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Is maternal thyroid function of influence?

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Contents

Chapter 1

General introduction and outline of the thesis

SECTION I

The first part of this thesis focuses on perinatal morbidity, induction of labor and trends in CS during the past decade in the Netherlands. Analyses are performed on a macro-level, to look at the effects of changing obstetric practice in the Netherlands.

Perinatal outcome

Perinatal mortality is an important parameter when analysing obstetric care. The Peristat project, a European collaborative study in which indicators for perinatal health have been defined, has resulted in an increased awareness to perinatal mortality figures in the Netherlands[1-4]. The Netherlands have higher perinatal mortality rates compared to other European countries, especially when compared to countries with a similar socio-economic position. Many reports have since then been published about this subject, focusing on possible mechanisms to explain those relatively high figures. The discussion has put forward that obstetric care should be critically evaluated[1-4].

During the past decade the perinatal mortality rate in the Netherlands has dropped, from 11.4 per 1000 in Peristat I (1999)[5], to 7.0 per 1000 in Peristat II (2004), to 5.1 per 1000 in Peristat III (2011)[6]. The ranking compared to other European countries has also improved, although the position of the Netherlands still remains unfavourable[6].

The main causes of perinatal mortality in the Netherlands are one or more of the so-called "big-four" causes; congenital malformations, preterm labor, intra-uterine growth restriction and APGAR-score below seven after five minutes[2]. These four causes of perinatal mortality, together account for about 85% of all perinatal deaths in the Netherlands[2]. To prevent those big-four problems multiple initiatives have been implemented. The main changes in management have been: the introduction of perinatal audits[7], team training for obstetric emergencies[8,9] and a structural ultrasound scan at 20 weeks gestation for all pregnant women since 2007[2].

The management of suspected intra-uterine growth restriction (IUGR) - which is an estimated fetal weight (EFW) of <10th percentile (p10) or an abdominal circumference (AC)

<p10 or flattening of the fetal growth curve - has changed tremendously in recent years. The outcome of a large randomized multi-centre trial in the Netherlands in 2010 (DIGITAT) has shown that, when comparing induction of labor to expectant management in suspected fetal IUGR, no benefit was found regarding neonatal outcomes or operative delivery rates when practicing expectant management[10]. In this study induction of labor is therefore considered a 'rational option' to prevent stillbirth and neonatal morbidity[10].

Induction of labor

Not only the DIGITAT study has possibly resulted in higher induction rates. Worldwide an increasing trend in induction rates is seen[11]. Many other large clinical trials have been performed, for example in hypertension and pre-eclampsia at term, showing a more beneficial maternal outcome in the induced group compared to expectant management[12]. The need for induction in pregnancies at or beyond term, remains a topic of debate. A higher incidence of meconium stained amniotic fluid (MSAF) is seen with advancing gestational age[13]. Although the pathophysiologic phenomenon of the presence of MSAF remains indistinct, its presence puts neonates at risk for the meconium aspiration syndrome[14]. The meconium aspiration syndrome still has a high perinatal mortality rate today and is thus of clinical importance[14]. A Cochrane review of 2012 has shown that induction of labor leads to less overall perinatal mortality and a decrease in CS, although the number needed to treat is high[15]. Furthermore, significantly less infants had the meconium aspiration syndrome in the induced group. The suggestion of the authors is, to offer women the option of induction for postdate pregnancies after extensive counseling[15]. Furthermore, many elective inductions are performed, as the increase of inductions is higher than the increase of medical complications, for which a medical indicated induction should be performed[11].

The relation between induction rates and increased risk of CS remains controversial[16-20]. Many reports have shown an association between induction and CS in general, compared to women in spontaneous labor[16,17]. However, Caughey et al. have introduced the concept that induction of labor should not be compared to spontaneous labor, but to expectant management instead[18]. In every day practice, expectant management can still result in induction of labor at a later time due to changing circumstances. Therefore, a comparison between expectant management and induction of labor has to be performed for every

gestational week. When induction of labor is compared to expectant management for each gestational week, no increased odds for CS are found when labor is induced[18-20].

Caesarean sections

CS rates are increasing globally, but there are concerns that this worldwide trend does not lead to improved perinatal outcomes[21,22], but instead leads to increased maternal morbidity in the index and possible subsequent pregnancies[23-25]. Risks of (multiple) CS are uterine rupture, placenta accreta and emergency peripartum hysterectomy[23-25]. The World Health Organization has stated that CS-rates >15% cannot be justified in any centre[26], but currently this rate is much higher in most developed countries. An international study from Ye et al. has confirmed that a CS rate above 10% does not improve maternal or neonatal outcome any further and is thus not desirable[27].

Reasons for increased CS rates could possibly be induction of labor as discussed above, but also a trend is seen towards more complicated pregnancies, with a higher risk of CS, due to for example obesity and increasing maternal age in nulliparous women[28,29]. Furthermore, there is unwillingness of both patients and doctors to take a risk for intrapartum asphyxia. One of the historic determinants of fetal distress, meconium-stained amniotic fluid, is still associated with higher CS-rates today[30]. CS on maternal request is another topic of debate and currently occurs in about 3% of all deliveries in the US[31]. There are some studies that report less neonatal morbidity and mortality when an elective CS is performed at term compared to expectant management[32], but most studies do not report any reduction in health risks of mothers or children[31].

SECTION II

The second part of this thesis will assess perinatal and maternal outcome at a "micro-level". The thyroid gland is found to be an important factor in many major obstetric outcome measures. That is why the second part of this thesis focuses on maternal thyroid (dys)function during pregnancy and its effects on the mode of delivery and perinatal outcomes.

Thyroid function in pregnancy

The thyroid gland produces the hormones thyroxine (T4) and triiodothyronine (T3) which are important for human metabolism. During pregnancy the thyroid gland enlarges and becomes hypervascularized. The thyroid hormones are stimulated by thyrotrophine-stimulating hormone (TSH) which has structural homology to beta-humane chorionic gonadotropin (β-hCG). β-hCG is highest in the first trimester of pregnancy. As β-hCG mimics the function of TSH, the levels of T4 will physiologically be 30-100% higher in the first trimester of pregnancy compared to pre-pregnancy values[32-34]. The availability of T4 and T3 is further enhanced by the increased availability of thyroxine binding globuline (TBG), which carries the thyroid hormones into the bloodstream[35]. The TBG production in the liver is increased during pregnancy and degradation is prolonged due to higher estrogen-levels[33,35,37]. TBG shows a plateau around 24 weeks, whilst the plateau for T4 is around 20 weeks[35]. TSH is suppressed in the first trimester of pregnancy and then increases during the course of pregnancy and is highest during the last trimester[34,36]. Due to these physiologic changes, trimester-specific reference ranges should be used when assessing thyroid function (preferentially of TPO-Ab negative women with sufficient iodine intake)[33,35,37-39].

Measurement methods

Although there is consensus about the need for trimester-specific reference ranges for thyroid dysfunction, there is still controversy about the proper cut off values and the methodology that should be used for thyroid function tests. It is advised that trimester-

specific reference ranges are determined for each laboratory individually, preferentially in TPO-Ab negative women, as both the methodology used and the iodine status of individuals determines the reference ranges[39-43]. When population-based trimester-specific reference ranges are not available the current guidelines recommend a cut-off value for TSH of 2.5 mU/L in the first trimester and 3.0 mU/L in the second and third trimester of pregnancy[42-44]. Ethnicity also plays an important role when assessing thyroid function; in the Generation R study 18% of the diagnoses of thyroid dysfunction had to be revised when using ethnicity specific reference ranges, compared to reference ranges for the total population[44].

There are different assays to test TSH and fT4. Especially the measurement of fT4 is challenging, as small amounts of free hormone should be detected, compared to high amounts of protein-bound analyte[45]. In pregnancy there is an increased chance of error when using immunoassays[46]. When analyzing the literature for thyroid function in pregnancy the variety in tests used is enormous for fT4 measurements.

Overt hypothyroidism (OH) in pregnancy is defined as both a high TSH and a low fT4, for the reference ranges of pregnancy. Subclinical hypothyroidism (SCH) is defined as a higher TSH than the pregnancy reference ranges, but a normal fT4. The prevalence of OH is 0.2-0.5% , compared to 2-2.5% for SCH[41]. Isolated hypothyroxinemia is also described in pregnancy[47] and refers to fT4 in the lower reference range with normal TSH and is preferentially seen in iodine deficient areas. Hyperthyroidism is defined as a low TSH and high fT4. Because most research focus on the possible detrimental effect of (sub)clinical hypothyroidism on obstetric outcome, hyperthyroidism is not further discussed in this thesis.

Screening

Apart from the difficulties measuring and interpreting thyroid function test in pregnancy, much discussion remains about which women to test and when to test them. The urgency for universal screening is currently being debated[39,48-51]. Universal screening has already been proven cost effective, even when compared to selective screening for high risk women[52,53]. It is known that up to 50% of cases of thyroid dysfunction are missed when targeted case-finding is performed, when compared to universal screening at the beginning of pregnancy[48]. Levothyroxine treatment has shown no disadvantageous side effects on newborns. However, it has shown beneficial effects on many important obstetric outcomes,

including childhood cognitive effects, although the benefit of treatment remains unclear for some outcomes in mild thyroid dysfunction[39,49,54]. In women undergoing assisted reproductive techniques the benefit of treatment before conception in order to prevent miscarriages has been demonstrated in some studies[55]. However, to date, despite beneficial effects of treatment with levothyroxine, universal screening is not currently recommended by the European Thyroid Association nor by the American Thyroid Association, as there is lack of grade 1 evidence[39,43]. However, the topic remains controversial, even within the team of the guideline development[39].

Maternal thyroid function and obstetric outcome

Obstetric outcome in women with suboptimal thyroid function has been studied widely. Effects of OH have been more distinct[56], although in many studies associations with poor obstetric outcome have also been found for women with SCH. Thyroid dysfunction is common in women of reproductive age, with SCH occurring in about 2-3% of all pregnancies[57]. However, this figure differs for women of different ethnicities and iodine-intake[39]. In developed countries the most common etiology of SCH is autoimmune, while in developing countries this condition mostly occurs due to (severe) iodine deficiency[39]. Treatment of hypothyroidism with levothyroxine is currently advised for women with OH, while treatment of women with SCH (with or without TPO-Ab), as well as for euthyroid pregnant women with autoimmune antibodies (TPO-Ab) is still debated[43,58]

Pregnancy loss is more prevalent in women with SCH, as has been described in multiple studies[59-61]. In a meta-analysis from Velkeniers et al. a beneficial effect of levothyroxine treatment was observed in the prevention of miscarriages in a population undergoing fertility treatment, with a number needed to treat of three[55]. Negro et al. have found that in euthyroid women with TPO-Ab, treatment with levothyroxine has beneficial effects on the reduction of miscarriages as well[58].

Complications during pregnancy such as gestational diabetes and pre-eclampsia are more common in women with SCH[62-64]. The relation between gestational diabetes and SCH can be biologically explained by the synergistic working of T3 and insulin. Increased insulin resistance is found in case of hypothyroidism, due to less glucose disposal in peripheral

tissues[65]. The insulin resistance found in patients with OH and SCH are similar, suggesting that the absolute levels of thyrothropine and thyroxine are of limited influence[65]. Pre-eclampsia and hypertensive disorders in pregnancy in relation to SCH can be explained by endothelial cell activation, which is thought to be the cause of multi-organ involvement in pre-eclampsia[64]. There is evidence in non-pregnant individuals that SCH is associated with a number of cardiovascular conditions, such as coronary heart disease, which are caused by chronic endothelial cell damage[66]. Furthermore, a hypothyroid state leads to increased arterial stiffness, which in turn might lead to hypertensive disorders[67,68].

It has been indicated that maternal hypothyroxinemia is associated with poor fetal neurodevelopment and impaired psychomotor development in early childhood[69]. During the first half of gestation the fetus is totally dependent on maternal thyroid hormones. After this period the fetus begins to excrete its own thyroid hormones. However, maternal transfer of T4 continues to play an important role in fetal neurodevelopment throughout pregnancy[70,71].

There have been a few studies that address fetal growth in women with SCH, but those have shown conflicting results[72-75]. Perinatal mortality rates have not been studied widely in relation to SCH. However, there are some studies that have shown higher rates of fetal distress and even of higher perinatal mortality rates for women with (overt) hypothyroidism[61,72,76]. There have been no studies that have assessed meconium stained amniotic fluid in relation to SCH and besides, the association between MSAF and fetal distress itself remains controversial. CS-rates in women with hypothyroidism have been assessed in some studies, but the evidence for higher CS rates is scarce, especially for women with SCH[72,76,77].

Research questions

The main questions of the current thesis are:

1. Did the induction and Caesarean section rates increase over the past decade in the Netherlands?

2. Did a possible increase of Caesarean sections improve perinatal and maternal outcomes?

3. Is suboptimal maternal thyroid function of influence on Caesarean section rates?

4. Is suboptimal maternal thyroid function of influence on perinatal outcomes?

Outline of the thesis

In **chapter 2** a general overview is given of induction- and CS-rates. Changes in trends in obstetric interventions have been studied over the past decade. We have determined whether possible trend changes of inductions and CS have influenced perinatal and maternal outcomes.

The two main reasons to perform a CS during labor are failure to progress or (suspected) fetal distress.

In **chapter 3** the results of the analysis of 872 women in spontaneous labor were analyzed. We determined whether maternal thyroid function was of influence on the risks of instrumental vaginal deliveries or CS, mainly focusing on failure to progress.

One of the historic determinants of fetal distress is meconium stained amniotic fluid. In **chapter 4** the literature is reviewed regarding meconium stained amniotic fluid. Is meconium stained amniotic fluid indeed a sign of fetal distress? In this chapter the etiology of MSAF is discussed.

In **chapter 5** the association between maternal thyroid function and meconium stained amniotic fluid is studied in detail. An analysis of 1051 term pregnancies was performed.

One of the main reasons for induction of labor is suspected fetal intra-uterine growth restriction, as this is one of the “big four” causes of perinatal mortality. In **chapter 6** we determined whether suboptimal maternal thyroid function is a risk factor for small for gestational age offspring.

Chapter 7 is a general discussion of this thesis.

In **chapter 8** a summary of this thesis is provided in English and in **chapter 9** in Dutch.

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Chapter 2

Changing obstetric practice and effect on outcomes - is there a connection?

Manuscript in preparation for submission

Abstract

Background – During recent years there has been a change in obstetric practice worldwide, leading to higher rates of inductions and Caesarean sections (CS). It is important to analyze if those changes have led to improved maternal and/or neonatal outcomes. In order to compare and contrast obstetric care across different units, a valid and uniform classification system should be used, such as the 'Ten Group Classification System'. In this system all pregnant women are classified in one individual group, determined by different obstetric parameters. In the Netherlands such a system has not been implemented yet.
We analyzed if there were changes in the induction and CS rates in the Netherlands during the past decade and whether this has led to any measurable alterations to perinatal and maternal outcomes.

Methods – In this retrospective cohort study, all pregnancies ≥24 weeks from 2000 to 2009, were extracted from the Netherlands Perinatal Registry (PRN) database, a linked database consisting of almost all (>95%) hospital and home births in the Netherlands. Data from the current pregnancy, as well as the medical and obstetric history were retrieved. For all births the course of labor and delivery were recorded (spontaneous, induction or planned CS) and the mode of delivery. Furthermore, neonatal and maternal outcomes were collected. All pregnancies were classified according to the Ten Group Classification System. Differences were calculated using chi-square tests. For trend analyses the Cohran-Armitage test was used.

Results – We found an increase in induction rates for nulliparous women over the years, from 16.5% in 2000 to 19.7% in 2009 ($p<0.001$). For multiparous women we did not find a statistically significant increase in induction rates. An overall increase in CS from 13.0% in 2000 to 15.4% in 2009 was observed ($p<0.001$). The changes in induction rates and CS did not follow the same pattern. Postpartum hemorrhage showed a gradual increase over the years and was highest in groups 2 and 4 (single cephalic births with an induction or planned CS) ($p<0.001$). The overall number of stillbirths has dropped significantly by more than 100% ($p<0.001$).

Conclusions – We found an increase in both induction rates and CS-rates over the past decade, although no direct association between inductions and CS was found. Maternal morbidity has increased over the years, while stillbirth rates have decreased. As a CS might also influence maternal morbidity in a possible subsequent pregnancy individualized care is very important. One should focus on a safe, vaginal, first birth. To analyze the effects of our changes in obstetric care, it is of uttermost importance to collect the best quality of data. To achieve this, a uniform classification system should be used, so that different obstetric care units can be compared.

Introduction

In recent years there has been a change in obstetric practice. The Term Breech Trial and Hypitat trial are examples of randomized controlled trials that have changed obstetric practice. The Term Breech Trial has resulted in an increase in Caesarean sections (CS) for breech presentations, whereas the Hypitat trial has led to increased induction rates in women with hypertensive disorders in pregnancy[1-3]. Clinicians have a responsibility to practice 'evidenced based medicine' but they also have a responsibility to collect 'the evidence' to ensure that the best quality of care is being given to their patients[4]. It is therefore important to examine what the effect of changes in practice are and in particular to evaluate a possible benefit. The quality of obstetric care can be measured in several ways; for example through assessing rates of perinatal and maternal morbidity and mortality. Another attitude is to evaluate induction- and CS-rates. In general the best level of obstetric care can be defined by an optimal ratio, between the lowest level of maternal and neonatal morbidity and mortality, at the lowest level of intervention.

During the last decades, a rising trend in CS-rates is observed worldwide, which has resulted in a discussion about appropriate CS rates[4-6] and concerns that there is no additional perinatal health gain[7,8] but that extra maternal morbidity and additional costs[9] are involved. The consequences of high CS rates are higher maternal morbidity and mortality rates, both in the index pregnancy as well as in any subsequent pregnancies. There is a higher risk of placenta praevia or accreta, uterine rupture and necessity for peripartum hysterectomy[8,10,11]. The risk reduction for the fetus for perinatal asphyxia and birth trauma is often used to support the decision to perform a CS[12], but the perinatal health gain by performing a CS is subject to discussion[7,8].

There are many factors contributing to the increasing CS rates, including more obese women and higher maternal age. Those women are more likely to need a CS[13,14]. Furthermore, psychosocial factors (including CS on maternal request) or physical complaints and medico-legal consequences play an important role[15-16]. Currently about 3% of the deliveries in the US are CS on maternal request[17].

One of the traditional risk factors of a CS has always thought to be induction of labor[18,19]. This has recently been questioned and opinion remains divided[20-23]. Fact is, that during the

last decades, there has been an increase in the number of inductions of labor, both elective and for medical reasons[23]. Due to the large amount of current clinical trials studying the influence of induction of labor, on neonatal and maternal outcomes for many different factors (pre-eclampsia, postterm pregnancies), with overall favorable outcomes for induction, we expect a continuation of this rising trend of inductions[3,24].

An important parameter when analyzing obstetric care is perinatal mortality. The Peristat project, a European collaborative study in which indicators for perinatal health have been defined, has led to increased attention to perinatal mortality in the Netherlands in recent years, as the Netherlands had relatively high perinatal mortality rates[25-28]. Especially when compared to countries with a similar socio-economic status the Netherlands was in an unfavourable position regarding perinatal mortality.

Another parameter of relevance when evaluating the quality of obstetric care is maternal morbidity, which can be defined by many outcomes measures. The most frequently used outcome for the definition of maternal morbidity in the Netherlands is (severe) postpartum hemorrhage[29]. Therefore we have considered postpartum hemorrhage as an appropriate reflection of maternal obstetric outcome. Known risk factors for postpartum hemorrhage are induction of labor and CS and therefore we hypothesize that with increasing rates of these obstetric interventions, there will be an increase in maternal morbidity.

