation between possible confounders and the dependent variable is shown. (demographic characteristics, obstetrical features and risk factors of depression in general). As can be seen, at 12 weeks' gestation, a decreased TSH (subclinical hyperthyroidism) and elevated titers of TPO-Ab significantly were related to depression as well as several possible confounders; at 24 weeks' gestation, an elevated titer of TPO-Ab was significantly related to depression as well as other confounders while at 36 weeks' gestation, no thyroid parameters were related to depression.

Subsequently, in Table 4, the set of variables was put into a multiple logistic regression analysis with the dependent variable: a syndromal diagnosis on the CIDI at different trimesters of pregnancy. Only the significant Odds Ratio's are shown.

As can be seen in Table 4, also at a multivariate level thyroid parameters remained significantly related to depression until 24 week's gestation. At the first trimester, women with a non-planned pregnancy were significantly at risk to suffer from depres-

sion. Moreover, smoking was shown to be an independent risk factor. The other variables at all three assessments, which significantly correlated with depression, were high anxiety and the occurrence of recent major life events.

Table 4 Multiple logistic regression analysis in 1017 women at three different assessments during gestation. Dependent variable: depression according to CIDI. (O.R., 95% CI). Only significant O.R. are shown

	O.R.	95%CI
12 weeks' gestation		
Not-planned pregnancy	3.0	1.8-6.6
Smoking during gestation	2.2	1.2-4.7
Occurrence of stress-full life event in first trimester	2.3	1.6-6.1
Anxiety: (scores > 90th percentile)	3.9	1.9-8.1
Sub-clinical hyperthyroidism	3.6	1.2-10.2
Increased TPO-Ab titers (> 35)	2.1	1.1-5.8
24 weeks' gestation		
Previous history of depression in life	1.5	1.2-2.1
Occurrence of stress-full life event in second trimester	3.1	1.6-6.1
Anxiety: (scores > 90th percentile)	6.3	3.2-12.8
Increased TPO-Ab titers (> 35)	2.8	1.9-7.1
36 weeks' gestation		
Occurrence of stress-full life event in third trimester	2.4	1.3-5.9
Anxiety: (scores > 90th percentile)	4.1	1.6-9.8

O.R.= odds ratio; CI= confidence interval

Discussion

This study in a large sample of pregnant women of the general population shows that the prevalence of major depression varies from 2.9 to 5.4% depending on the time of assessment during gestation. Besides, it demonstrates that, depending on the time of assessment, different variables predict depression at one hand, while on the other hand some factors are related to depression at all assessments. During early gestation thyroid parameters have an independent relation to depression: decreased TSH levels and elevated titers of TPO-Ab at first trimester, while, at second trimester, an

elevated titer of TPO-Ab is the only thyroid parameter that correlated significantly with depression.

A recent review of the literature concerning depression during gestation using similar methods of syndromal diagnosis showed a prevalence rate of major depression varying from 3.1 to 4.9% depending on the time of assessment, which is in accordance with the findings of the current study (1). The prevalence rate of depression during gestation is lower compared to that of depression in the general female non-childbearing population of similar age (10 – 12%) as shown in a large population study of 6000 adults between 18 – 65 years of age in The Netherlands (26). Although a definite explanation is lacking, a possible reason that might partly explain this difference is the down regulation of the immune system during gestation. Depression has a multifactorial origin in which biological, immune, psychological and environmental factors are thought to play an important role. In psychoneuroimmunology it has long time been described that perturbations of the immune system might be associated with depression or vice versa (27). Because of the down regulation of the immune system it might be argued that the effect of an auto-immune phenomenon as a possible trigger of depression decreases during gestation resulting in lower prevalence rates of depression. In the current study, the prevalence rate of depression dropped from 5.3 to 2.9% in line with the prevalence rate of elevated titers of TPO-Ab which dropped from 8.4 to 6.5% (Table 2).

As has been shown earlier, several authors reported a relation between thyroid autoimmunity and depression *in general*. Haggerty et al.(13) 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 unipolar depression and the non-psychiatric control group. One recent study reported an increased mean level of thyroid antibodies in depressed patients compared to controls (19) and another study of a community based sample reported a higher life-time prevalence of anxiety and mood disorder in subjects with increased TPO-Ab titers (20). The association between elevated TPO-Ab and depression has also been confirmed in perimenopausal women (18). The relation between depression and thyroid dysfunction has been well studied during the *postpartum period*. Kent et al.(14) found no relationship between thyroid antibody concentrations (TPO-Ab or MsAb) and depression at six months post partum. How-

ever, others have found high TPO-Ab levels to be associated with depression. Harris and colleagues (15) found elevated antibody concentrations to be related to high depressive symptomatology in the postpartum, regardless of thyroid function and Pop and associates found that women who had elevated TPO-Ab concentrations during early pregnancy had a slightly increased risk for postpartum depression (16).

The only two reports looking at a possible relation *during gestation* reported inconclusive data. Kuijpens et al. – using a similar design as the current study but in a smaller sample – also found a relation between depression and TPO-Ab, only at 12 weeks' gestation and not at 32 weeks' gestation (17). However, important confounders were not taken into account such as the co-morbidity of anxiety and obstetrical factors such as planning of pregnancy. Oretti et al. found no differences of prevalence rates of depressive symptoms between 61 antibody positive women and 66 antibody negative women (21). However, they used no syndromal diagnosis of depression and their study did not use a representative sample of the general population, which was the case in the current study.

The finding that sub-clinical hyperthyroidism during early pregnancy was related to depression is interesting and not to be explained by changes in the immune system during gestation. In general, one of the most important causes of sub-clinical hyperthyroidism is inadequate substitution or suppression dose of women with hypo- and hyperthyroidism, respectively. However, these women were excluded from the study. The 30 women with sub-clinical hyperthyroidism in the current study had a similar prevalence rate of elevated TPO-Ab titers (6.4%, data not shown) compared to the group as a whole, which suggests that thyroid-autoimmunity is not the cause either. In comparison: 18 (55%) of the 33 women with sub-clinical hypothyroidism (which is most of the time of auto-immune origin) did have elevated titers of TPO-Ab. It might be suggested that low TSH (with normal FT4 levels) especially during early gestation reflects high peaks of human chorionic gonadotrophin (hCG), which is known for its effect on the TSH receptor because of a structural analogy with TSH (28, 29). Future studies are needed to look directly at a possible relation between hCG levels and depression during early gestation.

But there is another argument that might support a relation between depression and thyroid autoimmunity: when looking at the literature concerning the relation between depression and obstetrical problems at one hand, and between elevated titers of

TPO-Ab and obstetrical problems on the other hand, it is interesting to see that there are many similarities. Both depression and TPO-Ab have been associated with increased rate of premature delivery, gestational hypertension and subsequent pre-eclampsia, spontaneous abortion, bleeding during gestation, neonatal growth retardation, spontaneous early labour, foetal death and low birth weight in babies (3 -8, 30). It is a matter of speculation whether the negative effect of TPO-Ab on obstetrical outcome might be partly explained by the higher risk of depression in TPO-Ab positive women. Besides thyroid parameters, smoking and a non-planned pregnancy were shown to be an independent risk factor of depression during early gestation. The relation between smoking and depression in general has been well documented (31) and smoking habits might moderate the finding that depression might interfere with low birth weight of the neonate. The fact that a non-planned pregnancy was an important risk factor of depression during early gestation has been described earlier and is another argument that these women need special attention during regular antenatal controls (1).

Anxiety was independently related to depression at all trimesters. This is not surprising given the fact that nowadays depression shows a co-morbidity with anxiety in up to 80% of the cases. Depression and anxiety very often co-occur (32). Because anxiety has been shown to be an important determinant of impaired obstetrical outcome it might be argued that a possible negative effect of depression on obstetrics might be moderated by anxiety.

At all trimesters 'classical' psychosocial determinants of depression were independently related to depression such as high levels of anxiety and the occurrence of major life events. These risk factors of depression by no means differ from risk factors of depression in general.

Several limitations of the study need to be mentioned. Anxiety was the most stable risk factor of depression throughout pregnancy but was only assessed using self-rating scales. Because its major negative impact on obstetrics and apparently the offspring syndromal diagnosis should be preferred. Secondly, when looking at a possible relation between thyroid parameters and depression it is important to look at possible confounders. In the current study, important psychological confounders were taken into account. Ideally, other biological parameters (hCG, oestradiol, pro-

gesterone, cortisol) should also take into account when looking at an independent biological parameter of depression.

In summary, this study suggests that during pregnancy the model to predict depression contains different parameters at different trimesters of gestation, in line with the down regulation of the immune system: an immune and biological (TPO-Ab, TSH and perhaps hCG) component during early gestation with some psycho-social trimester specific determinants; and a rather 'stable' psychological set of variables (anxiety, major life events) throughout whole pregnancy.

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References

1.Gaynes BH, Gavin N, Meltzer-Brody S, Lohr KN, Swinson T, Gartlehner S, Brody S, Miller WC. 2005 Perinatal depression: prevelance, screening accuraty and screening outcomes. Evid Rep Technol Assess **119**:1-8.

2. Stocky A, Lynch J. 2000 Acute psychiatric disturbance in pregnancy and the puerperium. Baillieres Best Pract Res Clin Obstet Gynaecol **14(1)**:73–87.

3. Preti A, Cardascia L, Zen T, Pellizzari P, Marchetti M, Favaretto G, Miotto P.2000 Obstetric complications in patients with depression—a population-based case-control study. J Affect Disord **61**:101–6.

4. Chung TK, Lau TK, Yip AS, Chiu HF, Lee DT. 2001 Antepartum depressive symptomatology is associated with adverse obstetric and neonatal outcomes. Psychosom Med **63**:830–4.

5. Field T, Diego M, Hernandez-Reif M, Salman F, Schanberg S, Kuhn C, Yando R, Bendell D.2002 Prenatal anger effects on the fetus and neonate. J Obstet Gynaecol **22**:260–6.

6. Dayan J, Creveuil C, Herlicoviez M, Herbel C, Baranger E, Savoye C, Thouin 2002 A. Role of anxiety and depression in the onset of spontaneous preterm labor. Am J Epidemiol **155**:293–301.

7. Orr ST, James SA, Blackmore PC.2002 Maternal prenatal depressive symptoms and spontaneous preterm births among African-American women in Baltimore, Maryland. Am J Epidemiol **156**:797–802.

8. Ashman SB, Dawson G, Panagiotides H, Yamada E, Wilkins CW.2002 Stress hormone levels of children of depressed mothers. Dev Psychopathol 14:333–49.

9. Brockington I. 2004 Postpartum psychiatric disorders. The Lancet Vol 363, jan 24

10.Musselman DL, Nemeroff CB.1996 Depression and endocrine disorders: focus on the thyroid and adrenal system. British Journal of Psychiatry. 168:123-128.

11. Esposito S, Prange AJ Jr, Golden RN. 1997 The thyroid axis and mood disorders: overview and future prospects. Psychopharmacol Bull. 33(2):205-17

12. Hendrick V, Altshuler L, Whybrow P. 1998 Psychoneuroendocrinology of mood disorders. The hypothalamic-pituitary-thyroid axis.Psychiatr Clin North Am. 21(2):277-92

13. Haggerty JJ, Silva SG, Marquardt M, Mason GA, Chang HY, Evans DL, Golden RN, Pedersen C.1997 Prevalence of antithyroid antibodies in mood disorders. Depression and Anxiety. 5:91-96.

14. Kent GN, Stuckey BG, Allen JR, Lambert T, Gee V. 1999 Postpartum thyroid dysfunction: clinical assessment and relationship to psychiatric affective morbidity. Clinical Endocrinology. 54:429-438.

15.Harris B, Huckle P, Thomas R, Johns S, Fung H.1989 The use of rating scales to identify post-natal depression.Br J Psychiatry. 154:813-7.

16. Pop VJ, De Rooy HA, Vader HL, Van der Heide D, Van Son MM, Komproe IH . 1993 Microsomal antibodies during gestation in relation to postpartum thyroid dysfunction and depression. Acta Endocrinologica. 129:26-30.

17. Kuijpens JL, Vader HL, Drexhage HA, Wiersinga WM, van Son MJ, Pop VJ. 2001 Thyroid peroxidase antibodies during gestation are a marker for subsequent depression postpartum. Eur J Endocrinol. 145(5): 579-84

18. Pop VJM, Maartens LH, Leusink G, Van Son MM, Knottnerus AA, Ward AM, Metcalfe R, Weetman AP.1998 Are autoimmune thyroid dysfunction and depression related? Journal of Clinical Endocrinology. 83:3194-3197.

19. Fountoulakis KN, Iacovides A, Grammaticos P, St Kaprinis G, Bech P. 2004 Thyroid function in clinical subtypes of major depression: an exploratory study.BMC Psychiatry. 15;4(1):6.

20. Carta MG, Loviselli A, Hardoy MC, Massa S, Gadeddu M, Sardu C, Carpiniello B, Dell Osso L, Mariotti S. 2004 The link between thyroid autoimmunity (antithyroid peroxidase autoantibodies) with anxiety and mood disorders in the community: a field of interest for public health in the future .BMC Psychiatry. 18;4(1):25.

21. Oretti RG, Hunter C, Lazarus JH, Parkes AB, Harris B.1997 Antenatal depression and thyroid antibodies. Biological Psychiatry. 41:1143-1146.

22. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth edition, Text Revision. Washington, DC: American Psychiatric Association, 2000.

23. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical descriptions and diagnostic guidelines. Geneva: World Health Organization, 1992.

24. Derogatis LR, Lipman RS, Covi L. 1973 SCL-90: an outpatient psychiatric rating scale--preliminary report. Psychopharmacol Bull. 9(1):13-28.

25. Arindel WA, Ettema JH. SCL-90. Een Multidemensionele Psychopathologie Indicator. Lisse: Swets & Zeitlinger.

26. Bijl RV, Rayelli A, van Zessen G. 1998 Prevalence of psychiatric disorder in the general population: results of The Netherlands Mental Health Survey and Incidence Study (NEMESIS).Soc Psychiatry Psychiatr Epidemiol. 33(12):587-95.

27. Ader R, Cohen N, Felten D.1995 Psychoneuroimmunology: interactions between the nervous system and the immune system. Lancet 345:99-103

28. Herschman JM. 1999 Human chorionic gonadotropin and the thyroid: hyperemesis gravidarum and trophoblastic tumors. Thyroid. 9(7):653-7. Review.

29. Glinoer D. 1998: Thyroid hyperfunction during pregnancy. Thyroid 8:859-64.

30. Poppe K, Glinoer D, Tournaye H, Devroey P, Van Steirteghem A, Kaufman L, Velkeniers B. 2003. Assisted reproduction and thyroid immunity: an unfortunate combination ? J Clin Endocrinol Metab 88:4149-4152.

31. Cuijpers P, Schoevers RA. 2004 . Increased mortality in depressive disorders: a review. Curr Psychiatry Rep. 6(6):430-7.

32. Gorman JM. 1997 Comorbid depression and anxiety spectrum disorders. Depression and Anxiety. 4:160-168.

Chapter IV

LOW CONCENTRATIONS OF MATERNAL THYROXIN DURING EARLY GESTATION: A RISK FACTOR OF BREECH PRESENTATION?

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Introduction

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

The negative impact of maternal hypothyroxinemia (low free thyroid hormone concentration (fT4) with thyrotrophin hormone (TSH) concentration within the reference range) during early gestation on subsequent infant development at one and two years of age has recently been demonstrated [7]. At one and two years of age, children of women with hypothyroxinemia showed an 8-to-10 point index delay on the motor scale compared to children of women with fT4 between the 50th and 90th percentiles. Since 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 [8]. Thyroid hormone is extremely important for the development of the foetal central nervous system: overt maternal hypothyroidism during pregnancy or major iodine (a major key-stone of thyroid hormone synthesis) deficiency has been associated with the poor obstetrical and developmental outcome of the infant [9].

Little is known about the aetiology of breech presentation. Together, factors such as prematurity, intra-uterine growth retardation, gemelli, pelvic abnormalities, as well as uterine anomalies, placenta praevia, polyhydramnion, multiparity, umbilical

cord problems, and congenital foetal abnormalities only explain 15% of breech presentations [10]. However, there are several aetiological factors (umbilical cord problems, congenital akinesia syndrome) that might be related to foetal movements during pregnancy [11,12] . It is interesting to note that, in a few congenital endocrinological syndromes (Prader-Willi, pituitary agenesis) in which hypothalamic function is impaired (and, as a consequence, foetal thyroid function), the rate of breech presentations is very high: up to 20% [13].

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

Methods

Subjects

Between January 1997 and April 1998, all pregnant women (n=1881), living in and around the city of Eindhoven, the Netherlands, were invited to participate into the study at their first antenatal control with a community midwife (figure 1). Only Dutch Caucasian women (n=1722) were eligible of whom 1361 (79%) consented to participate. Thyroid parameters (TSH, fT4 and TPO-Ab) were assessed at 12 weeks' gestation. Because of ethical reasons, women with overt hyperthyroidism (n = 7) and hypothyroidism (n = 1) were sent to their general practitioner with an advice for treatment and were excluded. In the first 220 of the remaining 1353 women, the lowest tenth and the 50^{th} - 90^{th} fT4 percentiles were calculated within the first ten weeks' of inclusion: 12.1 and 15.4-19.0 pmol/l, respectively. Thereafter, a further calculation was performed after every consecutive 150 women, which, after minor changes, resulted in the final cut-off scores for the total sample for the tenth (12.4 pmol/l) and 50^{th} - 90^{th} (15.6-19.1 pmol/l) percentiles. The 135 women in the lowest fT4 percentile were matched for parity and gravidity with an equal number of women whose fT4 values

were between the 50th and 90th percentiles. All these women (n = 270) were invited to participate in a follow-up study (figure 1).

Figure 1 Flow-chart of inclusion and exclusion of women during follow-up in pregnancy.

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

data analysis refers to a group of 204 women of whom 108 with an ft4 < 10th and 96 with an fT4 between 50 – 90th percentile at 12 weeks' gestation

Twelve declined to participate, and 20 were excluded, based on previously determined exclusion criteria (fertility problems; presence of autoimmune diseases such as rheumatoid arthritis, or insulin-dependent diabetes mellitus). The remaining 238 women were visited at home at 24 and 32 weeks' gestation for repeated assessments of thyroid function and gestational complications. No thyroid parameters were noted in 21 women at 24 and/or 32 weeks' gestation. Thirteen women with obstetrical complications such as abortion, gemelli pregnancy, and pre-term delivery (<37 weeks' gestation) were excluded. Therefore, analysis of the data covers 204 women.

The characteristics of these women (demographic features, lifestyle habits, obstetrical and thyroid parameters) for the group as a whole are shown in Table 1.

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

Measurements

Thyroid parameters

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

Foetal presentation at term delivery

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

Statistical analysis

Statistical analysis was performed using the Statistical Package of Social Science and Problems Solutions (SPSS). Differences in characteristics between the various subgroups were analysed by means of the chi-square test. OR's (with 95 % CI) were calculated by means of multiple logistic regression analysis.

Results

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

At term gestation (>37 weeks' gestation) twelve women showed foetal position in breech presentation (of whom in one of them cephalic position was reached after external version at 38 weeks' gestation). Of these twelve women, ten (85%) belonged to the subjects with an fT4< 10^{th} percentile at 12 weeks' gestation and two (15%) to the controls with an fT4 between 50-90^{th} percentiles at 12 weeks' gestation ($p = 0.03$, chi-square: 4.7, df=1). Three of the women with foetal breech presentation had a spontaneous vaginal delivery, one women (after external version in cephalic position at 38 weeks' gestation) delivered by vacuum extraction vaginally and the remaining eight delivered by elective Caesarean section. In Table 2a, the relation between breech presentation at term gestation (> 37 weeks') and several

Table 1 Characteristics of the sample: 204 women with gestational age > 37 week's.

	n	(%)
Socio-economic status		
educational level		
low	26	(13)
middle	111	(54)
high	67	(33)
educational level of father		
low	39	(19)
middle	90	(44)
high	75	(37)
income of parents / year		
low (<25.000 US$)	31	(15)
middle (<40.000 US$)	69	(34)
high (>40.000 US$)	88	(43)
unknown	16	(8)
Life style habits during pregnancy		
Smoking	54	(22)
Alcohol intake	26	(13)
Caffeine	159	(78)
Obstetrical parameters		
Parity		
Primiparity	84	(41)
Multiparity	120	(59)
Mean gestational age, weeks (SD)	39.4	(1.4)
Manner of delivery:		
spontaneous at home	92	(45)
spontaneous in hospital	47	(23)
after induction vaginally	20	(10)
forceps/vacuum	26	(13)
Caesarean section	19	(9)
Foetal position at term gestation (>37 weeks')		
Cephalic	192	(94)
Breech	12	(6)
Thyroid parameters		
Sub-clinical hypothyroidism during gestation at:		
12 weeks'	35	(17)
24 weeks'	26	(13)
32 weeks'	21	(10)
Sub-clinical hyperthyroidism during gestation at:		
12 weeks'	6	(3)
24 weeks'	-	-
32 weeks'	-	-
Elevated TPO-Ab titre at 12 weeks' gestation		
> 35 IU/ml	22	(11)
≥ 100 IU/ml	14	(7)

Table 2a **Uni-variate logistic regression** analysis of 204 women: dependent variable breech presentation at term gestation (>37 weeks'), method enter

	O.R.	95%CI
Primiparity	**3.0**	**1.1-10**
Caffeine consumption	1.3	0.3-4.8
Smoking	1.9	0.8-4.9
Alcohol consumption	1.1	0.4-4.6
Low income	1.2	0.5-5.1
Low education	1.1	0.3-3.1
fT4 < 10th percentile		
at 12 wks	**4.7**	**1.1-19**
at 24 wks	3.4	0.8-14
at 32 wks	1.9	0.4-9.5
subclinical hypothyroidism		
at 12 wks	1.2	0.2-5.8
at 24 wks	1.4	0.3-6.7
at 32 wks	1.8	0.4-7.1
subclinical hyperthyroidism		
at 12 wks	1.1	0.4-1.9
TPO-Ab > 35 IU/ml at 12 weeks'	1.4	0.2-6.1
TPO-Ab > 100 IU/ml at 12 weeks'	1.1	0.1-4.7

Table 2b **Multiple logistic regression** analysis of 204 women: dependent variable: breech presentation at term gestation (> 37 weeks'), method enter

	O.R.	95%CI
Primiparity	**4.7**	**1.3-15**
Caffeine consumption	1.1	0.2-3.7
Smoking	1.9	0.4-3.6
Alcohol consumption	1.2	0.4-5.1
Low income	1.1	0.3-3.1
Low education	1.1	0.6-3.7
fT4 < 10th percentile		
at 12 wks	**5.1**	**1.2-22**
at 24 wks	2.7	0.9-18
at 32 wks	1.7	0.2-19
subclinical hypothyroidism		
at 12 wks	1.2	0.2-18
at 24 wks	1.3	0.3-22
at 32 wks	1.1	0.1-19
subclinical hyperthyroidism		
at 12 wks	1.2	0.2-22
TPO-Ab > 35 IU/ml at 12 weeks'	1.1	0.1-16
TPO-Ab > 100 IU/ml at 12 weeks'	1.2	0.2-19

O.R.= odds ratio; CI= confidence interval

independent variables are shown using uni-variate logistic regression analysis (OR, 95% CI).

The risk of breech presentation at term gestation proved to be increased more than fourfold in those women with an fT4 < 10th percentile at 12 weeks' gestation (OR: 4.7; 95% CI: 1.1 – 19) while low fT4 levels at 24 and 32 weeks' gestation was not related to foetal position at term (OR: 3.4; 95% CI: 0.8 – 14 and OR: 1.9; 95% CI: 0.4 – 9.5, respectively). Subclinical hypo-as well as hyperthyroidism was not related to breech position. Primiparity increased the risk for breech presentation threefold (OR:3.0, 95% CI: 1.1 – 10). Finally, in Table 2b, multiple logistic regression showed that breech presentation at term gestation proved to be independently related to low fT4 levels at 12 weeks' gestation as well as to primiparity (O.R.: 5.1, 95% CI: 1.2 – 22 and OR: 4.7, 95% CI: 1.3 – 15, respectively).

Discussion

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

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

The mechanism that could explain the association between maternal hypothyroxinemia and an increased rate of breech deliveries still remains to be explained.

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

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

Several limitations of the present study need to be mentioned. Firstly, the rather low number of women undergoing breech deliveries. Since statistically significant differences were found in rather small numbers in the present study, larger studies with more epidemiological power are needed in order to confirm the association between maternal hypothyroxinemia and the breech position. Only then can interventional trials with thyroxin replacement possibly be considered. Secondly, after screening of a large sample, only women with two well-defined ranges of thyroid hormone concen-

tration (< 10th versus 50-90th percentile) were included for reasons that have been published elsewhere[7] . Preferentially, the relation between thyroid hormone and breech position should be investigated in a large open pregnant population in which fT4 is equally distributed and thyroid function is assessed at different times during gestation.

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

References

1. Hickok D.E., Gordon D.C., Milberg J.A., Williams M.A., Daling J.R. (1992). The frequency of breech presentation by gestational age at birth: a large population-based study. *American Journal of Obstetrics and Gynaecology* **166** 851-852.
2. Hannah M.E., Hannah W.J., Hewson S.A., Hodnett E.D., Saigal S., Willan A.R. (2000). Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. Term Breech Trial Collaborative Group. *Lancet* **356** 1375-1383.
3. Roosmalen J Rosendaal F (2002). There is still room for disagreement about vaginal delivery of breech at term. *British Journal of Obstetrics and Gynaecology* **109**; 967-969.
4. Van Ham M.A., Van Dongen P.W., Mulder J. (1997). Maternal consequences of caesarean section: a retrospective study of intra-operative and postoperative maternal complications of caesarean section during a 10-year period. *European J of Obstetrics, Gynaecology and Reproductive Biology* **74** 1-6.
5. Petrou S & Glazener C (2002) The economic costs of alternative modes of delivery during the first two months postpartum: results from a Scottish observational study. *British Journal of Obstetrics and Gynaecology* **109:** 214217.
6. Healey M., Porter R., Galimberti A. (1997) Introducing external cephalic version at 36 weeks or more in a district general hospital: a review and an audit. *British Journal of Obstetrics and Gynaecology* **104** 1073-1079.
7. Pop V.J., Brouwers E.P., Van Baar A.L., Vader H.L., Vulsma T., De Vijlder J.J. Maternal hypothyroxinemia during early pregnancy and subsequent child development: a 3 year follow-up study.(2003) Clin*ical Endocrinology Oxf*, **59**:282-288.
8. Burrow G.N., Fisher D.A., Larsen P.R. (1994). Maternal and fetal thyroid function. *New England Journal of Medicine* **331** 1072-1078.
9. Glinoer D. (1997). The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocrine Reviews* **18** 404-433.
10. Rayl J., Gibson P.J., Hickok D.E. (1996). A population-based case-control study of risk factors for breech presentation. *American Journal of Obstetrics and Gynaecology* **174** 28-32.
11. Soernes T., Bakke T. (1986). The length of the human umbilical cord in vertex and breech presentations. *American Journal of Obstetrics and Gynaecology* **154** 1086-1087.
12. Adinma J.I. (1993). The umbilical cord: a study of 1,000 consecutive deliveries. *International Journal of Fertility and Menopausal Studies* **38** 175-179.
13. Butler M.G. (1990). Prader-Willi syndrome: current understanding of cause and diagnosis. *American Journal of Medicine and Genetics* **35** 319-332.
14. Kozuma S., Okai T., Ryo E., Nishina H., Nemoto A., Kagawa H., Sakai M., Taketani Y. (1998). Differential developmental process of respective behavioral states in human fetuses. *American Journal of Perinatology* **15** 203-208.
15. Ten Hof J., Nijhuis I.J., Nijhuis J.G., Narayan H., Taylor D.J., Visser G.H., Mulder E.J. (1999). Quantitative analysis of fetal general movements: methodological considerations. *Early Human Development* **56** 57-73.
16. Delange F. (1999). The disorders induced by iodine deficiency. *Thyroid* **4** 107-128.
17. Utiger R.D. (1999). Maternal hypothyroidism and fetal development. *New England Journal of Medicine* **34** 601-602.
18. Lazarus J.H. (1999). Thyroid hormones and neurodevelopment. *Clinical Endocrinology* **50** 47-48.
19. Pop V.J., Van Baar A.L., Vulsma T. (1999). Should all pregnant women be screened for hypothyroidism? *Lancet* **354** 1224-1225.