In order to compare and contrast obstetric outcomes between different countries and centres it is crucial to have a uniform classification system. In this way both low- and high-risk pregnancies can be compared. The Ten Group Classification System (TGCS) or Robson Classification, has substantially contributed to the realization of appropriate comparisons of obstetric outcome between different institutions[30]. Each group is characterised by their own clinical identity and each group has its own characteristics and epidemiological importance. The 10 groups are totally inclusive, meaning that each patient can be placed in one group. The 10 groups are also mutually exclusive, meaning that each patient can only be classified in one group. In this way a valid comparison can be made when comparing obstetric outcome in different institutes. In addition, the sizes and distribution of the groups themselves reveal much about the type of care provided in a particular obstetric care unit. Many facilities and countries have incorporated the TGCS in their routine clinical practice

and its value has been proven unequivocally[31]. In the Netherlands, such a classification system has not been implemented yet. It is important to note that although popularized for looking at Caesarean sections it can also be used to classify other obstetric outcome measures.

Group 1 and 2 represent nulliparous women at term, with a single fetus in a cephalic position and group 5 represent women with at least one previous CS at term. It is generally agreed that for most populations group 1, 2 and 5 are the main contributors to the overall CS rate[32,33]. In order to stabilize or even reduce CS-rates, attention should mainly focus on these groups.

We evaluated the effect of changes in obstetric care on perinatal and maternal outcome in the Netherlands comparing data from the Netherlands Perinatal Registry from 2000 to 2009. To the best of our knowledge this is the first study in which the unique obstetric system of the Netherlands is classified according to the TGCS. Our primary aim was to analyze if there were changes in the induction and CS rates in the Netherlands during this decade. Our secondary aim was to assess whether those changes have resulted in any measurable alterations to perinatal and maternal outcomes.

Methods

In this retrospective cohort study all data were obtained from the Netherlands Perinatal Registry (PRN) database, which is a linked professional database of all pregnancies beyond 16 weeks. Data from primary care (midwives and general practitioners) (LVR-1), secondary and tertiary care (LVR-2) and neonatologists (LNR) are collected in the dataset. More than 95% of all approximately 180,000 annual deliveries (both hospital and home births) in the Netherlands are registered. This study was conducted with permission of the PRN, representing all professionals involved in the data registration.

All pregnancies ≥24 weeks between 2000 and 2009 were extracted from the PRN database in a one record per mother format. Information on the current pregnancy and obstetric history were obtained, as well as data of the delivery and neonatal outcome, including stillbirths.

For all births the course of labor and delivery was recorded (spontaneous, induction or planned CS) and the mode of delivery. The mode of delivery was considered spontaneous when there was no CS or instrumental vaginal delivery (ventouse or forceps). A planned CS was defined as a CS that was agreed on before labor, despite the fact that a woman could go into labor before the set date and have her planned CS at an emergency time. An emergency CS was defined as a CS during labor, when a CS was not planned during the course of pregnancy. Postpartum hemorrhage (HPP) was defined as blood loss ≥1000mL. Perinatal mortality was defined as the stillbirth rate. All data were classified according to the Ten Group Classification System[30] (table I). All deliveries in the Netherlands, including home births, were assessed.

Table I – The Ten Group Classification System (TGCS)[30]

Group	Definition
1	Nulliparous, single cephalic, ≥37 weeks, in spontaneous labor
2	Combination of groups 2a and 2b
2a	Nulliparous, single cephalic, ≥37 weeks, induced labor
2b	Nulliparous, single cephalic, ≥37 weeks, planned CS
3	Multiparous, single cephalic, ≥37 weeks, in spontaneous labor
4	Combination of groups 4a and 4b
4a	Multiparous, single cephalic, ≥37 weeks, induced labor
4b	Multiparous, single cephalic, ≥37 weeks, planned CS
5	Previous CS, single cephalic, ≥37 weeks
6	Nulliparous breech
7	Multiparous breech
8	Multiple pregnancies
9	Oblique lies
10	Single cephalic, <37 weeks

CS – Caesarean section

For our primary outcome, to study the changes in induction and CS-rates, we have assessed all births between 2000 and 2009 in the Netherlands. Our secondary aim was to study the relationship between obstetric interventions (inductions and CS) and maternal and perinatal outcome. For the latter, we have only looked at groups 1-4, the single cephalic term births. In the other smaller and more diverse groups the relationship is probably more complex.

Statistical analysis was performed using the statistical software from SAS 9.3. Differences between categorical variables were analyzed using chi-square test. The Cochran-Armitage test was used for trend analyses. A p-value <0.05 was considered statistically significant.

Results

The CS-rates in all groups in 2000 and 2009 are shown in table IIA and IIB.

Table IIA - Robson groups and contribution to Caesarean section rates in 2000 for all births in the Netherlands. Total number of births 182.493, overall Caesarean section rate was 13.0%. Missing values 1.3%.

Groups	Number of CS over total number of women in each group	Relative size of groups (%) of total 182.493	CS rate in each group (%)	Contribution made by each group to overall CS rate (%)
1	4681/59791	32.8	7.8	2.5
2	*3356/12873*	*7.1*	*26.1*	*1.8*
2a	2502/12019	6.6	20.8	1.4
2b	854/854	0.5	100	0.5
3	1277/64886	35.6	2.0	0.7
4	*2284/14358*	*7.9*	*15.9*	*1.2*
4a	711/12785	7.0	5.6	0.4
4b	1573/1573	0.9	100	0.9
5	3245/7358	4.0	44.1	1.8
6	3543/5814	3.2	60.9	1.9
7	1624/3564	2.0	45.6	0.9
8	1197/3774	2.0	31.7	0.7
9	534/557	0.3	95.9	0.3
10	2028/9518	5.2	21.3	1.1

Table IIB - Robson groups and contribution to Caesarean section rates in 2009 for all births in the Netherlands. Total number of births 171.964, overall Caesarean section rate was 15.4%. Missing values 1.7%.

Groups	Number of CS over total number of women in each group	Relative size of groups (%) of total 171.964	CS rate in each group (%)	Contribution made by each group to overall CS rate (%)
1	5302/54019	31.4	9.8	3.0
2	*4117/14410*	*8.2*	*28.6*	*2.4*
2a	3187/13480	7.8	23.6	1.8
2b	930/930	0.5	100	0.5
3	1403/61021	35.5	2.3	0.8
4	*3216/15418*	*8.8*	*20.9*	*1.8*
4a	842/13044	7.6	6.5	0.5
4b	2374/2374	1.4	100	1.4
5	3886/8172	4.8	47.6	2.2
6	3471/4316	2.5	80.4	2.0
7	1779/2457	1.4	72.4	1.0
8	1251/3172	1.8	39.4	0.7
9	550/599	0.4	91.8	0.3
10	1880/8380	4.9	22.4	1.1

In 2000 the overall CS-rate (planned and emergency) was 13.0% and it has gradually increased to 15.4% in 2009. In table IIa and IIb an overview is given for both the years 2000 and 2009. In column II the absolute number of CS is shown, with the largest number in group 1 (nulliparous women, in spontaneous labor at term, single cephalic fetus) for both years. In column III the group sizes are displayed. Groups 1 and 3 are the largest groups (spontaneous labor at term of a single cephalic fetus) in both years. There is an increase in induced labors and planned CS for at term women with a single cephalic fetus (group 2 and group 4). For the nulliparous women this increase is largest, from 7.1% to 8.4% of the population. In column IV the CS rates in each group are shown. The CS rates have increased for every group from 2000 to 2009 (except for group 9). The highest CS rates are seen for the non-cephalic groups (6, 7 and 9). In column V the contribution of each group to the overall CS rate is displayed. This is a combination of both the size of the group, as well as the CS-rate within that group. It enables us to see in which group the largest contributors to the overall CS-rate were found. In 2000 the largest contributors to the CS-rate were group 1, 2 and 6 (nulliparous women at term, single cephalic fetus in spontaneous labor and induced and

nulliparous breeches at term). In 2009 the largest contributors to the absolute number of CS were groups 1, 2 and 5 (previous CS).

In figure I the induction rates and CS rates for group 1 and 2 are displayed. The induction rates were calculated by dividing group 2A (induction) by the total number of women in groups 1 and 2 combined (all single cephalic nulliparous women at term). There is an increase in induction of term nulliparous women of 16.5% (12019/72664) in 2000 to 19.7% (13480/68429) in 2009 ($p<0.001$). The CS-rates have increased as well in group 1 and 2; from 11.1% in 2000 to 13.8% in 2009 ($p<0.001$). The CS-rate for groups 1 and 2 remained stable between 2001-2005 with an increase afterwards. Overall, the CS rates show a statistically significantly rising trend over the years but with a different pattern than the induction rates. Maternal obstetric hemorrhage has steadily increased over the years, from 4.4% in 2000 to 6.8% in 2009. Maternal obstetric hemorrhage (HPP) shows a statistically significantly rising trend over the years, with a similar pattern as the CS rates. Stillbirth rates in groups 1 and 2 have been halved; from 2.0/1000 in 2001 to 1.0/1000 in 2009 ($p<0.001$).

Figure I – group 1 and 2 as a cohort, all deliveries of nulliparous women with a single cephalic pregnancy at term. Induction and Caesarean section rates (both planned and emergency) are outlined against stillbirths and maternal postpartum hemorrhage (blood loss >1000mL).

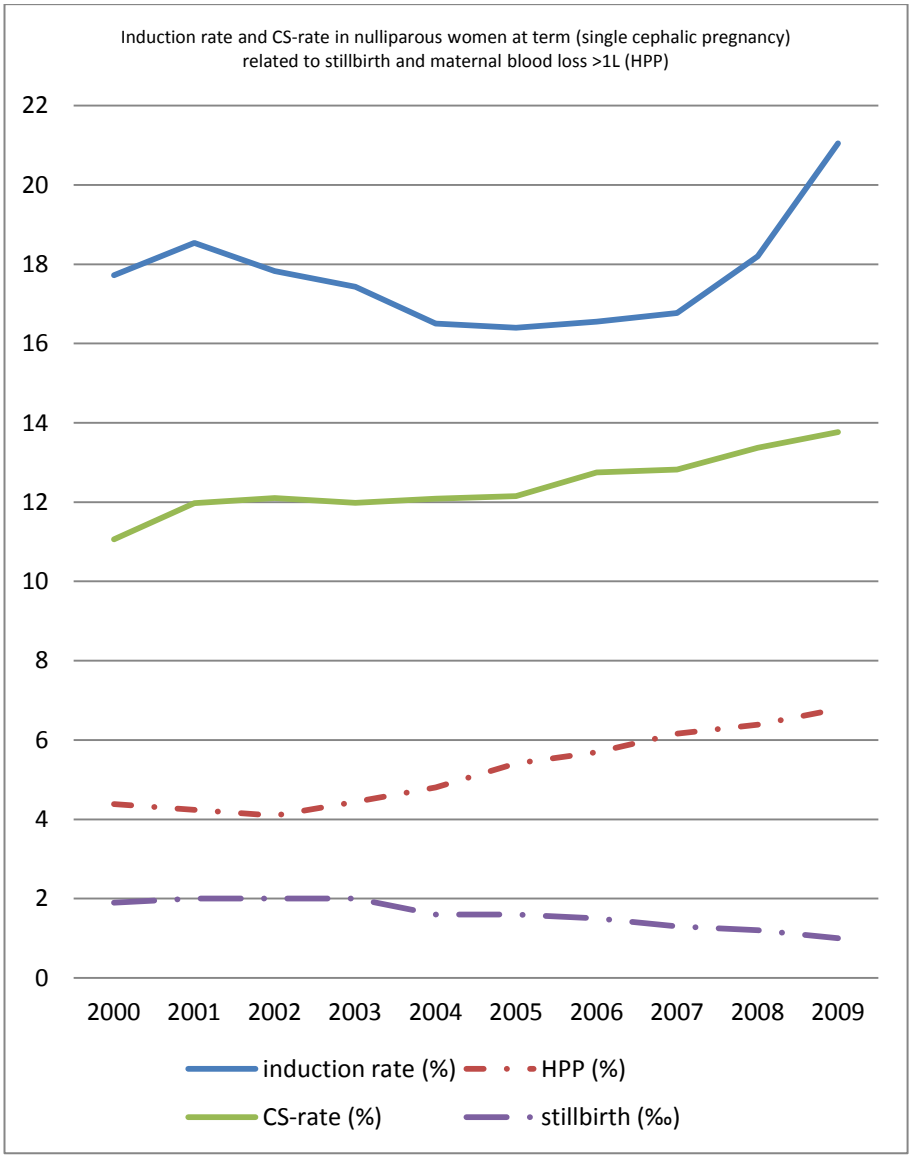
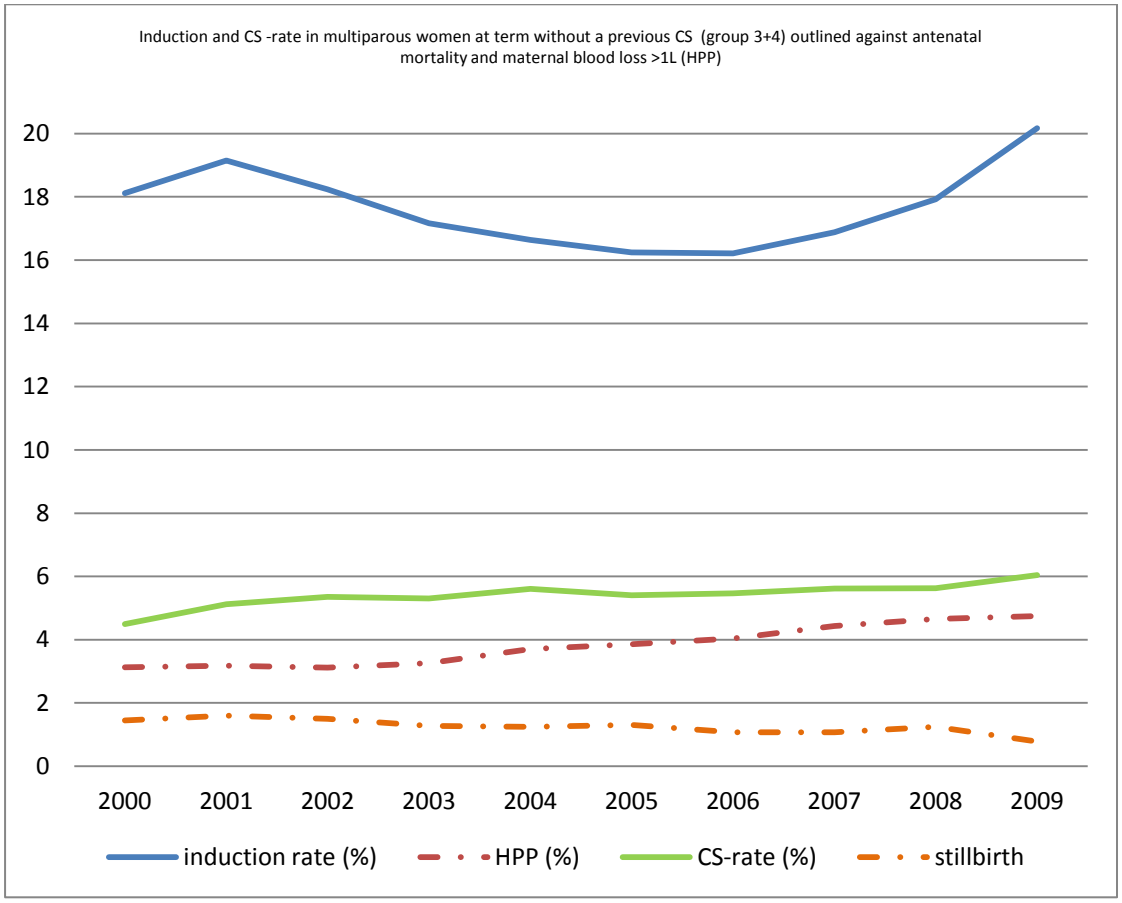


Figure I: all trends shown are statistically significant (P<0.001)

In Figure II induction and CS-rates for groups 3 and 4 are shown. These are the multiparous women at term with a single cephalic fetus, without a previous CS. After an initial decrease of induction rates, an increase from 2006-2009 is noted (from 13.4% to 17.1%). The CS-rates show a statistically significant rising trend, from 4.5% in 2000 to 6.0% in 2009 (p<0.001).

However, the trend of inductions and CS have a different pattern. Maternal HPP has shown a statistically significant increase from 3.1% in 2000 to 4.8% in 2009 ($p<0.001$). Stillbirths have decreased in this cohort of group 3 and 4 from 1.45/1000 in 2000 to 0.78/1000 in 2009 ($P<0.001$).

Figure II – cohort of group 3 and 4 combined, all deliveries of multiparous women without a previous CS, with a single cephalic pregnancy at term. Induction and Caesarean section (both planned and emergency) rates are outlined against perinatal mortality and maternal obstetric hemorrhage (blood loss >1000mL).



There is no significant trend for induction rates, all other trends are statistically significant ($p<0.001$).

In figure III the maternal postpartum hemorrhage is shown in more detail. In all groups a statistically significant rising trend is observed ($P<0.001$). The highest HPP-rates are found in the intervention groups of induction and planned CS (groups 2 and 4).

Figure III – postpartum hemorrhage (blood loss >1000mL) in the Netherlands for all single cephalic births at term, excluding previous CS (groups 1-4).

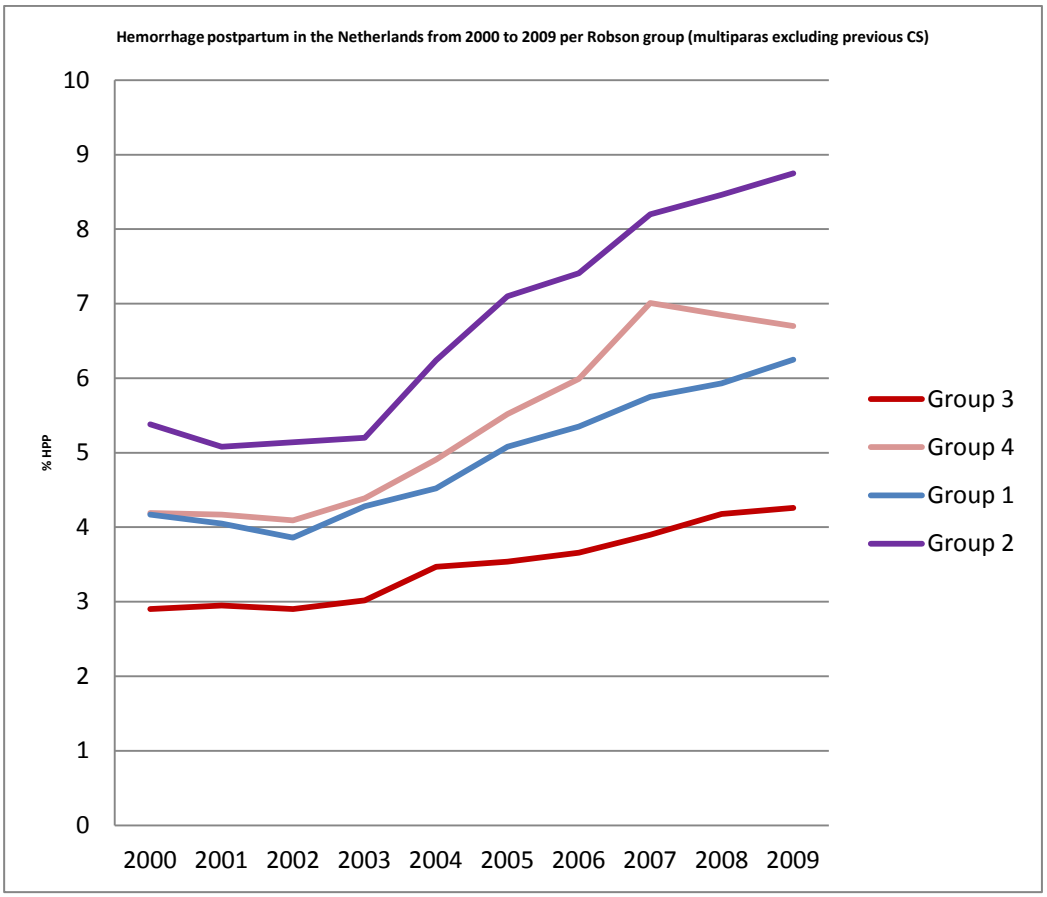


Figure III: all trends shown are statistically significant (P<0.001)

Discussion

Main findings

The distribution within the 'Ten Groups' has changed over the years 2000-2009. An increase of inductions and planned CS was seen for both nulli- and multiparous (without a previous CS) women at term with a single cephalic pregnancy. The largest contributors to the absolute number of CS in 2009 were groups 1, 2 and 5. This is consistent with the current international literature[32,33].

The induction rates decreased up until 2006 for both nulli- and multiparous women. From 2006 onwards a sharp increase in induction rates is seen, similar for nulli- and multiparous women. The increase in inductions as seen in our cohort, is also seen worldwide. The effect is largest from 2007 onwards, which could be the result of the preliminary results of the nationwide HYPITAT-study, which came out in 2007. This study showed that induction of labor is associated with improved maternal outcome and should be advised for women with mild hypertensive disease beyond 37 weeks gestation. However overall induction rates in the current study, are between 15-20%, which is generally lower compared to international induction figures[34].

There is ongoing controversy in the literature whether induction of labor after 37 weeks is associated with increased CS rate or not. Many studies describe an association between induction of labor and CS when compared to women in spontaneous labor[18,19]. However, Caughey et al. have introduced the concept that induction of labor should not be compared to spontaneous labor, but to expectant management instead[20]. When induction of labor is compared to expectant management, most studies don't find increased odds for CS when an induction of labor is performed[21-23]. Our study confirms this finding. From Figure I and II it can be seen that the rising trend of CS rates follows a different pattern than the rise in induction rates.

The overall CS-rate rose statistically significant from 13.0% to 15.4% between 2000 and 2009. Compared to international literature, this CS-rate is low, a well known feature of the Dutch obstetric system[35]. One of the reasons could be the strict division between midwife-

led care and obstetrician-led care. It is argued that midwifery-led care in general results in less obstetric interventions[36].

Postpartum hemorrhage has increased over the years and is higher in nulliparous women than in multiparous women. The overall international incidence of obstetric hemorrhage is 6%, which is comparable to our results[37]. Known risk-factors are induction of labor, CS and nulliparity[38]. This is confirmed in our study where we found the highest incidence of HPP in the intervention groups, group 2 and 4 (Figure III). However, from Figure I and II it can be seen that the rising trend of HPP rates follows a different pattern than the rising induction rates. Since obstetric hemorrhage is a marker for the quality of labor management, it is interesting to note that in all groups there is an increase in HPP. However, there has been more attention for the registration of postpartum hemorrhage in recent years after a large nationwide trial, so the increasing trend could (partially) be due to improved registration[29]. Additionally the number of women at-risk for HPP has increased due to the increased incidence of inductions and CS.

The overall number of stillbirths has dropped significantly by more than 100% (from 995 to 441 cases ($p<0.001$)). Much attention has been gained in recent years to the relatively high perinatal mortality in the Netherlands, due to the European Peristat results[26-28]. There have been multiple initiatives to improve perinatal outcomes (e.g. teamtraining for obstetric emergencies and structural ultrasound scans at 20 weeks gestation)[26]. The stillbirth rate has decreased over the studied period and is now more comparable to other European countries.

Strengths

A major strength of this study is that in the Dutch perinatal database, there is an almost 100% registration of all births in the Netherlands, leading to the evaluation of a large cohort of almost 2 million women. No women were double registered. Furthermore, there has been long experience in the validation of the linkage system between the different registration systems used (LVR-1, LVR-2 and LNR), resulting in a database of good quality[35].

Limitations

In the study of large databases there is a risk of incomplete or incorrect data collection. The Ten Group Classification System could be used for validation of our database, as certain

figures are obligatory. For example group 9 should not exceed 0,5% of the total population and should have a 100% CS rate. Furthermore, there should be no missing values, as every woman should be placed in one individual group (totally inclusive system). In our database less than 2% of the data are missing, resulting in an almost complete database. In group 9 the total figures are correct (less than 0,5%), but there is not a 100% CS rate, meaning that some women in this group are misplaced. Furthermore, the CS-rate in group 4 (single cephalic multiparous women without a previous CS) is relatively high, meaning that there might be women with a previous CS (group 5) inadvertently included in group 4.

Another limitation is that in this observational cohort study, trends are analyzed. One of the main methodological problems is that (planned) induction or CS are not compared to expectant monitoring. This is one of the main challenges when analyzing the effect of obstetric interventions[20]. Therefore no direct causal conclusion can be drawn from this study: increased induction and CS-rates have not necessarily influenced perinatal mortality and maternal morbidity directly. Because of the retrospective design of the study, we could not correct for a possible change of attitude over time. Women and caregivers are increasingly less tolerant of adverse fetal outcomes, and, in the belief that CS will decrease the likelihood of this eventuality, tend to undergo CS more frequently.

Another limitation is that for the analysis of maternal outcome maternal mortality was not considered. The most important cause of maternal mortality in the Netherlands used to be pre-eclampsia[39]. However, since the introduction of the results of the nationwide HYPITAT-study, maternal outcome improved and pre-eclampsia is now no longer the first cause. Severe maternal morbidity can therefore be reflected by HPP.

Future expectations

For the future: we hypothesize that induction rates will increase further. We don't expect the same rise in CS or HPP. It is of great importance to evaluate the effect of obstetric interventions to be able to provide the best quality of care. In order to make international comparisons, monitoring obstetric interventions and outcomes should be done by a uniform classification system, such as the TGCS (Ten Group Classification System).

Conclusion

In our cohort there is no direct association between induction rates and CS-rates. Stillbirths have decreased with higher induction and CS-rates, but at the same time there has been an increased incidence of maternal obstetric hemorrhage. Maternal morbidity due to increased CS is not only of importance in the index pregnancy, but also in subsequent pregnancies, so management should be individualized and specific attention should be drawn to a safe vaginal birth for nulliparous women. It is of great importance to evaluate the effect of obstetric interventions in a uniform way, to be able to provide the best quality of care.

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Chapter 3

High-normal maternal TSH and low-normal maternal FT4 are associated with a higher operative delivery rate in low-risk pregnancies: a prospective cohort study.

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Abstract

Background – The increasing number of operative deliveries is a topic of major concern in modern obstetrics. Maternal thyroid function is of known influence on many obstetric parameters. Our objective was to investigate a possible relation between maternal thyroid function, and operative deliveries. Secondary outcome was to explore whether thyroid function was related to specific reasons for operative deliveries.

Methods – In this prospective cohort study, low-risk pregnant Caucasian women were included. Women with known auto-immune disease, a pre-labor Caesarean section, induction of labor, breech presentation or preterm delivery were excluded. In all trimesters of pregnancy the thyroid function was assessed. Differences in mean TSH and fT4 were calculated using t-test. Mean TSH and fT4 levels for operative deliveries were determined by one way ANOVA. Repeated measurement analyses were performed, adjusting for several confounders.

Results - At 36 weeks gestation women who had an operative delivery had a significantly higher mean TSH (1.63mIU/L versus 1.46mIU/L, p=0.025) and lower mean fT4 (12.9pmol/L versus 13.3pmol/L, p=0.007)) compared to women who had a spontaneous delivery. Mean TSH was significantly higher (p=0.026) and mean fT4 significantly lower (p=0.030) throughout pregnancy for women with an operative delivery due to failure to progress in second stage of labor, compared to women with a spontaneous delivery or operative delivery for other reasons, corrected for BMI, parity, and maternal age.

Conclusions – High-normal TSH and low-normal fT4 are associated with more operative vaginal deliveries and Caesarean sections (especially due to failure to progress in second stage of labor), possibly to be explained by less efficient uterine action.

Introduction

Increasing rates of Caesarean Sections (CS) is a topic of major concern in obstetrics. Both the incidences of planned and emergency CS are rising, without necessarily better neonatal outcomes[1,2]. Operative vaginal deliveries (OVD) have shown a slowly decreasing trend, but OVD are still common, especially in nulliparous women. Maternal morbidity and mortality rates are higher for women with a CS or OVD[2,3]. Many studies have been performed to determine risk factors associated with operative deliveries. The main risk factors for CS and OVD are nulliparity, induction of labor, increasing maternal age, abnormal position of the fetus, high maternal body mass index (BMI) and previous CS[4-6]. Most CS and OVD are performed due to failure to progress, especially in nulliparous women[6]. The main reason is inefficient uterine action and to a lesser extent cephalopelvic disproportion. In fact, efficient uterine action is more and more considered as the key to normal delivery[7,8].

In previous studies it has been demonstrated that suboptimal maternal thyroid function is associated with adverse pregnancy outcomes[9-12]. Women with suboptimal thyroid function; mainly those with TPO-antibodies (thyroid-peroxidase-antibodies), are at risk for miscarriage and preterm birth[9,10]. Furthermore, there is evidence that high maternal TSH might interfere with normal obstetric outcome at term, with higher incidences of small for gestational age neonates[11], gestational diabetes[10] and meconium stained amniotic fluid[12].

Little research is done into the relation between maternal thyroid function and uterine contractions. However, there is some evidence that suboptimal maternal thyroid function might be associated with more breech presentations, possibly due to increased stiffness of the myometrium[13]. This increased stiffness in patients with suboptimal thyroid function has been demonstrated in previous research in vascular smooth muscle cells as well[14,15].

In the current study we evaluated a possible relationship between suboptimal maternal thyroid function and inefficient uterine action at term. Primary outcome was to investigate a possible relation between maternal thyroid function and incidence of CS and OVD. Secondary outcome was to explore whether thyroid function was related to specific reasons for operative deliveries: due to fetal distress or failure to progress. In order to create a representative low-risk group we excluded the women at high risk for operative deliveries (previous CS, inductions, breech presentations, multiple pregnancies).

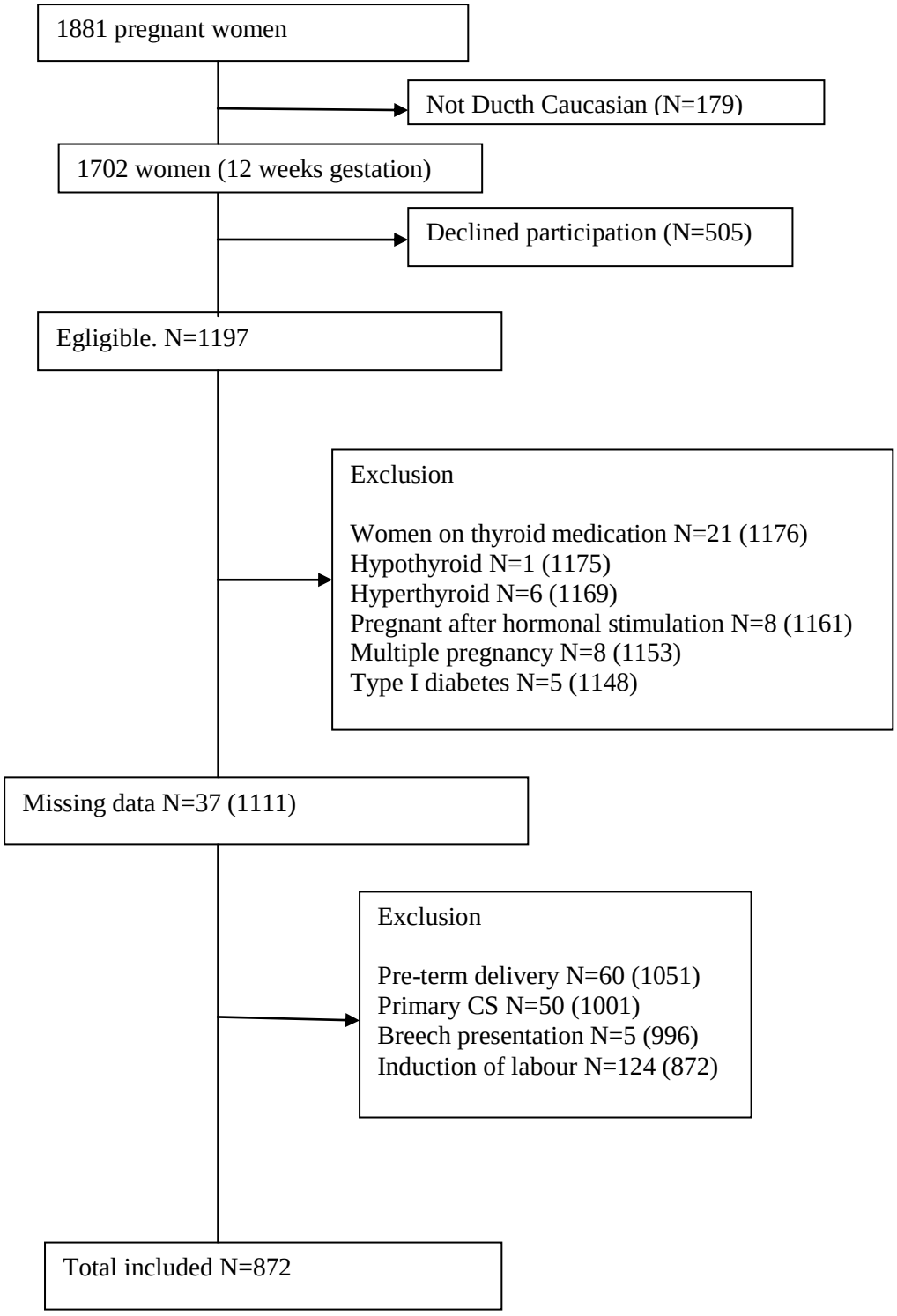
Methods

Design and participants

During a period of two years, 1702 women who booked for antenatal visits at 12 weeks gestation were followed in five community midwife practices in the vicinity of Eindhoven (the Netherlands). Only Dutch Caucasian women (n = 1507) were eligible to avoid language problems and confounding factors of ethnicity. Seventy-nine percent (n = 1197) of the women gave informed consent; the non-responders did not differ from the responders regarding maternal age, educational level and parity (data not shown). Women on thyroid medication (n = 21), with a new diagnosis of hypothyroidism (n = 1) or hyperthyroidism (n = 6) at screening, pregnant as a result of hormonal stimulation (n = 8), with multiple pregnancy (n = 8), and with Type 1 diabetes (n = 5) were excluded. Data were missing in 37 women. Of the remaining 1111 women a low-risk population was defined, with the exclusion of preterm deliveries, breech presentations and induction of labor. There were 60 women who delivered before 37 weeks gestation and 50 women who had a planned CS (45 for breech presentation). There were 5 more women with a fetus in breech presentation. Furthermore, there were 124 women who had an induction of labor. Therefore, data-analysis refers to 872 women. The selection process is shown in figure 1 and the characteristics are shown in Table 1.

Delivery was considered an OVD when there was a ventouse or forceps delivery. In cases without CS or OVD, delivery was defined as spontaneous. The reasons for OVD and CS were classified as fetal distress, failure to progress in first stage of labor (prolonged dilatation) or failure to progress in second stage of labor (prolonged expulsion). Fetal distress was defined as a non-reassuring fetal heart rate with cardiotocography. This study was approved by the Medical Ethical Committee of Máxima Medical Centre in Eindhoven/Veldhoven. (METC project number: 0116).

Figure 1, selection process.



Analysis

TSH was measured in serum at 12, 24 and 36 weeks 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 non-pregnant reference range of TSH is 0.45 - 4.5 mIU/L. FT4 concentration was measured in serum at 12, 24 and 36 weeks 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. TPO-Antibodies were determined in serum at 12, 24 and 36 weeks by means of the IMMULITE Anti-TPO-Ab kit. The inter-assay coefficients of variation for this analysis were 9% and 9.5% for concentrations of 40 kU/ml and 526 kU/ml, respectively. The anti-TPO assay is standardized in terms of the International Reference Preparation for anti-TPO MRC 66/387. Women were defined as TPO-Ab-negative when the titer was below 35 kU/ml at 12 weeks gestation. All measurements were performed in one laboratory.

Statistical analysis

Statistical analysis was performed using the Statistical Package of Social Science (SPSS, 19.0). TSH and fT4 concentrations were not normally distributed. However, because the cohort size of all subgroups was large (n > 30) we calculated differences in means (SD) of thyroid hormones concentration levels using Welch T-test (two-tailed). Differences in prevalence were calculated by chi-square. We compared mean TSH and fT4 levels in different groups of etiology of non-spontaneous delivery using one way ANOVA. We compared the changes of mean fT4 and TSH throughout pregnancy in women with and without a spontaneous delivery using repeated measurement analyses, adjusting for confounders such as parity, BMI and maternal age.

Results

Table 1 shows that women who undergo an operative delivery have a higher pre-pregnancy BMI (26.3kg/m^2 versus 25.0kg/m^2) and have a longer gestational age (40.3 versus 39.8 weeks gestation). There were no statistically significant differences between a history of thyroid dysfunction in the family or the prevalence of positive TPO-antibodies. However, at 36 weeks gestation (third trimester) women who had an OVD or CS had a significantly higher

mean TSH and lower mean fT4 compared to women who had a spontaneous delivery (TSH 1.63 mIU/L versus 1.46 mIU/L and FT4 12.9 pmol/L versus 13.4 pmol/L respectively).

Table 1 - Characteristics of a group of 872 women who delivered at term (≥37 weeks of gestation), comparing spontaneous deliveries and operative vaginal deliveries or secondary CS. Primary CS were excluded.

	All deliveries (872)		Spontaneous deliveries (747)		Operative deliveries (125)		p-value
	Mean (SD)	N(%)	Mean (SD)	N(%)	Mean (SD)	N(%)	t-test X^2
Age ≥35 yrs	30.5(3.6)		30.6(3.7)		30.0 (3.4)		0.08
Low education		69 (8)		62 (8)		7 (6)	0.47
BMI before pregnancy(kg/m2)	**25.2(4.3)**		**25.0 (4.2)**		**26.3(4.7)**		**0.002**
Primiparity		**366(42)**		**268(36)**		**98 (78)**	**<0.001**
Miscarriage in obstetric history		164(19)		148(20)		16 (13)	0.06
Thyroid function							
12 weeks gestation TSH (mIU/L) fT4 (pmol/L)	 1.30 (2.97) 16.2 (2.5)		 1.21(0.80) 16.2 (2.5)		 1.88(0.76) 16.2 (2.5)		 0.33 0.98
24 weeks gestation TSH (mIU/L) fT4 (pmol/L)	 1.33 (0.69) 13.9 (2.0)		 1.32(0.65) 13.9 (2.0)		 1.45(0.89) 13.7 (1.8)		 0.11 0.20
36 weeks gestation **TSH (mIU/L)**	 **1.49(0.75)**		 **1.46(0.73)**		 **1.63(0.86)**		 **0.025**

fT4 (pmol/L)	**13.3 (2.2)**		**13.4 (2.2)**		**12.9 (2.1)**		**0.007**
TPO-Ab >35IU/mL		75 (8.6)		60 (8.0)		15(12)	0.14
Family history thyroid dysfunction		158(18)		137(18)		21 (17)	0.80
Neonatal outcome:							
Term at delivery (wks)	**39.9(1.1)**		**39.8 (1.1)**		**40.3 (1.0)**		**<0.001**
Birth weight (gr)	3545(457)		3539(457)		3582(454)		0.33
Male offspring		451(52)		380(51)		71(57)	0.20

* Variables in bold are statistically significant (P<0.05).

The different modes of delivery and the reasons for OVD and CS are shown in table 2.