Chapter V

HIGH MATERNAL ANXIETY DURING LATE GESTATION PREDICTS PROTRACTION OF LABOR

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Introduction

Maternal stress and anxiety during gestation has been related to increased rates of abortion, structural fetal malformations, pre-eclampsia, pre-term delivery, and low birth weight [1,2,3]. Animal research also suggests that stress may affect delivery. A wild mare in the first stage of labor is capable – when observing wolves – to stop dilatation and run for her life in order to continue parturition many hours or even several days later when the safe environment is found [4]. Similarly, stress exposure in rats and mice during parturition delays birth [5,6].

However, studies investigating the relation between anxiety and obstetrical complications in women resulted in inconclusive data, mainly because of problems in the method and timing of anxiety assessment during gestation. Moreover, most studies concentrated on the effect of maternal stress on pre-term delivery [1,7,8]. To our knowledge, there are no studies on the relationship between maternal mental state and the different stages of labor and mode of delivery under the most optimal (and common) conditions: spontaneous onset of labor at term with fetus in the vertex occipito anterior position.

Investigation of this issue is important for several reasons. First, maternal neuroendocrine factors may affect delivery, e.g., (sub)clinical maternal thyroid dysfunction and maternal hypothyroxinemia are related to obstetrical complications and breech presentation [9,10] . Corticotropin-releasing hormone (CRH) may prevent premature myometrical contractions in 'at risk' pregnancies[11], while oxytocin allows CRH to facilitate dilatation and delivery in 'at term' pregnancies [12]. However, anxiety is inversely related to levels of oxytocin in humans[13,14]. Animal research suggests that stress exposure during parturition blocks the increase of oxytocin in the brain, which, in turn, inhibits delivery [5]. Hence, the oxytocin-dampening effect of maternal anxiety might increase the risk for protraction of dilatation time in women who report much stress.

Second, research on stress-management interventions during labor has resulted in national practical guidelines in the USA, Canada and UK which promote a 1:1 continuous support of all women from especially trained care givers during labor [15,16]. However, the cost-effectiveness of this approach has been questioned and a recent

randomized trial failed to show any effect of professional intervention during labor on caesarean section rate. [17] Among other things, little is known about the modulating effect of maternal anxiety on the outcome of these interventions. Hence, taking into account individual differences in anxiety level may be an effective way to monitor behavioral intervention towards the emotional needs of women during end gestation and delivery.

Therefore, the current study investigates the relation between maternal anxiety and the duration of dilatation and expulsion phase in women who delivered after 37 weeks' gestation with the fetus in vertex occipito anterior position, adjusting for psychological and biological confounders (e.g., depression, maternal thyroid function) and other risk factors.

Methods

Participants

During a period of two years (October 2002 and October 2004), out of a total sample of 1985 pregnant women of the community, 1507 Dutch Caucasian pregnant women of four community midwives practices, living in and around the city of Eindhoven, the Netherlands, were invited to participate into the study at their first obstetric control visit (10-12 weeks' gestation). These midwife practices covered a catchments area of 100.000 Dutch Caucasian inhabitants. It should be noticed that, in The Netherlands, women deliver at home or in hospital with a community midwife or in hospital with an obstetrician. The prospective follow-up of the participants in figure 1 shows that for various reasons women were excluded, leaving 908 women for data analysis, 399 primiparous and 509 multiparous women, all of who presented in spontaneous labor at term with the fetus in the occipito-anterior cephalic position.

During follow-up, one midwife saw all participants at 24 and 36 weeks' gestation (HW) who was unaware of biochemical and psychological parameters. During the 36 week's visit, the participants completed anxiety and depression questionnaires. All community midwives used the same protocol to describe onset and progression of labor. Women who delivered primarily in hospital by

Figure 1 Flow-chart of inclusion and exclusion of women during follow-up in pregnancy.

			total n
10-12 wks	Invitation of pregnant women of the community at first obstetric control gestation visit during 24 consecutive months		1985
	Eligible for participation (Caucasian, no auto-immune disease, no fertility problems with hormonal stimulation)		1507
	Informed consent (79%): assessment of general, medical and obstetrical history and thyroid parameters		1191
	Exclusion (n=38) because of:		
	overt (previously unknown) thyroid dysfunction	10	
	twin pregnancy	13	
	uterus anomaly	2	
	late abortion	13	
			1153
24 wks gestation	Assessment of general, medical and obstetrical history and thyroid parameters		
between 24-36 wks gestation	Exclusion (n=60) because of:		
	moving out of the area	14	
	pre-term delivery	46	
			1093
36 wks gestation	Assessment of general, medical and obstetrical history, thyroid function		
	Assessment of anxiety and depressive symp toms		
	Ultrasound of fetal condition and of possible malfor mations		
at delivery	Exclusion (n=185) because of:		
	primary Caesarean Section	4	
	fetes in non-cephalic position	53	
	fetes in cephalic position not occipito-anterior	67	
	ruptured membranes >48 hours, no spontaneous contractions	23	
	children with severe (congenital) malformations	4	
	women who did not complete all questionnaires	34	
number of women who completed the whole study with term gestation and fetus in occipito-anterior position with spontaneous onset of labor			**908**

data analysis refers to a group of 908 women; n=399 primiparous women and n=509 multiparous women.

the obstetrician and women who had - during labor - to be referred by the community midwife to the hospital delivered in one obstetric center: Máxima Medical Center

Veldhoven. All obstetricians working in this hospital use one standardized protocol when and how to intervene in case of protraction of labor. When labor started, all women, who did not deliver with a community midwife, were first seen by a hospital midwife, who followed the same protocol as the community midwife to describe the start and progression of labor and who were also unaware of the biochemical and psychological parameters of the women.

This study was approved by the Medical Ethical Committee of Máxima Medical Center Eindhoven / Veldhoven (the Netherlands).

Study Outcomes

Primary study outcome measures were dilatation in hours and expulsion time in minutes. Secondary outcome measures were obstetrical complications. Dilatation time was expressed in hours from the initiation of labor, which was defined when strong uterus contractions did start regularly (at least every 3 – 5 minutes), lasting at least sixty seconds and resulting in effacement and dilatation of the uterine cervix to ten centimeter. Dilatation time was categorized in quartiles and long dilatation time was defined by a cut-off of the 75^{th} percentile. Similarly, expulsion time was expressed in minutes, starting from the moment the woman actively began bearing down after reaching full dilatation and lasting until expulsion of the baby. Expulsion time was also categorized in quartiles and long expulsion time was defined above the 75^{th} percentile. Obstetrical outcome was defined as shown in table 1. Moreover, the use of pain relief medication (including epidural anesthesia) during labor was carefully assessed.

The independent variable was the intensity of anxiety symptoms at 36 weeks' gestation.

The occurrence of depressive symptoms at 36 weeks' gestation and thyroid parameters were taken into account as possible confounders. Several risk factors, known from literature possibly to interfere with protraction of labor, were also assessed: a previous history of depression in the woman's life, as well as life style habits (smoking, alcohol intake and BMI) and the birth weight of the baby. In multipara, the occurrence of complications during previous deliveries was also noticed.

Table 1 Characteristics of a sample of 908 women with gestational age > 37 weeks with fetus in most physiological position (vertex occipito anterior)

	Primipara N = 399		Multipara N = 509		$\chi^2(1)$	P	t(906) P	
	Mn (SD)	N (%)	Mn (SD)	N (%)				
Demographic features								
Age	29.1 (3.5)		31.6 (3.3)				11	< 0.001
Range	19 42		21 41					
Educational level								
Low		22 (5.5)		49 (10)		ns		
Middle		237 (59)		280 (55)		ns		
High		140 (35)		183 (36)		ns		
Marital status: single		9 (2)		6 (1)		ns		
Working outside home		368 (92)		412 (81)	23.5	< 0.001		
Lifestyle habits								
Smoking		54 (14)		48 (11)		ns		
Alcohol intake		36 (9)		84 (16)	10.7	0.001		
BMI	24.9 4.3		25.6 4.6				2.3	0.019
BMI > 30		49 (12)		80 (16)		ns		
Previous obstetrical history								
Abortion		42 (11)		128 (25)	314	< 0.001		
Mode of previous delivery								
Spontaneous at home				210 (41)				
Spontaneous in hospital				139 (27)				
After stimulation vaginally				79 (16)				
Per vacuum extraction				50 (10)				
Emergency Caesarean Section				31 (6)				
Previous psychiatric history								
Previous episode of depression		52 (13)		68 (13)		ns		
Previous treatment depression		41 (10)		60 (12)		ns		
Use of antidepressants		2 (0.5)		2 (0.4)				ns

Current obstetrical history										
blood loss			3	(0.7)		6	(1.1)		ns	
pre-eclampsia / HELLP			37	(9.2)		15	(2.9)	16.7	< 0.001	
less foetal movement			7	(1.7)		2	(0.3)	4.3	0.04*	
postmaturity (> 42 weeks)			25	(6.2)		23	(4.5)		ns	
(Suite)										
Mental state at 36 weeks'										
Anxiety scores	2.67	(3.6)			2.71	(3.7)				ns
N with scores >90th percentile			48	(12)		57	(11)		ns	
Depression scores on EDS	3.9	(3.6)			4.5	(3.9)				1.9	0.048
N with scores > 11 (= case)	27	(7)			37	(7)			ns	
Thyroid parameters at 36 weeks'										
TPO Ab >35			24	(6)		35	(7)		ns	
sub clinical hypothyroidism			3	(0.8)		9	(1.8)		ns	
sub clinical hyperthyroidism			10	(2.5)		16	(3.1)		ns	
Current delivery history										
delivery by midwife			145	(36)		349	(69)	93.6	<0.001	
spontaneous at home			120	(30)		298	(58)	73.8	< 0.001	
spontaneous in hospital			119	(30)		131	(26)		ns	
after stimulation vaginally			70	(18)		63	(12)		ns	
per vacuum extraction			65	(16)		10	(2)	60.8	< 0.001	
emergency Caesarean Section			25	(6)		7	(1)	15.8	< 0.001	
pain relief medication:										
No			312	(78)		481	(94)	52.7	< 0.001	
Sedativa			9	(2)		7	(1)		ns	
Pethidine			19	(5)		11	(2)	4.7	= 0.03	
Epidural			58	(15)		10	(2)	51.2	< 0.001	
requested by woman			24	(6)		3	(0.6)	22.8	< 0.001	
term at delivery in weeks	40	(1.2)			39.6	(1.1)			ns	
duration dilatation in hours	10.4	(7.1)			5.2	(3.7)				14.3	< 0.001
duration expulsion in minutes	47.6	(32)			14.1	(12.9)				19.2	< 0.001
Neonatal characteristics										
weight of the baby (grams)	3476	(444)			3625	(478)				4.8	< 0.001
n with weight >4000 grams			38	(10)		104	(20)	20	< 0.001	
apgar score after 5 minutes <7			3	(0.8)		2	(0.4)		ns	

Mn = mean; SD = Standard Deviation, * = Fisher Exact test

Instruments

Anxiety

Anxiety was measured using the 10-item Anxiety subscale of the Symptom Check List (SCL-90, Derogatis 1977) [18]. This self-report measure comprises ten items that are scored on a 0-4 response scale (total score ranges between 0 and 40) and is a reliable and valid measure of anxiety. The SCL-90 has been validated before in The Netherlands and its use as well as the use of several subscales only has revealed appropriate psychometric properties [19], also through different countries [20]. It was recently used in a Dutch study to document the detrimental effect of anxiety on long-term prognosis in patients recovering from an acute myocardial infarction [21]. Cronbach's alpha of the SCL-90 was 0.86 in the present study, indicating good internal consistency. High levels of anxiety were defined by a score above the 90th percentile (scores that are regarded as indicative of severe anxiety).

Biological and psychological confounders

Depressive symptoms were assessed using the Edinburgh Depression Scale. This instrument was originally developed for use during the postpartum period (Edinburgh Postnatal Depression Scale) but has also been validated in non-childbearing women [22, 23]. The Dutch version of the E(P)DS has been validated among postpartum women in The Netherlands and in a group of non-childbearing women as well, resulting in new nomenclature: Edinburgh Depression Scale (EDS) [24,25]. The total score on the 10 items ranges between 0 and 30, with a cut-off score of 12 and higher indicating mild to severe depressive symptoms. The Cronbach's Alpha of the EDS in the current study was 0.84 also implying appropriate internal consistency.

Thyroid parameters were also assessed. TSH (thyroid-stimulating hormone, reference range for women aged between 20 and 40 years: 0.4-3.1 mIU/l, (IMMULITE, Diagnostic Corporation, Los Angeles, CA). The FT4 concentration (free thyroxin, reference range for women aged between 20 and 40 years: 10.2–21 pmol/l) was also measured by an immulite essay. Hypothyroxinemia was defined as an FT4 < 10th percentile with TSH between reference range. Sub-clinical thyroid dysfunction was defined by an FT4 within reference range with abnormal TSH, while clinical

thyroid dysfunction was defined by both FT4 and TSH levels outside reference range. The IMMULITE Anti-TPO Ab kit was used to determine antibodies against thyroid peroxidase (TPO-Ab). A concentration of $\geq$ 35 IU/ml was defined as being elevated.

Possible risk factors

Demographic features (age, marital status and education level), life style habits (smoking, alcohol intake and BMI) and a general medical history (including previous episodes of depression) were assessed at 12 week's gestation. Moreover, obstetrical complications during gestation and possible use of medication were assessed prospectively until delivery.

Statistics

Differences in socio demographic characteristics between the study groups were analyzed using χ^2 tests with continuity correction (or Fisher's exact test when appropriate) for categorical data and Student T-tests for continuous data. The reliability of the screenings instruments was evaluated by calculation of Cronbach's alpha. Univariate and multiple logistic regression analyses were performed. Firstly, the relation between the independent variable (anxiety) and the primary outcome measures (dilatation and expulsion time) was analyzed using univariate logistic regression analysis. To understand the relative importance of confounders and risk factors adjusted Odd Ratio's (ORs with 95% confidence intervals [95% CI's]) were calculated with sequential multiple logistic regression analyses. Because parity is an important predictor of long dilatation and expulsion time separate multiple logistic regression analyses were performed for nulliparous and multiparous women. In multipara, complications during a previous pregnancy resulting in technical interventions (Caesarean section) are a well-known risk factor for protraction of labor in future labor. Therefore, this confounder was also put into the multiple regression analysis of multipara. Finally, with regard to the secondary outcome measure (the relation between dilatation time and obstetrical outcome), a univariate logistic regression analysis was performed for nullipara and multipara separately.

All statistical analyses were performed using the Statistical Package of Social Science version 12.0 (SPSS).

Results

Characteristics of the participants as well as obstetrical and thyroid parameters are shown in Table 1. The mean duration of dilation (10.4 versus 5.2 hours) and expulsion (48 versus 14 minutes) was significantly higher in primiparous women as compared to multiparous women, $t(906)=12.4$, $p<.001$ and $t(906)=17.2$, $p<.001$, respectively. Mean anxiety scores as well as the number of women with anxiety scores above the 90th percentile were similar in nulli- and multipara. (Table 1).

Figure 2 shows the prevalence rates of high anxiety scores (> 90th percentile) in 57 multipara (Figure 2a) and 48 nullipara (figure 2b) according to different quartiles of dilatation time (in hours). In both groups, the distribution of high anxiety scores was similar (between 10-11%) in the lowest three quartiles of dilatation time while in the highest quartile (>75) the prevalence of women with high anxiety scores was substantially higher in multipara (17%) and significantly higher (20%) in nullipara ($\chi 2(3)$: 7.9, $p = 0.04$). Long expulsion time (> 75th percentile: 67 and 16 minutes for nulli- and primipara, respectively) was not related to anxiety scores (data not shown). Subsequent univariate logistic regression analysis with long dilatation time (>75th percentile) as dependent variable and high anxiety score (> 90th percentile) as independent variable revealed for nullipara an OR of 2.3 (95% CI: 1.2 - 4.4) and for multipara an OR of 1.9 (95% CI: 1.1 - 3.4). As can be seen in Table 1, there were 24 primipara and 3 multipara women who received epidural pain relief intervention on their own request during labor. However, the actual number of women who, during labor, asked for pain relief was 34, 29 nullipara and 5 multipara. These seven women did not receive pain relief because the request was done during labor at a dilatation at or over eight centimeter. Of the 34 women who asked for epidural anesthesia there were 11 (32%) women with high anxiety scores at 36 weeks' gestation which was significantly different from the 874 women who did not ask for pain relief of whom 96

Figure 2a: Distribution of women (n=57) with high anxiety scores (> 90th centile) according to dilatation time (quartiles) in 509 multipara

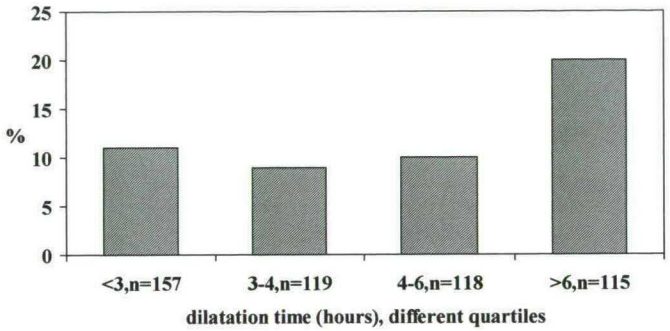

Figure 2b: Distribution of women (n=48) with high anxiety scores (> 90th centile) according to dilatation time (quartiles) in 399 primipara

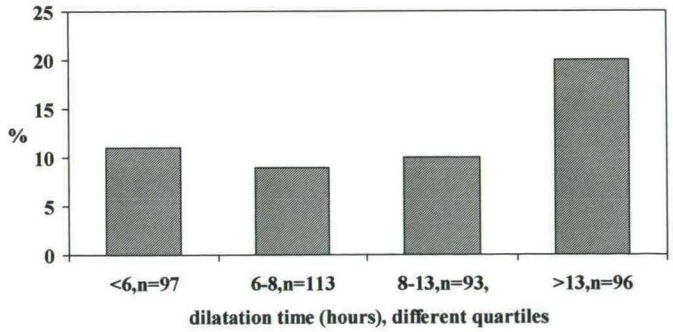

Table 2 Multiple logistic regression analysis of pregnant women with > 37 week's term gestation and the fetus in cephalic occipito-anterior position. (O.R., 95% CI). Dependent variable:

A. Long duration of dilatation time (> 75th percentile: > 13 hours), **nullipara, n = 399**

	O.R.	95%CI
High age of the mother	1.2	0.7-1.8
Depression (EDS > 11) at 36 weeks' gestation	1.3	0.6-3.5
Previous history of depression in life	2.1	0.8-4.8
Anxiety: (SCL-90 subscale scores > 90th percentile) at 36 weeks'	**2.6**	**1.3-5.1**
Obstetric factors		
Previous pregnancy with complicated delivery	--	-------
term of gestation	1.1	0.8-1.9
pre-eclampsia	1.5	0.7-3.8
high birth weight of the baby (> P 90 = 4200 gram)	1.6	0.6-3.2
Life style habits		
Smoking during gestation	1.8	0.7-3.1
alcohol intake	1.6	0.8-3.9
high BMI (> 30 at 12 weeks' gestation)	1.2	0.6-2.4
Thyroid parameters		
increased TPO-Ab titers	2.1	0.6-4.0
sub-clinical hyperthyroidism (TSH < 0.4 IU/l)	1.5	0.3-6.1
sub-clinical hypothyroidism (TSH > 3.1 IU/l)	2.1	0.5-7.1

(Suite)
B. Long duration of dilatation time (> 75th percentile: > 6 hours), **multipara, n= 509**

	O.R.	95%CI
High age of the mother	**1.5**	**1.2-2.4**
Depression (EDS > 11) at 36 weeks' gestation	2.5	0.8-4.8
Previous history of depression in life	1.1	0.5-2.7
Anxiety: (SCL-90 subscale scores > 90th percentile) at 36 weeks'	**2.3**	**1.2-4.6**
Obstetric factors		
previous history of Caesarean section	**5.4**	**2.6-9.1**
term of gestation	**1.2**	**1.1-1.5**
pre-eclampsia	1.2	0.6-1.7
high birth weight of the baby (> P 90 = 4200 gram)	1.6	0.8-3.4
Life style habits		
smoking during gestation	1.7	0.8-3.2
alcohol intake	1.4	0.7-3.1
high BMI (> 30 at 12 weeks' gestation)	1.6	0.8-3.4
Thyroid parameters		
increased TPO-Ab titers	1.1	0.5-2.6
sub-clinical hyperthyroidism (TSH < 0.4 IU/l)	1.3	0.5-5.2
sub-clinical hypothyroidism (TSH > 3.1 IU/l)	1.4	0.5-4.1

O.R.=odds ratio; CI= confidence interval

Table 3 Obstetrical outcome and pain relief interventions in relation to long duration of dilation ($\geq 75^{th}$ percentile) in 908 women with term > 37 weeks' gestation with fetus in physiological presentation (vertex occipito anterior) according to parity.

Table 3 a Mode of delivery

Primiparous, n = 399

	Dilatation <75th percentile N = 304 n (%)	Dilatation $\geq 75^{th}$ percentile ($\geq$13 hrs) N = 95 n (%)	X^2 (1)	p
			27	p<0.001
spontaneous	203 (67)	35 (38)	6	p=0.01
after induction vaginally	45 (15)	25 (26)	11	p=0.001
with forceps / vacuum	39 (13)	26 (27)	1.8	p=0.18
emergency Caesarean section	17 (5)	9 (9)		

Multiparous, n = 509

	Dilatation <75th percentile N = 395 n (%)	Dilatation $\geq 75^{th}$ percentile ($\geq$6 hrs) N = 114 n (%)	X^2 (1)	p
Spontaneous	353 (89)	76 (67)	84	p<0.001
after induction vaginally	37 (9.5)	26 (23)	10.7	p= 0.001
with forceps / vacuum (Suite)	3 (1)	7 (6)	13	p<0.001
emergency Caesarean section	2 (0.5)	5 (4)	9.8	P= 0.002

Table 3 b **Pain relief intervention**

Primiparous, n = 399

	Dilatation <75th percentile	Dilatation ≥75th percentile (≥13 hrs)		
	N = 304	N = 95		
	n (%)	n (%)	X^2 (1)	p
no intervention	267 (88)	46 (48)	66	p<0.001
sedation and pethidin	13 (4)	15 (16)	14.7	p<0.001
epidural anesthesia	24 (8)	34 (36)	45	p<0.001

Multiparous, n = 509

	Dilatation <75th percentile	Dilatation ≥75th percentile (≥6 hrs)		
	N = 395	N = 114		
	n (%)	n (%)	X^2 (1)	p
no intervention	387 (98)	94 (83)	40	p<0.001
sedation and pethidin	7 (1)	11 (10)	16	p<0.001
epidural anesthesia	1 (0.3)	9 (8)	26	p<0.001

showed (11%) high anxiety scores ($\chi 2(1)$: 7.6, p = 0.006). Univariate logisticregression analyses revealed that depressive symptoms (scores > 11 on the EDS) were not related to protraction of dilatation in nullipara (OR: 1.2, 95% CI: 0.6 - 21) or in multipara (OR: 1.2, 95% CI: 0.7 - 1.9).In Table 2, estimates of a sequential multiple logistic regressions are shown with the dependent variable dilatation time > 75th percentile and the independent variable high anxiety scores (> 90th percentile) and several risk factors, for nullipara (Table 2a) as well as multipara (Table 2b). The age of the mother was categorized in 4 groups of 5 years.

In primiparous women (Table 2a), high anxiety levels were significantly related to long duration of dilatation (OR: 2.6, CI: 95% 1.3 - 5.1). In multiparous women, in addition to high anxiety levels, high age of the mother, a previous history of caesarean section and term of gestation were independently related to long dilatation time (Table 2b).

For the other main outcome variable *long expulsion time*, in primipara no relations were found with high anxiety at a univariate or with any variable at a multiple level (data not shown). In multipara women, a BMI > 30 and higher age were significantly related to long expulsion time, OR: 1.5, 95% CI: 1.1 - 2.2 and OR: 1.6, 95% CI: 1.2 - 2.4, respectively. Depressive symptoms as well as thyroid parameters were not related to long dilatation or expulsion time in both primipara and multipara..

Table 3 shows the relationships between increased dilatation time and both mode of delivery and different types of pain relieve interventions according to parity. In primipara, all prevalence rates of modes of delivery (except for emergency Caesarean section) differed significantly with regard to dilatation time. In multiparous women all four modes of delivery differed significantly with regard to dilatation time (Table 3a). Similarly, prevalence rates of a long duration of dilation were significantly different in primipara and multipara women with regard to different pain relief interventions (Table 3b). Finally, when, for the group as a whole, parturition was dichotomized into spontaneous versus non-spontaneous delivery, univariate logistic regression analysis showed an OR of 5.2 (95% CI: 3.3 -7.7) of a dilatation time > 75th percentile to deliver non-spontaneously and an OR of 3.0 (95% CI: 1.3 – 6.6) to deliver by caesarean section.

Comment

This prospective follow-up study of a community sample of 399 nullipara and 509 multipara, with term of gestation over 37 weeks' and the fetus in occipito-anterior position and a spontaneous onset of labor shows that anxiety, assessed at 36 week's gestation, is an independent predictor of long dilatation time during delivery and not of expulsion time (primary outcome). Increased dilatation time in turn is associated with obstetrical complications such as increased rate of technical interventions and emergency caesarean section (secondary outcome).

By selecting only women with occipito-anterior position of the fetus with term over 37 weeks' gestation, an important confounder that might interfere with dilatation time but the effect of which is difficult to standardize (e.g. abnormal fetal position), could be excluded from the analysis. It should be realized that occipito-anterior position is the most optimal and common position that favors fetal passage through the birth canal and represents up to 85% of all term deliveries. No relation was found between thyroid parameters and obstetrical outcome in the current study. Thyroid parameters – especially clinical thyroid dysfunction, elevated TPO-Ab and hypothyroxinemia – have been associated with pre-term delivery and breech presentation but these women were excluded from the analysis [9,10,26].

There are several reports studying the relation between maternal anxiety during gestation and pre-term labor [27,28] or the occurrence of stress-full life events and pre-term labor [29]. Some studies showed a significant relation between depression / anxiety and operative deliveries, however not taken into account fetal position when delivery started [30] while other studies could not find a significant impact of anxiety and depression on mode of delivery [8,30]. Most of these studies did not discriminate between the different stages of labor and did not restrict to women with the most physiological fetal presentation at term or suffered from methodological problems as summarize elsewhere [8].

In the current study, depressive symptoms were not related to protraction of labor, even not at univariate level, which is in line with a recent study using a similar instrument to assess depression [31]. In psycho-cardiology, it has also recently been demonstrated that anxiety rather than depression shows to be a better predictor of

poor prognosis after myocardial infarction with regard to new cardiac episodes or death [21].

With regard to pain relief interventions an interesting relation with anxiety was also found. Pain relief interventions in The Netherlands during labor in general (including epidural anesthesia) are (still) rare and a consequence rather than a cause of obstetrical problems. The fact that women who asked for pain relief during labor showed significantly more often high anxiety scores suggests that asking for pain relief might be a symptom of high anxiety symptoms.

How to explain the relation between anxiety and protraction of dilatation time? Neuroendocrine studies have shown that exposure to hostile conditions initiates stress-responses (including the hypothalamic-pituitary-adrenocortical axis) organized to enhance the probability of survival, as is the case in the foaling mare [32,4]. Stress response includes increased secretion of epinephrine and norepinephrine, release of corticotropin-releasing hormone (CRH) and vasopressin and of pituitary adrenocorticotropin (ACTH). Some studies report that CRH acts as a 'stress peptide' that is synthesized in increased amount in 'at risk' pregnancies to try to prevent premature myometrical contractions [11,33]. At term these protective mechanism are disabled under the influence of the oxytocin receptor, allowing CRH via an alternative route to participate in mechanism that enhances dilatation and expulsion of the fetus [12]. In mice, stress exposure during parturition halted subsequent delivery with no increase of oxytocin in the brain, as is the case in normal parturition [5]. Administration of oxytocics in stress-exposed mice restored parturition. Moreover, administration of beta-adrenergic antagonist restored stress-delayed birth while administration of a beta-agonist delayed birth in non-stressed mice [6]. Recent studies in human have shown that participants who receive (nasal) oxytocin exhibit lower cortisol concentrations during stress exposure [13] and that greater partner support was linked to higher plasma oxytocin, suggesting that there is an inverse relation between oxytocin levels and anxiety [14]. A tentative explanation of the findings of the current study might be that anxious women produce larger amounts of CRH, which will overrule the oxytocin receptor, dampening myometrical contractility. Besides, adrenergic mechanisms are involved in delaying birth.