Table 2 – Mode of delivery in 872 women at term in whom labor started spontaneously. ANOVA analyses for influence of maternal thyroid function at every trimester on mode of delivery (df=3).

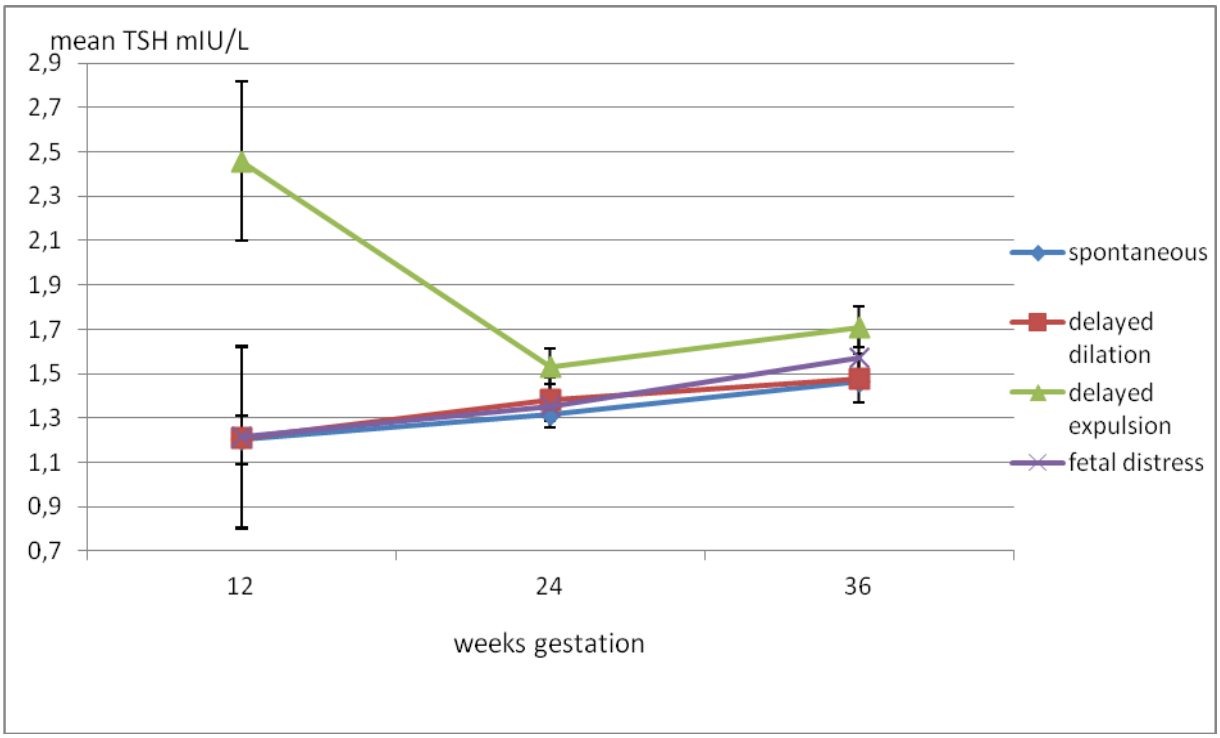
	Spontaneous delivery N=699 (80.2%)	Failure to progress in 1st stage of labor (prolonged dilatation) N=51 (5.8%)	Failure to progress in 2nd stage of labor (prolonged expulsion) N=69 (7.9%)	Fetal distress N=53 (6.1%)	P
12 weeks gestation					
TSH(mIU/L) mean(SD)	1.20 (0.80)	1.21 (0.63)	2.01 (0.92)	1.21 (0.79)	0.010
fT4(pmol/L) mean(SD)	16.2 (2.75)	16.4 (1.98)	15.5 (2.60)	16.6 (2.23)	0.070
24 weeks gestation					
TSH(mIU/L) mean(SD)	1.31 (0.65)	1.38 (0.68)	1.53 (0.85)	1.35 (0.65)	0.093
fT4(pmol/L) mean(SD)	13.9 (2.0)	13.6 (1.6)	13.5 (1.7)	14.2 (2.0)	0.16
36 weeks gestation					
TSH(mIU/L) mean(SD)	1.46 (0.73)	1.48 (0.74)	1.71 (0.96)	1.57 (0.68)	0.066
fT4(pmol/L) mean(SD)	13.4 (1.9)	13.4 (2.2)	12.7 (1.9)	13.3 (2.1)	0.080

80.2% of the women had a spontaneous delivery and in 19.8% of the women an OVD or CS was performed. In 5.8% of the deliveries there was an OVD or CS due to failure to progress in first stage of labor, in 7.9% of the deliveries there was failure to progress in second stage of labor and 6.1% of all deliveries were terminated due to fetal distress. Mean fT4 and mean

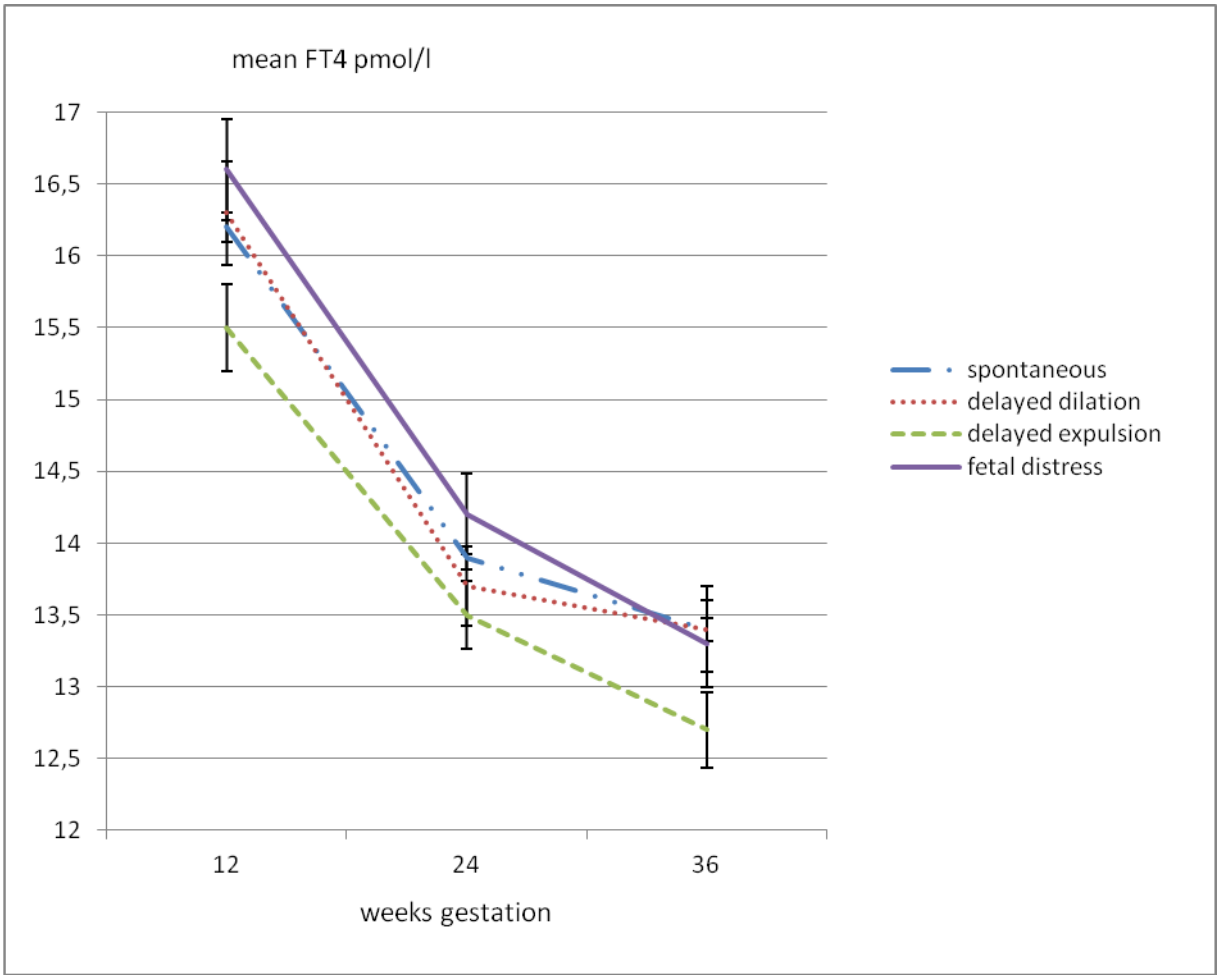
TSH were compared between these subgroups using one way ANOVA. As shown in table 2, mean TSH was significantly higher at 12 weeks of gestation and at a 90% significant level at 24 and 36 weeks gestation for women with an operative delivery due to failure to progress in second stage of labor. Mean fT4 was lower at a 90% significance level at the first and third trimester of pregnancy for women with failure to progress in second stage of labor.

Subsequently, repeated measures ANOVA was performed to determine whether the changes of TSH and fT4 during pregnancy were associated with the mode of delivery and the different reasons for OVD or CS. As shown in figure 2, women who had an OVD or CS for failure to progress in the second stage of labor (delayed expulsion) had higher mean TSH levels (p=0.026) at all trimester adjusted for age, parity, BMI and gestational age, compared to women who had a spontaneous delivery or an OVD or CS for other reasons.

Figure 2: The relation between mean TSH at all trimesters and the mode of delivery in 872 term women in whom labor started spontaneously: women who had an operative vaginal delivery or Caesarean section because of prolonged expulsion had significantly higher mean TSH throughout gestation (repeated measures ANOVA, F = 3.1, p = 0.026.), adjusted for age, parity, gestational age and BMI.



In figure 3 it is shown that women with an OVD or CS for failure to progress in second stage of labor, had a significant lower mean fT4 in all trimesters, adjusted for age, parity, BMI and gestational age, compared to women with a spontaneous delivery (p = 0.030) or OVD or CS for other reasons. There were no differences in maternal thyroid function between women who had a spontaneous delivery compared to women who underwent an OVD or CS for fetal distress or failure to progress in the first stage of labor (delayed dilatation).



Discussion

Main findings

In this study we found a significant association between high normal maternal TSH and low normal fT4 and the risk of operative delivery for women in spontaneous labor at term. Our cohort consisted of 872 Caucasian women with a low-risk pregnancy. Planned Caesarean sections, inductions of labor, preterm deliveries and breech presentations were excluded. Our cohort was representative in terms of thyroid function and obstetric outcome. We did find a higher incidence of TPO-Ab in our study (8.2%) compared to another large cohort study in the Netherlands (5.6%)[16], but this can be explained by the large number of African-European women in their sample (up to 40%), in whom TPO-Ab occur less frequently[17], while our sample included only Caucasian women. Mean TSH and fT4 levels of the current study are comparable to their sample. Obstetric outcome was proportionate to a large cohort study carried out in the Netherlands to analyse trends in obstetric interventions[1]. They found a CS rate of 7.5% for nulliparous women in spontaneous labor and an OVD rate of around 10% between 1993-2002, with an increase in CS rates over the years[1]. Our total operative delivery rate was 20%, for OVD and CS combined.

The current study showed that women who undergo a CS or OVD had a higher pre-pregnancy BMI and delivered at a later gestational age. This finding is consistent with previous reports[8,18-20]. We also found that women with an operative delivery for failure to progress in second stage of labor had higher mean TSH levels and lower mean fT4 levels throughout pregnancy, compared to women who delivered spontaneously or had an operative delivery for another reason. This finding was adjusted for maternal age, pre-pregnancy BMI, parity and gestational age at time of delivery.

Strength and limitations

One of the main strengths of this study is the fact that maternal thyroid function was assessed prospectively throughout pregnancy at fixed time-intervals. Repeated measurement analysis was performed to assess changes in thyroid function within and between subjects. Furthermore, we corrected for important confounders, including BMI, which is one of the known risk factors for operative deliveries[8,18,19]. We have not used cut off values for suboptimal maternal thyroid function. We believe that this is a strength of this

study, as there is considerable discussion about the proper cut off values and the definition of, for example, subclinical hypothyroidism in pregnancy[21,22].

A limitation of the study is the fact that this was an observational study and therefore no conclusions on causality of the associations can be drawn. Furthermore, no strict definition of fetal distress was used. Diagnosis of fetal distress was made on the basis of a non-reassuring fetal heart pattern. As only healthy Dutch Caucasian women were analysed in this study, extrapolation of the results to women with other ethnicities or to high-risk pregnant women with for example hypertension or diabetes must be taken with caution.

Interpretation

Higher TSH and lower fT4 in this euthyroid sample were associated with higher operative delivery rates. However, TSH and fT4 were still in the normal ranges for all groups. In a large retrospective cohort study from Männistö et al. increased odds for CS (both prelabor and during labor) were found in women with primary hypothyroidism[23]. From that study however, it was not clear for what reasons the CS were performed.

The main difference in the current study, according to maternal TSH and fT4, is found in OVD and CS due to failure to progress in second stage of labor. It is known that the most important factor in the expulsion of the fetus is the thickness of the myometrium and thus the strength of the contractions, despite the pushing efforts of the mother[24]. It has not been well established whether the spontaneous contractions are stronger during the second stage of labor than during the first stage of labor, but it is known that during Valsalva the power of the contractions is significantly higher in the second stage of labor[25]. With Valsalva it is not only smooth muscle cell contractions, but contractions of the skeleton muscles of the abdominal wall as well, that determine the expulsive power. It is well known that thyroid hormones are of influence on the contractile phenotype of skeletal muscles[26]. The most effective uterine action is needed in the second stage of labor and factors that are of influence on the strength of the contractions will therefore become most apparent during this stage.

Calcium influx is necessary for excitation of the smooth muscle cells and therefore for the myometrial contractility required during labor. Parija et al. have demonstrated that hypothyroidism reduces calcium channel function in uterine tissue of the pregnant rat[27]. A

study from Corriveau et al. has found that the amplitude and time course of contractions is enhanced in patients treated with thyroid hormone compared to controls[28]. This suggests that thyroid function is of direct influence on myometrial contractility. Besides the absolute strength of the contractions, it has also been found in vascular research that hypothyroidism leads to impaired smooth muscle cell relaxation, leading to increased arterial stiffness[14,15]. Moreover, women with failed external cephalic version had higher TSH values, probably because of impaired uterine relaxation which is essential for the breech baby to turn[29]. The combination of the strength of the contractions and the impaired relaxation of the myometrium might lead to less efficient uterine action in women with suboptimal thyroid function in this study. Future research should confirm this finding in a larger population and determine whether treatment of suboptimal maternal thyroid function leads to less failure to progress.

Conclusion

High normal maternal TSH and low normal maternal fT4 in this euthyroid sample, are independently related to higher rates of instrumental deliveries for women in spontaneous labor at term. Suboptimal maternal thyroid function is associated with more OVD and CS especially due to failure to progress in second stage of labor, possibly to be explained by less efficient uterine action. The conclusions of this study are very relevant, as the increasing incidence of CS is one of the major concerns in modern obstetrics. Future research should confirm our findings and focus on determining the direct effect of maternal thyroid hormones on uterine contractions in vivo.

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Chapter 4

The aetiology of meconium stained amniotic fluid: pathologic hypoxia or physiologic fetal ripening? a review.

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Abstract

Introduction - despite the many efforts to study the (patho)physiology of meconium release before delivery, it still remains an indistinct subject. Some studies have reported a relationship between hypoxia and meconium stained amniotic fluid (MSAF), whilst others have not. The most common association found however, is between MSAF and the term of gestation.

Methods - MEDLINE, EMBASE and the Cochrane library were electronically searched. Papers about the (patho)fysiology of meconium stained amniotic fluid in English were included. Papers about management strategies were excluded.

Results - different theories have been proposed including acute or chronic hypoxia, physiologic fetal ripening and peripartum infection.

Conclusion - we suggest that meconium stained amniotic fluid should be regarded as a symptom rather than a syndrome becoming more prevalent with increasing term and which might be associated with higher levels of infection or asphyxia.

Introduction

As a result of passing of fetal colonic contents, meconium stained amniotic fluid (MSAF) can be observed in 7-22% of all deliveries at term[1]. Historically MSAF has been regarded as an indicator of fetal asphyxia. In 1962 Leonard has already suggested a possible relation between fetal anoxia, fetal distress, perinatal death and MSAF[2]. Since then, many studies have been performed to evaluate the clinical relevance of MSAF in terms of prediction of fetal asphyxia.

Despite the many efforts to study the (patho)physiology of meconium release before delivery, it still remains an indistinct subject. Some studies have reported a relationship between hypoxia and MSAF, whilst others have not. The most common association found however, is between MSAF and the term of gestation. In post-date pregnancies incidences of MSAF of up to 40% have been described[3].

In this systematic review we want to give an overview of the aetiology and pathophysiology of MSAF. Until now, the presence of MSAF results in an increase of interventions during delivery, as described in most studies; perhaps due to more fetal distress, but definitely enhanced by the `historic meaning` of MSAF [4-7].

Methods

Search strategy

MEDLINE, EMBASE and the Cochrane library were electronically searched through May 2013. The search comprised the terms 'meconium stained amniotic fluid', 'aetiology', 'pathophysiology', 'fetal distress' and related entry terms. In addition, reference lists of identified articles and related reviews were hand searched. Titles, abstracts and entire texts were searched for potentially relevant articles. Papers were included when the aetiology or (patho)physiology of meconium stained amniotic fluid were analysed. Both human and animal studies have been included. Retrospective studies as well as prospective studies, reviews and experimental researches have been included (Table I). Publications about the management strategies were excluded. There was a language restriction to English. There were no restrictions concerning the year of publication. The most important reports on the

aetiology of meconium stained amniotic fluid are presented in table I. Based on the included papers, the aetiology of MSAF could be divided into three categories: fetal hypoxia, fetal ripening and peripartum infection.

Results and discussion

1. Hypoxia

In many studies MSAF is related to poorer neonatal outcome[4,7-12]. This includes lower APGAR-scores and lower cord blood pH-levels. Furthermore, in some studies more neonatal admittance to intensive care units is described[7,11] and more perinatal deaths[7,9]. This association is seen as a prove that hypoxia leads to more intra-uterine meconium release. One of the known risks of MSAF is the meconium aspiration syndrome (MAS). About 5% of the infants with MSAF develop MAS, which still has a mortality rate of 2.5% in the developed world and up to 35% in the developing world[13,14]. The lower APGAR-scores, the more admittance to a neonatal ICU and the higher perinatal death figures could therefore be an effect of MAS rather than that it supports the theory that fetal hypoxia leads to more MSAF. Lower pH-levels and thus more acidosis on the other hand cannot be related to MAS only and supports the theory of fetal hypoxia leading to MSAF. However, in some studies no differences in pH levels are found in case of MSAF[15,16].

In a study of Ciftici et al. in rats, the aortas were clamped to effectuate hypoxic stress; none of the animals released meconium[17]. Therefore the authors suggested that the association between MSAF and poor neonatal outcome might be due to reduced clearance of meconium, rather than due to increased meconium release[17]. Furthermore they performed sympathectomy in animal models and then put those animals in a hypoxic environment. Compared to controls, there was no meconium release in the sympathectomised animals, but all animals in the control group did defecate after the hypoxic event. Furthermore, meconium by itself can have a vasoconstrictive effect on the umbilical cord and lead to necrosis and ulceration of the cord[18] which can result in more fetal hypoxia. This does not necessarily mean that more hypoxia leads to fetal meconium release. Therefore, we cannot determine the exact pathophysiologic mechanism underlying the association between MSAF and fetal hypoxia.

In a small study, placentas from neonates with MSAF have been pathologically examined and placenta´s thickening of the basal membrane was observed and more apoptosis was found[12]. These findings have also been described in growth-restricted infants and placentas of infants with fetal distress and are therefore suggested to be ultra-structural changes to hypoxia. Small for gestational age is also an independent risk factor for meconium stained amniotic fluid[19]. In an experimental animal study it has been indicated that hypoxemic stress leads to reduced swallowing of meconium stained amniotic fluid, instead of more meconium release[17]. This might explain the association between more meconium stained amniotic fluid and poor perinatal outcome, but not in the pathophysiologic way as previously proposed.