Several limitations of the study need to be mentioned. Firstly, it might be questioned whether anxious women in general contact their midwife or obstetrician more rapidly

when contractions start at term. If so, it might be hypothesized that the findings of the current study are biased because the midwife/obstetrician register the start of labor at an earlier stage in anxious women compared to non-anxious women. However, all women – at home or in hospital – were (first) seen by a midwife once they asked for obstetrical care because they believed labor started. The midwife decided (by anamnesis and vaginal examination) whether labor had started or not: contractions of at least sixty seconds at regular intervals of 3-5 minutes resulting in effacement and dilatation of the uterine cervix. When there was no effacement or dilatation there was no question of onset of labor. In total, twenty midwives (ten in hospital and ten in the community) participated into the study following this protocol and who were all unaware of the woman's biochemical and psychological parameters. It is obvious that inter assessor variability might have influenced the registration of total time of dilatation but there is no argument to suggest that possible errors will have been made more frequently in anxious women. Secondly, anxiety was assessed according to the mental state in the previous seven days. Ideally, in order to assess anxiety during labor, this scale should be taken off just before labor starts or within the first postpartum days. The first option is impossible for obvious reasons (in spontaneously delivering women) and the second option is less desirable because during the first postpartum days many women are susceptible to major mood fluctuations (blues) resulting in recall bias [34].

The findings in this study have several relevant implications. First, as mentioned before, the cost-effectiveness of national practical guidelines which promotes a 1:1 continuous support from especially trained care givers during labor has been questioned [17]. With regard to the findings of the current study an important implication for future research could be that the effect of (professional) support during labor should preferentially be investigated in women with high anxiety levels at late term. Secondly, obstetric care by community midwives in The Netherlands can only exist because of severe selection of low-risk women of obstetrical problems on the basic of strict criteria, which are applied rigorously by all midwives. Surprisingly, these criteria almost all refer to somatic and physical aspects of the pregnant woman. There are no standardized psychological instruments used in daily practice to detect high-risk women with regard to anxiety. Given the fact that several instruments to detect anxiety do exist (self-rating scales) which are easily to complete in several minutes, the

findings of the current study support the promotion of assessment of anxiety during (late) gestation as part of selecting high risk women for obstetrical complications.

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References:

1. Dayan J, Crevuil C, Herlicoviez M, Herbel C, Baranger E, Savoye C, Thouin A. Role of anxiety and depression in the onset of spontaneous preterm labor. Am J Epidemiol. 2002;155(4):293-301.
2. Andersson L, Sundström-Poromaa I, Wulff M, Åström M, Bixo M. Implications of antenatal depression and anxiety for obstetric outcome. Obstet Gynecol. 2004;104(3):467-76.
3. Wadhwa PD. Psychoneuroendocrine processes in human pregnancy influence fetal development and health. . Psychoneuroendocrinology. 2005;30(8):724-43
4. Naaktgeboren C, Bontekoe EH. Vergleichend-geburtskundliche Betrachtungen und experimentelle Untersuchungen über psychosomatische Störungen der Schwangerschaft und des Geburtsablaufes. Z Tierzüchtung und Züchtungsbiol. 1976;93:264-320
5. Douglas AJ, Leng G, Russell JA. The importance of oxytocin mechanisms in the control of mouse parturition. Reproduction. 2002;123(4):543-52.
6. Douglas AJ, G, Russell JA. Endogenous opioid regulation of oxytocin and ACTH secretion during pregnancy and parturition. Prog Brain Res. 2001;133:67-82
7. Johnson RC, Slade P. Obstetric complications and anxiety during pregnancy: is there a relationship? J Psychosom Obstet Gynaecol. 2003 Mar;24(1):1-14.
8. Wu J, Viguera A, Riley L, Cohen L, Ecker J. Mood disturbance in pregnancy and the mode of delivery. Am J Obstet Gynecol. 2002;187(4):864-7.
9. Morreale de Escobar G, Obregon MJ, Escobar del Rey F. Role of thyroid hormone during early brain development. European Journal of Endocrinology. 2004;151:1-14.
10. Pop VJ, Brouwers EP, Wijnen H, Oei G, Essed GG, Vader HL. Low concentrations of maternal thyroxin during early gestation: a risk factor of breech presentation? BJOG. 2004;111(9):925-30.
11. Grammatopoulos DK, Chrousos GP,Functional characteristics of CRH receptors and potential clinical applications of CRH-receptor antagonists. Trends Endocrinol Metab. 2002;13(10):436-44. Review.
12. Hillhouse EW, Grammatopoulos DK. Role of stress peptides during human pregnancy and labour. Reproduction. 2002;124(3):323-9. Review.
13. Heinrichs M, Baumgartner T, Kirschbaum C, Ehlert U. Social support and oxytocin interact to suppress cortisol and subjective responses to psychosocial stress. Biol Psychiatry 2003; 54:1389-1398.
14. Grewen KM, Girdler SS, Amico J, Light KC. Effects of partner support on resting oxytocin, cortisol, norepinephrine, and blood pressure before and after warm partner contact. Psychosom Med. 2005;67(4):531-8.
15. Kennell J, Klaus H, Mc Grath S, Robertson S, Hinkley C. Continuous emotional support during labor in a US hospital. A randomized controlled trial. JAMA. 1991;265(17):2197-201.
16. Hodnett ED, Gates S, Hofmeyr GJ, Sakala C. Continuous support for women during childbirth.
Cochrane Database Syst Rev. 2003;(3):CD003766. Review.
17. Hodnett ED, Lowe NK, Hannah ME, Willan AR, Stevens B, Weston JA, Ohlsson A, Gafni A, Muir HA, Myhr TL, Stremler R; Nursing Supportive Care in Labor Trial Group. Effectiveness of nurses as providers of birth labor support in North American hospitals: a randomized controlled trial.
JAMA. 2002 18;288(11):1373-81.
18. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale--preliminary report. Psychopharmacol Bull. 1973;9(1):13-28.
19. Arindelll WA, Ettema JH. Dimensional structure, reliability and validity of the Dutch version of the Symptom Cecklist (SCL-90). Ned Tijdschr Psychologie. 1981;43:381-7.
20. Zvolensky MJ, Arrindell WA, Taylor S, Bouvard M, Cox BJ, Stewart SH, Sandin B, Cardenas SJ, Eifert GH. Anxiety sensitivity in six countries. Behav Res Ther. 2003;41(7):841-59.

21. Strik JJ, Denollet J, Lousberg R, Honig A. Comparing symptoms of depression and anxiety as predictors of cardiac events and increased health care consumption after myocardial infarction. J Am Coll Cardiol. 2003;42(10):1801-7.
22. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale.Br J Psychiatry. 1987;150:782-6.
23. Cox JL, Chapman G, Murray D, Jones P.Validation of the Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women. J Affect Disord. 1996;39(3):185-9.
24. Pop VJ, Komproe IH, van Son MJ. Characteristics of the Edinburgh Post Natal Depression Scale in The Netherlands. J Affect Disord. 1992;26(2):105-10.
25. Becht MC, van Erp CF, Teeuwisse TM, van Heck GL, van Son MJ, Pop VJ. Measuring depression in women around menopausal age: towards a validation of the Edinburgh Depression Scale. J Affect Disord. 2001;63(1-3):209-13.
26. Prummel MF, Wiersinga WM. Thyroid autoimmunity and miscarriage. Eur J Endocrinol. 2004;150(6):751-5. Review.
27. Hedegaard M, Hendriksen TB, Secher NJ, Hatch MC, Sabroe S. Do stressful life events affect duration of gestation and risk of preterm delivery? Epidemiology. 1996 ;7(4):339-45.
28. Chung TK, Lau Tk, Yip AS, Chiu HF, Lee DT. Antepartum depressive symptomatology is associated with adverse obstetric and neonatal outcomes. Psychosom Med. 2001;63(5):830-4.
29. Andersson L, Sundström-Poromaa I, Wulff M, Åström M, Bixo M. Implications of antenatal depression and anxiety for obstetric outcome. Obstet Gynecol. 2004;104(3):467-76.
30. Perkin MR, Bland JM, Peacock JL, Anderson HR. The effect of anxiety and depression during pregnancy on obstetric complications.Br J Obstet Gynaecol. 1993;100(7):629-34.
31. Larsson C, Sydsjo G, Josefsson A. Health, sociodemographic data, and pregnancy outcome in women with antepartum depressive symptoms. Obstet Gynecol. 2004;104(3):459-66.
32. Carrasco GA, van de Kar LD. Neuroendocrine pharmacology of stress. Eur J Pharmacol. 2003;463(1-3):235-72. Review
33. Challis JR, Matthews SG, Gibb W, Lye SJ. Endocrine and paracrine regulation of birth at term and preterm. Endocr Rev. 2000;21(5):514-50. Review.
34. Brockington I. Postpartum psychiatric disorders. Lancet. 2004;363(9405):303-10. Review.

Chapter VI

VERTEX POSITION DURING LABOUR IN RELATION TO MATERNAL THYROID FUNCTION

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Introduction

At term up to 95% of the foetus presents in cephalic presentation. Within this group, around 90% presents in vertex occipito-anterior position which is regarded as the most physiological position. The efficient way for the foetus to negotiate the birth canal is in vertex presentation which enables the biparietal plane of the fetal head entering the pelvic inlet during labour (1). As the head continues to descent beyond this point, pressure and resistance on the vertex result in flexion of the fetal neck. The remaining cardinal movements of labour follow: internal rotation at the neck, extension of the head, external rotation (restitution) and finally complete expulsion of the foetus (1).

In general it is accepted that abnormal labour can be the result of one or more anatomical abnormalities of the cervix, the uterus (including placental localisation) and maternal pelvis, or the foetus as well as abnormal functional factors such as uterus contractions (2). These factors have been defined elsewhere as: 'the pelvis, the power and the passenger' (3).

Overt thyroid dysfunction during pregnancy has repeatedly been associated with poor obstetrical outcome such as increased rate of abortion, foetal death, preterm-delivery, neonatal tachycardy (4). Similarly, the presence of elevated titres of thyroid peroxidase antibody (TPO-Ab) – even in the absence of overt thyroid dysfunction - has been associated with increased rate of miscarriage, gestational hypertension and increased foetal death (5). During the last two decades several studies reported an increased risk of psychomotor problems in the offspring of mothers with hypothyroxinemia (fT4 levels at the lower range with normal thyroid stimulating hormone (TSH)) during gestation (6). It might be hypothesized that, when psychomotor problems of the offspring postpartum are related to maternal thyroid hormone concentrations during gestation, psychomotor retardation should also be present in the foetus.

In human, thyroid hormone is important for normal muscle tonus and neurological reflexes. Therefore, it seems reasonable to assume that obstetrical outcome (and more specifically protraction of labour) might reflect an indirect way of looking at foetal motor development.

The present study investigated the relation between maternal thyroid hormone concentrations and obstetrical outcome with regard to foetal position during the second stage of delivery (the expulsion of the foetus) and mode of delivery in healthy pregnant women who present with the foetus in cephalic position at term.

Methods

Subjects

This study was approved by the Medical Ethical Committee of the Máxima Medical Centre Veldhoven / Eindhoven, The Netherlands.
Between July 2002 and December 2004, healthy Dutch Caucasian singleton pregnant women of five community midwives practices, living in and around the city of Eindhoven, the Netherlands, were invited to participate in the study at their first antenatal control (10 weeks' gestation). Women with a history of thyroid dysfunction or other autoimmune disease, uterine anomalies, or fertility problems prior to the current pregnancy were not included in the study. After women had given informed consent, thyroid parameters (TSH, fT4 and TPO-Ab) were assessed at 12 weeks' gestation. Women with previously unknown overt hyperthyroidism and hypothyroidism at their first assessment were excluded. Women with late pregnancy failure - delivery before 37 weeks of gestation, a baby in non-cephalic presentation at 37 weeks, as well as those who had a primary Caesarean section - were excluded. Finally, women who had a child with severe congenital anomalies were excluded from the study.

Measurements

Thyroid parameters

Thyroid parameters were assessed at 12, 24 and 36 weeks, but for the purpose of this analysis, only measurements at 36 weeks of gestation were used. We measured TSH (reference range for women aged between 20 and 40 years: 0.04-3.1 mIU/l) using a solid-phase, two-site, chemiluminescent enzyme immunometric assay (IM-

MULITE third generation TSH, Diagnostic Corporation, Los Angeles, CA). The inter-assay coefficients of variation were 5.0% and 4.4% at concentrations 0.22 mIU/l and 2.9mIU/l, respectively. The fT4 concentration (reference range for women aged between 20 and 40 years: 10.2–21 pmol/l) was also measured by means of a solid-phase immunometric assay (IMMULITE Free T4, Diagnostic Corporation, Los Angeles, CA). The inter-assay coefficients of variation for this technique were 6.7% and 4.4% at concentrations of 11.6 pmol/l and 31.5 pmol/l, respectively.
The IMMULITE Anti-TPO Ab kit was used to determine antibodies against thyroid peroxidase (TPO). The inter-assay coefficients of variation for this analysis were 9% and 9.5% for concentrations of 40 kU/l and 526 kU/l, respectively. The anti-TPO assay was standardized according to the International Reference Preparation for anti-TPO MRC 66/387. A concentration of between 35 and 100 IU/ml was regarded as being elevated.

Foetal position at term delivery

At delivery, the thyroid status of the patient was unknown for the midwife or gynaecologist assisting with the delivery. The cephalic position (vertex occipito-anterior versus other cephalic position) was carefully assessed during first and/or secondary stage of labour. At birth, vertex presentation in occipito anterior position was defined as anterior position. All other cephalic presentations were categorized as abnormal vertex positions, thus including occipito posterior position, brow and face position and asynclitism. Moreover, the mode of delivery in both groups was categorized as spontaneous delivery, assisted vaginal delivery (forceps or ventouse) or secondary Caesarean section.

Statistical analysis

To evaluate whether the outcome of labour was related to the thyroid status of the patient, we studied the associations between fT4 and TSH with the position of the foetal head (anterior/posterior versus other) and the mode of delivery (spontaneous versus non-spontaneous). First, we assessed the linearity of fT4 and TSH on one

hand, and the outcome of labour on the other hand, using spline functions (7). Non-linear associations were redefined, based on these spline functions. We then performed univariable and multiple logistic regression analyses with the position of the foetal head (anterior versus other) and outcome of delivery (instrumental versus spontaneous delivery) as dependent variables. In the multiple regression analysis we corrected for maternal age, induction by amniotomy and /or use of prostaglandin's, foetal weight, parity, gestational age, maternal height and weight, as well as for the position of the foetal head.

Results

In the study period, 1,475 women were seen, of whom 68 were not included due to a history of thyroid dysfunction or other autoimmune disease, uterine anomalies, or fertility problems prior to the current pregnancy. Of the remaining 1,407, 1,065 (76%) consented to participate, and thyroid parameters (TSH, fT4 and TPO-Ab) were assessed at 12 weeks' gestation. After this assessment, women with (unknown) overt hyperthyroidism (n = 8) and hypothyroidism (n = 2) at their first assessment were sent to their general practitioner with an advice for treatment.

Of the 1,055 remaining women, 13 delivered prior to 37 weeks, 32 women had a non-cephalic position at the start of delivery, 47 had a primary caesarean section, and 3 had an unknown position of the foetal head at the start of labour, leaving 960 women with cephalic presentation at term for analysis, Table 1.

Of these 960 women, 891 (93%) presented with the foetus in vertex occipto-anterior position. Table 2 shows the distribution of FT4 and TSH among women with an anterior position of the foetal head as compared to women with the foetal head in another cephalic position, both for the whole group as well after stratification for parity and mode of delivery. Women with a vertex anterior position of the foetal head had statistically significant higher levels of FT4 compared to those with an abnormal cephalic presentation (Wilcoxon test, P-value .02), which was not the case for TSH (Wilcoxon test, P-value .58) or TPO-Ab (Wilcoxon test, P-value .52, data not shown).

Table 1 Characteristics of a sample of 960 women in whom thyroid parameters were assessed at 36 weeks' gestation with parturition at gestational age >37 weeks with foetal cephalic position.

			n	(%)
Demographic features				
age (mean, SD)			29	(0.6)
marital status				
With partner			901	(98)
Single			15	(2)
educational level				
Low			78	(9)
Middle			409	(45)
High			354	(38)
Academic			74	(8)
working outside home				
Yes			791	(86)
No			123	(14)
Life style habits				
Smoking:	never		504	(55)
	stopped earlier in life		211	(23)
	stopped during pregnancy		86	(9)
	yes:	< 10 / day	100	(11)
		> 10 / day	16	(2)
Alcohol intake:	never		271	(30)
	stopped during pregnancy		517	(56)
	≥ 2 consumptions / week		127	(14)
Body mass index	:	<20	56	(6)
	between 20 and 25		425	(46)
	between 26 and 30		308	(33)
	>30		138	(15)
Obstetrical features				
During gestation				
Parity				
Primiparity			561	(58)
Multiparity			400	(42)
previous history of Caesarean section			36	(3.9)
At delivery:				
Term at gestation				
mean (SD) in weeks		39.9 (1.2)		
range in weeks		37.0-42.6		
Weigth (gr) of the baby at birth				
Mean (SD)		3545 (472)		
Range		1840-4990		

Table 2

Median and range of FT4 and TSH in women delivering with the foetal head in anterior position or other cephalic position, stratified for parity and mode of delivery.

	FT4 (pmol/l)				TSH (mIU/L)	
	Anterior position		Other cephalic position		Anterior position	Other cephalic position
All	N=891	13.3 (7.2 to 37)	N=69	12.6 (8.9 to 20.6)	1.4 (.05 to 5.)	1.3 (.45 to 4.8)
Multiparous						
Spontaneous delivery	N=419	13.3 (7.2 to 37)	N=10	14.0 (10.6 to 16.5)	1.4 (.10 to 5.0)	1.4 (.45 to 2.4)
Assisted delivery	N=96	12.9 (8.1 to 18)	N=36	11.9 (8.9 to 20.6)	1.6 (.20 to 4.6)	1.4 (.52 to 4.8)
Nulliparous						
Spontaneous delivery	N=366	13.3 (8.6 to 18)	N=16	12.3 (10 to 16.7)	1.4 (.05 to 4.5)	1.1 (.45 to 3.5)
Assisted delivery	N=11	12.7 (9.9 to 15)	N=7	12.6 (9.5 to 14.9)	1.3 (.31 to 1.8)	1.4 (.50 to 2.4)

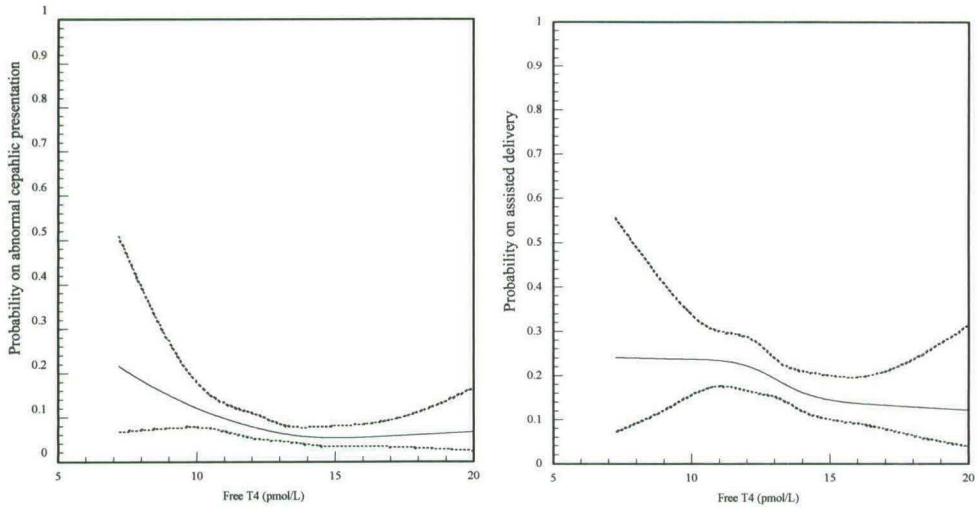

Figure 1. **Figure 1A shows the relation between FT4 and the probability of an abnormal position of the foetal head. Figure 1B shows the probability of an instrumental delivery in nulliparous women who had the foetal head in normal position. In both analyses, the spline analysis did not show a significant cut-off point. (_____ estimated probability, ------- 95% confidence interval).**

Figure 1A shows the relation between FT4 and the probability of an abnormal position of the foetal head. There was no significant cut-off point for FT4. Figure 1B shows the probability of an instrumental delivery in nulliparous women who had the foetal head in normal position. Again, the spline analysis did not show a significant cut-off point. As a consequence, FT4 was considered to be a linear continuous variable at further analysis.

Table 3 shows the results of the logistic regression analysis with the risk of an abnormal position of the foetal head as dependent variable.

Table 3 **Logistic regression analysis showing the risk of an abnormal position of the foetal head.**

	Risk for abnormal position of the foetal head			
	Univariable analysis		Multivariable analysis	
	OR	95% CI	OR	95% CI
FT4 (per pmol/L)	.87	.77 to .99	.88	.77 to .99
TSH (per mIU/L)	.99	.71 to 1.4	.94	.67 to 1.3
TPO-Ab	1.0	.99 to 1.01	1.0	.99 to 1.01
Maternal age (per year)	.99	.96 to 1.03	1.0	.96 to 1.0
Amniotomy	1.2	.15 to 8.9	1.3	.15 to 10.3
Prostaglandin induction	1.6	.82 to 3.2	1.6	.79 to 3.2
Foetal weight (per gram)	1.0	.99 to 1.0	1.0	.99 to 1.0
Multiparity	.68	.40 to 1.1	.64	.37 to 1.1
Gestational age (per week)	1.0	.83 to 1.2	.96	.76 to 1.2
Maternal height (per cm)	1.0	.99 to 1.02	1.0	.99 to 1.0
Maternal weight (per kg)	.99	.98 to 1.01	1.0	.98 to 1.02

OR = odds ratio; CI = confidence interval

Both in the univariable and in the multivariable analysis, there was a statistically significant decreased risk of an abnormal position of the foetal head in case the FT4

increased (odds ratios .87 [95% CI .77 to .99]) and .88 [95% CI .77 to .99], respectively). The TSH concentration was not associated with the position of the foetal head, as were any of the other factors.

Table 4 shows the results of the logistic regression analysis with the risk of an instrumental delivery as the dependent variable. In the univariable analysis, the association between FT4 and instrumental delivery was statistically significant (OR .87, 95% CI .79 to .95). In the multivariable analysis, the difference became borderline statistically significant (OR .90, 95% CI .80 to 1.02). Other statistically significant predictors of a non-spontaneous pregnancy in the multivariable analysis were induction with prostaglandin's, parity and maternal weight.

Table 4 **Logistic regression analysis showing the risk for instrumental delivery among women with a anterior position of the foetal head**

	Risk for instrumental delivery			
	Univariable analysis		Multivariable analysis	
	OR	95% CI	OR	95% CI
FT4 (per pmol/L)	.87	.79 to .95	.90	.80 to 1.02
TSH (per mIU/L)	1.3	.85 to 2.1	1.2	.89 o 1.5
TPO-Ab	1.0	.99 to 1.01	1.0	.99 to 1.01
Abnormal cephalic position	12	7 to 21	25	.56 to 999
Interaction FT4 and cephalic position			.97	.73 to 1.3
Maternal age (per year)	1.1	1.0 to 1.3	1.02	.97 to 1.1
Prostaglandin induction	2.6	1.1 to 6.2	2.0	1.1 to 3.5
Foetal weight (per gram)	1.001	1.0 to 1.002	1.0	.99 to 1.01
Multiparity	.19	.07 to .56	.12	.07 to .22
Gestational age (per week)	1.9	1.4 to 2.8	1.4	1.2 to 1.7
Maternal height (per cm)	1.0	.97 to 1.02	.99	.97 to 1.0
Maternal weight (per kg)	1.03	1.0 to 1.05	1.02	1.0 to 1.03

OR = odds ratio; CI = confidence interval

Discussion

As far as we know, this is the first paper showing a relationship between low maternal thyroid hormone concentration and non-physiological cephalic presentation of the foetus in a large sample of healthy (no thyroid dysfunction) pregnant women. Women with a low FT4 concentration at 36 weeks' gestation had an increased risk of abnormal cephalic presentation and instrumental delivery. There existed also an increased

risk for instrumental delivery, and this risk remained virtually present after correction for the abnormal position of the foetal head.

The number of women with anterior / posterior position is similar to other recent studies in large samples of term vertex presenting pregnant women (8,9). The increased risk of women with posterior position of complications during labour that we found is similar to the risk found in a study of over 6000 pregnant women with vertex presentation at term: only 26% of the nulliparas and up to 57% of the multiparous showed spontaneous delivery (8), compared to 12% and 61% in the current study.

The association between thyroid hormone in women without thyroid dysfunction and cephalic presentation of the foetus has never been described. There is substantial evidence suggesting a relation between sub-clinical and overt thyroid dysfunction as well as elevated concentrations of TPO-Ab and impaired obstetrical outcome: increased rates of miscarriage, foetal abnormalities, gestational hypertension and stillbirths have been described in women with clinical hypothyroidism and / or increased concentrations of TPO-Ab (4,5). In the present study, however, both TSH and TPO-Ab were not related to non-physiological presentation of the foetus at term. Moreover, all women had an fT4 within physiologic ranges, most of them with normal TSH, a condition that is not regarded as thyroid dysfunction (10).

Several determinants of posterior position have been described such as congenital anomalies of the foetus, pelvic disproportion, placental location and low birth weight (11,12). During early labour up to one third of foetus's present in posterior position, a number which deceases to 20% at full dilatation (13). However, a large number of the remaining posterior positions rotate during labour to the anterior position. An early report suggested that the persistence of posterior position was related to malrotation during labour rather than absence of rotation from an initially posterior position (14) while a recent report found the opposite (13).

How can a relationship between low maternal thyroid hormone concentration and non-physiological cephalic position be explained? With regard to the above mentioned triad of 'pelvis, power and passenger' a recent paper reported that the persistence of posterior position is less likely to be related to 'power': women with foetuses in posterior position did not show lower intra-uterine pressure levels immediately before or during the second stage of labour (15). This hypothesis is strengthened, as after statistical correction for confounding by and abnormal position of the foetal

head, women with low fT4 values were still at increased risk for instrumental delivery. Another study showed that occiput position was less likely to be related to pelvic abnormalities (16). This suggests that one should focus more on the role of the 'passenger' in relation to non-anterior position. In this view, the consistent findings of a delay of motor development at one and two years of age of the offspring of hypothyroxinemia pregnant women might be of relevance (17). If impaired motor development post-natally is related to low maternal thyroid hormone concentrations during gestation, it might be hypothesized that this impaired motor development already exists during gestation resulting in poor foetal movements and as a consequence impaired foetal internal rotation during labour. It is interesting to note that, in a few congenital endocrinological syndromes (Prader-Willi, pituitary agenesis) in which hypothalamic function is impaired (and, as a consequence, foetal thyroid function), the rate of abnormal foetal presentations is very high: up to 25%. Longitudinal follow-up studies of children with congenital hypothyroidism showed motor developmental delays at preschool age, likely to be related to sub-optimal substitution and / or late onset with thyroxin after birth (18,19). In adults, thyroid hormone is of importance to keep normal muscle tonus. From old clinical studies it is known that patients with (severe) hypothyroidism have an increased achilles tendon reflex relaxation time (20).

Several limitations of the study need to be mentioned. Obviously, looking at obstetrical outcome as a parameter of foetal movements and motor development in relation to maternal thyroid hormone levels is a rather indirect way of looking at a possible relationship. Direct echo graphical assessment of foetal movements has recently been developed (21,22). However, the standard procedure is to assess foetal movements for a period of at least 40-60 minutes. Up until now, it has not been ascertained whether such long-duration echo graphical examinations have any negative effects on the foetus, which makes it difficult to use this instrument as a standard research tool for assessing foetal movement.

What might be the clinical relevance of these findings? There is an ongoing discussion concerning screening of all pregnant women during gestation because of the high prevalence of thyroid dysfunction in the general female population of fertile age (2-4%), its negative impact on obstetrical outcome and the rather insidious nature of clinical signs and symptoms of both (sub) clinical hyper-and hypothyroidism (23).