Chronic or acute hypoxia

If MSAF is indeed associated with fetal distress the question is whether MSAF is related to an acute hypoxic event or if MSAF is a symptom of chronic distress. In some studies a distinction has been made between thin and thick meconium[5,6]; thick but not thin meconium stained amniotic fluid was associated with poor neonatal outcomes in one of them[5], while the other study from Ohja et al. found the opposite effect[6]. This difference of effect might be related to the timing of the proposed hypoxic event, in which thin meconium stained amniotic fluid would represent chronic, while thick MSAF would, rather represent acute hypoxemic stress. Thick meconium stained amniotic fluid has a higher risk of causing MAS, which could (partially) explain the differences in perinatal outcome. Erythropoetine (EPO) is a cytokine for erythropoiesis and is released in case of hypoxemia[20]. The peak of EPO is 12 hours after the onset of the hypoxic event, suggesting that it is a marker for chronic hypoxic stress[21]. In several studies an association between fetal erythropoietin (EPO) levels and MSAF was found[8,16,22]. EPO has not only been related to MSAF, but to longer duration of pregnancy as well[16]. However, when corrected for gestational age, EPO still remained significantly associated with MSAF. The lactate-creatinine ratio (L/C ratio) in first passed urine of newborns has been used to indicate intra-partum asphyxia. In a study form Ojha et al. higher L/C-ratios have been found in those newborn born through thin meconium, but not thick[6]. Thin meconium might therefore be related to chronic hypoxic stress. In rats, MSAF was associated with increased action of corticotrophin releasing factor (CRF)[23]. CRF is part of the stress-hormone family. In adults, CRF is known for its effect on colonic motility[24].

Increased colonic motility after CRF exposure, would suggest that meconium release is enhanced by acute hypoxic stress.

In conclusion, both acute and chronic hypoxia have been related to MSAF.

Primary MSAF versus new-onset MSAF

In several studies a distinction has been made between primary and secondary MSAF[25-27]. MSAF is considered primary when there is meconium staining at the time of membrane rupture. MSAF is considered new-onset or secondary when the liquor changes from clear to meconium-stained during labor. Hiersch et al. have again studied the difference between primary and secondary MSAF. They have confirmed the association between secondary, but not primary, MSAF and adverse neonatal outcome, suggesting that a change in colour of the liquor might reflect fetal distress whereas primary MSAF is a sign of fetal ripening[25].

2. Fetal ripening

Another explanation of MSAF is the physiologic ripening of the fetal gastro-intestinal tract. The most consistent association with meconium stained amniotic fluid is gestational age[3,11,15,16,28]. Meconium stained amniotic fluid is rare before 32 weeks of gestation and it mostly occurs in pregnancies 37 weeks and over[23], although it has been described from 16 weeks of gestation onwards [18]. It is known that MSAF is subject to ethnic differences[29,30]. The incidence is increased more than 80% in African-American and African-European women[30]. It has been shown in over 122.000 pregnancies that the mean gestational age is also shorter in African women, indicating a possibility for enhanced ripening of the fetus[29]. This enhanced ripening increases the risk of MSAF. In 1996 Ciftci et al. have already proposed the theory that fetal defecation might be a physiologic phenomenon[31]. They have performed several animal experiments in which they showed that non-stressed goats and rats do defecate in utero as well and also that hypoxic stress does not necessarily lead to more often meconium release.

3. Infection

Meconium stained amniotic fluid has been independently related to peripartum infection (RR 1.28) and thick meconium has a stronger association than thin meconium[32]. Wen et al. have also indicated in a case-control study (N=200) that MSAF is related to a higher incidence of intra-amniotic infection[33] which was supported in a small retrospective study from Chapman[34]. Meconium might inhibit normal bacteriostatic function of the amniotic fluid and result in intra-uterine infections[1]. In a large Cochrane review the effect of antibiotics on neonatal and maternal infection in MSAF was analyzed. A significant reduction in chorio-amnionitis was found, but there was no effect on neonatal sepsis, NICU admission or postpartum endometritis[1].

Table I - Reports of aetiology of Meconium Stained Amniotic Fluid

Author	Year of publication	Hypoxia	Infection	Maturation	Number of subjects (N) and type of article
Meis	1982	+/-	-	-	N=128 cases, N=134 controls. Case-control study.
Wen	1993	-	+	-	N=200. Retrospective case-control study.
Chapman	1995	-	+	-	N=200. Retrospective case-control study.
Richey	1995	+/-	-	-	N=56. Case-control study. No difference in cord pH were found, however elevated EPO levels
Maymon	1998	+	+	-	N=37085. Cross-sectional cohort study.
Piper	1998	-	+	-	N=936. Cohort study.
Sienko	1999	+	-	-	N=4. Histologic study.*
Ciftici	1999	+/-	-	-	N=16. Rat study.*
Jazayeri	2000	+/-	-	+	N=203 (N=70 with MSAF). Higher EPO levels but no differences in cord pH or APGAR.
Sheiner	2002	+/-	-	-	Prospective study. N=586. (N=106 with MSAF).
Ahanya	2005	+	+	+	Review.
Locatelli	2005	+	-	-	N=19090. Cohort study.
Ohja	2006	+/-	-	-	N=52 cases, N=42 controls. Case-control study.
Modarressnejad	2006	+	-	-	N=400. Prospective study.
Oyelese	2006	-	-	+	N=6403. Retrospective study.
Lakshmanan	2007	+	-	-	N=12 cases, N=12 controls. Rat study.*
Shaikh	2010	+	-	-	N=250 cases, N=250 controls. Cross sectional study.
Balchin	2011	+	-	++	N=499096. Retrospective study.
Lee	2011	+	-	+	N=4376. Retrospective cohort study.

Brailovschi	2012	+/-	-	-	N=204102. Case-control study to intrapartum death.
Kumari	2012	+	-	-	N=75. Observational study.
Yurdakul	2012	+	-	-	N=13 cases, N=24 controls. Histologic study.*
Gun Eriyilmaz	2013	+	-	-	N=40 cases, N=40 controls. Cross sectional cohort study.

* - low number of subjects due to study type; histologic or animal studies.

Summary and conclusion

A lot of research has been done into the (patho)physiology of meconium release. Some authors claim the association between fetal distress and meconium release and therefore suggest that it is a pathologic event, while others have found only an association between gestational age and MSAF and not with fetal distress, suggesting a more physiological role. Different theories have been proposed in the last years, including impaired swallowing of meconium after physiologic defecation in utero. Furthermore, meconium has been associated with higher levels of intra-amniotic infections. The meaning of MSAF still remains subject to discussion.

In conclusion, we suggest that meconium stained amniotic fluid should be regarded as a symptom rather than a syndrome, becoming more prevalent with increasing term and which might be associated with higher levels of infection or asphyxia. Irrespective of the possible cause, MSAF increases the risk of the meconium aspiration syndrome and hence perinatal death. In order to interpret MSAF properly we believe that other symptoms should also be taken into account, such as (non) re-assuring intra-partum cardiotocography or the presence of maternal fever.

Key points

There are three major causes for meconium passage in utero, hypoxia, maturation and infection.

- Hypoxic stress may lead to MSAF, due to enhanced meconium passage or decreased swallowing of the foetus.
- MSAF might reflect both acute and chronic hypoxia.
- Secondary MSAF, with a change in liquor colour during labor, is associated with poorer neonatal outcomes than primary MSAF.
- MSAF is associated with fetal maturation, where gestational age is the most important predictor of MSAF.
- MSAF is independently related to peripartum infections.

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Chapter 5

Maternal thyrothropine in euthyroid women is related to meconium stained amniotic fluid in women who deliver at or over 41 weeks of gestation

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Abstract

Background - Maternal thyroid dysfunction is of known influence on pregnancies in the preterm period. However little is known about its effect on term and post term pregnancies. Meconium stained amniotic fluid (MSAF) is known to occur preferentially in (post)term pregnancies.

Aims – To assess a possible independent relation between maternal thyroid function and MSAF.

Study design and subjects – 1051 women, in whom thyroid function was assessed at each trimester, were followed prospectively (delivery ≥37 weeks). We compared the difference in mean TSH and fT4 between women with (152) and without (889) MSAF using one way ANOVA. Thyroid function was assessed in subgroups regarding gestational age. Finally we performed multiple logistic regression analysis with MSAF as dependent variable and TSH as independent variable adjusting for various confounders.

Results – Maternal thyroid function was not associated with the incidence of MSAF when analysing all deliveries >37 weeks. However, in the "at-risk" group for MSAF (>41 weeks), multiple logistic regression showed an independent relation between MSAF and TSH (O.R. 1,61, 95%CI: 1.10-2.43).

Conclusions – The present study shows that in women delivering ≥41 weeks of gestation, higher TSH is independently related to MSAF.

Introduction

Overt thyroid disease has since long been associated with poor fetal outcome, as miscarriage and preterm birth[1,2]. But also sub-clinical thyroid dysfunction which is present in approximately 5% of pregnant women is related to the similar complications[1]. Although it is known that maternal thyroid function is crucial in fetal organ maturation[3], little is known about the relation between thyroid function and fetal outcome in term and post-term pregnancies. To the best of our knowledge, a study in which maternal thyroid function (thyrothropine-stimulating hormone (TSH), thyroxine (fT4) and thyroid peroxidase antibody (TPO-Ab)) is followed prospectively during gestation and related to the occurrence of MSAF has not been published yet. Therefore, we investigated the occurrence of MSAF in a large cohort without a history of thyroid dysfunction, who were followed prospectively from 12 weeks of gestation and in whom thyroid function was assessed at each trimester and who delivered at term. The study outcome was to investigate a possible independent relation between maternal thyroid function and the incidence of MSAF in those who delivered at term.

Materials and methods

Subjects

Women

During a period of two years, 1702 women who booked for antenatal visits at 12 weeks of gestation were followed in five community midwife practices in the vicinity of the city of Eindhoven (the Netherlands), known to be an iodine sufficient area[4]. In order to avoid language problems (several questionnaires were used) and possible confounding of ethnic origin, only Dutch Caucasian women (n = 1507) were invited to participate. Seventy-nine percent (n = 1197) of the women signed a consent form; the non-responders did not differ from the responders with regard to age, parity, or educational level (data not shown). Women on thyroid medication (n = 21), diagnosed as clinically hypothyroid (n = 1) or hyperthyroid (n = 6) at screening, pregnant as a result of hormonal stimulation (n = 8), with multiple pregnancy (n = 8), and with Type 1 diabetes (n = 5) were excluded. This left 1148 women eligible for participation who were followed up at 24 and 36 weeks of gestation. Of

these women, data were missing for 37 women. Of the remaining 1111 women there were 60 women who delivered preterm leaving 1051 women who delivered at term. Therefore, data-analysis refers to these 1051 women of whom the characteristics are shown in Table I. This study was approved by the Medical Ethical Committee of Máxima Medical Centre in Eindhoven/Veldhoven.

Assessments

Thyrothropine stimulating hormone (TSH) was measured in serum at 12, 24 and 36 weeks 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 non-pregnant reference ranges of TSH is 0.45 - 4.5 mIU/L.

Free thyroxine (fT4) concentration was measured in serum at 12, 24 and 36 weeks 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. The non-pregnant reference range of fT4 is 10.3 - 25.7 pmol/L.

TPO-Antibodies (TPO-Ab) were determined in serum at 12, 24 and 36 weeks by means of the IMMULITE Anti-TPO-Ab kit. The inter-assay coefficients of variation for this analysis were 9% and 9.5% for concentrations of 40 IU/ml and 526 kU/ml, respectively. The anti-TPO assay is standardized in terms of the International Reference Preparation for anti-TPO MRC 66/387. Women were defined as TPO-Ab-positive when the titer was > 35 kU/ml at 12 weeks of gestation.

Table I - Characteristics of a sample of 1051 women who delivered at term (≥37 weeks gestation), 889 women without MSAF and 152 women in whom MSAF was diagnosed.

	Total Group (N=1051)		**No MSAF** (N=889)		**MSAF** (N=152)		P-value
	Mean (SD)	N (%)	Mean (SD)	N (%)	Mean (SD)	N(%)	T Chi2
Age ≥35 yrs	**30.5 (3.5)**		**30.6 (3.6)**		**30.0 (3.7)**		**0.04**
Low education		82 (8)		68 (8)		14 (9)	
Smoking (yes/no)		127 (12)		105 (12)		22 (14)	
Alcohol use (yes/no)		137 (13)		118 (13)		19 (13)	
BMI (kg/m2)	25.5 (4.6)		25.4 (4.6)		25.8 (4.4)		
Primiparity		**482 (46)**		**399 (44)**		**83 (45)**	**0.03**
Family history thyroid dysfunction		184 (17)		159 (18)		25 (16)	
Miscarriage earlier in life		196 (17)		169 (19)		27 (19)	
Fetal distress		115 (11)		95 (11)		20 (13)	
Mean hours first stage of labour	**7.3 (6.2)**		**7.1 (6.1)**		**8.7 (6.9)**		**0.003**
Mode of delivery:							
Spontaneous		686 (65)		587 (65)		99 (65)	
After induction		150(14)		126 (14)		24 (16)	
Instrumental		97 (10)		82 (9)		15 (10)	
Caesarean section		118 (11)		104 (12)		14 (9)	
Thyroid function:							
12 weeks gestation:							
TSH mIU/L	1.23 (0.78)		1.22 (0.78)		1.29 (0.82)		
FT4 pmol/L	16.0 (2.3)		16.1 (2.1)		16.1 (2.4)		
TPO-Ab >35IU/mL		86 (8.2)		73 (8.0)		13 (9)	
24 weeks gestation:							
TSH mIU/L	1.42 (0.67)		1.35 (0.65)		1.41 (0.76)		
FT4 pmol/L	13.8 (2.0)		13.8 (1.9)		13.7 (1.8)		

TPO-Ab >35IU/mL		74 (7)		65 (7)	9 (6)
36 weeks gestation:					
TSH mIU/L	1.51 (0.74)		1.50 (0.73)	1.57 (0.75)	
FT4 pmol/L	13.3 (2.0)		13.3 (1.9)	13.2 (1.8)	
TPO-Ab >35IU/mL		67 (6)		59 (7)	8 (5)
Neonatal outcome:					
Term at delivery (wks)	**39.9 (1.2)**		**39.7 (1.2)**	**40.4 (1.0)**	**<0.001**
Birth weight (gr)	**3526 (483)**		**3511 (494)**	**3596 (425)**	**0.03**
Placental weight (gr)	**623 (127)**		**618 (126)**	**648 (130)**	**0.01**
Male		558 (53)		478 (53)	79 (52)

Chi^2: df = 1
Welch T-test Bold data indicate p<0.05.

Statistical analysis

Statistical analysis was performed using the Statistical Package of Social Science (SPSS, 19.0). TSH and fT4 were not normally distributed. However, as the cohort size of all subgroups was substantial (n > 30), differences in means (SD) of thyroid hormones concentration levels were compared using Welch T-test (two-tailed)[5]. Differences of prevalence rates were calculated by chi-square. Also, we compared the difference in mean TSH and fT4 between women with and without MSAF using one way ANOVA. Thereafter we defined a group of women with high TSH at each trimester using the 97.5^{th} percentile as cut-off and compared the prevalence of MSAF in these different sub-groups. Finally we performed multiple logistic regression analysis with MSAF as dependent variable and TSH as independent variable, adjusting for several confounders such as elevated titers of TPO-Ab at 12 weeks of gestation, parity, duration of first stage of labor, smoking status and alcohol intake during gestation and pre-pregnancy BMI.

Results

As can be seen in Table I, there were 152 (14.5%) women with MSAF who delivered $\geq$ 37 weeks. Women with MSAF were significantly younger, were significantly more often primiparous, and had neonates with a significantly higher birth and placental weight (P <

0.001, Student-T-test). The mean TSH and fT4 were comparable in the two groups as was the case for the number of women with elevated TPO-Ab titers. The number of fetuses with fetal distress during labor was similar in both groups (determined by CTG and APGAR-scores). There were no differences in mode of delivery (spontaneous, instrumental) between the two groups (Table I). Life style habits were also similar in both groups. MSAF occurred significantly more often at higher gestational age. There were no significant differences of thyroid function throughout pregnancy, in relation to gestational age at delivery (data not shown). In figure 1 the incidence of MSAF is shown according to gestational age at delivery.

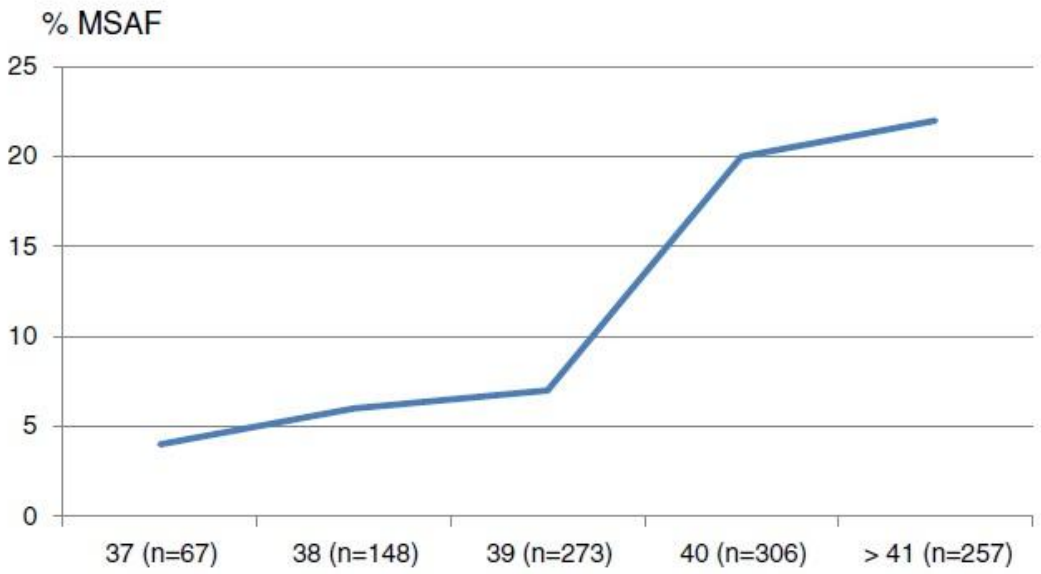


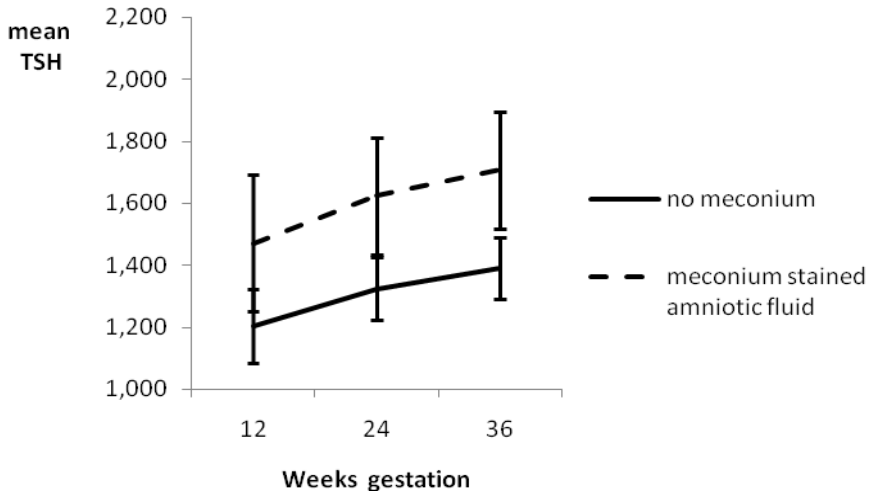
Fig. 1. Percentage of MSAF according to gestational age at delivery in weeks (+0–6 days).