Moreover, up to 8% of the general pregnant population have elevated titres of TPO-Ab which are also related to obstetrical problems (5). So far, a panel of experts has argued against screening because there are no evidence based arguments of adequate benefit / risk and costs ratios (24). However, the same panel is in favour of treatment of women with mild thyroid dysfunction (mostly sub-clinical hypothyroidism as reflected by elevated TSH with normal FT4) although evidence based benefit does not exist either. A recent commentary also argued that on the basic of this attitude treatment of women with hypothyroxinemia during gestation is worth to be considered (24). Whenever hypothyroxinemia shows also to be a risk factor for non-physiological foetal presentation at term – resulting in more complications during labour with increased foetal and maternal morbidity – another argument might be added in favour of screening or even more standard assessment of thyroid hormone at the third trimester of pregnancy. From an ethical point of view, placebo controlled studies in which thyroxin is substituted to hypothyroxinemic women are difficult to promote given the reported relation with impaired neurodevelopment and very recently behavioural problems (ADHD) of the offspring (10,25,26). The current study strongly supports further research into the benefit of thyroid hormone substitution in healthy women with thyroid hormone levels in the lower range in relation to obstetrical outcome.

References

1. Cunningham FG, MacDonald PC, Gant NF, Leveno KJ, Gilstrap LC. Williams Obstetrics. 21st ed. Prentice-Hall International Inc. 1993
2. American College of Obstetrics and Gynecology Committee on Practice Bulletins-Obstetrics. ACOG Practice Bulletin Number 49, December 2003: Dystocia and augmentation of labor. *Obstet Gynecol.* 2003;**102(6):**1445-54.
3. Norwitz ER. Physiology of parturition .*UpToDate* 2005; online version **13.1.**
4. Poppe K, Glinoer D. Thyroid autoimmunity and hypothyroidism before and during pregnancy. *Hum Reprod Update*. 2003;**9(2):**149-61.
5. Prummel MF, Wiersinga WM.Thyroid autoimmunity and miscarriage.*Eur J Endocrinol.* 2004;**150(6):**751-5.
6. Morreale de Escobar G, Obregon MJ, Escobar del Rey F. Role of thyroid hormone during early brain development. *Eur J Endocrinol* 2004; **151:** 1-14.
7. Harrell FE Jr., Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. *J Natl Cancer Inst.* 1988;**80(15):**1198-202. Review.
8. Ponkey SE, Cohen AP, Heffner LJ, Lieberman E. Persistent fetal occiput posterior position: obstetric outcomes. *Obstet Gynecol.* 2003;**101:**915-20.
9. Fitzpatrick M, McQuillan K, O'Herlihy C. Influence of persistent posterior position on delivery outcome. *Obstet Gynecol.* 2001;**98(6):**1027-31.
10. Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Maternal hypothyroxinaemia during early pregnancy and subsequent child development: a 3-year follow-up study. *Clin Endocrinol.* 2003;**59:**282-8.
11. Gardberg M, Tuppurainene M. Anterior placental location predisposes for occiput posterior presentation near term. *Acta Obstet Gynecol Scand.* 1994; **73(2):**151-2.
12. Sizer AR, Nirmal DM. Occipito posterior position: associated factors and obstetric outcome in nulliparas. *Obstet Gynecol.* 2000;**96:**749-52.
13. Akmal S, Tsoi E, Howard R, Osei E, Nicolaides KH. Investigation of occiput posterior delivery by intrapartum sonography. *Ultrasound Obstet Gynecol.* 2004; **24(4):**425-8.
14. Gardberg M, Laakkonen E. Salevaara M. Intrapartum sonography and persistent occiput posterior position: a study of 408 deliveries. *Obstet Gynecol.* 1998; **91:**746-9.
15. Buhimschi CS, Buhimschi IA, Malinow AM, Weiner CP. Uterine contractility in women whose fetus is delivered in the occipitoposterior position. *Am J Obstet Gynecol.* 2003;**188(3):**734-9.
16. Marpeau L, Sergent F, Manson F, Verspyck E, Eurin D. Mechanisms of the stagnation of dilatation in the active phase of labor. *Gynecol Obstet Fertil.* 2002;**30(4):**282-5.
17. Sallam Hn, Abdel-Dayem A, Sakr RA, Sallam A, Loutfy I. Mathematical relationships between uterine concentrations, cervical dilatation, descent and rotation in spontaneous vertex deliveries. *Int J Gynaecol Obstet.* 1999;**64(2):**135-9.
18. Butler MG. Prader-Willi syndrome: current understanding of cause and diagnosis. *American Journal of Medicine and Genetics.* 1990; **35:** 319-332.
19. Kooistra L, Laane C, Vulsma T, Schellekens JM, van der Meere JJ, Kalverboer AF. Motor and cognitive development in children with congenital hypothyroidism: a long-term evaluation of the effects of neonatal treatment. *J Pediatr.* 1994;**124(6):**903-9.
20. Rives KL, Furth ED, Becker DV. Limitations of the ankle jerk test: intercomparison with other tests of thyroid function. *An Intern Med* 1965;**62**:1139.
21. Bargagna S, Canepa G, Costagli C, Dinetti D, Marcheschi M, Millepiedi S et al. Neuropsychological follow-up in early-treated congenital hypothyroidism: a problem-oriented approach. *Thyroid.* 2000;**10(3):**243-9.
22. Kozuma S., Okai T., Ryo E., Nishina H., Nemoto A., Kagawa H et al. Differential developmental process of respective behavioral states in human fetuses. *American Journal of Perinatology* 1998;**15:** 203-208.

23. Ten Hof J., Nijhuis I.J., Nijhuis J.G., Narayan H., Taylor D.J., Visser GH et al. Quantitative analysis of fetal general movements: methodological considerations. *Early Human Development* 1999; **56(1):**57-73.
24. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA.* 2004; **291:** 228-33.
25. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med.* 1999; **341:** 549-55.
26. Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G et al. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency disorder in developed countries. *J Endocrinol Metab.* 2004; **89:** 6054-60.

Chapter VII

VALIDATION OF THE "KEMPEN CONFINEMENT SELF-RATING" SCALE

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Introduction

The Netherlands is one of the few western countries where home delivery frequently occurs, although the numbers have dropped during the last two decades: from 45% in the late eighties to 30% at the beginning of the new century. 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 standardized forms are used by gynaecologist and midwife to describe the mode of delivery. The following categories can be discriminated: (1) spontaneous 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. With the increase of hospital deliveries, the number of technical intervention during labour has increased in general, and especially in the case of for abnormal foetal presentation at term such as breech position. After Hannah's publication concerning elective Caesarean section in the case of breech presentation at end term, the number of sections in case of breech presentation has increased substantially [1,2]. This is remarkable while others report no increased risk of vaginal delivery in case of breech position[3] . Moreover, the longitudinal follow-up of children who were born vaginally in Hannah's trial showed no neurodevelopmental delay to those delivered by Casarean section, as suggested earlier[1,4] .

Surprisingly, very little research has been carried out concerning the way women in general perceive labour and the first confinement days. Aspects in the normal spectrum of mental well-being, which one considers as being relevant going through this major event are poorly documented. At the more pathological spectrum of mental well-being there is a growing literature that childbearing might result in post-traumatic stress symptoms, which is beyond the scope of this paper.

This study describes the construction and validation of a self-rating scale assessing the way in which labour and confinement days are perceived by childbearing women.

Methods

Development of the self-rating scale

For the construction of the scale, three different groups were formed. The first group consisted of four experienced community midwives and four maternity nurses who discussed several dimensions concerning the way women perceive delivery and confinement days, which were transformed into open questions. Subsequently, two focus groups were formed. A focus group is a type of group interview in which the interaction between the participants is vital. The moderator of the focus group has to make sure that communication goes smoothly and that every participant receives the opportunity to participate fully into the discussion. These interviews of three hours were taken off in two groups of women. The first group consisted of eight women (four primiparous and four multiparous women with term over 34 weeks' gestation) and the second group consisted of eight recently (less than six weeks') delivered women (four primi- and four multiparous). Both group interviews occurred under the supervision of two staff members of the Department of Clinical Health Psychology of Tilburg University (JV, GH). Apart from the open questions all aspects that the participants found relevant to delivery and recovery during the confinement days with regard to emotional experiences, were discussed and tape recorded. At the university, the most relevant and frequently mentioned topics during these interviews were taken together and constructed as items into a self-rating scale that contained 40 items. The items could be scored on a four point scale rating from: totally agree to totally disagree. The higher the score, the less positive delivery and confinement were perceived. This scale was subsequently distributed in several midwife offices for validation research.

Participants

During a period of one year (2001), all women who booked in for antenatal controls in eight community midwife offices were invited to participate into the study. Only Dutch

Caucasian women were invited (n=1280) of whom 1067 (83%) consented to participate. These women had to complete the questionnaire at the seventh postpartum day. At the last postpartum visit, the midwife collected the questionnaires and checked appropriate completion of the self-rating scale resulting in 998 fully completed questionnaires. The first 500 women who were included into the study were used for construct validity and content validity, the second half of the sample was used for confirmatory analysis. The characteristics of the first group are shown in Table 1, that of the second group were similar (data not shown).

Table 1. Characteristics of a sample of 500 women of the general population who recently (< 1 week) delivered

		N	%
Age			
Mean (SD)	30 (3.4)		
Range	18 – 42		
Parity			
Primipara		240	48
Multipara		260	52
Number of children			
No children		215	43
One		205	41
Two		70	14
> 2		10	2
Education level			
Low		105	21
Middle		195	39
High		180	36
Academic		20	4
Marital status			
Married / partner		495	99
Divorced		5	1
Working outside home			
No		145	29
Yes		355	71
Continuation after delivery of these 355:			
	Yes	276	78
	No	79	22

Measurements

Together with the KCS, the Edinburgh Postnatal Depression Scale (EPDS, Cox et.) was assessed in the first postpartum week [5,6]. The Dutch version of the E(P)DS has been

validated among postpartum women in The Netherlands and revealed appropriate psychometric characteristics[7,8]. It consists of ten items, to be completed within five minutes. The total score ranges between 0 and 30, with cut-off scores between 11 and 13 [9,10].

Statistical analysis

Statistics were performed using the Social Package for Social Sciences (SPSS, 12.2). Content validity was studied in two ways. First, exploratory factor analysis was performed in the first 500 women (group 1), using the Scree test (Catell, 1966) for determining the number of factors. Cronbach's alphas were calculated for each group and for the scale as a whole and for possible subscales that derived from factor analysis. Construct validity (does the KCS assesses what it intend to assess) in the second group was calculated using Pearson correlations with the EPDS. Moreover, mean scores on the KCS between different sub-groups of women according to the mode of delivery were compared using ANOVA (one way).

Results

Content validity

Exploratory factor analysis with Scree test revealed four different factors (total variance 39.2%). Therefore, three, four and five factor solutions were examined. Based on the face validity of the items, three different sub-scales could be discriminated: the way delivery was perceived emotionally, the way the confinement days were perceived emotionally and a sub-scale related to perception of social support during the confinement (partner, family, relatives and maternity nurse). Therefore, another factor analysis was performed with varimax rotation using a three factor structure. There were six items that did not have a factor loading above 0.30, and another three items had secondary loadings. The remaining 31 items revealed three subscales: delivery (11 items), confinement (14 items) and support (6 items). A Cronbach alpha analysis showed that the sub-scales could be reduced further: delivery (10 items, alpha 0.85), confinement (8 items, alpha: 0.83) and support (3 items, alpha: 0.77).

With this final scale, another 3-factor analysis was performed with varimax rotation. Eigen values and factor loadings of the three different sub-scales are shown in (Table 2).

Table 2 Factor analysis with varimax rotation in 500 recently delivered women who completed a delivery and confinement self-rating scale. For full text of items see appendix.

	Component 1	**Component 2**	**Component 3**
	delivery 8 - items	confinement 10 - items	support 3 - items
Eigenvalue	4.75	2.21	1.45
Explained variance (%)	22	11	7
Factor loading items			
1: labour / unsatisfied	0.58		
2. labour / not confident	0.73		
3. after delivery / not confident		0.46	
4. after delivery / lonely		0.46	
5. after delivery / proud		0.50	
6. labour / safe	0.54		
7. learned of maternity nurse			0.77
8. after delivery / guilt		0.44	
9. after delivery / tense		0.50	
10. labour / turned out different	0.46		
11. labour / wrong	0.54		
12. after delivery / disappointed		0.44	
13. labour / coping	0.71		
14. labour / panic	0.75		
15. after delivery / joy		0.79	
16. after delivery / turned out different		0.68	
17. after delivery / advices			0.66
18. after delivery / crying		0.41	
19. after delivery / support			0.67
20. labour / relax	0.64		
21. after delivery / cozy		0.75	
Alpha Cronbach	0.85	0.84	0.77

This 21 item scale was called the Kempen Confinement Self - rating scale, KCS. The higher the scores, the poorer the outcome. Subsequently, the KCS was completed by the second group of women (n=498) who also completed the EPDS. Three-factor analysis in this group revealed Eigenvalues of 4.70, 2.18 and 1.40 with ex-

plained variance of 22, 10 and 6%, respectively. The alpha Cronbach of the total scale was 0.85, the subscale delivery, confinement and support: 0.84, 0.82 and 0.77, respectively.

Construct validity

In Table 3a, the means of the total scale and the subscales of the KCS and the mean scores of the EPDS are shown. The correlations between the EPDS and the KCS (sub)scales are shown in Table 3b. As can be seen in Table 3b, except for the KCS sub-scale support all correlations were highly significant. Moreover, the total KCS as well as the confinement sub-scale showed high correlations with the EPDS. The KCS sub-scale support correlated significantly with the sub-scale confinement but not with the other sub-scale. Finally, in Table 4, the mean scores are shown of the EPDS and the three sub-scales of the KCS in relation to the mode of delivery. As can be seen in Table 4, the mean scores on all scales increased the more delivery became more complicated. The differences in mean scores between the groups on the different subscales were all significant (at a level of $P < 0.001$) using ANOVA ($df = 4$, one-way). The EPDS with an $F = 16.7$, the delivery sub-scale with an $F = 17.1$, the confinement sub-scale with an $F = 16.7$. For the sub-scale support the $F = 1.9$ ($p = 0.11$).

Table 3a Ranges, mean scores (SD) of the EPDS and the KCS scale as a whole as well as the three sub-scale (N = 498).

		range	mean	(SD)
EPDS (10 items)		0 - 25	4.26	3.7
KCS				
Total	(21 items)	21-72	36.5	8.1
Subscale delivery	(8 items)	8-31	15.4	4.8
Subscale confinement	(10 items)	10-39	15.8	4.5
Subscale support	(3 items)	3-12	5.3	1.8

Table 3b Pearson correlations between different (sub)scales, 2-tailed

	EPDS	Total	Delivery	Confinement	Support
EPDS		**0.60**	**0.37**	**0.68**	0.07
KCS					
Total			**0.80**	**0.81**	0.12
Delivery				**0.38**	0.06
Confinement					0.14*
Support					

bold : p<0.0001; * p,0.05

Table 4 Mode of delivery in 498 women in relation to mean scores on the EPDS and the sub-scales of the KCS

		EPDS Mn (SD)	delivery Mn (SD)	confinement Mn (SD)	support Mn (SD)
Mode of delivery	N				
Spontaneous at home	218	3.3(3.4)	14.1(4.1)	14.6(3.6)	5.3(1.8)
Spontaneous in hospital	147	3.8(3.6)	15.5(4.8)	15.6(4.2)	5.3(1.8)
After stimulation vaginally					
Forceps / vacuum	49	5.9(3.3)	19.1(4.9)	18.5(4.3)	5.9(3.3)
Caesarean section	14	7.2(6.1)	19.1(4.5)	21.5(6.1)	7.2(6.1)

Discussion

As far as we know, this is the first scale especially developed for the way women perceive labour and the confinement days. Based on the focus groups with interviews in women who were pregnant or recently delivered and subsequent quantitative analyses, a 21-items self-rating scale was developed (the Kempen Confinement Self-rating Scale, KCS) assessing three sub-scales: 8 items related to delivery, 10 items related to confinement and 3 items related to the perceived support from the maternity nurse. The higher the scores, the poorer the outcome. The scale as a whole shows appropriate psychometric aspects and is easy to complete (within 5 minutes).

Looking at the face validity of the items (see appendix), the delivery subscales contain aspects of feelings of guilt not coping adequately with labour, feelings and thoughts about expectations of labour that turned out to be different, aspects of panic whether the woman can cope with labour and feelings of loneliness or feeling safe. The confinement self-rating scale contains similar aspects: feeling confident or disappointed, feelings of loneliness, guilt and tension.

These sub-scales highly correlated with the EPDS which is a widely validated self-rating scale to assess depressive symptoms although there is growing evidence that anxiety is also partly assessed [11]. The fact that the EPDS does not correlate with the sub-scale support is easy to understand. The three items of the support scale all relate to very practical help that is given by the maternity nurse to the woman including: advice how to feed the baby, how to take care of the baby and how to take care of the woman's own body after delivery. Moreover, in The Netherlands, the maternity nurse is at the woman's house during the day for the first postpartum week, taking care of the cooking and cleaning of the house and possible other children. An interesting cultural phenomenon of The Netherlands was reflected in the development of this scale. During the interviews the women reported that support perceived from the partner was an important issue. However, due to the presence of the maternity nurse, most partners of recently delivered women only stay at home for one or more weeks after the nurse has left. This might explain why several items of the original

forty items scale referring to support perceived from the partner did not load at all and that the Cronbach's alpha substantially increased once the items were deleted.

The fact that the scores of the sub-scale delivery and sub-scale confinement significantly differed between the groups according to the complications at delivery is an important argument that these scales actually assess what is intended: emotional aspects during labour and during the first postpartum week.

The clinical relevance of this scale might be high. In The Netherlands there is a growing interest in hospital deliveries, even in women without a medical reason of referral, with all the consequences of technical interventions. Future research will elucidate whether women who deliver at home will have better scores on the delivery and confinement sub-scales compared to those who deliver spontaneously in hospital or after technical intervention. As suggested in this study by the high correlation between the EPDS and the KCS scale, a negative perception of delivery and confinement might contribute to depressive symptoms during the first postpartum week, the latter being a major risk factor for the development of a major depressive episode during the postpartum. Looking at the face validity of several items of the KCS, several might correlate with items of several self-rating scales which are used in research of post-traumatic stress symptoms (PTSS)[12]. Future research is needed to evaluate whether high scores on he KCS might predict high post-traumatic symptoms (PTS).

References

1 Hannah ME, Hannah WJ, Hewson SA, Hodnett ED, Saigal S, Willan AR.: Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. Term Breech Trial Collaborative Group. Lancet. 2000 Oct 21;356(9239):1375-83.

2 Rietberg GC, Elferink-Stinkens PM, Visser GH. The effect of the Term Breech Trial on medical intervention behaviour and neonatal outcome in The Netherlands: an analysis of 35,453 term breech infants. BJOG. 2005;112(2):205-9.

3 Krupitz H, Arzt W, Ebner T, Sommergruber M, Steininger E, Tews G. Assisted vaginal delivery versus caesarean section in breech presentation.Acta Obstet Gynecol Scand. 2005;84(6):588-92.

4 Whyte H, Hannah ME, Saigal S, Hannah WJ, Hewson S, Amankwah K, Cheng M, Gafni A, Guselle P, Helewa M, Hodnett ED, Hutton E, Kung R, McKay D, Ross S, Willan A; Term Breech Trial Collaborative Group. Outcomes of children at 2 years after planned cesarean birth versus planned vaginal birth for breech presentation at term: the International Randomized Term Breech Trial. Am J Obstet Gynecol. 2004 Sep;191(3):864-71.

5 Cox JL, Chapman G, Murray D, Jones P.Validation of the Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women. J Affect Disord. 1996;39(3):185-9

6 Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale.Br J Psychiatry. 1987;150:782-6.

7 Pop VJ, Komproe IH, van Son MJ. Characteristics of the Edinburgh Post Natal Depression Scale in The Netherlands. J Affect Disord. 1992;26(2):105-10.

8 Becht MC, van Erp CF, Teeuwisse TM, van Heck GL, van Son MJ, Pop VJ. Measuring depression in women around menopausal age: towards a validation of the Edinburgh Depression Scale. J Affect Disord. 2001;63(1-3):209-13.

9 Harris B, Huckle P, Thomas R, Johns S, Fung H. The use of rating scales to identify post-natal depression.Br J Psychiatry. 1989;154:813-7.

10 Murray L, Carotuers AD. The validation of the Edinburgh Post-natal Depression Scale on a community sample. Br J Psychiatry. 1990;157:288-90.

11 Pop VJ, Komproe IH, van Son MJ. Characteristics of the Edinburgh Post Natal Depression
Scale in The Netherlands. J Affect Disord. 1992;26(2):105-10.

12 van der Velden PG, van den Burg S, Steinmetz CH, van den Bout J. Slachtoffers van bankovervallen [Victims of bank robberies] . Houten: Bohn Stafleu van Loghum. 1992.

Appendix

The Kempen Confinement Self-rating Scale. Experience of labour and confinement period.

Following below are some statements which relate to different aspects of labour and the confinement period (roughly the first eight days after labour). For each statement there are four possible answers:
-totally disagree, -disagree, -agree, -totally agree, and only one answer can be given.
Please read carefully and answer all questions.

	totally disagree	disagree	agree	totally agree
1. labour was very unsatisfactory	□	□	□	□
2. during labour I was not confident	□	□	□	□
3. after labour I felt not confident	□	□	□	□
4. after labour I have felt lonely	□	□	□	□
5. during the confinement period I was very proud	□	□	□	□
6. during labour I have felt safe	□	□	□	□
7. I have learned a lot from the maternity nurse	□	□	□	□
8. during the confinement period I often had feelings of guilt	□	□	□	□
9. after labour I felt very tense	□	□	□	□
10. labour turned out completely different than I had intended	□	□	□	□
11. during labour I did many things wrong	□	□	□	□
12. after labour I was very disappointed	□	□	□	□
13. during labour I doubted whether I could cope with it	□	□	□	□
14. during labour I panicked	□	□	□	□
15. I enjoyed my confinement period	□	□	□	□
16. after labour every thing turned out completely different than I had intended	□	□	□	□
17. I got valuable advice during the confinement period	□	□	□	□
18. after labour I cried several times	□	□	□	□
19. I received lots of support from the maternity nurse	□	□	□	□
20. during labour I could relax very well	□	□	□	□
21. the confinement period was very cosy	□	□	□	□

Chapter VIII

HOME AND HOSPITAL DELIVERY, WHICH LADY SINGS THE BLUES?

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Introduction

The number of technical interventions during delivery is increasing. An important explanation is the paper of Hannah et al. in 2002 that showed that a vaginal delivery in the case of breech position of the foetus at term should be regarded as obsolete[1,2]. Although others have criticized this paper or did found no differences, many gynecologists in general practice have started since to choose for primary Caesarean section in case of breech presentation.

Technical interventions increase the costs of delivery and postpartum confinement days and the risk for future complications in case of another pregnancy and delivery[3]. Moreover, recent papers have shown that a substantial number of women suffer from posttraumatic stress symptoms after delivery and that technical interventions have been shown to be independently related to the intensity of these symptoms[4]. Postnatal depression occurs in 10 to 15% of the women and an important predictor is the way the first postpartum week is emotionally perceived by the mother[5]. For example, severe depressive and anxiety symptoms during this first postpartum week can be a prodromen of subsequent postpartum psychosis. Also, the occurrence of severe blues - interfering with maternal mood state during the first postpartum week- has been shown to be an independent risk factor of subsequent postnatal depression[5].

Maternal thyroid function during gestation has been shown to be an independent risk factor for maternal depression during and after gestation[6]. Besides, it has been shown recently that maternal thyroid function is an independent risk factor for protraction of labour, which in turn increases the risk of non-spontaneous delivery dramatically[7]. Another independent determinant of protraction of labour is maternal anxiety at end term[8].

This study investigated the way women emotionally perceive delivery and the confinement days in relation to mode of delivery, taken into account possible confounders such as psychosocial well-being during end gestation, as well as thyroid function.

Methods

Subjects

Between July 2002 and November 2004, 1507 healthy Dutch Caucasian singleton pregnant women of five community midwives practices, living in and around the city of Eindhoven, the Netherlands, were invited to participate into the study at their first antenatal control (12 weeks' gestation). These low risk women did not have a history of thyroid disease or other autoimmune disease, of uterus anomalies, or a history of fertility problems prior to the current pregnancy. Of these, 79% (n=1191) consented to participate and in whom thyroid parameters (TSH, fT4 and TPO-Ab) were assessed at 12, 24 and 36 weeks' gestation. Women with overt hyperthyroidism (n = 8) and hypothyroidism (n = 2) at their first assessment were excluded. In 82 women thyroid parameters were not obtained and 8 women had late miscarriage. In the remaining 1091 a careful obstetrical history was assessed at 24 and 36 weeks' gestation by one midwife who was blinded for the biochemical results. Women with premature delivery (n=43, < 37 weeks' gestation) were excluded. Of the 1048 remaining women, in 42 women not all obstetrical parameters were available and another 87 did not properly complete several questionnaires and were also excluded. Therefore, data analysis refers to 919 women of whom the characteristics are summarized in Table 1.
This study was approved by the Medical Ethical Committee of Máxima Medical Centre Eindhoven / Veldhoven (the Netherlands).

Measurements

Dependent variable

The way delivery and the confinement days were perceived was assessed using the Kempen Confinement Self-rating scale (KCS) which was developed at Tilburg University and which has been validated in earlier research in a large sample of child

Table 1 Characteristics of a sample of 919 women with gestational age > 37 weeks

		n (%)	T	P
Demographic features				
age (mean, SD)	29 (0.5)			
marital status				
with partner		901 (98)		
single		18 (2)		
educational level				
low		83 (9)		
middle		414 (45)		
high		349 (38)		
academic		73 (8)		
working outside home				
yes		790 (86)		
no		129 (14)		
Mood and anxiety (Mn, SD)				
EDS scores at 36 weeks' gestation	4.2 (3.9)			
EDS scores at 1 week postpartum	4.7(4.5)			
Anxiety scores at 36 weeks" gestation	12.7(3.6)			
Anxiety scores at 1 week postpartum	12.9(4.7)			
Life style habits				
Smoking				
never		506 (55)		
stopped earlier in life		202 (22)		
stopped during pregnancy		92 (10)		
yes: < 10 / day		92 (10)		
> 10 / day		27 (3)		
Alcohol intake				
never		276 (30)		
stopped during pregnancy		524 (57)		
≥2 consumptions / week		119 (13)		
Body Mass Index				
< 20		55 (6)		
between 20 and 25		423 (6)		
between 26 and 30		303 (33)		
> 30		138 (15)		
Obstetrical features				
Parity				
primiparity		423 (46)		
multiparity		496 (54)		
At delivery:				
Term at gestation				
mean (SD) in weeks	39.9(1.2)			
range in weeks	37.0 - 42.6			
Weigth (gr) of the baby at birth				
Mean (SD)	3545 (472)			
Range	1840 – 4990			

(Suite)			
Duration of dilatation (mn in hrs, SD)			
primiparous	multiparous		T=11.5 p<0.0001
10.2 (6.7)	5.6 (4.1)		
Expulsion time (mn in minutes, SD)			
primiparous	multiparous		T=17 p<0.0001
48 (32)	16 (15)		
Mode of delivery			
Spontaneous at home		395 (42.9)	
Spontaneous in hospital		232 (25.3)	
After induction vaginally		120 (13)	
Vacuum extraction		87 (9.5)	
Caesarean Section		85 (9.3)	
At seventh postpartum day			
Scores on the confinement scale			
Delivery sub-scale (10 items, Mn, SD)	15.9(5.0)		
Confinement sub-scale (8 items, Mn, SD)	16.3(4.9)		
Support subscale (3 items, Mn, SD)	5.4(1.9)		

bearing women[9]. The 21-items scale consists of three subscales. One subscale refers to the way delivery is perceived (delivery, 10 items), one subscale is related to the way the first postpartum week is perceived (confinement, 8 items) and one subscale (support, 3 items) the way the practical support by the maternity nurse is perceived. These scales (total as well the different sub-scales) have been shown in previous research to have appropriate psychometric characteristics[9]. All items have to be scored on a four point rating scale varying from not at all to totally agree. The higher the score, the poorer the outcome. No cut-off scores are discriminated but for the current study a cut-off of > 1 SD > mean defined high scores on the delivery and the confinement scale, which were used as dependent variables.