It can be seen that the prevalence of MSAF increased from 3 /67 (4.4%) in women who delivered at 37 weeks of gestation to 57 / 257 (22%) in those who delivered at ≥ 41 weeks of gestation. In women who delivered before 41 weeks of gestation, no differences were found in TSH and fT4 between clear and meconium deliveries (data not shown).

However, as shown in figure 2, in women who delivered ≥ 41 weeks of gestation (n=257), the mean TSH was significantly higher throughout gestation in women with a history of MSAF (n=57), compared to those women who delivered at the same period of gestation

without MSAF (n=200): [ANOVA, F(1256) =8.0, p=0.005]. For fT4 no differences were found throughout gestation [ANOVA, F(1.256)=0.98, p=0.34].

Figure 2 - Mean TSH scores in a group of 257 women who deliver > 41 weeks gestation, comparing those with (n = 57) and without (n = 200) a history of MSAF. (ANOVA, F = 8.0, p =0.005).



We finally performed several multiple logistic regression analyses. First we performed an analysis in the whole group with MSAF as dependent variable and TSH at the last trimester as independent variable, adjusted for: gestational age at delivery, maternal age, smoking, BMI, alcohol intake, education level, parity, sex of the baby and the occurrence of fetal distress during labor. The only factor that was statistically significant related to MSAF was gestational age at delivery: O.R.: 1.63 (95% CI: 1.39 – 1.96, p < 0.001). With every week of increasing gestational age (from 37 weeks on) the likelihood of MSAF increased with 63%. TSH at the last trimester was not related to MSAF. When we repeated the logistic regression analysis using the same model in all different groups according to gestational age at delivery as shown in figure 1, with MSAF as dependent variable and TSH as independent variable, adjusting for the same variables no relations were found between any of the factors in the model and MSAF in the group of women who delivered at 37, 38, 39 and 40 weeks of gestation (data not shown). We then performed a logistic regression analysis in the group of women who delivered $\geq$ 41 weeks of gestation (n = 257) with MSAF as dependent variable

and TSH at 36 weeks as independent variable, adjusting for the same variables. As shown in Table 2, every mIU/l higher maternal TSH at the last trimester was associated with a 61% higher likelihood of MSAF at delivery at or after 41 weeks of gestation. Also primparous women had an O.R. of 2 to have MSAF at this term of delivery. Fetal distress during labor and the duration of first stage of labor were not associated with MSAF.

Table II Multiple logistic regression analysis in 257 women who delivered ≥ 41 weeks gestation with MSAF as dependent variable (n = 57) and high maternal TSH at 36 week gestation as independent variable, adjusted for possible confounders.

	O.R.	95% CI	P
High maternal age	0.98	0.89 – 1.09	0.71
Low education	1.68	0.43 – 6.56	0.45
Any alcohol intake	0.69	0.24 – 1.96	0.46
Duration of first stage of labour (hours)	0.98	0.92 – 1.03	0.43
Primiparity	**2.01**	**1.17 – 4.89**	**0.025**
Fetal distress during labour	1.12	0.35 – 2.38	0.86
Female neonate	0.95	0.75 – 1.49	0.31
Smoking	0.73	0.62 – 1.78	0.87
BMI	1.01	0.94 – 1.08	0.81
TSH mIU/l at last trimester	**1.61**	**1.10 – 2.43**	**0.013**

MSAF: meconium stained amniotic fluid.

Discussion

In the current study, the incidence of MSAF was 2.2% in those who delivered at 37 weeks of gestation compared to 22% in those who delivered at ≥41 weeks of gestation which is in line with the literature[6]. Thyroid function (TSH/fT4/TPO-Ab) was not different in women delivering at term or post-term and also, no relation was found between maternal thyroid function and MSAF, when looking at all term and post-term pregnancies combined. However, the sample size of the current study enabled to perform analyses in different subgroups according to gestational age at delivery. In women who delivered ≥41 weeks of gestation, TSH at the last trimester was independently related to the occurrence of MSAF (O.R.: 1.61, 95% CI: 1.10 – 2.43). Moreover, in this “at-risk” group (>41 weeks) for MSAF, the MSAF women had significantly higher mean TSH at all trimesters compared to those without MSAF. The mechanism behind this association is still unclear. However, it is known that maternal thyroid function is important for optimal placental function[7]. As placental function decreases with increasing gestational age, suboptimal maternal thyroid function (as

reflected by high normal TSH throughout pregnancy) might have an additional negative effect on placental function[8,9]. As such, women at or over 41 weeks of gestation with higher TSH are at increased risk of MSAF.

Also, elevated maternal TSH might directly impact uterine relaxation, thereby negatively affecting placental circulation and predisposing to fetal distress. Empirical evidence of such a direct effect is seen in vascular smooth muscle[10,11]. High normal TSH leads to increased arterial stiffness and impaired diastolic function which can be neutralized by thyroxine replacement[12]. The same mechanism could be true in the smooth muscle cells of the uterus. The fact that no association was found between MSAF and fT4, might be explained by the questionable reliability of fT4 measurements in late pregnancy[13]. Recently, the group of Cunningham showed an association between high TSH (sub-clinical hypothyroidism) and the occurrence of diabetes gravidarum, as well as hypertension during gestation, which also underlines the relevance of possible negative impact of high TSH during gestation on obstetric outcome[14,15].

The current study has several strengths. Firstly, because of the power of our large cohort we were able to look at different subgroups of women, according to gestational age. Secondly, TSH was assessed at all trimesters showing a persistent higher TSH level in those women delivering $\geq$41 weeks with MSAF. Also, the upper limit of TSH during gestation was 6.2 mIU/l (table I), suggesting that we did indeed study a relatively healthy euthyroid sample.

A limitation of the study is that fetal distress at birth – which, according to the literature, might be an important cause of MSAF - was assessed according to APGAR scores and not to other denominators (e.g. umbilical artery pH-assessment).

Future research should confirm a possible relation between maternal thyroid function and MSAF, especially in those delivering at advancing gestational age with more objectively assessing of fetal distress.

In conclusion, our current study shows that in women delivering ≥41 weeks of gestation, higher TSH (indicating less maternal thyroid functioning) is independently related to MSAF.

Key points

- Meconium stained amniotic fluid is known to occur mostly in post-date pregnancies (≥41 weeks).
- In this study we found primiparity and high maternal TSH in the last trimester of pregnancy to be independent risk factors for the presence of MSAF in pregnancies ≥41 weeks.
- MSAF was not related to lower APGAR scores nor to the mode of delivery.

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Chapter 6

Maternal thyrothropine is independently related to Small for Gestational Age neonates at term.

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Abstract

Objective - Small for gestational age (SGA) newborns constitute still a major cause of perinatal morbidity and mortality. Overt thyroid disease is a known cause of preterm birth and low birth weight but in its untreated condition it is rare today. In this study we investigated the possible relation between maternal thyroid function assessed in euthyroid women at each trimester and the incidence of term born SGA neonates.

Design – A prospective cohort study was performed.

Patients - Thyroid function was assessed at 12, 24 and 36 weeks gestation in 1051 healthy Caucasian women who delivered at $\geq$ 37 weeks gestation.

Measurements - One-way ANOVA was used to compare mean TSH and fT4 levels between women with SGA neonates and controls. Multiple logistic regression analysis was performed to adjust for known risk factors of SGA.

Results – Seventy (6.7%) SGA neonates were identified and they were significantly more often born to women with a TSH $\geq 97.5^{th}$ at first and third trimester. Multiple logistic regression analysis showed that smoking (O.R: 4.4, 95% CI: 2.49 – 7.64), pre-eclampsia (O.R.: 2.8, 95% CI: 1.19 -6.78) and TSH $\geq 97.5^{th}$ percentile (OR 3.3, 95% CI 1.39 – 7.53) were significantly related to SGA. Maternal fT4 levels and TPO-Ab status were not associated with SGA offspring.

Conclusions – Our data show that TSH levels in the upper range of the reference interval at different trimesters (3.0-3.29 mIU/L) are independently related to an increased risk of delivering SGA neonates at term.

Introduction

Intra-uterine growth restriction is an important cause of perinatal morbidity and mortality[1,2]. Small for gestational age (SGA) neonates are predisposed to adult metabolic syndrome due to altered metabolic homeostasis[3,4]. Several determinants of SGA have been described such as: maternal age
>35 years, smoking, pre-eclampsia, low pre-pregnancy BMI and primiparity[2]. Overt thyroid dysfunction has long been recognized as an important risk factor of preterm birth and miscarriage[5-8]. Suboptimal maternal thyroid function (sub-clinical hypothyroidism and elevated titers of thyroid peroxidase antibodies [TPO-Ab]) has been related to poor perinatal outcome as well[9,10]. Research into a possible association between maternal TSH and fT4 levels, and SGA is scarce and has resulted in inconclusive data[11,12]. A recent paper of a large cohort from Rotterdam found a relation between high maternal fT4 during early gestation and SGA, with no effect for maternal TSH or TPO-Ab status[13].

The present study investigates the occurrence of SGA in a cohort of more than 1000 women without a history of thyroid dysfunction, who were followed prospectively throughout gestation with thyroid function assessment at each trimester. Primary outcome was to investigate the possible relation between the incidence of SGA in those who delivered at term and maternal thyroid function, at a cross-sectional level (each trimester). Secondary outcome was to find out whether this possible relation persisted after adjustment for other factors which are known to be related to SGA.

Materials and methods

Subjects

Women

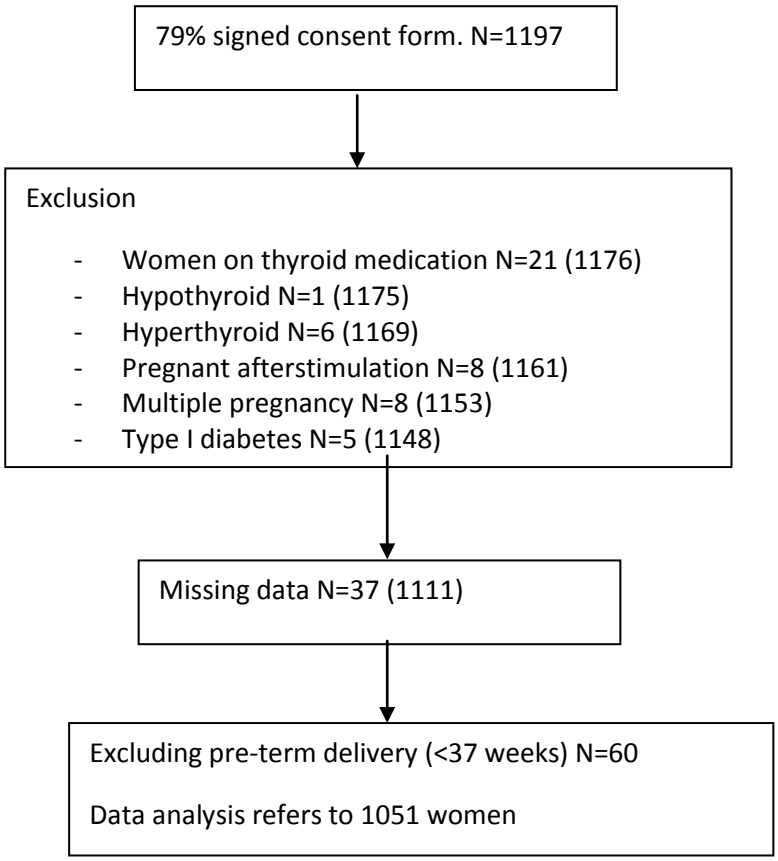
During a period of two years, 1702 women who booked for antenatal visits at 12 weeks gestation were followed in five community midwife practices in the vicinity of Eindhoven (the Netherlands), known to be an iodine sufficient area[14]. In order to avoid language problems (several questionnaires were used) and possible confounding of ethnic origin, only Dutch Caucasian women (n = 1507) were eligible. Seventy-nine percent (n = 1197) of the women signed a consent form; the non-responders did not differ from the responders with

regard to age, parity, or educational level (data not shown). Women on thyroid medication (n = 21), diagnosed as clinically hypothyroid (n = 1) or hyperthyroid (n = 6) at screening, pregnant as a result of hormonal stimulation (n = 8), with multiple pregnancy (n = 8), and with Type 1 diabetes (n = 5) were excluded. Data were missing in 37 women. Of the remaining 1111 women, there were 60 women who delivered before 37 weeks gestation (in whom 11 had SGA neonates). Therefore, data analysis refers to 1051 women. This sample included 14 (1.3%) women with low pre-pregnancy BMI according to WHO classification (<18.4). The selection process is shown in figure 1 and the characteristics are shown in table 1. This study was approved by the Medical Ethical Committee of Máxima Medical Centre in Eindhoven/Veldhoven.

Neonates

The Netherlands Perinatal Registry (PRN) was used to define SGA neonates. In this registration system, >95% of all hospital and home births in the Netherlands are registered. The definition of SGA was based on population based birth weight percentiles using the lowest 10^{th} percentile cut-off[2,15]. Although the cut-off for the definition of SGA and intra-uterine growth restriction is arbitrary, in most large studies the lowest 10^{th} percentile is used[16,17]. To define SGA appropriately birth weight is corrected for: gestational age, sex of the baby and parity.

Figure 1, selection of participants.



Assessments

TSH was measured in serum at 12, 24 and 36 weeks using a solid-phase, two site chemiluminescent enzyme immunometric assay (IMMULITE Third generation TSH, Diagnostic Products Corporation, Los Angeles, CA, 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 non-pregnant reference range of TSH is 0.45 - 4.5 mIU/L

Free thyroxin (fT4) concentration was measured in serum at 12, 24 and 36 weeks 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. The non-pregnant reference range of fT4 is 10.3 - 25.7 pmol/L.

TPO-Ab were determined in serum at 12, 24 and 36 weeks by means of the IMMULITE Anti-TPO-Ab kit. The inter-assay coefficients of variation for this analysis were 9% and 9.5% for concentrations of 40 IU/ml and 526 IU/ml, respectively. The anti-TPO assay is standardized in terms of the International Reference Preparation for anti-TPO MRC 66/387. A woman with TPO-Ab titer > 35 kU/ml at 12 weeks gestation was defined as moderately immunologically compromised, while a woman with TPO-Ab titer $\geq$ 100 kU/ml was defined as distinctly compromised, even if the titer fell during pregnancy. Women were defined as TPO-Ab-negative when the titer was below 35 kU/ml at 12 weeks gestation. All measurements were performed in one laboratory.

Statistical analysis

Statistical analysis was performed using the Statistical Package of Social Science (IBM SPSS statistics for Windows. Version 19.0. Armonk, NY: IBM Corp.). TSH and fT4 concentrations were not normally distributed. However, because the cohort size of all subgroups was substantial (n > 30) we were able to calculate differences in means (SD) of thyroid hormones concentration levels using Welch T-test (two-tailed)[18]. Differences of prevalence rates were calculated by chi-square. We compared the changes of fT4 and TSH means in women with and without SGA neonates by means of one-way ANOVA. Thereafter we defined a group of women with high TSH at each trimester using 97.5th percentile as cut-off and compared the prevalence of SGA in these different sub-groups by chi-square with Bonferroni correction for multiple testing. Finally we performed multiple logistic regression analysis with SGA as dependent variable and high TSH as independent variable, adjusting for multiple possible confounders.

Results

In our study, 70 (6.7%) SGA neonates (<10th percentile) were detected, of whom the characteristics are shown in Table I. There were 42 (4%) and 23 (2.2%) SGA neonates using the 5th and 2.3rd percentiles, respectively. None of the women who were included after 12 weeks gestation developed overt thyroid dysfunction throughout pregnancy.

Table I: Characteristics of a sample of 1051 women who delivered at term (≥37 weeks gestation), 981 women with neonates with normal or high birth weight (AGA/LGA) and 70 neonates who were Small for Gestational Age (SGA).

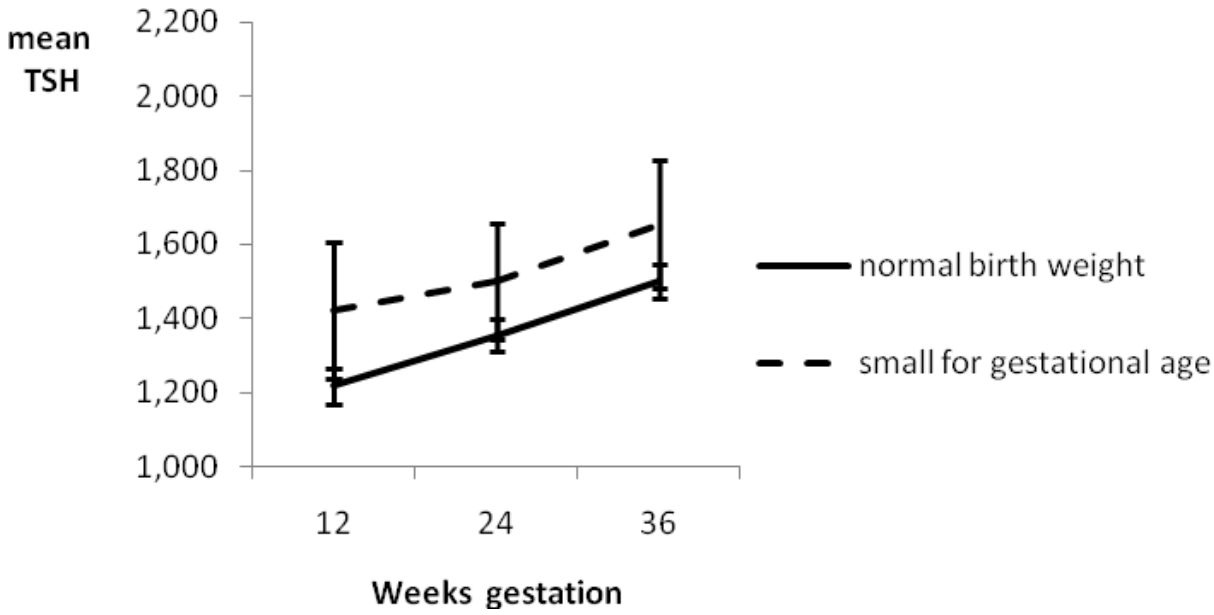
	Total Group (N=1051)		AGA/LGA (n=981)		SGA (n=70)		P-value
	Mean (SD)	n (%)	mean (SD)	n (%)	mean (SD)	n(%)	T Chi2
Age	30.5 (3.5)		30.5 (3.6)		30.6 (3.6)		
Smoking (yes/no)		**127(12)**		**105(11)**		**22(31)**	**<0.01**
Alcohol use (yes/no)		137(13)		127(13)		10(14)	
BMI (kg/m2)	25.5 (4.6)		25.5 (4.6)		24.7 (4.6)		0.14
Primiparity		482(46)		450(47)		32(46)	
Multiparity		569(54)		531(53)		38(54)	
Miscarriage earlier in life		196(17)		180(19)		16(22)	
Pre-eclampsia		59 (5.8)		52 (5.3)		7 (10)	0.10
Thyroid dysfunction in family		184(17)		170(18)		14(20)	
12 weeks gestation:							
TSH mIU/L	1.23 (0.78)		1.21 (0.76)		1.42(0.99)		0.12
FT4 pmol/L	16.0 (2.3)		16.1 (2.3)		15.9 (2.1)		0.63
TPO-Ab >35IU/mL		86 (8.2)		66 (8.0)		5 (7.1)	
24 weeks gestation:							
TSH mIU/L	1.42 (0.67)		1.41 (0.69)		1.52(0.71)		0.13
FT4 pmol/L	13.8 (2.0)		13.8 (2.3)		14.1 (1.8)		0.53
TPO-Ab >35IU/mL		74 (7)		69(7)		4(5.7)	
36 weeks gestation:							
TSH mIU/L	1.51 (0.74)		1.50 (0.72)		1.65(0.98)		0.18
FT4 pmol/L	13.3 (2.0)		13.3 (2.1)		13.4 (2.2)		0.75
TPO-Ab >35IU/mL		67 (6.2)		63(6.4)		4(5.7)	
Neonatal outcome:							
Term at delivery (wks)	39.9 (1.2)		39.9 (1.3)		39.8 (1.1)		
Birth weight (gr)	**3526 (483)**		**3582 (447)**		**2753(259)**		**<0.001**
Placental weight (gr)	**623 (127)**		**632 (124)**		**482 (78)**		**<0.001**
Male		558(53)		515(53)		43(61)	0.15
Female		493(47)		466(47)		27(39)	

The range for TSH at 12 weeks was between 0.04 and 5.2 mIU/L, at 24 weeks between 0.3 and 5.7mIU/L and at 36 weeks between 0.4 and 6.2mIU/L. For fT4 the range at 12 weeks gestation was between 9.1 and 26 pmol/L, at 24 weeks between 8.4 and 24 pmol/L and at 36 weeks gestation between 7.2 and 23pmol/L. This indicates that the studies population maintained normal thyroid function throughout the whole gestation.

Women with appropriate for gestational age (AGA) or large for gestational age (LGA) neonates smoked significantly less often ($p<0.001$). Also, the birth weight and placental weight were significantly higher in the AGA/LGA group ($P<0.001$, Welch-T-test). Gender was not significantly different in the SGA group compared with the AGA/LGA group. Although at a cross-sectional level at each trimester, the mean TSH was higher in the SGA group, this

difference was not significant. Mean fT4 was rather similar in both groups and so was elevated TPO-Ab. In figure 2, the relation between SGA neonates and changes of mean TSH (figure 2) throughout gestation is shown.

Figure 2 - Mean maternal TSH levels throughout pregnancy in relation to small for gestational age offspring.



As shown, in both groups, mean TSH did increase towards end gestation but during all trimesters, the mean TSH in the SGA group remained significantly higher compared to the women with AGA/LGA neonates ($p<0.001$). For mean fT4, no differences were found between the two groups related to SGA (data not shown).

We subsequently defined high TSH at each trimester using the group as its own reference using an upper reference limit of $\geq$ 97.5th percentile. These cut-offs were 3.28 mIU/L, 3.0 mIU/L and 3.29 mIU/L, at 12, 24 and 36 weeks, respectively.

We defined a group of women who had a TSH $\geq$ 97.5th percentile at least at one trimester (n=53). Within this group, there were significantly more SGA neonates born; 17% in the high TSH group (9) and 6% (61) in the remaining 998 women [RR 3.8 (95% CI 1.8-8.1)]. Of the 53 women with a TSH $\geq$ 97.5th percentile at least at one trimester, 20 (37.7%) had elevated TPO-

Ab titers at 12 weeks gestation, compared with 66 (6.6%) in the group of women below this cut-off (p<0.001). We subsequently used other cut-offs to define SGA. When the lowest 5th percentile was used, high TSH at the third trimester (>97.5th percentile) was significantly associated with SGA, OR: 4.5 (CI: 1.5-13.7, p=0.008) When we used the lowest 2.3rd SGA cut-off, high TSH at the last trimester was associated with SGA but only at a 90% significance level: OR 3.8, 95% CI: 0.85-17, p=0.08).

We finally performed multiple logistic regression analysis with SGA (10th percentile) as dependent variable and high TSH ($\geq$97.5th percentile) as independent variable, adjusting for possible confounders (Table 2).

Table 2 Multiple logistic regression analysis with SGA as dependent variable and high maternal TSH during gestation as independent variable, adjusted for possible confounders in 1052 women who delivered at term (>= 37 weeks gestation).

	Odds Ratio	95% CI	P-value
Maternal age > 35 years	1.03	0.96 – 1.09	0.42
Low education	1.29	0.84 - 3.02	0.23
Alcohol intake (yes/no)	1.07	0.52 – 2.19	0.84
Work outside home (yes/no)	0.88	0.44 – 1.55	0.56
Primiparity	1.13	0.65 – 1.96	0.61
Term of gestation at delivery	1.01	0.83 – 1.23	0.81
Female neonate	0.77	0.46 – 1.49	0.31
Smoking	**4.38**	**2.49 – 7.64**	**<0.001**
BMI	0.95	0.89 – 1.008	0.08
High TSH*	**3.31**	**1.39 – 7.53**	**0.007**
Thyroid dysfunction in family	0.57	0.26 – 1.23	0.15
Pre-eclampsia	**2.84**	**1.19 – 6.78**	**0.018**

SGA: small for gestational age: birth weight in the lowest 10th percentile corrected for gender, parity and term at delivery

*TSH $\geq$97.5th percentile at any trimester

As indicated, high TSH ($\geq$ 97.5th percentile at one or more trimesters) (OR 3.31, 95% CI: 1.39-7.53), the occurrence of pre-eclampsia (OR 2.8, 95% CI: 1.19-6.78) and smoking (OR 4.4, 95% CI: 2.49-7.64) were independently related to SGA.

Discussion

The current study, with a prospective design in which thyroid function was evaluated at each trimester in a cohort of more than 1000 euthyroid pregnant women who delivered at term, showed that TSH $\geq$97.5th percentile at any trimester was independently related to SGA (O.R.: 3.3, 95% CI: 1.39 – 7.53), adjusted for confounders of SGA such as smoking and the occurrence of pre-eclampsia.

The prospective design of the study enabled to show that women with SGA neonates had an increase of TSH throughout gestation at a level which was consistently higher and significantly different from those with mothers of appropriate or large for gestational age (AGA/LGA) neonates. In detecting an upper limit of TSH that was associated with an increased risk of SGA, the 97.5th percentile proved to be associated with an increased risk of SGA. This might suggest that the optimal upper limit of TSH, regarding SGA offspring, during gestation ranges between 3.0 - 3.29 mIU/L, depending on the trimester. Low levels of TSH and fT4 levels were not related to SGA.

In our study population we found 6.7% SGA, which is slightly lower than expected for the <10th percentile. This could be explained by the fact that we only included healthy women and women who delivered at term. We found no differences in the SGA and AGA/LGA groups in terms of alcohol use, BMI, family history of thyroid dysfunction or term of delivery (table I). The only statistically significant difference that we found in the patient characteristics was smoking status and the occurrence of pre-eclampsia, which are known risk factors for SGA[2,19,20]. When comparing our cohort to the large recent study from Rotterdam, we see comparable figures regarding mean TSH and fT4, suggesting that we included a representative population[13]. We did find a higher incidence of TPO-Ab (8.2% in the first trimester compared with 5.6% in the study from Rotterdam), but this could be explained by the large number of African-European women in their sample (up to 40%), in whom TPO-Ab occur less frequent[21].

In previous studies the relationship between overt thyroid disease and SGA has been well established[5-8]. Studies about a possible relation between SGA and fT4 and TSH ranges in euthyroid women are scarce and have shown conflicting results[9,11,12,22]. An explanation for these inconclusive findings is first, the different time of assessment of maternal thyroid function, which is important when relating it to SGA outcome. Moreover, different definitions for SGA (birth weight percentiles should be corrected for parity, sex and term of gestation) and different cut-offs have been used (<10th percentile and <2.3th percentile). Finally, a possible relation between maternal thyroid function and SGA should be adjusted for other important confounders, such as pre-eclampsia or smoking.

Two studies have found no differences in maternal thyroid function in SGA neonates[11,12]. The sample size was, however, small in one study (N=89)[11] and in the other study thyroid function was only assessed between 11 and 13 weeks of gestation[12]. By contrast, however, the study from Shields et al. had found an association between high maternal fT4 levels at 28 weeks gestation and lower birth weight of the offspring. A 10% increase in fT4 resulted in 59 g decrease in absolute birth weight (thus not necessarily SGA). A very recent, large cohort study from Rotterdam has endorsed the finding that high free T4 levels, in euthyroid women, but not TSH levels, are related to SGA[13]. However, in this study thyroid function was assessed only once at around thirteen weeks of gestation, so no prospective changes in thyroid function could be observed. Furthermore, in contrast to TSH assessment, there have been concerns about the reliability of the measurement methods used of free T4 levels in pregnancy[23]. Recently, the International Federation of Clinical Chemistry Working Group has set-up a procedure to standardize fT4 assessments[24]. This recently developed reference measurement system is a key advance towards improved standardization and clinical validity of free thyroid hormone measurements and should preferentially be implemented in future research[25]. The study from Rotterdam consisted of only 62,2% Dutch or other Western immigrants, which is substantially different from the general Dutch population[26] and the current study in which only Caucasian women were included.

Casey et al.[9] showed in a retrospective study of over 15.000 pregnancies that there was a significant relation between higher TSH levels and poor obstetric outcome, which was not the case for low TSH or fT4 in upper or lower reference ranges. In a more recent study, the same group showed a relation between high TSH and the development of severe pre-

eclampsia[27]. Pre-eclampsia by itself is an independent risk factor for SGA[2]. In the current study this is shown as well, but even after adjustment for pre-eclampsia, the independent relation between high TSH and SGA persisted. Maternal thyroid function is important for fetal growth, due to the need of trans-placental passage of T4[25]. Thyroid hormones enhance fetal growth by anabolic action on fetal metabolism and their influence on different growth factors (i.e. insulin-like growth factors)[29]. This might explain why in the current study, women with TSH in the upper reference ranges (suboptimal maternal thyroid function) were at risk to deliver term SGA neonates. Another explanation could be the role of thyroid hormones on placentation. Karagiannis et al. studied the role of thyroid hormones in placentation and found no association[12]. However, there is some evidence that high fT3 and fT4 levels do have a role in vascularization, proliferation and differentiation of the placenta[30,31]. A recent meta-analysis on levothyroxine treatment in women with subclinical hypothyroidism undergoing assisted reproductive techniques, has indicated that T4-replacement therapy is beneficial on pregnancy outcomes, possibly indicating a role for thyroid hormones on placentation as well[32].

The current study has several strengths. First, maternal thyroid function was assessed at each trimester enabling to look at the dynamic pattern of thyroid function changes during gestation in relation to SGA. Secondly, trimester specific upper limits of TSH were defined using generally accepted cut-offs of 97.5th percentiles. Thirdly, the upper limit of TSH during gestation was 6.2 mIU/L (table I), suggesting that the cut-offs of high TSH (> 97.5th percentiles) refer to women without severely high TSH. This means that the relation between higher TSH and SGA, is analyzed in a healthy euthyroid sample. Fourth, the definition of SGA was corrected for parity, sex and gestational age. In international literature different definitions of SGA are used, including ≤-2SD for gestational age (<2.3rd percentile)[32], <3rd percentile and <5th percentile[33], but most recent studies have used the <10th percentile definition as described previously. Furthermore, a recent survey in Ireland has identified that the opinion of most clinicians is that the lowest 10th percentile should be used to define intrauterine growth restriction.[17] The best definition however, is based on customized percentiles and individual growth potential, to rule out the effects of, for example, ethnicity[15]. As only Dutch Caucasians were included in our study population, population based percentiles from the Netherlands perinatal registry are appropriate for the definition

of SGA in our cohort. Finally, factors that are known to be related to SGA such as smoking and pre-eclampsia, were also independently related to SGA in the current study, suggesting that the women in this cohort refer to a representative sample.

Several limitations of the study need to be mentioned. First we did not consider iodine status. A study from Alvarez et all. showed that low iodine levels in maternal urine are related to a higher incidence of SGA[34]. However, the iodine intake in our region has recently been shown to be generally sufficient[14]. Moreover, results of congenital heel screening in 886 neonates born in the sample showed 13 (1.5%) newborns with a TSH >5 mIU/L, a figure which is below 3%, a generally accepted cut-off showing sufficient iodine intake at a population level[35,36]. Furthermore, although the number of women who were prospectively followed was relatively large, the absolute number of SGA was only 70. Finally, our population was a selected cohort of women without medical disease, such as hypertension or diabetes and all from the same ethnic origin. The results found should therefore be validated in cohort studies with women from different ethnic backgrounds. Also, in future research one should be aware to obtain appropriate trimester specific reference levels of the TSH cut-offs, as those can differ for different methodology used at different centers and in women with different iodine intake.

In conclusion, the current study supports the evidence that TSH levels in euthyroid women at different trimesters in the upper range of the reference interval (3.0 to 3.29 mIU/L) are independently related to an increased risk of delivering SGA neonates at term.

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Chapter 7

General discussion and future perspectives

In this thesis the evaluation of obstetric interventions over more than one decade and the association between suboptimal maternal thyroid function and several obstetric outcomes have been discussed.

Obstetric interventions

In **chapter 2** we have analyzed the obstetric interventions and outcomes in a ten-year period in the Netherlands. The answers to research questions 1 and 2 – *"Did the Caesarean section rates and induction rates increase over the past decade in the Netherlands?"* and *"did the increase in Caesarean sections improve perinatal and maternal outcomes?"* – are found in this chapter. We have used the Ten-Group Classification System, which is a generally accepted classification system to compare and contrast figures regarding CS and other obstetric outcomes[1,2]. We found an increase in CS and induction rates in the period from 2000-2009, which is comparable to international literature. Traditionally obstetric interventions are low in the Netherlands and despite the increase that is seen, the figures for CS and inductions remain low when compared to other developed countries[3]. One of the major reasons is the large proportion of midwifery-led care, which is a known protective factor against obstetric interventions[4]. We observed an improvement in perinatal and antenatal mortality and in perinatal morbidity (defined by less neonates with low Apgar-scores) in the studied period. On the one hand, this could be due to increased interventions. On the other hand many initiatives have been implemented in the Netherlands over the past decade, as a consequence of the unfavorable position of the Netherlands in the European Peristat study to perinatal mortality[5,6]. The improved perinatal outcomes could thus be related to a combination of more interventions and non-invasive improvements (e.g. more team training for obstetric emergencies)[7]. Contrary, we found an increase in maternal morbidity, reflected by a gradual increase in postpartum hemorrhage (HPP) in the 10-year study period. Partially this could be due to better registration after a nationwide study to severe maternal morbidity[8], but it could also be due to more obstetric interventions, as both inductions and CS are known independent risk factors for HPP[9].

The association between inductions and increased odds for CS are currently being debated[10,11]. In our study no direct association was found between increased inductions and CS.

As CS do not only influence maternal and neonatal health during this pregnancy, but also in a possible subsequent pregnancy we suggest to balance the risk-benefit ratio thoroughly for every (planned) CS. It is of uttermost importance to try and avoid the first CS -when a woman has the highest chance of a vaginal delivery- to stabilize or even decrease the CS-rate nationwide[12]. As the relation between inductions and CS is not yet fully determined the outcome of currently ongoing large randomized trials might give more decisive answers whether to perform an induction of labor or not for specific situations.

Obstetric interventions and the thyroid

To answer research question 3 – *"Is suboptimal maternal thyroid function of influence on Caesarean section rates?"* – we have analyzed a group of low-risk women prospectively. We have found that suboptimal maternal thyroid function is indeed associated with more CS and operative vaginal deliveries at term, as described in **chapter 3**. Mean TSH was significantly higher (p=0.026) and mean FT4 was significantly lower (p=0.030) throughout the entire pregnancy in women with an operative delivery for failure to progress in second stage of labor, when compared to women with a spontaneous delivery or operative delivery for a different reason, although the mean levels of TSH and FT4 remained within the normal reference ranges. How can this finding be explained?

It is known that the most efficient uterine action is needed in the second stage of labor and that it is mostly the thickness of the myometrium that determines the effectiveness of the contractions, despite the pushing maneuvers of the mother[13,14]. This means that probably not the skeleton muscles of the abdominal wall are most important for effective expulsion of the fetus, but the smooth muscle cells of the myometrium. We argue that the impaired smooth muscle cell function in women with suboptimal thyroid function is binary. Firstly, there is evidence for impaired relaxation of smooth muscle cells leading to increased arterial stiffness in hypothyroid women in vascular research[15,16]. Secondary, there is evidence for decreased contractions of smooth muscle cells in hypothyroidism. Both impaired relaxation

and contraction are thought to be due to impaired functioning of calcium channels as is seen in the uteri of hypothyroid rats[17,18]. Furthermore, when treatment with T3 hormone is given, the amplitude and duration of myometrial contractions is enhanced[19]. However, TSH receptors have not been identified on the myometrium of the uterus yet. Future research is needed to investigate if there indeed is a TSH-receptor on uterine tissue, which could then be directly targeted in case of for example dystocia during labor.

Meconium stained amniotic fluid and fetal distress

In **chapter 5** we have discussed the association between high maternal TSH and meconium stained amniotic fluid (MSAF) to answer the first part of research question 4 – *"Is suboptimal maternal thyroid function of influence on perinatal outcomes?".* We found that high normal TSH at 36 weeks gestation was an independent risk factor for the presence of MSAF in pregnancies ≥41 weeks gestation (n=157) with an O.R. of 1.61, corrected for multiple confounders such as fetal distress, the duration of the first stage of labor and maternal age. We only found an association for pregnancies beyond term (≥41 weeks), but it is known that advancing gestational age is the most important determinant of MSAF[20-22]. To our knowledge our study is the first to describe this association and therefore the mechanism behind this association is still unknown. However, the concept of increased myometrial stiffness, as described in the section above, might be one of the reasons for the observed association. It is suggested that the increased myometrial stiffness might lead to impaired placental circulation, thereby enhancing fetal distress. Besides, it is known that maternal TSH is necessary for normal placental development[23]. As the function of the placenta decreases with advancing gestational age[24], the suboptimal maternal thyroid function might be of an additional negative influence on the placenta, thereby further augmenting fetal distress. However, in our study we did not find differences for fetal distress (as determined by a non-reassuring fetal heart rate pattern) or operative deliveries in the MSAF or non-MSAF groups.

In the review presented in **chapter 4** we have discussed the controversy about the association between MSAF and fetal distress. Some studies did find an association between lower Apgar-scores, lower cord-blood pH's and biochemical effects of hypoxia[25-27]. The results however are conflicting across different studies[28]. It might therefore be possible that the results described in **chapter 5** do reflect fetal hypoxia and therefore defecation in utero

due to increased stiffness of the myometrium, but that it did not lead to severe fetal distress with the need for obstetric interventions. Future research should determine whether our finding is consistent and which underlying mechanisms could be responsible for this association. Furthermore, we did not have an objective form of describing fetal distress. Ideally cord pHs should be measured alongside Apgar-scores in future research.

Small for gestational age

In **chapter 6** we have discussed the results of a prospective cohort study to maternal thyroid function and small for gestational age offspring at term, to answer the second part of research question 4 – "*Is suboptimal maternal thyroid function of influence on perinatal outcomes?"*. It was found using multiple logistic regression analyses that there were three independent risk factors in our cohort of low-risk pregnant women for getting SGA neonates; smoking (O.R. 4.4), preeclampsia (O.R. 2.8) and high TSH at any trimester (O.R.3.3). High TSH was defined as the ≥97.5th percentile at any trimester, with the study population as its own reference. The cut-offs for high TSH in our study were 3.28mIU/L, 3.0mIU/L and 3.29mIU/L at the three trimesters respectively. This is comparable to international literature and suggests we performed our study in a representative study population[29]. FT4 and TPO-antibodies were not associated with SGA. Preeclampsia and smoking are known independent risk factors for SGA offspring[30]. The relation between sub-clinical hypothyroidism (SCH) and small for gestational age offspring or neonates with low birth weight (not corrected for parity, gestational age and sex of the baby) has been confirmed by some authors, but has been denied by others[31-34]. A reason for the conflicting results could be found in the measurements of the thyroid hormones (methodology and timing), as well as in the definition of SGA (corrected for confounders, different percentiles used). The association between thyroid function and SGA found in some studies, including ours, could be explained by the role of thyroid hormones in placentation. In *in vitro* and animal studies a role for thyroid hormones has been demonstrated in placentation, as vascular endothelial growth factor (VEGF) and epidermal growth factor expression are enhanced if thyroid hormones are administered[35,36]. As placental dysfunction is the most common cause of IUGR impaired placentation might be of great importance to the subject. However, SGA was not only associated with suboptimal maternal thyroid function in the first trimester when

placentation took place. The association throughout pregnancy could be explained by the fact the transplacental T4 is needed for fetal growth throughout pregnancy. High TSH might actually reflect poor transfer of maternal FT4 through the placenta.