Independent variable

Obstetrical parameters were carefully assessed by the nationwide used standardized criteria of the Dutch Midwife and Obstetrics & Gynaecology Association. Dilatation time was expressed in hours starting from the first time that strong uterus contractions did start regularly (at least every 3 – 5 minutes) resulting in effacement and dilatation of the uterine cervix. The mean duration of dilation in primiparous women

was 10.3 hours compared to 5.4 hours in multiparous women (T= 11.2, $p < 0.00001$, two tailed). Long duration of dilatation time was defined by a cut-off of the 90th percentile (> 14 hours). Similarly, expulsion time was expressed in minutes, starting from the moment the woman actively began bearing down after reaching full dilatation and lasting until expulsion of the baby. The mean duration of expulsion of primaparous women was significantly higher compared to multiparous women, 46 versus 16 minutes, respectively ($T = 16.8$, $p < 0.00001$). Long expulsion time was defined also at or above the 90th percentile: > 72 minutes. In The Netherlands the following different categories of way of delivery can be discriminated: spontaneously at home or in hospital, after induction vaginally, with vacuum/forceps extraction and (primary or secondary) Caesarean section. Obstetrical parameters are summarized in Table 1.
However, it should be noticed that of the women who deliver spontaneously in hospital, a number of them made the choice to deliver in hospital already at antenatal booking while the remaining women had to deliver in hospital because of previous obstetrical problems or because they were referred with obstetrical complications during gestation.

Confounders

Factors, which are known to interfere with emotional perception of major events in general, were also assessed. At 36 weeks' gestation and during the first postpartum week, *depressive symptoms* were assessed using the Edinburgh Depression Scale (EDS; Cox et al., 1996)[10], which was originally developed for use during the postpartum period and was called the Edinburgh Postnatal Depression Scale (EPDS; Cox et al., 1987)[11]. The Dutch version of the E(P)DS has been validated among postpartum women in The Netherlands by Pop et al. (1992), and revealed appropriate psychometric characteristics[12]. Recently, the EPDS was validated in a group of non-childbearing mothers[10,13], resulting in new nomenclature: Edinburgh Depression Scale (EDS). It consists of ten items, to be completed within five minutes. The total score ranges between 0 and 30, with cut-off scores between 11 and 13[14,15]. In the present study, women with a score above 11 were defined as suffering from depression.

Similarly, *anxiety* was measured using the 10-items anxiety subscale (range 10 – 50) of the SCL-90 scale of Derogatis[16]. The SCL-90 is a self-rating scale consisting of six subscales measuring all kind of psychopathology. The item score ranges from one to five. The SCL-90 has been validated before in The Netherlands and its use as well as the use of several subscales only has revealed appropriate psychometric properties[17] . Normally, no cut-off levels are used but in the present study scores at and above 1 SD above the mean defined high levels of anxiety.

The occurrence of *blues* was assessed using the Pitts' criteria[18]. Moreover, the intensity of blues was assessed discriminating between: only at interval during several hours during one day, at interval during almost one whole day and at intervals during hours at more than one day.

Mean scores (SD) of the EDS, the SCL-anxiety subscale and the KCS scale and its sub-scale are summarized in Table 1.

Demographic features, life style habits and general medical history were taken off at antenatal booking as well as the occurrence of stress-full life events during gestation.

Because *thyroid parameters* have recently been shown to interfere with obstetrical outcome and also might interfere with mood, thyroid function was assessed. TSH (reference range for women aged between 20 and 40 years: 0.04-3.1 mIU/l) was measured using a solid-phase, two-site, chemiluminescent enzyme immunometric assay (IMMULITE third generation TSH, Diagnostic Corporation, Los Angeles, CA). The inter-assay coefficients of variation were 5.0% and 4.4% at concentrations 0.22 mIU/l and 2.9mIU/l, respectively. Sub-clinical hypothyroidism was defined as a TSH > 3.1 mIU/l with an FT4 between reference range.

The fT4 concentration (reference range for women aged between 20 and 40 years: 10.2–21 pmol/l) was also measured by means of a solid-phase immunometric assay (IMMULITE Free T4). The inter-assay coefficients of variation for this technique were 6.7% and 4.4% at concentrations of 11.6 pmol/l and 31.5 pmol/l, respectively.

Hypothyroxinemia was defined as an FT4 < 10^{th} percentile with TSH between reference range and hyperthyroxinemia by an FT4 at or above the 90^{th} percentile with normal TSH. Subclinical thyroid dysfunction was defined by an fT4 within reference range with abnormal TSH, while clinical thyroid dysfunction was defined by both fT4 and TSH levels outside reference range.

The IMMULITE Anti-TPO Ab kit was used to determine antibodies against thyroid peroxidase (TPO). The inter-assay coefficients of variation for this analysis were 9% and 9.5% for concentrations of 40 kU/l and 526 kU/l, respectively. The anti-TPO assay was standardized according to the International Reference Preparation for anti-TPO MRC 66/387. A concentration of $\geq$ 35 IU/ml was defined as being elevated. Thyroid parameters at 36 weeks' gestation are summarized in Table 1.

Statistical analysis

Statistical analysis was performed using the Statistical Package of Social Sciences (SPSS). Differences in characteristics between the various subgroups were analysed by means of t-test and ANOVA (one way). Post hoc analysis was performed using Scheffe technique. A factor and reliability analysis of the KCS scale was performed. OR's (with 95 % CI) were calculated by means of (multiple) logistic regression analysis. Dependent variables were: high score on the delivery elf-rating subscale ($\geq 90^{th}$ percentile) and the confinement self-rating scale ($\geq 90^{th}$ percentile).

Results

Factor analysis of the KCS and its subscales revealed similar structures as previously described[9]. The Cronbach alphas of the scale in the current study as a whole were 0.86, of the subscales delivery, confinement and support, 0.83, 0.85 and 0.79, respectively. As can be seen in Table 1, the mean scores on the EDS increased significantly from 36 weeks' gestation to one week postpartum, T= 2.7 (p=0.007). The scores on the anxiety sub-scale also increased although not significantly (T= 1.3, p = 0.19).

In Table 2, the mode of delivery is shown in more detail with a distinction between primary and secondary Caesarean section in relation to scores on the delivery and

confinement subs-scale. As can be seen, the highest scores were found in women with secondary Caesarean section, the lowest scores in women who delivered spon

Table 2 Mean scores (SD) on the delivery and confinement sub-scales in relation to mode of delivery (n = 919).

		delivery	confinement
		Mn (SD	Mn (SD)
Mode of delivery	N		
1. Spontaneous at home	395	14.2 (3.9)	15.6 (4.3)
Spontaneous in hospital	232		
2. woman's own choice	69	16.2 (6.2)	16.1 (4.9)
3. after referral	154	16.6 (4.8)	15.9 (4.1)
4. After stimulation vaginally	120	16.8 (4.9)	17.1 (4.7)
5. Forceps / vacuum	87	18.6 (4.7)	16.9 (4.5)
6. Primary Caesarean	36	15.9 (3.8)	18.7 (4.8)
7. Secondary Caesarean	49	19.6 (4.3)	21.4 (9.1)

taneously at home and to a lesser degree in hospital without an obstetrical indication (no referral).

ANOVA showed that both the means of the delivery scale and the confinement scale differed significantly (df = 6, $p < 0.001$), F = 20 and F = 14, respectively. Post hoc analysis with Scheffe showed significant differences between groups 1 versus 3, 4, 5, and 6 ($p < 0.001$), between 2 and 7 ($p = 0.01$), between 3 and 7 ($p = 0.009$), between 4 and 7 ($p = 0.02$) and between 6 and 7 ($p = 0.02$).

In Table 3, differences in mean scores on the sub-scale delivery and confinement of the KCS are shown of several groups defined as possible confounders. Protraction of labour with regard to increased dilatation time significantly differed on both sub-scales. Moreover, depression and anxiety at 36 weeks' gestation as well as during the first postpartum week and the occurrence of blues resulted in significantly higher scores. A previous episode of depression in the woman's life also increased the scores. Of the thyroid parameters, only hypothyroxinemia at 36 weeks' gestation was related to increased scores on the self-rating scales.

Table 3 **Differences in mean scores on delivery and confinement scale at the seventh postpartum day between different groups of 919 women who delivered > 36 weeks' gestation. (T-test, two tailed).**

	N	delivery scale Mn(SD)	T	P	confinement scale Mn(SD)	T	P
Obstetrical parameters							
Parity:							
Nulliparous	**423**	**16.6 (5.1)**	**3.7**	**0.0001**	**17.2 (5.2)**	**4.7**	**0.0001**
Multiparous	**496**	**15.3 (4.9)**			**15.6 (4.5)**		
Dilatation > 1 SD > mn	**79**	**19.4 (5.1)**	**6.6**	**0.0001**	**18.1 (5.8)**	**3.5**	**0.0001**
Less dilatation time	**743**	**15.5 (4.9)**			**16.1 (4.7)**		
Expulsion > 1 SD > mn	80	16.9 (4.4)	1.8	0.68	16.7 (3.9)	0.73	0.467
Less expulsion time	742	15.8 (5.1)			16.3 (4.9)		
Mood and anxiety							
During gestation							
Depressed (EDS >11)	**55**	**18.8 (5.5)**	**4.2**	**0.0001**	**19.5 (5.8)**	**4.7**	**0.0001**
Non-depressed	**864**	**15.7 (4.9)**			**16.1 (4.7)**		
Anxious (> 1 sd > mn)	**83**	**18.1 (5.2)**	**3.8**	**0.0001**	**18.7 (5.7)**	**4.4**	**0.0001**
Not anxious	**836**	**15.7 (5.0)**			**16.1 (4.7)**		
At postpartum							
Depressed (EDS >11)	**74**	**19.8 (5.6)**	**6.7**	**0.0001**	**25.4 (5.0)**	**15.7**	**0.0001**
Non-depressed	**845**	**15.6 (4.8)**			**15.5 (3.9)**		
Anxious (> 1 SD > mn)	**101**	**18.6 (5.6)**	**5.5**	**0.0001**	**22.2 (6.1)**	**10.0**	**0.0001**
Not-anxious	**818**	**15.6 (4.8)**			**15.6 (4.1)**		
Blues: yes	**616**	----	---	---	**17.9 (4.9)**	**12.9**	**0.0001**
Blues: no	**303**	----			**13.7 (3.7)**		
Psycho-social parameters							
Low education	64	16.6 (5.4)	1.1	0.25	17.4 (5.2)	1.8	0.071
Middle / high	855	15.8 (5.0)			16.2 (4.8)		
Working outside home	799	15.9 (5.0)	0.2	0.81	16.4 (4.8)	0.5	0.554
Not working	120	15.8 (5.0)			16.0 (5.3)		
Pregnancy planned	855	15.9 (5.0)	1.0	0.31	16.3 (4.8)	0.5	0.611
Not planned	64	16.6 (5.3)			16.6 (5.8)		
Recent SLE	92	15.7 (5.4)	0.3	0.70	16.9 (5.2)	1.2	0.217
No SLE	827	15.9 (5.0)			16.2 (4.8)		
Earlier depressed	110	16.8 (5.5)	1.8	0.06	**17.3 (5.0)**	**2.1**	**0.030**
Not depressed	809	15.8 (5.0)			**16.2 (4.8)**		

(Suite)							
Thyroid parameters							
Hypothyroidism	2	20 (8.5)	1.1	0.25	17.1 (5.6)	019	0.84
Euthyroidism	797	15.9 (5.0)			16.3 (4.9)		
Hyperthyroidism	0		--	--		--	--
Euthyroidism	797	15.9 (5.0)			16.3 (4.9)		
Sub-clinical hyper	7	14.1 (3.8)	1.1	0.3	13.6 (3.5)	1.5	0.13
Euthyroidism	797	15.9 (5.0)			16.3 (4.9)		
Sub-clinical hypo	16	16.8 (5.2)	0.7	0.41	13.6 (3.5)	1.5	0.13
Euthyroidism	797	15.9 (5.0)			16.3 (4.9)		
Hypothyroxinemia	**79**	**15.5 (4.9)**	**2.1**	**0.04**	**16.2 (4.8)**	**2.2**	**0.03**
FT4 between 10-90th	**644**	**16.9 (5.5)**			**17.5 (4.9)**		
Hyperthyroxinemia	99	16.1 (5.1)	1.5	0.13	16.3 (4.8)	0.3	0.75
FT4 between 10-90th	644	15.2 (4.6)			16.5 (5.3)		
TPO-Ab + (>35)	52	15.2 (5.1)	1.0	0.29	16.4 (4.9)	1.8	0.07
TPO-Ab <36	720	15.9 (4.5)			15.2 (4.6)		

Subsequently, the variables that showed significance differences on ANOVA and T-test were entered into a multiple logistic regression analysis (method enter), one with a high score on the delivery subscale (> 1 SD > mean, Table 4a) and one with a high score on the confinement sub-scale (> 1 SD > mean, Table 4b) as dependent variable. Scores on the support subscale were entered as a dichotomised independent variable (> 1 SD > mean) in the analysis of the confinement subscale.

Table 4 Multiple logistic regression analysis of 919 pregnant women who delivered > 37 week's term gestation . (O.R., 95% CI). Dependent variable:

A. Negative perception of delivery (scores of > 1 SD > mean)

	O.R.	95%CI
Depression (EDS > 11) at 36 weeks' gestation	1.7	0.8 - 3.8
Depression (EDS > 11) at seventh postpartum day	**3.1**	**1.6 - 6.2**
Anxiety: (scores > 90th percentile) at 36 weeks' gestation	1.2	0.5 - 2.4
Anxiety: (scores > 90th percentile) at seventh postpartum	**1.7**	**1.1 - 3.2**
Non-spontaneous delivery	**1.5**	**1.2 - 2.8**
Ventouse	**2.2**	**1.2 - 4.2**
Secondary Caesarean section	**3.2**	**1.6 - 6.5**
Primiparity	1.1	0.7 - 1.5
Increased dilatation time	**1.8**	**1.1 - 3.0**
Hypothyroxinemia at 36 weeks' gestation	1.1	0.5 - 1.9

B. Negative perception of confinement days (scores of > 1 SD > mean)

	O.R.	95%CI
Depression (EDS > 11) at 36 weeks' gestation	1.8	0.8 - 4.0
Depression (EDS > 11) at seventh postpartum day	**12**	**8.2 - 19**
Anxiety: (scores > 90th percentile) at 36 weeks' gestation	1.2	0.5 - 2.2
Anxiety: (scores > 90th percentile) at seventh postpartum	1.4	0.7 - 2.7
Previous episode of depression	1.7	**0.8 - 2.9**
The occurrence of severe blues	**4.4**	**2.3 - 8.4**
Non-spontaneous delivery	**1.9**	**1.2 - 4.2**
Secondary Caesarean section	**5.9**	**2.4 - 12.4**
Primiparity	1.1	0.7 - 1.6
Increased dilatation time	1.8	**0.8 - 4.1**
Hypothyroxinemia at 36 weeks' gestation	1.1	0.5 - 1.9
Low support perceived from maternity nurse	**3.4**	**1.5 - 7.1**

As can be seen on Table 4a, at a multivariate level, obstetrical outcome (non-spontaneous delivery, secondary Caesarean section and an increased dilatation time during labour) were independently related to high scores on the delivery sub-scale.
Of the possible confounders, depression and anxiety during the first postpartum week were independently related to high scores of the delivery sub-scale. In Table 4b, the set of obstetrical independent variables that significantly increased the risk of high scores on the confinement scale included non-spontaneous delivery and secondary Caesarean section. Of the confounders, blues, depression during the first postpartum week and a previous episode of depression earlier in life were significantly related to high scores. High scores on the sub-scale support (practical advices received from the maternity nurse) were also independently related to a negative perception of the confinement sub-scale.

Discussion

This study in a large group of healthy pregnant women with a gestation term over 37 weeks' shows, that the way delivery is perceived is independently related to obstetrical parameters such as non-spontaneous delivery, secondary Caesarean section and an increased dilatation time during labour. Moreover, several confounders increased the risk of high scores: anxiety and depression during the first postpartum week, increased dilatation time and non-spontaneous delivery. An almost identical set of variables is independently related to the way the confinement days are perceived including confounders such a previous history of depression earlier in life, the occurrence of severe blues, and support as perceived form the maternity nurse.
From an obstetrical point of view it is interesting to see that both long dilatation time and non-spontaneous delivery contribute to a negative perception of delivery. At one hand, long dilatation time – because it implies poor perception of delivery – could be a reason for an obstetrician for technical intervention. However, on the other hand, a technical intervention (non-spontaneous delivery) also predicts a negative perception of labour. Does the fact that secondary rather than primary Caesarean section did contribute to high scores on the delivery self-rating scale supports advocating of even

more primary interventions at end term before labour starts (as is the case currently when the foetus present in breech)? In case of primary Caesarean section the woman often participates in the discussion (breech presentation, yes or no vaginal delivery). Therefore she is more in control of time and mode of delivery, which might explain the difference in scores compared to secondary section. However Caesarean delivery is associated with increased maternal morbidity and mortality, for the current as well as future pregnancy and delivery, such as anaesthesia related complications, uterine rupture, bladder injuries, uterine atony, placenta accreta, secondary infertility [3, 19, 20.] . Therefore, the finding that primary Caesarean section is not related to poor scores might be better interpreted by the statement that optimal information and preparation of the woman what might happen during labour is important. The fact that recently anxiety during end gestation has been shown to be independently related to protraction of labour (which increases the risk of technical intervention)[8], implies that when preparing women for labour it is important to look not only at practical advices but also at psychological aspects such as anxiety and depression. Until now, most antenatal classes, which are set up to give women the opportunity to learn more about the process of labour itself, restrict to practical rather than psychological advices (how to breath during contractions, how to relax between the contractions e.g.).
Blues were significantly related to poor scores on the confinement self-rating scale. The *baby blues* are a common experience (up to 70%) amongst mothers in the first days postpartum. They can include transient feelings of being overly happy or sad and bouts of unexplainable crying[18.] The 'baby blues' usually resolve within two weeks and require no formal treatment. However, severe blues might be a prodromen of postpartum depression or even postpartum psychosis.[5] The fact that severe blues within this study was independently related to poor perception of confinement days – after correction for depression – suggests that it is a mood change distinct from depression and should alert a midwife or maternity nurse.
The support as perceived from the maternity nurse proved to be an important factor of positive perception of the confinement days. Although this seems to be obvious, this finding could be used to convince the health authorities in The Netherlands not to decrease the number of days of maternity nurse support further: from ten days in the eighties to seven days now.

The literature concerning the effect of technical intervention during labour on the occurrence of posttraumatic stress symptoms (PTSS) is growing. In a study performed in the same area as the current study, technical intervention was an independent risk factor for high PTSS[4]. Moreover, within the current study, it was shown that women who reported high levels of negative emotions during and shortly after childbirth were more likely to develop PTSD symptoms than women who did not[21]. Looking at risk factors of PTSS several categories have been discriminated: (1) *prenatal factors (including* traumatic deliveries) (2) *nature and circumstances of delivery*, e.g. long, hard and extremely painful labour, forceps delivery, emergency caesarean section, lack of control; and (3) *subjective factors during childbirth*, e.g. feelings of powerlessness, staff experienced as unsympathetic, lack of social support during the delivery and afterwards[22]. Several aspects of these risk factors are included in some items of the delivery and confinement sub-scale. Future research should focus on similarities between predictors of high scores on scales that measures both PTSS and perception of delivery and confinement days.

In conclusion, this study supports the idea that when a midwife - as a major task of her care giving during pregnancy - tries to achieve optimal risk selection for obstetrical outcome, she should include psychological aspects also. The obstetrician – when deciding if and how to intervene during labour - should realize that instrumental delivery when not strictly needed because of foetal complications – might contribute to negative emotions of the mother with regard to peripartum events.

References

1. Rietberg GC, Elferink-Stinkens PM, Visser GH. The effect of the Term Breech Trial on medical intervention behaviour and neonatal outcome in The Netherlands: an analysis of 35,453 term breech infants. BJOG. 2005;112(2):205-9.
2. Hannah ME, Hannah WJ, Hewson SA, Hodnett ED, Saigal S, Willan AR. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. Term Breech Trial Collaborative Group. Lancet 2000;356:1375– 1383.
3. Krupitz H, Arzt W, Ebner T, Sommergruber M, Steininger E, Tews G. Assisted vaginal delivery versus caesarean section in breech presentation.Acta Obstet Gynecol Scand. 2005;84(6):588-92.
4. Van Son M, van der Hart O, Verkerk G, Pop V, Komproe I. Prenatal Depression, Mode of Delivery, and Perinatal Dissociation as Predictors of Postpartum Posttraumatic Stress: An Empirical Study. Clin. Psychol. Psychother.2005;12:297–312.
5. Brockington I. Postpartum Psychiatric disorders. The Lancet Vol 363 jan 24,2004.
6. Kuijpens JL, Vader HL, Drexhage HA, Wiersinga WM, van Son MJ, Pop VJ. Thyroid peroxidase antibodies during gestation are a marker for subsequent depression postpartum. Eur J Endocrinol. 2001 ;145(5): 579-84
7. Wijnen HA, Vader HL, Essed GG, Mol BW, Oei G, Nadisauskiene R, Pop VJ. Vertex position during labour in relation to maternal thyroid function. Submitted.
8. Wijnen HA, Essed GG, van Son MJ, Bonevicius R,, Pop VJ. Maternal anxiety at end term and protraction of labour. Submitted.
9. Pop VJ, de Vries J, van Heck GL, Wijnen HA. Validation of the "Kempen Confinement Selfrating Scale" Submitted.
10. Cox JL, Chapman G, Murray D, Jones P.Validation of the Edinburgh Postnatal Depression Scale (EPDS) in non-postnatal women. J Affect Disord. 1996;39(3):185-9
11. Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale.Br J Psychiatry. 1987;150:782-6.
12. Pop VJ, Komproe IH, van Son MJ. Characteristics of the Edinburgh Post Natal Depression Scale in The Netherlands. J Affect Disord. 1992;26(2):105-10.
13. Becht MC, van Erp CF, Teeuwisse TM, van Heck GL, van Son MJ, Pop VJ. Measuring depression in women around menopausal age: towards a validation of the Edinburgh Depression Scale. J Affect Disord. 2001;63(1-3):209-13.
14. Harris B, Huckle P, Thomas R, Johns S, Fung H. The use of rating scales to identify post-natal depression.Br J Psychiatry. 1989;154:813-7.
15. Murray L, Carotuers AD. The validation of the Edinburgh Post-natal Depression Scale on a community sample. Br J Psychiatry. 1990;157:288-90.
16. Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale--preliminary report. Psychopharmacol Bull. 1973;9(1):13-28.
17. Arindel WA, Ettema JH. SCL-90. Een Multidemensionele Psychopathologie Indicator. Lisse: Swets & Zeitlinger.
18. Pitt B. 'Maternity blues'.Br J Psychiatry. 1973 Apr;122(569):431-3.
19. Smith GC, White IR, Pell JP, Dobbie R,. Predicting Cesarean Section and Uterine Rupture among Women Attempting Vaginal Birth after Prior Cesarean Section. PLoS Med. 2005;13;2(9):e252
20. Magann EF, Evans S, Hutchinson M, Collins R, Lanneau G, Morrison JC. Postpartum hemorrhage after cesarean delivery: an analysis of risk factors. South Med J. 2005 Jul;98(7):681-5.
21. Olde E, Hart van der O, Kleber RJ, Son van MJ, Wijnen HA, Pop VJ, Journal of Trauma & Dissociation, 2005, Vol 6 (3).:125-142.
22. Joseph S,Bailham D. Traumatic childbirth: what we know and what we can do. RCM Midwives 2004;7(6):258-61. Review

Chapter IX

BLUES AND DEPRESSION DURING EARLY POSTPARTUM: HOME VERSUS HOSPITAL DELIVERY

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OBSTETRICS

Blues and depression during early puerperium: home versus hospital deliveries

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ABSTRACT

Objective: To investigate whether women who give birth at home are less prone to mood disturbances during the early puerperium than those who give birth in hospital.

Design: A prospective study of 303 pregnant women who registered for antenatal care.

Setting: The antenatal clinic at St Joseph's Hospital, Veldhoven. The Netherlands, and five antenatal consultation programmes of local midwives working in the surrounding region.

Subjects: Three hundred and eighty-two consecutive caucasian women registering for antenatal care were approached. Of these, 303 consented to participate and 293 completed the study.

Main outcome measure: The predictor variable was the way in which the women gave birth: spontaneous vaginal parturition at home or in hospital as follows: spontaneously; vaginal parturition after stimulation with medication; vaginal parturition with forceps/vacuum extraction; or caesarean section. The outcome variables were blues and depression. The occurrence of blues was assessed at 4 weeks postpartum, using Pitt's criteria. The occurrence of depression was assessed at 4 weeks postpartum using the Research Diagnostic Criteria. The possible confounding effects of a set of obstetrical and psycho-social variables relating to the early puerperium were investigated using logistic regression analysis.

Results: Of the 293 women who completed the study, 52 % gave birth at home. Significantly more nullipara gave birth in hospital. Parturition occurred where it had been planned in 77 % of women; referral occurred later on in pregnancy in II % and during labour in 12 %. Nullipara had to be referred significantly more often than multipara. In general. there was no difference in the incidence of blues and depression between women who gave birth at home and those who gave birth in hospital. Obstetric factors were not related to the occurrence of blues or depression in the early puerperium.

Conclusions: Women who give birth in hospital are no more prone to postpartum mood disturbances, such as blues and depression, than women who give birth at home.

Up until 1900, home deliveries were quite common in Western Europe. It is only during the last few decades that in most Western countries it has become very unusual to give birth out of hospital. In The Netherlands about 35 % of women have their baby at home. compared with the UK where only I % of births take place out of hospital (Kloosterman 1984). Recently, discussions of this issue have been regenerated by the House of Commons Health Committee: "encouraging women to give birth in hospitals cannot be justified on the grounds of safety " ({Editorial BMJ 1992; Warden 1992) However, these discussions are mostly characterised by obstetric arguments (Schatzberger I 992).

It is generally accepted that postpartum women are vulnerable to mood distur-

bances, such as blues, postpartum depression and postpartum psychosis (Cox 1988). The aetiology is thought to be multifactorial: psychological factors, hormonal changes, obstetric factors; and social variables are all thought to play un important role (O'Hara & Zekoski 1988, O'Hara *et al.* 1991). Moreover, anthropological studies have suggested a possible relation between these mood disturbances and in our culture the lack of distinct protective measures designed to reflect the vulnerability or the new mother, such us social seclusion, mandatory rest and assistance from relatives (Stern & Kruckman (983). Another argument is the sophisticated and technical approach to parturition, especially in hospitals, and it has been suggested that the place of giving birth might be a contributing factor to the occurrence of postpartum depression (Cox 1988). However, most if not all studies into the aetiology of postpartum depression have been carried out in Western countries where women, as a rule, are delivered of their babies in a special maternity unit or in hospital.

Generally speaking, in The Netherlands there are three patterns of intrapartum care: 1. birth at home with the aid of a community midwife (or occasionally a general practitioner); 2. 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 3. 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). Within this system, the decision of where to give birth has usually been taken before or early in pregnancy, but quite often the woman has to be referred later on in pregnancy due to complications, such as vaginal bleeding or pregnancy-induced hypertension, or during labour due to dystocia or meconium stained amniotic fluid.

Our a priori hypothesis was that women who give birth at home are less prone to suffer from blues and depression during the early puerperium. We were also interested in finding out whether referral during late pregnancy or even during labour might influence mood in the early postpartum period.

Subjects and methods

Between November 1988 and April 1989, 382 caucasian women who had registered

for antenatal care were invited to participate in a screening programme. The study was carried out in a semi-urban, semi-rural region near the city of Eindhoven in the southern part of The Netherlands. The women were recruited by five midwives working in various communities and at the antenatal clinic of St Joseph's Hospital in Veldhoven on the outskirts of Eindhoven. The mean length of gestation at recruitment was 16 weeks. Three hundred and three women consented to participate, the recruitment rate being 79%. The demographic features (age, marital state, social class and number of children) were assessed. The nonparticipants did not differ in age, parity or social class. Of the 303 participants, there were 137 nullipara and 166 multipara. One woman was divorced, and all the others were married or had a partner. As expected, the mean age of the multipara (30.5 years) was higher than that of the nullipara (27.4 years). There was no significant difference in social class between the two groups. The women were assessed seven times: at 32 weeks gestation and 4 weeks postpartum, and thereafter at six weekly intervals until 34 weeks postpartum. The rationale for these frequent intervals was a parallel study on transient postpartum thyroid dysfunction (Pop *et al.* 1991). Assessment began in December 1988 and lasted until June 1990. Three women moved away from the area and were lost to follow up, two declined further screening and five became pregnant again during the period of screening. The data from these women were excluded from the analysis. Therefore, the results presented refer to 293 women (133 nullipara and 160 multipara) who completed the study; the drop-out rate was 3 %.