Conclusions of this thesis

The two main topics of this thesis are the increase in CS and induction rates in the Netherlands and the negative influence of suboptimal maternal thyroid function on obstetric outcomes.

Regarding the first topic, we came to the conclusion that CS rates and induction rates in the Netherlands did indeed increase during the past decade in the Netherlands, but CS are still low compared to international figures. Perinatal mortality rates have improved during the past decade. Furthermore, Apgar-scores <5 decreased in our study. Contrary, we saw an increase in maternal postpartum hemorrhage, the most important determinant of maternal morbidity.

We have shown that maternal thyroid function might be of influence on CS-rates in the Netherlands due to failure to progress in second stage of labor. Increased odds for CS are found in women with suboptimal thyroid function in our cohort. Furthermore, there is an association with more small for gestational age offspring and more meconium stained amniotic fluid in offspring from women with high normal TSH. Meconium stained amniotic fluid does not necessarily mean that there has been fetal distress, but despite the causes, there is an increased risk of perinatal morbidity and mortality due to the possibility of meconium aspiration syndrome. The associations found could be explained by less efficient placentation and increased myometrial stiffness in the presence of suboptimal maternal thyroid function.

Future perspectives

The induction rates are thought to rise even further in the coming decade, as the unwillingness of both patients and clinicians to wait for spontaneous labour, with the risk of stillbirth, decreases. Especially since more recent studies have found that the odds for CS are not increased with an induction of labor we expect to see rising induction rates, which will then become more comparable to international figures. Currently, many trials are running, e.g. to induction for postdates and to preterm induction for hypertension and preeclampsia. We expect that those results will lead to a further increase of induction rates.

Historically, the CS rates in the Netherlands were and still are low compared to other Western countries. However, we foresee a trend of CS that will continue to rise. Deliveries in the Netherlands become more medicalized, women are generally older, have a higher BMI and there are more women with a previous CS. Those women are all 'at-risk' for a CS.

Maternal thyroid function during pregnancy is a topic of ongoing interest. Currently there is much controversy about the need for universal screening, although the benefit of levothyroxine treatment and the cost-effectiveness of universal screening have already been proven[29,35,36]. This thesis can further contribute to the discussion, as besides the known effects of thyroid dysfunction on certain obstetric outcomes, such as preterm birth, it shows that suboptimal maternal thyroid function is associated with other major obstetric outcomes, such as CS rates, IUGR and MSAF. Basic future research should focus on determining whether there is a TSH-receptor on myometrial tissue. We advocate universal screening at the beginning of pregnancy, instead of individual case-finding based on non-specific symptoms, to offer pregnant women optimal care for themselves and their offspring. Diagnosis and treatment of suboptimal thyroid function might not only be important for optimal major obstetric outcomes, but also for the prevention and / or early recognition and treatment of maternal postpartum thyroid dysfunction. The possible benefit of rigorously monitoring maternal thyroid function during pregnancy on neurodevelopmental outcome off the offspring remains to be established.

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Chapter 8

Summary

Chapter 1 provides a general introduction of this thesis. Firstly, concerns about perinatal mortality in the Netherlands are discussed, after which trends in induction and Caesarean sections (CS) rates in the past decade are described. There is an increased trend in number of inductions, as well as in number of CS. The relation between inductions and the odds for CS are currently being debated. There are conflicting results about the perinatal and maternal outcome in relation to increased inductions and CS. In the second part of the introduction there is attention for the physiologic changes of the thyroid function during pregnancy and the known associations of suboptimal maternal thyroid function and obstetric outcome.

The aim of this thesis was to analyze whether increased induction and CS-rates in the Netherlands have led to better perinatal and maternal outcomes and whether suboptimal maternal thyroid function is of influence on those obstetric outcomes.

Chapter 2 describes the trends of induction and Caesarean section rates in relation to obstetric outcomes. It is a retrospective nationwide cohort study over a period of ten years with data from the Dutch perinatal registry. Women who delivered between 2000 and 2009 after 24 weeks gestation were included in the study and classified using the Ten Group Classification system. We found that the overall Caesarean section rate increased from 13.0% in 2000 to 15.4% in 2009. In 2000 the largest contributors to the CS-rate were groups 1, 2 and 6 (nulliparous women at term, single cephalic fetus in spontaneous labor and induced and nulliparous breeches at term). In 2009 there has been a shift. The largest contributors to the absolute number of CS were groups 1, 2 and 5 (previous CS). Furthermore, an increase in induction of labor and prelabor CS was seen in the period from 2000 to 2009. For the nulliparous women (groups 1 and 2) this trend was statistically significant ($P<0.001$), but for the multiparous women (groups 3 and 4) this was not the case ($p=0.78$). As the induction and CS-rates did not show similar trends we concluded that induction was not directly associated with CS in out cohort.

For groups 1-4 the stillbirths were analyzed. A decreasing trend was shown, with a decrease of more than 100% within the ten-year period. The largest decrease was seen in groups 2 and 4. Overall perinatal mortality was also steadily going down. Contrary, maternal postpartum hemorrhage was found to increase gradually over the years ($P<0.001$). The

highest rates of postpartum hemorrhage were seen in the intervention groups of prelabor CS and inductions. Perinatal morbidity, defined as an Apgar-score below 7 after 5 minutes, has slightly decreased over the ten-year period. Most low Apgar-scores are found in nulliparous women where an induction of labor or prelabor CS is performed (group 2).

Chapter 3 describes the association between maternal thyroid function and operative vaginal delivery rates and CS rates in a prospective cohort of women in spontaneous labor at term. Furthermore, the reasons for operative deliveries were determined. 872 women were included for data-analysis. In 19.9% (n=125) of those women a ventouse of forceps delivery was performed or a CS. Women who underwent an operative vaginal delivery (OVD) or CS had a significantly higher TSH and lower fT4 at 12 weeks gestation (TSH 1.63 mIU/L versus 1.46 mIU/L and fT4 12.9 pmol/L versus 13.4 pmol/L respectively). Women who underwent an OVD or CS for failure to progress in second stage of labor (delayed expulsion) had higher mean TSH levels (p=0.026) and lower mean fT4 levels (p=0.030) in all trimesters, adjusted for BMI, maternal age, parity and gestational age when compared to women with a spontaneous delivery or an OVD or CS for different reasons.

Chapter 4 provides a literature review on the topic of meconium stained amniotic fluid (MSAF). Some authors have found an association between fetal distress and MSAF whilst other have not. The latter suggest that MSAF should be seen as a physiologic sign of fetal ripening. Some authors claim that a distinction should be made between primary MSAF, which is present at the time of membrane rupture, and new-onset or secondary MSAF. Primary MSAF is associated with fetal ripening and thus physiology, whilst secondary MSAF is a sign of fetal distress. Furthermore, there have been some reports which have shown an independent association between MSAF and peripartum infections.

In conclusion we suggest that MSAF should be seen as a symptom, rather than a syndrome and that it should be interpreted against other factors, such as the fetal heart rate pattern or the presence of maternal fever.

Chapter 5 is a prospective cohort study, which analyses the association between maternal thyroid function and the presence of MSAF. 1051 women with a term delivery (≥37 weeks) were included for analysis. When assessing all births, there was no difference found in thyroid function for women with or without MSAF. However, it is known that the most

important risk factor for the presence of MSAF is the term of gestation. In our cohort the likelihood of MSAF increased by 63% for every week of gestation from 37 weeks onwards. When the 'at-risk' population for MSAF was analyzed in more detail, we found that high normal TSH at 36 weeks gestation was an independent risk factor for the presence of MSAF in pregnancies ≥41 weeks gestation (n=157) with an O.R. of 1.61, corrected for multiple confounders such as fetal distress, the duration of the first stage of labor and maternal age. Another independent risk factor for the presence of MSAF ≥41 weeks gestation was nulliparity, with an O.R. of 2.0. Maternal fT4 was not associated with an increased risk of MSAF.

Chapter 6 describes the relation between maternal thyroid function and small for gestational age neonates (SGA). SGA was defined as the lowest 10^{th} percentile of population based birth weight percentiles, corrected for parity, gestational age and sex of the baby. We included only deliveries that were at term (≥37 weeks), with a total number of 1051 deliveries. Of those, there were 70 (6.7%) SGA neonates. We defined high TSH at each trimester using the group as its own reference, with an upper reference limit of $\geq$ 97.5^{th} percentile. These cut-offs were 3.28 mIU/L, 3.0 mIU/L and 3.29 mIU/L, at 12, 24 and 36 weeks, respectively. SGA neonates were significantly more often born to the women with a high TSH. With multiple logistic regression analysis with SGA as dependent variable and high TSH at any trimester as independent variable, adjusting for multiple confounders, we found that the occurrence of smoking, pre-eclampsia and high TSH were independent risk factors for SGA neonates. High TSH at any trimester had an O.R. of 3.3 (95% C.I. 1.39-7.53) for the birth of SGA neonates. Low TSH (≤2.5^{th} percentile) and FT4 were not associated with the incidence of SGA neonates.

Chapter 7 consists of a general discussion of this thesis. Conclusions to the main research questions are drawn and future perspectives are discussed.

Chapter 9

Nederlandse samenvatting

In **hoofdstuk 1** wordt een inleiding van dit proefschrift gegeven. Als eerste wordt er aandacht besteed aan zorgen rondom de perinatale sterfte in Nederland en vervolgens worden de trends van keizersneden en inleidingen in de afgelopen tien jaar besproken. Er wordt een toenemende trend gezien in het aantal inleidingen en in het aantal (geplande) keizersneden. Momenteel is er een discussie gaande over de mogelijke relatie tussen het inleiden van de baring en een verhoogd risico op het krijgen van een keizersnede. Daarnaast zijn er in de literatuur tegenstrijdige resultaten beschreven over het verhoogde aantal inleidingen en keizersneden en het effect hiervan op perinatale en maternale uitkomsten. In het tweede deel van de introductie is aandacht voor de fysiologische veranderingen van de schildklier tijdens de zwangerschap en de bekende associaties tussen suboptimale maternale schildklierfunctie en obstetrische uitkomsten.

Het doel van dit proefschrift was enerzijds om te analyseren of meer inleidingen en keizersneden hebben geleid tot betere perinatale en maternale uitkomsten, en anderzijds om te onderzoeken of suboptimale maternale schildklierfunctie van invloed is op obstetrische uitkomsten.

In **hoofdstuk 2** wordt de inductie- en keizersnedetrend in Nederland beschreven en de effecten hiervan op obstetrische uitkomsten. Het is een landelijke, retrospectieve cohortstudie over een periode van 10 jaar, met data van Perinatale Registratie Nederland (PRN). Alle vrouwen die tussen 2000 en 2009 bevielen na een zwangerschapsduur van 24 weken werden geïncludeerd. Zij werden ingedeeld volgens het tien-groepen classificatie systeem, ook wel “Robson-systeem”. Het algemene keizersnedepercentage is in de studieperiode gestegen van 13.0% in 2000 tot 15.4% in 2009. In 2000 hadden de vrouwen in groep 1, 2 en 6 het grootste aandeel in het totaal aantal keizersneden (nulliparae à-terme met een eenling in hoofdligging, spontaan in partu of na inductie en nulliparae met een eenling in stuitligging). In 2009 heeft er een verschuiving plaatsgevonden en hadden groepen 1, 2 en 5 (eerdere keizersnede) het grootste aandeel in het totaal aantal keizersneden. Ook was er een verschuiving te zien naar een groter aantal vrouwen die ingeleid werden of een primaire sectio Caesarea kregen. Voor de nulliparae was deze trend statistisch significant ($P<0.001$). Voor de multiparae echter niet ($p=0.078$). De trendlijnen voor inleidingen en keizersneden over de studieperiode waren dusdanig verschillend dat wij concludeerden dat in ons cohort inleidingen geen direct effect hadden op het aantal uitgevoerde keizersneden.

In de studieperiode werd het aantal vrouwen met een antenatale sterfte in groep 1 t/m 4 bestudeerd (intra-uteriene vruchtdood, IUVD). Een dalende trend werd gezien voor het aantal IUVD's, met een daling van meer dan 100% over de 10 jaar. De grootste daling vond plaats in groepen 2 en 4. De totale perinatale sterfte is ook gedaald. Hier staat tegenover dat het aantal vrouwen met een fluxus postpartum (>1000mL bloedverlies) gestaag toenam over de jaren ($p<0.001$). De grootste aantallen fluxus werden gevonden in die groepen waar een obstetrische interventie (een inleiding of keizersnede) plaatsvond. Naast perinatale sterfte is ook het aantal kinderen met een lage apgar-score afgenomen gedurende de jaren. De meeste kinderen met een apgar-score onder de zeven na vijf minuten worden gevonden in groep 2, de nulliparae met een inleiding of geplande keizersnede.

Hoofdstuk 3 is een prospectieve cohortstudie naar vrouwen die spontaan in partu zijn, waarbij de associatie tussen suboptimale maternale schildklierfunctie en een hoger aantal kunstverlossingen wordt bestudeerd. Vervolgens werden de verschillende redenen voor een kunstverlossing nadere geanalyseerd. 872 vrouwen werden geïncludeerd, waarvan in 125 gevallen (19.9%) een vaginale kunstverlossing of keizersnede werd uitgevoerd. Vrouwen waarbij een kunstverlossing werd uitgevoerd hadden een significant hoger TSH (1.63mIU/L versus 1.46mIU/L) en significant lager fT4 (12.9 pmol/L versus 13.4 pmol/L) bij 12 weken zwangerschap. Vrouwen die een kunstverlossing ondergingen voor niet vorderen van de uitdrijving hadden een significant hoger TSH gedurende de hele zwangerschap ($P=0.026$) en een significant lager fT4 gedurende de hele zwangerschap ($P=0.030$), gecorrigeerd voor BMI, leeftijd, zwangerschapduur en pariteit, vergeleken met vrouwen met een spontane bevalling of een kunstverlossing voor een andere reden.

Hoofdstuk 4 is een overzicht van de literatuur over meconiumhoudend vruchtwater. Sommige studies laten een associatie zien tussen foetale nood en meconiumhoudend vruchtwater, terwijl andere studies dit niet aantonen. In die laatste studies wordt gesuggereerd dat meconiumlozing een fysiologisch mechanisme is door uitrijping van de foetus. Verder maken sommige auteurs onderscheid tussen primaire en secundaire meconiumlozing. Bij de eerste vorm is er al sprake van meconiumhoudend vruchtwater bij het breken van de vliezen, terwijl bij de tweede vorm er een verschuiving optreedt van helder naar meconiumhoudend vruchtwater. Primaire meconium zou samenhangen met fysiologische rijping van de foetus, terwijl secundaire meconium een teken is van foetale

nood. Daarnaast zijn er een aantal studies die een onafhankelijke relatie beschrijven tussen meconiumhoudend vruchtwater en peripartum infecties. Wij concluderen dan ook dat meconiumhoudend vruchtwater gezien moet worden als een symptoom, in plaats van als een syndroom, en dat het in het licht moet worden gezien van andere factoren, zoals het CTG.

Hoofdstuk 5 is een prospectieve studie die de associatie tussen maternale schildklierfunctie en meconiumhoudend vruchtwater bestudeerd bij à-terme zwangerschappen. 1051 vrouwen werden geïncludeerd voor deze studie. Voor de totale groep vrouwen werd geen verschil gevonden in schildklierwaardes bij vrouwen met helder of meconiumhoudend vruchtwater. Het is echter bekend dat de meeste belangrijke determinant voor het hebben van meconiumhoudend vruchtwater de zwangerschapsduur is. In ons cohort nam de kans op meconiumhoudend vruchtwater met 63% toe voor elke extra week zwangerschapsduur vanaf 37 weken. Bij een subgroepanalyse van de 'at-risk' vrouwen met een zwangerschapsduur ≥41 weken (n=157), vonden wij een onafhankelijke, statistisch significante relatie, tussen meconiumhoudend vruchtwater en een hoog normaal TSH bij 36 weken zwangerschap (O.R. 1.61). Bij deze regressie-analyse werd gecorrigeerd voor meerdere factoren, zoals de duur van de ontsluiting, foetale nood en maternale leeftijd. Ook nulliparitеit bleek een onafhankelijke risicofactor bij zwangerschappen ≥41 weken voor meconiumhoudend vruchtwater, met een O.R. van 2.0. Maternaal fT4 was niet geassocieerd met het voorkomen van meconiumhoudend vruchtwater.

Hoofdstuk 6 is een studie naar de relatie tussen maternale schildklierfunctie en het voorkomen van foetale groeibeperking (small for gestational age, SGA). SGA werd gedefinieerd als een geboortegewicht onder de 10^{e} percentiel, gecorrigeerd voor de zwangerschapsduur, pariteit en het geslacht van de baby. De curves die gebruikt werden zijn curves op populatieniveau van de PRN. In totaal werden 1051 à-terme vrouwen geïncludeerd. 70 kinderen voldeden aan de definitie van SGA (6.7%). Hoog TSH werd gedefinieerd als een TSH ≥97.5 percentiel ten opzichte van de rest van de onderzoekspopulatie op enig moment in de zwangerschap. De afkapwaardes die op deze manier werden gedefinieerd zijn 3.28 mIU/L, 3.0 mIU/L en 3.29mIU/L bij een zwangerschapsduur van respectievelijk 12, 24 en 36 weken. SGA kinderen werden significant vaker geboren bij moeders met een hoog TSH. Bij multivariate logistische regressie analyse

bleek dat roken, pre-eclamspie en hoog TSH onafhankelijke risicofactoren waren in ons cohort, voor het krijgen van een SGA kind. Hoog TSH had een O.R. van 3.3 (95% BI 1.39-7.53) voor het krijgen van een SGA neonaat. Laag TSH en fT4 waren niet geassocieerd met het krijgen van groeibeperkte kinderen.

Hoofdstuk 7 is een algemene discussie van dit proefschrift. Hierin worden de onderzoeksvragen beantwoord en worden er suggesties gedaan voor toekomstig onderzoek.

Chapter 10

Appendices

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Curriculum Vitae

Loes Monen werd op 02-03-1989 geboren te Eindhoven als enig kind. Zij doorliep zowel de basis- als de middelbare school in Eindhoven. In 2000 startte zij met de opleiding geneeskunde aan Maastricht University. In 2010 volgde zij een keuzecoschap gynaecologie en obstetrie in het Academisch Ziekenhuis Paramaribo te Suriname. Haar wetenschappelijke stage werd doorlopen bij de gynaecologie in het Orbis Medisch Centrum Sittard. Haar semi-arts stage werd in het Catharina ziekenhuis Eindhoven gevolgd, ook binnen de gynaecologie en obstetrie. Hier kon zij na haar afstuderen in 2012 direct aan de slag als arts niet in opleiding tot specialist (opleider Dr. S. Kuppens, plaatsvervangend opleider Dr. T. Hasaart). Hier werd ook het begin gemaakt van het promotie-onderzoek. In januari 2015 is zij gestart met de opleiding tot gynaecoloog binnen het cluster Maastricht in het Atrium Medisch Centrum te Heerlen (opleider Dr. P. Mercelina, plaatsvervangend opleider Dr. N. Smeets). Loes woont samen in Eindhoven met Rick van de Bunt.