Blues were defined by Pitt's criteria (Pitt 1973): the presence of both significant tearfulness und low mood, lasting for at least part of one during the first 10 days postpartum. This small set of criteria is potentially as useful as another (more extensive) set of blues criteria (O'Hara *et al.* 1991). The occurrence or blues was assessed retrospectively at four weeks postpartum. Women were rated as cases if they reported significant tearfulness and low mood during the first 10 days postpartum.

Depression during pregnancy and the postpartum was diagnosed in an interview using the Research Diagnostic Criteria (Spitzer *et al.* 1975) which, within the DSM-III-R system, discriminate between major and minor depression. The occurrence of depression was assessed at 32 weeks gestation and four weeks postpartum.

To evaluate their obstetric history at four weeks postpartum the women were asked

to report on the way in which they had given birth. The following responses could be given:

1. Spontaneous vaginal parturition at home;
2. Spontaneous vaginal parturition in hospital;
3. Vaginal parturition after stimulation with medication in hospital;
4. Vaginal parturition with forceps/vacuum extraction in hospital ;
5. Caesarean section in hospital.

Moreover, at four weeks postpartum we determined whether the mother had had to be referred to give birth in hospital during pregnancy or during labour.
Finally, the influence of several other (mostly) psychosocial confounding variables on the occurrence of blues was also investigated: social support as perceived by the woman from her partner or closest relatives, with the aid of the social support interview (Cox 1988; O'Hara *et al.* 1991); the infant's temperament, including those aspects of childcare contributing to the severity of the stress experienced by the recently delivered mother. using the Child Care Stress Inventory (Cutrona 1983). The latter contains two distinct subscales: one concerning the way in which the child is perceived as troublesome by the mother and the other concerning the actual amount of care, such as feeding at night. A previous history or depression or having had depressed parents in childhood (<18 years) are two other variables which frequently contribute to the explained variance of depression. Finally. the occurrence or stressful life events during pregnancy and postpartum, generally thought of as being precipitating factors in depression, was assessed using the Recent Life Events List (Willige *et al.* 1985).

Statistical analysis

To detect the prevalence rates of postpartum thyroid dysfunction (PPT) and postpartum depression (PPD), we used the Epistat computerised statistical program to evaluate the sample size. Because neither syndrome has yet been investigated in The Netherlands, we predicted a 5 % prevalence rate for PPT and a 10% rate for PPD, based on literature from the UK and Scandinavia. From a total population of

1050 pregnant women, we calculated that for a 95 % accurate estimation of prevalence rates we would need a sample size of 170 women for PPT and 122 for PPD. Bearing in mind possible drop-outs and an 80% informed consent rate, we decided to invite approximately 400 women to participate. There are no data available on the prevalence rates of depression or blues in home compared with hospital delivery. In general, the prevalence rate for postpartum depression in women who give birth in hospital is 10%. We decided that a difference of 10% in the prevalence rate for postpartum depression between the two groups would be the minimum difference for clinical significance.

We predicted a 5% prevalence of postpartum depression for home births and a 15 % prevalence for hospital births. Using Pocock's formula with a power of 0.8, the size of the groups of home and hospital births had to be 134 with a 95 % significance level, and 105 with a 90 % significance level (Pocock 1991). In both cases, the size of the home and hospital birth groups in our study was appropriate: 153 compared with 140.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS). Statistical testing was either by χ^2 or logistic regression. We hypothesised that the impact of the manner of giving birth on maternal mood (if any) would be most powerful during the early postpartum period. Therefore, we analysed the data from the first postpartum assessment taken at four weeks postpartum.

Results

One hundred and fifty-three women had a spontaneous vaginal delivery at home, while 140 women gave birth in hospital (Table I). Of these, 108 were 24-hour confinements and 32 were clinical deliveries in hospital. The decision of where the baby should be born was not related to socio-economic status. Confinement occurred where it had been planned for 76% of the women; 12% were referred to hospital later on during pregnancy, and 12% during labour.

Significantly more nullipara had to be referred during labour than multipara (Table 1).One hundred and nineteen women (41 %) reported blues. There was a significant difference in the occurrence of blues between home (*n* = 53, 34%) compared with hospital deliveries (*n* = 66, 47%): women who gave birth in hospital reported blues

Table I. Prevalence of home *versus* hospital deliveries and referral rate in 293 pregnant women.

	Nulliparity	Multiparity	Total	χ^2 (df=2)	P
Delivery					
Spontaneous vs nonspontaneous(*n*= 293)				7.0	0.003
spontaneous at home	59	94	153		
spontaneous in hospital	50	57	107		
nonspontaneous in hospital	24	9	33		
Nonspontaneous in hospital (*n* = 33)				5.9	0.06
after drug stimulation	6	6	12		
after forceps/vacuum	12	1	13		
caesarean section	6	2	8		
Referral rate to hospital (*n*=293)				9.3	0.009
no referral	92	131	223		
during pregnancy	17	18	35		
during labour	24	11	35		

significantly more often (χ^2 : 4.6, df = 1, *P* 0.03). However, in order to exclude the possible confounding effects of variables (e.g., obstetrical complications, blues) which are known to be differently distributed in nullipara and multipara or are known from the literature to interfere with blues, we analysed possible interactions using logistic regression analysis, both at a univariate and multivariate level (Table 2). At the multivariate level only variables with an odds ratio at a significance level of less than 0.1 at univariate level were entered into the regression.

At four weeks postpartum the point-prevalence of depression (RDC) was 9 % (*n* = 27); six women had major and 21 minor depression. Multiparous women (10 % of 160) tended to be depressed more often than nulliparous women (8 % of 133), but the difference was not significant. In Table 3, odds ratios are shown for several variables with depression as the dependent variable at univariate level. All variables with odds ratios at a significance level of < 0.1 were subsequently entered into the multivariate logistic regression (Table 3). Several psycho-social variables and the occurrence of depression assessed at 32 weeks' gestation were entered stepwise in a regression analysis with obstetrical complications (e.g., nonspontaneous delivery) as the dependent variable (Table 4).

Table 2. Logistic regression analysis including obstetric history and several confounding variables.Dependent variable: blues (n = 293)

	O.R.	95%CI	P
Univariate			
Obstetric history			
hospital delivery	1.7	1.1-2.6	0.02
labour complications	1.4	0.7-2.8	0.4
episiotomy	1.2	0.7-1.9	0.5
nulliparity	2.3	1.4-3.6	0.0006
breastfeeding	1.1	0.8-1.4	0.6
referral during pregnancy	1.4	0.9-1.9	0.05
referral during lahour	1.9	1.1-3.1	0.02
Psycho-social history			
depression in pregnancy	1.2	0.6-2.4	0.8
depression in parent	1.4	0.8-2.3	0.2
previous depression in life	0.6	0.3-1.5	0.3
low support from partner	1.0	0.8-1.2	0.6
low support from relatives	1.0	0.9-1.1	0.9
stressful life event	2.3	1.4-3.7	0.0007
Child temperament aspects			
much care demanding	1.0	0.8-1.1	0.06
perceived as troublesome by mother	1.0	0.9-1.2	0.06
Multivariate*			
Obstetric history			
hospital delivery	1.3	0.8-2.2	0.3
nulliparity	1.6	0.9-2.7	0.07
referral during pregnancy	1.6	0.9-3.0	0.1
referral during labour	0.9	0.5-1.4	0.6
Psycho-social history			
stressful life event	1.9	1.2-3.1	0.01
Child temperament aspects			
much care demanding	1.0	0.9-1.1	0.6
perceived as troublesome by mother	0.9	0.8-1.0	0.1

* Variables with OR at univariate level with $P < 0'1$ are entered
O.R. = odds ratio; CI = confidence interval

Table 3 Logistic regression analysis, including obstetric history and several confounding variables.Dependent variable: depression (n = 293)

	O.R.	95%CI	P
Univariate			
Obstetric history			
hospital delivery	0.9	0.5-2.3	0.9
labour complications	0.8	0.4-4.5	0.7
nulliparity	1.3	0.6-3.0	0.5
breastfeeding	1.6	0.8-2.9	0.1
blues	4.0	1.7-9.7	0.002
referral during pregnancy	0.8	0.4-1.5	0.5
referral during lahour	0.8	0.4-1.9	0.7
Psycho-social history			
depression in pregnancy	2.7	0.8-8.4	0.08
depression in parent	3.7	1.6-7.8	0.002
previous depression in life	4.9	1.7-11.7	0.002
low support from partner	1.0	0.8-1.1	0.1
low support from relatives	1.2	0.8-1.4	0.03
stressful life event	1.9	0.8-4.7	0.1
Child temperament aspects			
demanding much care	1.0	0.8-1.1	0.09
perceived as troublesome by mother	1.0	0.9-1.2	0.02
Multivariate*			
Obstetric history			
blues	4.3	1.5-12.0	0.006
Psycho-social history			
depression in pregnancy	3.3	0.9-9.1	0.08
depression in parent	2.3	0.9-5.7	0.08
previous depression	3.4	1.0-11.2	0.05
low support from relatives	0.8	0.7-1.0	0.05
Child temperament aspects			
demanding much care	1.0	0.9-1.1	0.4
perceived as troublesome by mother	0.9	0.8-1.0	0.06

* Variables with OR at univariate level with $P < 0.1$ are entered
O.R. = odds ratio; CI = confidence interval

Table 4 Multivariate logistic regression analysis, dependent variable: obstetric complication (e.g., nonspontaneous delivery, $n = 293$)

	O.R.	95%CI	*P*
Depression in pregnancy	1.1	0.2-5.5	0.9
Depression in parents	2.0	0.9-4.6	0.09
Previous depression	2.1	0.6-7.2	0.3
Educational level	1.1	0.6-1.8	0.8
Stressful life events	1.1	0.7-1.5	0.7
Nulliparity	7.3	3.0-18.2	0.0001

O.R. = odds ratio; CI confidence interval

Discussion

In the Netherlands there are strict criteria governing giving birth at home. Only spontaneous births to low risk women occur at home (Kloosterman 1984). The fact that significantly more multipara had their babies at home compared with nullipara is consistent with the general picture in obstetrics: nullipara are more prone to complications during labour than multipara. This finding was confirmed in the regression analysis: the only variable which predicted obstetrical complications was parity (Table 4). This was also reflected by the finding that nullipara had to be referred to hospital significantly more often than multipara. It was found that other variables which are sometimes hypothesised as being related to the way in which women give birth. such us depression or depressive feelings during pregnancy, did not contribute in any way (Oates 1989). Perkin *et al.* (1993) also found that anxiety and depression during pregnancy were of little importance in the evolution of obstetric complications. In their study, parity had the strongest relation with obstetric complications, as was also the case in our study.

Blues were reported significantly more often after hospital deliveries (χ^2 :1.7 increased risk at a univariate level) (Table 2). However, it should be realised that the occurrence of blues is often associated with parity. O'Hara & Zekoski (1988) found

that nullipara report blues more often than multipara, which was also the finding in our study. but nullipara give birth more frequently in hospital. After correction for parity, the occurrence of blues was shown not to be related to the place or manner of giving birth (Table 2).

The origin of blues is still unclear. Because of its frequent occurrence (30 – 70% after delivery), some authors consider it a normal physiological event. Recently. it was demonstrated that complaints relating to blues are specific to the puerperium and are essentially different from nonspecific mood fluctuations due to other forms of physical and emotional stress, such as post-operative or post-traumatic stress (Levy 1987; Iles *el al.* 1989; Kennerly & Gath 1989). Moreover in their prospective controlled study, O'Hara *el al.* (1991) showed that in the first week after delivery childbearing women show a fourfold higher rate of mild dysphoria compared with nonchildbearing women. It is assumed that the biological changes due to abrupt changes in levels of oestradiol, progesterone, cortisol and β endorphins in the first week postpartum are partly responsible in view of the timing and course of the symptoms (George & Sandler 1988; Harris *el al.* 1994). However, if abrupt changes of hormones are of importance, why do blues occur more often in nullipara than in multipura? Moreover, blues have also been reported in women who adopt children. In addition, a number of psycho-social factors have been shown to be positively associated with maternity blues: poor social adjustment, poor marital relationship, previous history of severe or moderate premenstrual tension, high neuroticism, and anxious and depressed mood during pregnancy (Kennerly & Gath 1989; Smith *el al.* 1990). Referral was not associated with increased risk for blues, which suggests that in nullipara the occurrence of blues might be not related to how stressful the confinement is perceived to be by the woman. Finally, the finding in our study that, after correction for possible confounding variables, the occurrence of significant life events (in which the occurrence of a complicated delivery is excluded) almost doubles the risk for blues to occur, is in favour of the hypothesis that the aetiology of blues is multifactorial. Life events that occur in a period when the woman is vulnerable contribute to the exacerbation of a mood disorder which might be specific to the postpartum period but cannot be entirely related to hormonal fluctuations.

The point-prevalence of postpartum depression in our study is similar to other studies which used the same criteria for postpartum depression and has been dis-

cussed in detail elsewhere (Pop *et al.* 1993). Moreover, most of the psycho-social variables which were found to correlate significantly with the dependent variable depression can also be found in other studies (Cutrona 1984; O'Hara *et al.* 1984). In our study obstetric history was not related to postpartum depression. Many studies have investigated the extent to which obstetric complications during pregnancy or labour play in the development of postpartumdepression. However, poor definition of what sort of features constitute obstetric complications and differing methodologies in the assessment or depression have resulted in rather conflicting data (O'Hara & Zekoski 1988). Some studies did not find a significant association while others showed a weak correlation. However, it is difficult to compare these studies because different definitions of obstetric complications were used, includingtoxaemia, anaemia, labour complications and level of birth technology. In one study an association was found in women after premature delivery (Kumar & Robson 1984). O'Hara *et al.* (1991). using a peripartum event scale which contained a number of stressful life events associated with late pregnancy, labour and delivery, found no relation with postpartum depression. In our study psycho-social factors were mostly responsible for increasing the risk of postpartum depression (Table 3). The fact that women who suffered from blues had four times the increased risk of depression occurring is consistent with data from other studies (O'Hara & Zekoski 1988).It might be questioned whether the attitude of women with regard to location of confinement is important to psychological wellbeing in the early puerperium. Do the psychological background features of women who prefer to give birth at home except for obstetric reasons-differ significantly from those who prefer to give birth in hospital? If so, it might be hypothesised that this could also influence the women's perceptions of the early puerperium. These factors were not taken into account in our study. In an urbanised sample of 170 nullipara Kleiverda *et al.* (1990) studied the women's motives and background variables in relation to the preferred location of confinement. In their study a high level of education, relatively low psychological wellbeing and anxiety concerning the birth during early pregnancy, and less traditional attitudes towards female social roles, predicted a preference for home confinement. In our study, level of education was not associated with preference for agiven location for confinement among either nulliparous or multiparous women. High anxiety levels, as a rule, are associated with depressed mood, suggesting that

women who give birth at home are less prone to mood disturbances in the early puerperium. However, in many studies it has been shown that low psychological wellbeing during pregnancy is a strong predictor for postpartum depression (O'Hara & Zekoski 1988). The data of K1eiverda *et al.* (1990) appears to indicate that women with a preference for home confinement would be at risk for postpartum mood disturbances. It should be mentioned that in the study by Kleiverda *et al.* (1990) and our own the referral rate in nullipara who chose home confinement was high: 59% and 54%, respectively, which is similar to other studies published in The Netherlands. This means that, in general. results of studies into the relation between attitudinal factors towards the location of confinement, as registered in early pregnancy, and the occurrence of postpartum depression will be complicated by a high referral rate.It has been suggested that the increasing "medicalisation" of childbirth has to some extent interrupted postpartum social customs which were more prominent in the past (Stern & Kruckman 1983). It is hypothesised that in other cultures women are protected against postpartum depression by various existing social rules. Moreover, it might be hypothesised that women who give birth at homebenefit the most from their social network or family and close friends. However, in our study no relation could be demonstrated between home versus hospital delivery and the occurrence of blues and postpartum depression.It can be hypothesised that these findings may influence the decision as to where to give birth, which is still possible in The Netherlands. The comments of the House or Commons Health Committee in the UK were based mainly on the fact that, provided home deliveries are reserved only for low risk pregnant women who are so defined during pregnancy by the use of strict criteria, the perinatal morbidity and mortality after home deliveries does not differ from hospital deliveries (Kloosterman 1984; Warden 1992). The discussion which the report has reopened is characterised primarily by technical (obstetric) arguments (Schatzberger 1992), and it has been reported recently that pregnant women in Britain requesting a home birth have been intimidated by their general practitioner (Court 1995). Because a woman's psychological wellbeing during and after labour has often been quoted as an important argument in favour of home delivery, we believe that studies which investigate the outcome of obstetric and psycho-social factors on a woman's mental health perinatally may contribute more to the discussion on this subject.

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References:

Court C. (1995) Childbirth trust calls for rights to home births. Br Med J 310, 212.

Cox J.L. (1988) The life event of childbirth: sociocultural aspects of postnatal depression. In Motherhood and

Mental Illness Vol 2 (R. Kumar & 1. F. Brockingtoll, eds), Wright, London, pp. 64-77.

Cutrona C.E. (1983) Causal attributions and perinatal depression. J Abnormal Psychol 92, 161-172_

Cutrona C.E. (1984) Social support and stress in the transition to parenthood. J Abnormal Psychol 93, 378-390.

Editorial (1992) Home truths about maternity services. Br Med J 304, 657.

George A.J. & Sandler M. (1988) Endocrine and biochemical studies in puerperal mental disorders .In Motherhood and Mental Illness Vo12 (R. Kumar & I. F. Brockington, eds), Wright, London, pp. 78-112.

Harris B., Lovett L, Newcombe R.G., Read G.F., Walker R. & Riad~Fahmy D. (1994) Maternity blues and major endocrine changes: Cardiff puerperal mood and hormone study II. Br Med J 308, 949-953.

Iles S., Gath D. & Kennerley H. (1989) Maternity blues: a comparison between post-operative women and post-natal women. Br J Psychiatry 155,363-366.

Kennerly H. & Gath D. (1989) Maternity blues II. Associations with obstetric, psychological, and psychiatric factors. Br J Psychiatry 155, 367- 373.

Kleiverda G., Steen A.M., Andersen I., Treffers P.E. & Everaerd W. (1990) Place of delivery in The Netherlands: maternal motives and background variables related to preferences for home or hospital confinement. Eur J Obstet Gynecol Reprod Biol 36, 1-9.

Kloostenman G. J. (1984) The Dutch experience of domiciliary confinements. In Pregnancy Care for the 1980's (I.G.Zander & G. Chamberlain. eds), The Royal Society of Medicine, London. pp. 115-125.

Kumar R. & Robson K. M. (I984) A prospective study of emotional disorders in childbearing women. Br. J. Psychiat 144, 35-47.

Levy V. (1987) The maternity blues in post-partum and post-operative women.Br J Psychiatry. 151:368-72.

Oates M (1989) Normal emotional changes in pregnancy and the puerperium. Baillieres Clin Obstet Gynaecol.; 3 (4):791-804. Review.

O'Hara M.W., Neunaber D.J. & Zekoski E.M.(1984) Prospective study of postpartum depression: prevalence, course,and predictive factors. J Abnorm Psychol. 93(2):158-71.

O'Hara M.W. &. Zekoski E.M.(1988) Postpartum depression, a comprehensive review. In Moth-

erhood and Mental Illness Vol 2 (R. Kumar & 1. F. Brockingtoll, eds), Wright, London, pp. 17-57

O'Hara M.W., Schlechte J.A., Lewis D.A. & Wright E..J. (1991) Controlled prospective study of postpartum mood disorders: psychological, environmental, and hormonal variables J Abnorm Psychol. 100(1):63-73.

Perkin M. R., Bland J. M., Peacock J. L. & Anderson H. R. (1993) The effect of anxiety and depression during pregnancy on obstetric complications Br J Obstet Gynaecol. 100 (7):629-34.

Pitt B. (1973) Maternity blues. Br J Psychiatry. 122.431 433

Pocock S.J. (1991) Clinical trials: A Practical Approach. John Wiley, Chichester, pp 123-141

Pop V.J., de Rooy H.A., Vader H.L. et al. (1991) Postpartum thyroid dysfunction and depression in an unselected population. N Engl J Med. 20;324(25):1815-6.

Pop V.J., Essed G.G., Geus C.A., Son van M.J. & Komproe J.(1993) Prevalence of postpartum depression or is it post-puerperium depression? Acta Obstet Gynecol Scand 72, 354 -358

Schatzberger P. (1992) Maternity services. Br Med J 304,663

Smith R., Cubis J., Brinsmead M. et al. (1990) Mood changes, obstetric experience and alterations in plasma cortisol, beta-endorphin and corticotrophin releasing hormone during pregnancy and the puerperium. J Psychosom Res.34(1):53-69.

Spitzer R.L. Endicott J. & Robins E (1975) Clinical criteria for psychiatric diagnosis and DSM-III. Am J Psychiatry. 132(11):1187-92.

Stern G. & Kruckman L. (l983) Multi-disciplinary perspectives on post-partum depression: an anthropological critique. Soc Sci Med. 17(15):1027-41

Warden J. (1992) Maternity landmark Br Med J .304, 662.

Willige G., Schreurs P., Tellegem B. & Zwart I. (1985) .An inventory of recent life events (de vragenlijst recent meegemaakte gebeurtenissen) Dutch J Psychol 40, 1-19.

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Chapter x

PERI-TRAUMATIC DISSOCIATION AND EMOTIONS AS PREDICTOR OF PTSD SYMPTOMS FOLLOWING CHILDBIRTH.

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ABSTRACT. The current study investigated the contributive role of perinatal dissociative and perinatal emotional responses to the development of PTSD symptoms following childbirth. Method: Using a prospective, longitudinal design, 140 women were studied who were followed from the first week after delivery to three months postpartum. Results: Three women (2.1%) met criteria for PTSD and 21.4% reported a traumatic childbirth experience. Both perinatal negative emotional reactions and perinatal dissociative reactions were the predictors of PTSD symptoms at three months postpartum. The effect of perinatal dissociation, however, was partially mediated by perinatal emotional reactions. Conclusion: Posttraumatic stress disorder can be a consequence of the experience of childbirth. Women who reported high levels of negative emotions during and shortly after childbirth were more likely to develop PTSD symptoms than women who did not. Women who experienced an instrumental delivery and also reported higher levels of psychoform perinatal dissociation, were at higher risk than women who reported higher levels of perinatal dissociation during a spontaneous delivery. These findings add to the growing body of literature regarding traumatic childbirth and indicate that perinatal dissociative and emotional phenomena are associated with posttraumatic stress.

KEYWORDS. Peritraumatic dissociation, posttraumatic stress, childbirth, emotional responses

Introduction

Recent studies have indicated that for some women childbirth may be a traumatic experience leading to the development of posttraumatic stress disorder (PTSD) and related disturbances. Between 2.8 and 5.6% of women suffer from PTSD as a consequence of childbirth at six weeks postpartum (Ayers & Pickering, 2001; Creedy, Shochet, & Horsfall, 2000; Czarnocka & Slade, 2000; Wijma, Soderquist, & Wijma, 1997). At approximately 6 months postpartum PTSD prevalence rates decrease to a level of around 1.5% (Ayers & Pickering, 2001; Wijma et al., 1997). Several studies investigated factors that may predict the development of childbirth-related PTSD and posttraumatic stress symptoms (Creedy et al., 2000; Soet, Brack, & Dilorio, 2003; Wijma et al., 1997). Personality traits, level of obstetric intervention, intense perinatal emotional reactions, negative contact with staff, and lack of social support have been found to be related to PTSD and posttraumatic stress symptoms. Similar factors have also been identified in studies focusing on other types of stressors (Brewin, Andrews, & Rose, 2000; Ozer, Best, Lipsey, & Weiss, 2003).

In recent years, much attention has been paid to the predictive role of psychological phenomena that occur during or directly after various traumatic incidents. Immediate reactions experienced at the time of the trauma, such as dissociation, extreme anxiety, panic, and negative emotions, may be important predictors of subsequent PTSD symptoms (Bernat, Ronfeldt, Calhoun, & Arias, 1998). One of the most important predictors appears to be peritraumatic dissociation. According to Marmar, Weiss, and Metzler (1998), peritraumatic dissociation is the occurrence of dissociative symptoms during or shortly after exposure to extreme events involving acute alterations in cognitive and perceptual functioning at the time of a traumatic event. Traumatized patients frequently report alterations in the experience of time, place and person, which lead to a sense of unreality as the event is occurring (Marmar et al., 1998).

Nijenhuis, Van Engen, Kusters, and Van der Hart (2001) suggested that peritraumatic dissociation – involving both psychoform and somatoform phenomena – is a manifestation of acute integrative failure, which sets the stage for the failure to synthesize and personify the traumatic experience in the long run. Psychoform phe-

nomena of dissociation refer to dissociative amnesia and identity fragmentation and may involve depersonalization and derealization. Somatoform dissociation designates dissociative symptoms that phenomenologically involve the body. The adjective "somatoform" indicates that the physical symptoms suggest, but cannot be explained by a physical condition or by the direct effect of a substance (Nijenhuis & Van der Hart, 1999). Somatoform dissociative phenomena include the inability to move and speak, anesthesia of various perceptual modalities, such as lack of pain perception (analgesia), tunnel vision, and bodily numbing (tactile and kinesthetic anesthesia; Nijenhuis, et al., 2001).

Ozer et al. (2003) performed a meta-analysis on predictors of PTSD and related symptoms following different forms of trauma (not including childbirth). Peritraumatic dissociation was found to be the strongest predictor for PTSD as compared to prior trauma, prior psychological adjustment, family history of psychopathology, perceived life threat during trauma, posttrauma social support, and peritraumatic emotional responses. Measures of peritraumatic dissociation have been found to predict PTSD and posttraumatic stress symptoms beyond the level of stress exposure, general dissociative tendencies, locus of control, and social support (Marmar et al., 1999; Shalev, Peri, Canetti, & Schreiber, 1996; Tichenor, Marmar, Weiss, Metzler, & Ronfeldt, 1996). Peritraumatic dissociation was also predictive in various groups of victims of trauma: Vietnam combat veterans (Kaufman et al., 2002; Tichenor et al., 1996), motor vehicle accident victims (Delahanty, Royer, Raimonde, & Spoonster, 2003; Fullerton et al., 2001; Ursano et al., 1999), victims of natural disasters (Koopman, Classen, & Spiegel, 1994), emergency service personnel (Marmar et al., 1999), and survivors of crime and assault (Freedman, Brandes, Peri, & Shalev, 1999; Shalev et al., 1996). A study on posttraumatic stress after pregnancy loss reported a relation between peritraumatic dissociation and PTSD. Peritraumatic dissociation was predicted by lower emotional control (Engelhard, Van den Hout, Kindt, Arntz, & Schouten, 2003). In the field of childbirth-related PTSD, the role of peritraumatic dissociation has been noticed (Moleman, Van der Hart, & Van der Kolk, 1992) but has been scarcely empirically studied (Van Son, Verkerk, Van der Hart, Komproe, & Pop, 2004).

Nevertheless, in the general trauma field the predictive role of peritraumatic dissociation has not been confirmed in several other studies. Marshall and Schell (2002)

examined the link between peritraumatic dissociation and symptoms of PTSD in a sample of survivors of community violence. Although peritraumatic dissociation at baseline correlated with subsequent PTSD symptom severity, it was not an independent predictor of chronic PTSD symptoms. In a study on motor vehicle accident victims (Holeva & Tarrier, 2001) peritraumatic dissociation was not found to be predictive of PTSD. According to Gershuny, Cloitre, and Otto (2003), little attention has been paid to possible mediating relationships between peritraumatic emotions and peritraumatic dissociation. These authors found in their study that the effect of peritraumatic dissociation was eliminated when controlling for peritraumatic emotions such as fear and loss of control. These studies indicate that the predictive role of peritraumatic dissociation is still indistinct.

PERITRAUMATIC EMOTIONS AND PERITRAUMATIC DISSOCIATION

The occurrence of negative emotional responses during or directly after the traumatic event has also been found to be predictive of PTSD and posttraumatic stress symptoms. Brewin et al. (2000) reported that intense levels of fear, helplessness and horror strongly predicted PTSD six months post-trauma. In their meta-analysis Ozer et al. (2003) found that peritraumatic emotional responses were the second strongest predictor of posttraumatic stress symptoms or current PTSD, after peritraumatic dissociation. Vehement emotional reactions during or shortly after the trauma such as intense fear, helplessness, loss of control and horror were found to be related to PTSD and posttraumatic stress symptoms in various groups of victims of potentially traumatizing experiences such as serious accidents and natural disasters (Bernat et al., 1998), violent crime (Brewin et al., 2000), motor vehicle accidents (Ehlers, Mayou, & Bryant, 1998), and terrorist attacks (Simeon, Greenberg, Knutelska, Schmeidler, & Hollander, 2003). With regard to childbirth-related PTSD, various studies reported associations between the occurrence of negative emotions and the development of PTSD (Czarnocka & Slade, 2000; Keogh, Ayers, & Francis, 2002; Lyons, 1998).

The occurrence of negative emotions such as fear and panic has been associated with perinatal dissociative reactions, as dissociation may be regarded as a mechanism to handle the extreme emotions associated with traumatic events

(Creedy et al., 2000; Moleman et al., 1992). Moleman et al. (1992) reported that women who panicked during delivery went into a dissociative state on order to escape the emotional event. Although this report was based on three case studies, it clearly illustrates how women may react during the course of delivery in anticipation of negative outcomes. Other studies have also suggested that dissociation is a response to overwhelming emotional and physiological arousal (Bernat et al., 1998; Van der Kolk & Van der Hart, 1989). Peritraumatic dissociation has been found to be related to greater perceived threat and greater externality in locus of control (Marmar, Weiss, Metzler, & Delucchi, 1996), loss of control, helplessness and anger (Simeon et al., 2003), and hyperarousal and anxiety (Sterlini & Bryant, 2002). Bernat et al. (1998) reported that the relationship between acute fear and peritraumatic dissociation was mediated by acute panic symptoms, and that peritraumatic dissociation is the proximal outcome of overwhelming traumatic fear and attendant physiological responding. According to Gershuny et al. (2003), peritraumatic dissociation could be conceptualized as part of a panic process. These authors suggested that fears about death and loss of control are cognitive components of panic. The cognitive appraisal of the traumatic event as unmanageable, as reflected by fears of death and losing control, may help elicit dissociation. In addition, fears of death and losing control mediated the relationship between peritraumatic dissociation and PTSD (Gershuny et al., 2003).

In a prospective study on soldiers in Army survival training, Morgan et al. (2001) found that a majority reported peritraumatic dissociation under stress, and that dissociative symptoms were common in healthy humans experiencing acute, highly intense stress. The authors reported that fearing for one's life significantly influenced the degree to which subjects experienced symptoms of dissociation. Morgan et al. (2001) stated that the causal link between peritraumatic dissociation and PTSD must be viewed with caution as acute stress-induced symptoms of dissociation were found to be very common among their subjects.

The current study aimed to prospectively test whether perinatal negative emotions and perinatal dissociation are associated with the development of posttraumatic stress symptoms related to childbirth. We prefer to use the term *perinatal* because childbirth is generally not considered a traumatic experience. On the basis of prior general trauma studies we hypothesized that both perinatal negative emotions and

perinatal dissociation would be positively correlated to PTSD symptoms. Based on earlier findings (Bernat et al., 1998; Moleman et al., 1992; Morgan et al., 2001), we assumed that negative perinatal emotions precede the occurrence of perinatal dissociation. Finally, we expected that both perinatal emotional reactions as well as perinatal dissociative reactions independently contributed to level of PTSD symptoms.

METHODS

Participants

Participants (N = 140) were pregnant Dutch women who lived in a suburban region in the southern part of the Netherlands. All participants were clients of midwives' practices in the region of the town of Veldhoven. Data were collected between September 2001 and December 2002 as part of a larger study on the effects of thyroid hormone level on the delivery, conducted by two of the authors (VP & HW). Of the 344 women who were asked to participate, 229 (66.6%) entered the study. Ten women (4.4%) were excluded from the study because of premature birth (birth before the 37th week of pregnancy). As this is a report of an ongoing longitudinal study we used data from those women who had completed all assessments, therefore 79 (34.5%) women could not enter the study. The demographics of the remaining 140 (61.1%) women were similar to those of the group as a whole, except that women participating in the current study (N = 140, M = 31.5, SD = 3.3) were significantly older compared to women with incomplete data (N=89, M = 30.5, SD = 3.4) as was found using a t-test (df = 227; t = -2.2; $p < .05$). No differences were found on level of education and number of deliveries. The average age of participants was 31.5 years (SD = 3.3, range = 22.0-40.1). For 41% of the sample this was their first delivery (primiparous). All women were currently married or living together with their partner. A large majority were employed (90%). This sample is representative for the Dutch population of pregnant women with regard to age, employment and education (Centraal Bureau voor de Statistiek, 2003).

Procedure

A longitudinal design makes it possible to investigate the development of PTSD symptoms and PTSD. Women were approached and informed about the study

during their pregnancy by the midwife (HW) at their first visit at the midwife practice. Informed consent was required before they were included in the study. There were two moments of assessment: in the first week postpartum and at three months postpartum. In the first week postpartum, participants filled out a self-report questionnaire that was given to them by their midwife during the last birth control at 36 weeks in pregnancy. The midwife collected the questionnaires during a visit at eight days postpartum. During the first assessment, peritraumatic risk factors were measured. These factors consisted of peritraumatic psychoform and somatoform dissociation, peritraumatic emotions, acute stress symptoms and depressive symptoms during the first week postpartum. At three months postpartum a self-report questionnaire was sent to the participants' home address by mail, which they could send back by using the return envelope. PTSD symptoms were measured at this time point.

Instruments

Characteristics of the delivery – mode of delivery, duration and other specific birth related aspects – were assessed by a *standardized form* that is regularly used by midwives and gynecologists in the Netherlands. The following possibilities of delivering a baby can be discriminated in the Netherlands: spontaneously at home with the aid of a midwife or GP, or in hospital (spontaneously, after induction vaginally, after forceps / vacuum extraction vaginally or by Caesarean section). Those deliveries that are not spontaneous will be labelled instrumental in the current study. Up to 90% of the women who deliver in hospital stay there for less than 24 hours. During the first postpartum week at home, all women are visited by the midwife to look after the mother and the baby. Moreover, the woman receives care during eight hours per day of a special trained "confinement" nurse (this is part of health insurance care in the Netherlands). A lconfinement nurse is a maternity caretaker who visits the mother during the first eight days after delivery, teaches the parents of the newborn child how to take care of the baby and carries out simple household tasks.

Psychoform perinatal dissociation was assessed by the Dutch version of the *Peritraumatic Dissociative Experiences Questionnaire-Self-Report Version* (PDEQ-SRV) (Marmar, Weiss, & Metzler, 1998; Dutch version: Kleber & Van der Hart, 1998), a ten-item self-report questionnaire for assessing subjects' recall of experiences

during the trauma which are characterized as psychoform dissociation. In the current study, the delivery was set as the critical event. Items include derealization, amnesia, out-of-body experiences and altered time perception, and are rated on a scale from 1 to 5. Phenomena assumed to be dissociative are related to constructs of depersonalization, derealization, altered sense of time, and altered sense of body image. Internal consistency for the PDEQ in the present sample was good (Cronbach's alpha = .85).

Perinatal somatoform dissociation was assessed by the *Somatoform Dissociation Questionnaire-Peritraumatic* (SDQ-P; Nijenhuis & Van der Hart, 1998) . The SDQ-P is a self-report questionnaire that evaluates somatoform manifestations of dissociation during or immediately following an overwhelming event. The items were derived from clinical observations, clinical reports in the literature and from the SDQ-20 (Nijenhuis, Spinhoven, Van Dyck, Van der Hart, & Vanderlinden 1996), which assesses the severity of current somatoform dissociation. Examples of items are: "It was like my body, or a part of it was paralyzed," and "It was like my body, or a part of it had disappeared." The SDQ-P has good internal consistency and convergent validity as it is strongly associated with the PDEQ (Nijenhuis et al., 2001). Internal consistency in the current study was satisfactory (Cronbach's alpha = .62)

Negative emotions were assessed using the *Peritraumatic Emotions List* (PEL; Van der Velden, Van der Burg, Steinmetz, & Van den Bout, 1992), a standardized list with 10 emotions that can be scored on a five-point Likert scale. Participants were asked to report which emotions they had experienced during a defined shocking event, for example, fear, powerlessness, horror and guilt. Childbirth is characterized by an ambiguous set of emotions. During delivery women may experience huge amounts of pain, fear and loss of control. Afterwards, feelings of happiness and pride may be experienced when they hold their baby in their arms. Therefore, we distinguished between emotions experienced during and emotions experienced shortly after delivery. Internal consistencies of the PEL during and after were satisfactory with Cronbach's alphas of .79 and .71, respectively.

The Dutch version of the *PTSD Symptom Scale-Self Report version* (PSS-SR; Foa, Riggs, Dancu, & Rothbaum, 1993; Dutch version: Arntz, 1993) was used to assess the frequency of the 17 PTSD symptoms according to the *DSM-IV* criteria for PTSD and to indicate whether women were fully symptomatic (i.e., reporting symp-

toms of intrusion, avoidance and hyperarousal, or not, at three months postpartum). The instrument has a four-point scale (0 = "not at all" to 3 = "five or more times a week/almost always"). The range of possible scores is 0 to 51, with higher scores indicating higher levels of PTSD symptoms. Internal consistency for the PSS-SR in the present sample was good (Cronbach's alpha = .81). The PSS-SR provides reliable and valid information of both PTSD diagnosis and symptom severity. In the current study the same method for assessing PTSD with this inventory was used as Dunmore, Clark, and Ehlers (1999) applied. Besides fulfilling the symptom criteria of one intrusion symptom, three avoidance symptoms, and two hyperarousal symptoms, they suggested a more conservative scoring method of a sum score of at least 18 on frequency of symptoms in order to assess a certain amount of symptom severity. Additionally, in order to meet the *DSM-IV* PTSD stressor (A) criterion, participants had to report feelings of fear, powerlessness or disgust, and they had to hold the idea that their or their baby's life was threatened, or that they or their baby were being harmed during childbirth.

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 11.5, personal computer version. The psychometric properties of the PDEQ, SDQ-P, PEL, and the PSS-SR were assessed using Cronbach's alpha for reliability. To determine the incidence and severity of PTSD symptoms, total scores on the PSS-SR were calculated. To determine the relationship between demographic variables, obstetric characteristics, perinatal dissociative and emotional responses, Pearson correlations were undertaken. In addition a hierarchical multiple regression analysis was conducted to analyze the predictive role of mode of delivery, perinatal dissociation and emotions in the development of PTSD symptoms. An alpha level of .05 was used for Pearson correlations. One-tailed correlations were assessed when the direction of the relation was also expected. In these cases an alpha level of .10 was used.

RESULTS

Incidence of Posttraumatic Stress Disorder

From the total sample of 140, 22 women (15.7%) reported no symptoms on the PSS-SR, 44 (31.4%) reported symptoms on one of the clusters of PTSD, 59 (42.1%) reported symptoms on two clusters of PTSD, and 15 women (10.7%) reported symptoms on all three clusters of PTSD. Symptoms of hyperarousal were most frequently reported. A total of 30 women (21.4%) of the total sample met the A-criterion. Three of the 15 fully symptomatic women fulfilled the criteria for PTSD at three months postpartum as they also met the A-criterion, which indicates a prevalence of 2.1% of PTSD in the total sample. A majority of women (67.1%) had a spontaneous delivery, whether at home or in the hospital (see Table 1). A t-test was performed to assess differences between instrumental and normal deliveries on PTSD symptom severity. No differences were found between the groups on the outcome variable (PSS-SR normal delivery: M = 4.2, SD = 0.4, PSS-SR instrumental delivery M = 5.0, SD =0.8; df = 134; t = -.9; p > .05).

TABLE 1. Characteristics of Mode of Delivery

Mode of delivery	N	%
Spontaneous home	66	47.1
Spontaneous hospital	28	20.0
After induction	16	11.4
Vacuum	15	10.7
EmCs*	8	2.1
ElCs**	3	5.7

Note: EmCs = Emergency Cesarean Section; ElCs = Elective Cesarean Section.

Perinatal Emotional and Dissociative Reactions as Predictors of PTSD Symptom Severity

In order to investigate whether negative emotional reactions during and shortly after delivery and perinatal dissociation were related to PTSD symptom sever-

ity, we examined whether their mutual correlations and the correlations between both constructs with PTSD symptoms were significant. We investigated Pearson correlation coefficients between emotional reactions during and shortly after delivery, perinatal dissociative reactions, and PTSD symptom severity. Both perinatal psychoform and somatoform dissociation correlated with negative emotional responses during delivery and with negative emotional responses shortly after delivery. As shown in Table 2, perinatal psychoform and somatoform dissociation were significantly related to PSS-SR scores. Negative emotions during and shortly after delivery also correlated significantly with PSS-SR scores (Table 2).

TABLE 2. Correlations (Pearson's *r*) Between Perinatal Dissociative Symptoms and Emotions and PTSD Reactions at Three Months Postpartum

	Perin somf diss	Neg emot during	Neg emot after	PTS sympt PSS-SR
Perin psychof diss	0.37**	0.31**	0.52**	0.31**
Perin somf diss		0.25**	0.18*	0.33**
Neg emot during			0.48**	0.32**
Neg emot after				0.28**

Note: Perin psychof diss = perinatal psychoform dissociation; Perin somf diss = perinatal somatoform dissociation; Neg emot during = negative emotions during delivery; Neg emot after = negative emotions shortly after delivery; PTS sympt = PTSD symptoms.
*$p < .05$ (2-tailed)
**$p < .01$ (2-tailed)

We computed a hierarchical multiple regression analysis in order to examine which factors contributed significantly to the variance on PTSD symptom severity (Table 3). In the first step we included four demographic factors: age, education, parity, and duration of delivery explaining 1.5% of the variance, which was not significant (see for all steps Table 3). In the second step we controlled for mode of delivery (spontaneous or instrumental). Mode of delivery did not significantly contribute to PTSD symptom severity. In step 3 negative emotional reactions during delivery were entered. Perinatal negative emotions accounted for significant increments in the change of variance in PSS-SR scores. Furthermore, negative emotions during delivery predicted PTSD symptom severity. Then perinatal psychoform and somatoform reactions were entered in the fourth step. We did not specify an order in which psy-

choform or somatoform dissociation would occur, therefore they were both entered in the fourth step of the model. Perinatal psychoform and somatoform dissociative reactions both significantly predicted level of PTSD symptoms and contributed significantly to the explained variance above and beyond age, education, parity, and duration and mode of delivery. Perinatal somatoform dissociative reactions significantly contributed to scores on the PSS-SR. Perinatal psychoform dissociation did significantly contribute to the explained variance. In step 5 negative emotional reactions shortly after delivery were entered. Negative emotional reactions shortly after delivery did not significantly contribute to the explained variance. The total model explained 21.0 % of the variance in PTSD symptoms. Perinatal negative emotional reactions during delivery and somatoform and psychoform dissociation were significant predictors of PTSD symptoms in the final model (Table 3).

TABLE 3. Hierarchical Multiple Regression Analyses Perinatal Variables Predicting Scores on the IES-R and the PSS-SR (N = 140)

Predictor	R^2	ΔR^2	B	SEB	β
Model 1	0.21**				
Step 1		0.02			
Age			0.12	0.15	0.09
Education			-0.23	0.30	-0.07
Parity			-0.38	0.49	-0.09
Duration			0.01	0.01	0.08
Step 2		<0.01			
Mode			0.57	0.97	0.06
Step 3		0.10**			
Neg em du			0.30*	0.08*	0.31*
Step 4		0.10**			
Psych Diss			0.12*	0.06*	0.18*
Som Diss			0.32*	0.13*	0.23*

Note: Regression coefficients were taken from the last step of the model. Neg em du = negative emotions during delivery; Psych Diss, psychoform dissociation; Som Diss, somatoform dissociation.

* $p < .05$

** $p <$. 01 (one-tailed)

DISCUSSION

The results of this study confirm that women may experience childbirth as a traumatic experience and subsequently develop PTSD symptoms (Ayers & Pickering, 2001; Creedy et al., 2000; Czarnocka & Slade, 2000; Wijma et al., 1997). In this study 2.1% of women developed all the symptoms needed for PTSD except the F-criterion. In order to assess symptom severity, we used a total score of 18 following Dunmore et al. (1999). The prevalence found in the current study at three months postpartum is quite similar to the findings of Ayers and Pickering (2001) who found an incidence rate of 2.8% at 6 weeks and 1.5% at six months. On the other hand, the prevalence is lower compared to findings of Creedy et al. (2000; 5.6% at 4 to 6 weeks postpartum) who used the same instrument, but did not apply the Dunmore et al. (1999) method of scoring higher than 18 on the PSS. Nevertheless, we should be careful interpreting the prevalence of PTSD, as we did not assess the F-criterion according to *DSM-IV*. These prevalence rates are all within that found in the general population for PTSD prevalence.

To our knowledge, the present study is the first longitudinal study that prospectively examined the role of perinatal emotions and perinatal dissociation as risk factors for PTSD symptoms after childbirth. Women who reported higher levels of perinatal psychoform and perinatal somatoform dissociation subsequently also reported higher levels of PTSD symptoms. This relationship has been found in other posttraumatic stress studies using psychoform dissociation only (Freedman et al., 1999; Marshall & Schell, 2002; Shalev et al., 1996). A higher level of negative perinatal emotions was also related to higher levels of PTSD symptoms. This finding is consistent with studies on other populations (Bernat et al., 1998; Brewin et al., 2000; Gershuny et al., 2003). Women in our study who reported higher levels of negative perinatal emotions also reported higher levels of perinatal psychoform and perinatal somatoform dissociation. This finding is comparable with other studies reporting associations between symptoms of hyperarousal, negative emotions, loss of control and the occurrence of peritraumatic psychoform dissociation (Bernat et al., 1998; Gershuny et al., 2003; Morgan et al., 2002; Sterlini & Bryant, 2002).

Negative emotions during delivery and perinatal psychoform and somatoform dissociation predicted PTSD symptom severity above parity, age, and duration and mode of delivery. Although both emotional reactions *during* delivery as well as

emotional reactions shortly *after* delivery were significantly correlated with PTSD symptoms, negative emotional reactions shortly *after* delivery did not predict PTSD symptoms. This finding might indicate that emotional reactions during the event play a larger role in the development of PTSD symptoms. Regarding PTSD symptom severity, perinatal somatoform and psychoform dissociation, and negative emotions during delivery were the strongest predictors of PTSD symptom severity. This finding is in contrast with the findings of Gershuny et al. (2003), who reported that the effect of peritraumatic dissociation (also assessed with the PDEQ) on posttraumatic stress symptoms was mediated by fear about death and loss of control. This difference may be due to the fact that Gershuny et al. (2003) investigated a more specific emotional response (fear of death and loss of control) whereas we investigated a larger variety of emotional responses (e.g., fear, panic, sadness, and shame). In addition, emotional responses during delivery were associated with dissociative responses, possibly indicating that negative emotional responses may elicit dissociative responses.

The results of this study with regard to peritraumatic psychoform dissociation are consistent with those of other studies in the general traumatic stress field that peritraumatic psychoform dissociation is a main predictor of PTSD symptom severity. However, a limitation in other studies is the weak conceptual base of the dissociation construct (Marshall, Spitzer, & Liebowitz, 1999; Nijenhuis, Van der Hart, & Steele, 2002; Van der Hart, Nijenhuis, Steele, & Brown, 2004). While this construct essentially refers to a division of doubling of consciousness or personality (Van der Hart et al., 2004), many scholars have subsumed under this heading phenomena such as absorption and imaginary involvement, and momentary confusion. Thus, the PDEQ used to measure psychoform peritraumatic dissociation includes items measuring changed sense of time and confusion, while it is questionable whether these phenomena should be regarded as dissociative in nature (Van der Hart et al., 2004). Given the central predictive role of peritraumatic dissociation, studies that critically examine the nature of this construct and involve operationalisations true to the basic understanding of dissociation and its relations to emotions are urgently needed.

Study Limitations

This study has several limitations, suggesting caution with regard to the generalizations of our results. First, we studied an experience that should not be

regarded as a very shocking event for the majority of women. However, this study as well as others, firmly showed that a minority of women may develop childbirth-related PTSD, and that a larger group develops PTSD symptoms. Second, we studied an event that can only be experienced by women, so generalizations to other groups than childbearing women is difficult. Third, we did not use standardized clinical interviews to assess PTSD, although the PSS-SR has been shown a useful tool for screening and assessing current PTSD (Foa et al., 1993). The findings of the prevalence of PTSD in the current study should also be regarded with caution, as we did not assess the F-criterion of PTSD. Fourth, perinatal dissociative and negative emotional responses were associated with each other, but due to the assessment procedure it is not possible to conclude that negative emotional responses precipitate perinatal dissociation. Nevertheless, the strong relation found between perinatal psychoform dissociation and negative emotions during and after delivery is similar to the findings of Marmar et al. (1996), Simeon et al. (2003) and Sterlini and Bryant (2002) with regard to other trauma populations. Finally, although we assessed perinatal dissociative and perinatal emotional reactions in the first week after delivery, there is still a gap of a few days between the experience and the assessment of perinatal responses. These data therefore have a slightly retrospective character.

CONCLUSION

The results of this study add to the findings of previous studies that for some women childbirth may indeed be a traumatic experience leading to the development of PTSD symptoms. We have focused on two peritraumatic risk factors. Perinatal negative emotions predicted the development of childbirth-related PTSD symptoms. In addition, the strong relation with perinatal negative emotions indicates that dissociative reactions might be part of a traumatic stress response. Future studies should examine relationships with other known predictors of childbirth-related PTSD symptoms, such as social support by partners and support of the medical staff. In addition, future studies should also differentiate between the kinds of emotional responses, whether these responses pertain to anger, helplessness, or shame and guilt, or a combination of any of them, in order to examine which combination of factors channels mostly on those individuals at risk.

REFERENCES

Arntz, A. (1993). *Dutch translation of the PSS-SR.* Universiteit Maastricht, the Netherlands: Author.

Ayers, S., & Pickering, A.D. (2001). Do women get posttraumatic stress disorder as a result of childbirth? A prospective study of incidence. *Birth, 28*, 111-118.

Bernat, J.A., Ronfeldt, H.M., Calhoun, K.S., & Arias, I. (1998). Prevalence of traumatic events and peritraumatic predictors of posttraumatic stress symptoms in a nonclinical sample of college students. *Journal of Traumatic Stress, 11*, 645-664.

Brewin, C.R., Andrews, B., & Rose, S. (2000). Fear, helplessness, and horror in posttraumatic stress disorder: Investigating DSM-IV criterion A2 in victims of violent crime. *Journal of Traumatic Stress, 13*, 499-509.

Centraal Bureau voor de Statistiek [Central Statistics Agency]. 2003. Retrieved from http://www.cbs.nl, December 2004.

Creedy, D.K., Shochet, I.M., & Horsfall, J. (2000). Childbirth and the development of acute trauma symptoms: Incidence and contributing factors. *Birth, 27*, 104-111.

Czarnocka, J., & Slade, P. (2000). Prevalence and predictors of post-traumatic stress symptoms following childbirth. *British Journal of Clinical Psychology, 39*, 35-51.

Delahanty, D.L., Royer, D.K., Raimonde, A.J., & Spoonster, E. (2003). Peritraumatic dissociation is inversely related to catecholamine levels in initial urine samples of motor vehicle accident victims. *Journal of Trauma & Dissociation, 4*(1), 65-80.

Dunmore, E., Clark, D.M., & Ehlers, A. (1999). Cognitive factors involved in the onset and maintenance of posttraumatic stress disorder (PTSD) after physical or sexual assault. *Behaviour Research and Therapy, 37*, 809-829.

Ehlers, A., Mayou, R.A., & Bryant, B. (1998). Psychological predictors of chronic posttraumatic stress disorder after motor vehicle accidents. *Journal of Abnormal Psychology, 107*, 508-519.

Engelhard, I.M., Van den Hout, M.A., Kindt, M., Arntz, A., & Schouten, E. (2003). Peritraumatic dissociation and posttraumatic stress after pregnancy loss: A prospective study. *Behaviour Research and Therapy, 41*, 67-78.

Foa, E.B., Riggs, D.S., Dancu, C.V., & Rothbaum, B.O. (1993). Reliability and validity of a brief instrument for assessing post-traumatic stress disorder. *Journal of Traumatic Stress, 6*, 459-473.

Freedman, S.A., Brandes, D., Peri, T., & Shalev, A. (1999). Predictors of chronic post-traumatic stress disorder: A prospective study. *British Journal of Psychiatry, 174*, 353-359.

Fullerton, C.S., Ursano, R.J., Epstein, R.S., Crowley, B., Vance, K., Kao, T.C., Dougall, A., & Baum, A. (2001). Gender differences in posttraumatic stress disorder after motor vehicle accidents. *American Journal of Psychiatry, 158*, 1486-1491.

Gershuny, B.S., Cloitre, M., & Otto, M.W. (2003). Peritraumatic dissociation and PTSD severity: Do event-related fears about death and control mediate their relation? *Behaviour Research and Therapy, 41*, 157-166.

Holeva, V., & Tarrier, N. (2001). Personality and peritraumatic dissociation in the prediction of PTSD in victims of road traffic accidents. *Journal of Psychosomatic Research, 51*, 687-692.

Kaufman, M.L., Kimble, M.O., Kaloupek, D.G., McTeague, L.M., Bachrach, P., Forti, A.M., & Keane, T.M. (2002). Peritraumatic dissociation and physiological response to trauma-relevant stimuli in Vietnam combat veterans with posttraumatic stress disorder. *Journal of Nervous and Mental Disease, 190*, 167-174.

Keogh, E., Ayers, S., & Francis, H. (2002). Does anxiety sensitivity predict post-traumatic stress symptoms following childbirth? A preliminary report. *Cognitive Behaviour Therapy, 31*, 145-155.

Kleber, R.J., & Van der Hart, O. (1998). Dutch translation of the PDEQ. Utrecht, The Netherlands: Authors.

Koopman, C., Classen, C., & Spiegel, D. (1994). Predictors of posttraumatic stress symptoms among survivors of the Oakland/Berkeley, Calif., firestorm. *American Journal of Psychiatry, 151*, 888-894.

Lyons, S. (1998). A prospective study of post traumatic stress symptoms 1 month following childbirth in a group of 42 first-time mothers. *Journal of Reproductive and Infant Psychology, 16*, 91-105.

Marmar, C.R., Weiss, D.S., Metzler, T.J. (1998). Peritraumatic dissociation and posttraumatic stress disorder. In J.D. Bremner & C.R. Marmar (Eds.), *Trauma, memory, and dissociation* (pp. 229-252). Washington, DC: American Psychiatric Press.

Marmar, C.R., Weiss, D.S., Metzler, T.J., & Delucchi, K. (1996). Characteristics of emergency services personnel related to peritraumatic dissociation during critical incident exposure. *American Journal of Psychiatry, 153*, 94-102.

Marmar, C.R., Weiss, D.S., Metzler, T.J., Delucchi, K.L., Best, S.R., & Wentworth, K.A. (1999). Longitudinal course and predictors of continuing distress following critical incident exposure in emergency services personnel. *Journal of Nervous and Mental Disease, 187*, 15-22.

Marshall, G.N., & Schell, T.L. (2002). Reappraising the link between peritraumatic dissociation and PTSD symptom severity: Evidence from a longitudinal study of community violence survivors. *Journal of Abnormal Psychology, 111*, 626-636.

Marshall, R.D., Spitzer, R., & Liebowitz, M.R. (1999). Review and critique of the new DSM-IV diagnosis of acute stress disorder. *American Journal of Psychiatry, 156*, 1677-1685.

Moleman, N., Van der Hart, O., & Van der Kolk, B.A. (1992). The partus stress reaction: A

neglected etiological factor in postpartum psychiatric disorders. *Journal of Nervous and Mental Disease, 180*, 271-272.

Morgan, C.A., 3rd, Hazlett, G., Wang, S., Richardson, E.G., Jr., Schnurr, P., & Southwick, S.M. (2001). Symptoms of dissociation in humans experiencing acute, uncontrollable stress: a prospective investigation. *American Journal Psychiatry, 158*, 1239-1247.

Nijenhuis, E., Van Engen, A., Kusters, I., & Van der Hart, O. (2001). Peritraumatic somatoform and psychological dissociation in relation to recall of childhood sexual abuse. *Journal of Trauma and Dissociation, 2*(3), 49-68.

Nijenhuis, E.R.S., Spinhoven, P., Van Dyck, R., Van der Hart, O., & Vanderlinden, J. (1996). The development and psychometric characteristics of the Somatoform Dissociation Questionnaire (SDQ-20). *Journal of Nervous and Mental Disease, 184*, 688-694.

Nijenhuis, E.R.S., & Van der Hart, O. (1998). *Somatoform Dissociation Questionnaire-Peritraumatic.* Unpublished Document

Nijenhuis, E.R.S., Van der Hart, O., & Steele, K. (2002). The emerging psychobiology of trauma-related dissociation and dissociative disorders. In D. D'Haenen, J. Den Boer, H. Westenberg, & P. Willner (Eds.), *Biological psychiatry* (pp. 1079-1098). London: Wiley.

Nijenhuis, E.R.S., & Van der Hart, O. (1999). Somatoform dissociative phenomena: A Janetian perspective. In J.M. Goodwin & R. Attias (Eds.), *Splintered reflections: Images of the body in trauma* (pp. 89-127). New York: Basic Books.

Ozer, E.J., Best, S.R., Lipsey, T.L., & Weiss, D.S. (2003). Predictors of posttraumatic stress disorder and symptoms in adults: A meta-analysis. *Psychological Bulletin, 129*, 52-73.

Shalev, A.Y., Peri, T., Canetti, L., & Schreiber, S. (1996). Predictors of PTSD in injured trauma survivors: A prospective study. *American Journal of Psychiatry, 153*, 219-225.

Simeon, D., Greenberg, J., Knutelska, M., Schmeidler, J., & Hollander, E. (2003). Peritraumatic reactions associated with the World Trade Center disaster. *American Journal of Psychiatry, 160*, 1702-1705.

Soet, J.E., Brack, G.A., & Dilorio, C. (2003). Prevalence and predictors of women's experience of psychological trauma during childbirth. *Birth, 30*, 36-46.

Sterlini, G.L., & Bryant, R.A. (2002). Hyperarousal and dissociation: A study of novice skydivers. *Behaviour Research and Therapy, 40*, 431-437.

Tichenor, V., Marmar, C.R., Weiss, D.S., Metzler, T.J., & Ronfeldt, H.M. (1996). The relationship of peritraumatic dissociation and posttraumatic stress: Findings in female Vietnam theater veterans. *Journal of Consulting and Clinical Psychology, 64*, 1054-1059.

Ursano, R.J., Fullerton, C.S., Epstein, R.S., Crowley, B., Vance, K., Kao, T.C., Baum, A. (1999). Peritraumatic dissociation and posttraumatic stress disorder following motor vehicle accidents. *American Journal of Psychiatry, 156*, 1808-1810.

Van der Hart, O., Nijenhuis, E.R.S., Steele, K., & Brown, D. (2004). Trauma-related dissociation: Conceptual clarity lost and found. *Australian and New Zealand Journal of Psychiatry, 38,* 906-914.

Van der Kolk, B.A., & Van der Hart, O. (1989). Pierre Janet and the breakdown of adaptation in psychological trauma. *American Journal of Psychiatry, 146*, 1530-1540.

Van der Velden, P.G., Van der Burg, S., Steinmetz, C.H.D., & Van den Bout, J. (1992). *Slachtoffers van bankovervallen* [Victims of bank robberies]. Houten: Bohn Stafleu Van Loghum.

Van Son, M.J.M., Verkerk, G.J.M., Van der Hart, O., Komproe, I. H., & Pop, V.J.M. (2004). *Prenatal depression, mode of delivery, and perinatal dissociation as predictors of postpartum posttraumatic stress: An empirical study*. Manuscript submitted for publication.

Wijma, K., Soderquist, J., & Wijma, B. (1997). Posttraumatic stress disorder after childbirth: A cross sectional study. *Journal of Anxiety Disorders, 11*, 587-597.

Chapter XI

GENERAL DISCUSSION

General discussion.

The present study focused on maternal well-being, obstetrical outcome and gestational thyroid function. Before coming to the final discussion and conclusions the background of this thesis should first be highlighted.

The background of the study in this thesis is a prospective ongoing research line of maternal well-being during gestation (and postpartum) in relation to thyroid function, obstetrical outcome and infant development, which started with the aid of the midwives of Veldhoven back in 1988. A that time a cohort of 300 women of the general population was formed and followed during late pregnancy and nine months postpartum (Kempen study I). In 1993, the 250 children of these women were followed (Kempen study II) and in 1996, another cohort of 300 women was formed in which women were followed from early gestation to eight months postpartum (Kempen study III). The children of these women were followed at the age of one year between 1997 – 1998 (Kempen study IV). In 1999 another cohort of women was formed, this time consisting of a low and high-risk group with regard to thyroid hormone concentrations during gestation and the children of these women were followed until 2002 (Kempen study V).

Study I reported the occurrence of postpartum depression and thyroid function but did not have assessments of depression and thyroid function during early gestation. Study II reported for the first time about the neurodevelopmental delay of 5-years aged children related to subtle maternal thyroid dysfunction, however only data on maternal thyroid function during the last trimester were available. Study III included assessment of maternal thyroid function in the first trimester but the sample size was to small to look at a possible relation between gestational depression and obstetrical outcome. Study IV showed neurodevelopmental delay of the offspring already at the age of 10 months in relation to maternal thyroid functioning during early gestation, but again the sample size was rather small for the development of an etiological model. Study V had sufficient epidemiological power to look more closely at the effect of maternal functioning during gestation and infant neurodevelopment at one and two years of age. Breech presentation occurred significantly more often in hypothyroxinemic women. Although no epidemiological power was achieved because of small

sample size the hypothesis of a possible relation between maternal thyroid function and physiological labour emerged.
Within this background, the current study of the thesis should be regarded as the VIth prospective study in this area in which 1000 women are followed during gestation and the first postpartum week and of whom the children will be followed during the next decade.

Three basic principles were of importance.

First, there is substantial literature concerning a possible role between thyroid dysfunction and impaired obstetrical outcome or a possible interaction between maternal depression and / or anxiety during gestation and obstetrical problems. However, hardly ever, studies have been published that looked at a possible relationship between normal thyroid function (TSH and FT4 within reference ranges) and labour at a physiological level (term gestation instead of premature delivery) or the effect on maternal depression and anxiety and physiological labour (instead of premature labour). This was the main reason that a large cohort was needed to have sufficient epidemiological power.
Secondly, when looking at a possible biological (dependent variable, thyroid hormone or hCG) model to explain anxiety, gestational nausea / vomiting or obstetrical complications (independent variable), other confounders were taken into account. Several reviews concerning these topics have stressed the point that in many studies in the past – when looking at a relation between a biological and psychological or somatic variable – possible confounders were not taken into account.
Thirdly, obstetrical care in The Netherlands of low risk women is primarily the area of the community midwife. Therefore an important aim of the study was that possible spin off and implementation of the results should fit within the main task of midwifes: selection of low risk women and where needed to start up realistic interventions to increase maternal well-being during gestation and the early postpartum.

Chapter II showed that severity of nausea and vomiting during gestation (NVP) – taking into account two biological factors – is largely dependent of psychological factors and more specifically psycho-neuroticism. The design of the study, however,

was cross-sectional and in order to get more reliable data concerning the incidence of NVP, prospective research is needed in which NVP is repeatedly assessed. Simple instruments – self rating scale containing 3 items - have been developed recently which are easy to complete during regular consultation in the midwife office. This gives the opportunity to register prospectively in the future women with severe symptoms. Severe symptomatology might be a sign of psychopathology, which in turn increases the risk of anxiety and depression. The latter two are risk factors of obstetrical, foetal, and neonatal complications as well as of impaired development of the offspring.

Chapter III showed that assessing depression at different trimesters revealed different models to explain depression. During early gestation thyroid autoimmunity was shown to be an independent risk factor of depression. Due to the down regulation of the immune system this association had disappeared at late gestation. However, the relation between thyroid antibodies (TPO-Ab) and depression during early gestation could be another argument to add to the discussion whether screening of thyroid function during early gestation should be implemented nationwide. Recently a panel of experts has concluded that the benefit / costs ratio does not favour screening. However, only medical arguments were used, no psychological arguments. It might be suggested that adding psychological arguments to the discussion might change this statement.
Anxiety was an important confounder or moderator of depression. It is becoming increasingly apparent that anxiety is of major importance to maternal and foetal well-being, not only in relation to risk of premature delivery but also in relation physiological labour (chapter V). An important conclusion therefore is that selection of low-risk women during gestation, the basic task of the community midwife, should also include selection of psychological risk factors. Instruments have been developed that can easily be completed within several minutes with final scores to be noted in the medical record of the midwife.

Chapter IV described the increased risk of women with low normal thyroid hormone concentrations (hypothyroxinemia) to have a breech presentation of the foetus at term (Kempen V). Although statistically significant, this correlation did not have ap-

propriate epidemiological power. This study was the main reason to start the current study of the thesis.

Chapter V showed that during physiological labour in term pregnant women, anxiety was an independent risk factor of protraction of labour. Because protraction of labour is a major risk factor of instrumental delivery this means that anxiety is directly related to poor obstetrical outcome. As discussed in the chapter, there are several studies reporting a relation between anxiety and premature delivery. Surprisingly, no study ever reported the relationship between anxiety and physiological labour taking into account the classical two stages of labour: dilation and expulsion. In other mammalians, similar findings have been described: in case of acute stress (life danger) a pregnant animal, when she is in the first stage of labour, is able to stop the contractions and to run for her life continuing parturition once she is in a safe place.

Chapter VI confirmed the basic question of the thesis which was derived from earlier publications in the Kempen studies: when a child of a mother with gestational hypothyroxinemia during gestation shows motor-developmental delay at the age of one or two years it is a matter of speculation whether these motor problems are already present during gestation. The findings of this study showed that FT4 levels not only at the lowest 10^{th} percentile but rather at the lowest 30^{th} percentile increased the risk of non physiological cephalic position, which in turn increase the risk of obstetrical complications. As explained in the introduction section, foetal muscle tonus is important during labour for flexion and deflexion of the head during passage of the birth canal.

Chapter VII reported the validation of a self-rating scale, that assesses emotional perception of labour and confinement days and that can easily be completed during the first postpartum week.

Chapter VIII showed that women who delivered at home had the most positive emotional perception of delivery and confinement days. Moreover, it showed that technical interventions increased the risk of poor scores of both delivery and confinement.

Important confounders such as anxiety and depression were also related to lower scores concerning the emotional perception of delivery and confinement days.

Chapter IX reported data of an earlier study (Kempen I) showing that obstetrical complications were not independently related to depression assessed at four weeks postpartum. However, the sample size was to small to discriminate between different subgroups of mode of deliveries, especially with regard to Caesarean section.

Chapter X confirmed the results of an earlier study in this area (Kempen IV) showing that instrumental deliveries increased the risk of perinatal negative emotions, which in turn increased the risk of high levels of posttraumatic stress symptoms at 3 months postpartum.

What kind *of* ***recommendations*** can be given on the basic of the results of this study?

As described in the introduction, a crucial aspect of the role of the midwife in the Dutch obstetrical health care system is low-risk selection. This means that the midwife should select those woman who should be referred to the second level of obstetrical health care (obstetrician) and those woman who can stay at the primary level and deliver at home. Surprisingly, only strictly medical aspect are used by the midwives when selecting high-risk women such as: hypertension, gestational diabetes, growth retardation etc. This thesis strongly favours the recommendation that psychological aspects should also be taken into account. Not only because of the general well-being of the mother, but also because of the well-being of the foetus and obstetrical outcome.

Risk selection during gestation should include:

- detection of women with high intensity of symptoms of nausea and vomiting which are classically regarded as being normal for pregnancy
- detection of women with high anxiety levels, especially during late gestation
- detection of women with depressive symptomatology at different intervals of consultations

This selection is easy to perform by means of the completion of self-rating scales (at home or during consultation). The results of the sum-scores should be carefully mentioned in the medical record of the patient. Subsequently, the midwife could spent more time during consultation to those women with high scores or – with the aid of the GP – refer the woman to a primary care health psychologist for further intervention.

At end term, risk selection should include similar protocols with special attention to anxiety. High scores should also be mentioned in the medical record form and when labour starts the midwife could decide to spend more time with the woman keeping in mind not only the time that contractions started but also the mental condition of the mother during the last visit. Another alternative could be to send the maternity nurse earlier to the woman's house to support her in coping with labour, especially during the first phase of dilatation. Nowadays, the maternity nurse is often called by the midwife at the woman's house shortly before the woman enters the expulsion stage of labour.

During the early postpartum the midwife should pay especially attention to women who - unexpectedly – went through a complicated delivery. Moreover, assessing anxiety and depression symptoms should also contribute to select high-risk women for developing mental problems in the postpartum week. At the last assessment at 6 weeks ' postpartum, apart from a general physical examination, the mental state should also be investigated, especially in those women who had high scores during gestation and shortly after delivery.

Because depression and anxiety have been shown to be highly chronic conditions throughout a life cycle, detection of high risk cases early in life, followed by efficient interventions is highly relevant with a possibly important task for the community midwife.

As far as the relation between thyroid function and non-physiological labour is concerned it is too early to advise screening of maternal thyroid function during late gestation. Placebo controlled intervention trials are needed first to evaluate whether screening is worthwile to perform. On the other hand, within the task of high-risk selection, it could be argued that knowing the thyroid function of the woman at end term might predict obstetrical problems. However, replications of these finding by

others should preferentially be done before implementation of this assessment into the standard protocol of appropriate primary obstetrical health care could be advocated.

SAMENVATTING

Samenvatting

De achtergrond van dit onderzoek is een prospectieve onderzoekslijn naar maternaal welbevinden tijdens de zwangerschap, het kraambed en de postpartum periode in relatie tot schildklier functie, verloskundige uitkomsten en ontwikkeling van het kind. Deze is gestart in 1988 met de hulp van de verloskundigen uit de Kempen. Toen werd een cohort van 300 vrouwen uit de algemene populatie gevormd en vervolgd tijdens het laatste trimester van de zwangerschap tot negen maanden postpartum (Kempen I studie). In 1993 werden 250 kinderen van deze vrouwen vervolgd (Kempen II studie) en in 1996 werd een volgend cohort van 300 vrouwen gevormd waarvan de vrouwen werden vervolgd vanaf het begin van de zwangerschap tot acht maanden postpartum (Kempen III studie). De kinderen van deze studie zijn vervolgd op eenjarige leeftijd tussen 1997-1998 (Kempen IV studie). In 1999 werd een ander cohort gevormd dat bestond uit vrouwen met een laag en hoog risico wat betreft schildklier hormoon concentraties tijdens de zwangerschap, De kinderen van deze groep werden vervolgd tot 2002 (Kempen V studie).

Studie I toonde een relatie aan tussen het optreden van postpartum depressie en schildklierfunctie maar had geen metingen van depressie of schildklierfunctie in de vroege zwangerschap.
Studie II rapporteerde als eerste over de neurologische ontwikkelingsachterstand bij 5-jarige kinderen gerelateerd aan subtiele maternale schildklier disfunctie. Hierbij waren echter alleen data over maternale schildklierfunctie tijdens het laatste trimester beschikbaar.
Studie III had wel metingen van maternale schildklier functie in het eerste trimester van de zwangerschap maar het cohort was te klein om te kunnen kijken naar een mogelijke relatie tussen depressie in de zwangerschap en verloskundige uitkomsten.
Studie IV toonde aan dat een achterstand in de neuropsychologische ontwikkeling van kinderen gerelateerd aan maternale schildklierfunctie in het eerste trimester van de zwangerschap reeds bij kinderen in de leeftijd van 10 maanden bestond, maar opnieuw was het cohort te klein voor het opzetten van een verklarend model.
Studie V had voldoende epidemiologische power om nader te kijken naar het effect van maternale schildklierfunctie tijdens de zwangerschap en neuropsychologische

ontwikkeling van het kind op de leeftijd van een en twee jaar. Stuit liggingen kwamen bovendien significant vaker voor bij vrouwen met hypothyroxinemie. Ofschoon er door het kleine cohort onvoldoende epidemiologische power werd verkregen ontstond toch de hypothese van een mogelijke relatie tussen maternale schildklierfunctie en een fysiologische bevalling.
Tegen deze achtergrond kan de huidige dissertatie gezien worden als de VI^{de} prospectieve Kempen studie waarin 1000 vrouwen vervolgd zijn tijdens de zwangerschap en het kraambed en waarvan de kinderen de komende 10 jaar vervolgd zullen worden.

Drie basis principes waren hierbij belangrijk.

Ten eerste, er is een grote hoeveelheid literatuur wat betreft een mogelijke rol tussen schildklier disfunctie en pathologische verloskundige uitkomsten, en een mogelijke relatie tussen maternale depressie tijdens de zwangerschap en verloskundige problemen. Er zijn echter bijna geen onderzoeken gepubliceerd waarbij gekeken is naar een mogelijke relatie tussen normale schildklier functie (TSH en fT4 binnen de referentiewaardes) en bevalling op een fysiologisch manier (à terme in plaats van premature bevalling). Tevens is het effect van maternale depressie en angst op de à terme bevallingen niet onderzocht. Het verkrijgen van voldoende epidemiologisch power was de belangrijkste reden voor de grootte van dit cohort.

Ten tweede, kijkend naar een mogelijke biologisch (afhankelijke variabele, schildklier hormoon of humaan chorion gonadotrofine (hCG)) model om angst, zwangerschapsmisselijkheid / braken of verloskundige complicaties (onafhankelijke variabele) te verklaren, werd rekening gehouden met andere verstorende factoren (confounders). Diverse literatuur overzichten over dit onderwerp hebben benadrukt dat in veel onderzoek er geen rekening gehouden werd met andere mogelijke confounders.

Ten derde, verloskundige zorg voor de laag risico vrouwen in Nederland wordt hoofdzakelijk verricht door eerstelijns verloskundigen. Daarom was een belangrijk doel van dit onderzoek dat mogelijke resultaten en implementatie zouden kunnen passen in het kader van het werk van deze verloskundigen: risico selectie bij zwan-

geren en waar nodig beginnen met realistisch interventies om het maternale welbevinden tijdens de zwangerschap en het kraambed te verbeteren.

Hoofdstuk II toont aan dat de ernst van misselijkheid en braken in de zwangerschap - rekening houdend met twee biologische factoren (schildklier en hCG) - voornamelijk afhangt van psychologische factoren. Het ontwerp van de studie was echter "cross-sectional" en om meer betrouwbare data te krijgen wat betreft de incidentie van zwangerschapsmisselijkheid en braken, is prospectief onderzoek nodig waarin misselijkheid en braken herhaaldelijk wordt gemeten in de vroege zwangerschap. Eenvoudige instrumenten – zelf in te vullen vragenlijsten van drie items – zijn recentelijk ontwikkeld en makkelijk in te vullen tijdens de routine zwangerschapscontrole bij de verloskundige. Dit geeft de gelegenheid om in de toekomst prospectief vrouwen met ernstige misselijkheid symptomen te registreren. Ernstige symptomen kunnen een teken zijn van psychopathologie, wat op zijn beurt de kans op angst en depressie verhoogt. Deze laatste twee zijn niet alleen risico factoren voor verloskundige, foetale en neonatale complicaties maar ook voor een verstoorde ontwikkeling van het kind.

Hoofdstuk III toonde aan dat het meten van depressie in verschillende trimesters van de zwangerschap verschillende modellen toont om depressie te verklaren. In de vroege zwangerschap werd aangetoond dat schildklier auto-immuniteit een onafhankelijke variabele was voor depressie. Door de verminderde werking van het immuunsysteem verdween deze associatie later in de zwangerschap. Schildklier antilichamen (TPO-Ab) komen bij ongeveer 8 tot 10% van de zwangeren voor. De relatie tussen schildklier antilichamen (TPO-Ab) en depressie in de vroege zwangerschap, zou een argument kunnen zijn in de discussie of screening van schildklier functie in de vroege zwangerschap zou moeten worden toegevoegd aan de routine screening voor zwangeren. Onlangs heeft een panel van experts geconcludeerd dat de kosten/baten verhouding tegen screening pleit. Daarbij werden echter alleen medische argumenten gebruikt en geen psychologische argumenten.

Hoofdstuk IV beschrijft het verhoogde risico voor vrouwen met lage normaal waardes van schildklier hormoon (hypothyroxinemie) op stuitligging van de baby à terme (Kempen V). Ofschoon statistisch significant had deze correlatie niet voldoende epi-

demiologische power. Dit onderzoek was echter de belangrijkste reden om de huidige studie te starten.

Hoofdstuk V toont aan dat bij een fysiologische bevalling à terme angst een onafhankelijke risico factor is voor een langdurige bevalling. Omdat een langdurige bevalling een grote risico factor is voor kunstverlossingen betekent het dat angst gerelateerd is aan verloskundige complicaties. Zoals beschreven in het hoofdstuk, zijn er diverse studies die een verband beschrijven tussen angst en prematuur bevallen. Echter, geen studie heeft de relatie beschreven tussen angst en fysiologisch bevallen rekening houdend met de klassieke twee verdeling van de bevalling: ontsluiting en uitdrijving. Van andere zoogdieren zijn soortgelijke bevindingen wel beschreven: in geval van acute stress (levensgevaar) kan een zwanger dier (o.a. paard, hert), in de eerste fase van de bevalling, de weeën stoppen, rennen voor haar leven en op een veilige plek doorgaan met de bevalling. Een belangrijke conclusie is daarom dat bij de risico selectie tijdens de zwangerschap – een van de belangrijkste taken van een eerstelijns verloskundige – ook psychologische factoren moeten worden bekeken. Er zijn instrumenten ontwikkeld om eenvoudig angst en depressie te meten, die in een paar minuten ingevuld kunnen worden en waarvan de uitslag vermeld kan worden in het dossier van de zwangere.

Hoofdstuk VI bevestigt de belangrijkste vraag van het onderzoek voortkomend uit eerdere publicaties van de Kempen studies: als een kind van een moeder met hypothyroxinemie tijdens de zwangerschap een motorische ontwikkelingsachterstand heeft op eenjarige en tweejarige leeftijd is het denkbeeldig dat deze motorische problemen al aanwezig zijn in de zwangerschap. De bevindingen uit deze studie tonen aan dat fT4 niet alleen vanaf de laagste 10^{de} percentiel maar al vanaf de 30^{ste} percentiel het risico vergroot op een niet fysiologische hoofdligging (niet aav), welke weer een groter risico is op verloskundige complicaties. Als verklaring zou kunnen worden aangevoerd dat foetale spiertonus belangrijk is voor de flexie en deflexie van het hoofdje tijdens de passage door het bekken. Bij volwassenen is schildklierhormoon belangrijk voor normale spiertonus.

Hoofdstuk VII beschrijft de validatie van een vragenlijst die emotionele beleving meet van bevalling en kraambed en die makkelijk ingevuld kan worden in de eerste week postpartum.

Hoofdstuk VIII toont aan dat vrouwen die thuis bevallen de meest positieve emotionele beleving van bevalling en kraambed hebben. Verder wordt aangetoond dat technische interventies het risico vergroten op negatieve scores voor zowel de beleving van de bevalling als van het kraambed. Ook belangrijke confounders zoals angst en depressie zijn gerelateerd aan lagere scores wat betreft de emotionele beleving van bevalling en kraambed.

Hoofdstuk IX beschrijft data van een eerdere studie (Kempen I) die aantonen dat verloskundige complicaties niet onafhankelijk gerelateerd zijn aan depressie gemeten vier weken postpartum. Het cohort was echter te klein om onderscheid te maken tussen diverse groepen wat betreft manier van bevallen, met name wat betreft de sectio.

Hoofdstuk X bevestigde de resultaten van een eerdere studie in deze omgeving (Kempen IV) waarin werd aangetoond dat kunstverlossingen het risico verhogen van perinatale negatieve emoties, die op hun beurt het risico vergroten op posttraumatisch stress symptomen gemeten drie maanden postpartum.

Welke **aanbevelingen** kunnen gegeven worden naar aanleiding van de resultaten van deze studie?
Zoals eerder genoemd, een zeer belangrijk aspect van de rol van de eerstelijns verloskundige in het Nederlandse verloskundig systeem is de risico selectie. Dit wil zeggen dat de verloskundige een zorgvuldige selectie maakt van vrouwen die verwezen moeten worden naar de tweede lijn en welke vrouwen in de eerstelijns zorg blijven en eventueel thuis kunnen bevallen. Voor deze selectie worden echter vaak alleen medisch/verloskundige criteria gebruikt zoals: hypertensie, dismaturiteit, zwangerschapsdiabetes etc. Deze dissertatie pleit ervoor om bij de risico selectie ook psychologische factoren mee te nemen. Niet alleen vanwege het algehele wel-

bevinden van de vrouw, maar ook voor het welbevinden van de baby en de verloskundige uitkomsten.

De risico selectie tijdens de zwangerschap zou moeten bevatten

- opsporen van vrouwen met hoge intensiteit van symptomen van misselijkheid en braken, wat klassiek gezien "normaal" wordt geacht voor de zwangerschap doch een teken van psychoneuroticisme kan zijn
- opsporen van vrouwen met hoge angst scores, speciaal in het laatste trimester van de zwangerschap
- opsporen van vrouwen met ernstige depressieve symptomen tijdens diverse tijdstippen van de zwangerschap

Dit opsporen is makkelijk uit te voeren met behulp van vragenlijsten (thuis of op het spreekuur). De resultaten van deze metingen zouden zorgvuldig moeten worden vermeld in het dossier van de zwangere. Vervolgens zou de verloskundige tijdens de zwangerschapscontroles meer tijd kunnen besteden aan de vrouwen met hoge scores of – in overleg met de huisarts – deze vrouwen door verwijzen voor psychologische hulp.
Bij hoge angst scores zou de verloskundige kunnen besluiten aan het begin van de bevalling meer tijd te besteden aan het begeleiden van de barende, niet alleen rekening houdend met de duur van de weeën maar ook met de psychische conditie van de vrouw. Een alternatief hiervoor zou zijn de kraamverzorgster in een zeer vroeg stadium van de baring op te roepen zodat die de vrouw kan ondersteunen bij het opvangen van de weeën.
Tevens kunnen metingen van angst en depressieve symptomen ertoe bijdragen om vrouwen op te sporen die een hoog risico hebben op het ontwikkelen van psychische problemen in het kraambed en daarna. Omdat de wijze van bevallen hierin ook een rol kan spelen zou de verloskundige in de eerste dagen van het kraambed speciale aandacht kunnen besteden aan vrouwen die – onverwachts – een moeilijke bevalling hebben gehad.
Bij de nacontrole zes weken postpartum zou, behalve het algemene lichamelijke onderzoek ook aandacht kunnen worden besteed aan de psychische conditie van de

vrouw, met name degene die hoge scores had tijdens de zwangerschap en het kraambed.

Omdat is aangetoond dat depressie en angst chronische aandoeningen zijn is het belangrijk vrouwen met een hoog risico vroeg op te sporen zodat tijdig kan worden begonnen met behandeling. In deze risico selectie zou de verloskundige een belangrijke rol kunnen spelen.

Wat betreft de relatie tussen schildklier functie en een niet-fysiologische bevalling is het te vroeg om screening van maternale schildklierfunctie in het laatste trimester van de zwangerschap aan te bevelen. Deze bevindingen dienen eerst door onderzoek in andere centra bevestigd te worden voordat de implementatie van schildklierfunctie metingen in het standaard protocol van eerstelijns verloskundige zorg aanbevolen kan worden.

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CURRICULUM VITAE

Hennie Wijnen is op 06-03-1950 geboren te Horst - Melderslo.
In het Academisch Ziekenhuis Utrecht is ze in 1972 geslaagd voor het diploma Verpleegkundige A. Als verloskundige is ze in 1975 aan de Rijkskweekschool voor Vroedvrouwen in Rotterdam afgestudeerd, waarna ze bijna drie jaar in Nieuw Zeeland gewerkt heeft.
Na haar terugkeer in Nederland is ze begonnen met de studie filosofie aan de Universiteit van Groningen, in combinatie met werk als verpleegkundige en verloskundige. Na twee jaar heeft ze deze studie afgebroken en is gaan werken als waarneemster.
Sinds september 1982 is ze werkzaam als eerstelijns verloskundige in Veldhoven, samen met een collega en vanaf juli 2001 met twee collega's.
Vanaf de oprichting is ze lid geweest van de Werkgroep Onderzoek en Scholing (WOS) en heeft de cursussen WOS-I (Prof. dr. Mark Keirse) en WOS-II (TNO) gevolgd.
Sedert 1988 is ze betrokken geweest bij de Kempenstudies. De resultaten van deze studies zijn door haar op een aantal internationale congressen gepresenteerd zoals Cambridge (U.K.1994), Basel (Zwitserland 1995), Oslo (Noorwegen 1996) en Iowa (USA 1998).