Successful external cephalic version in breech

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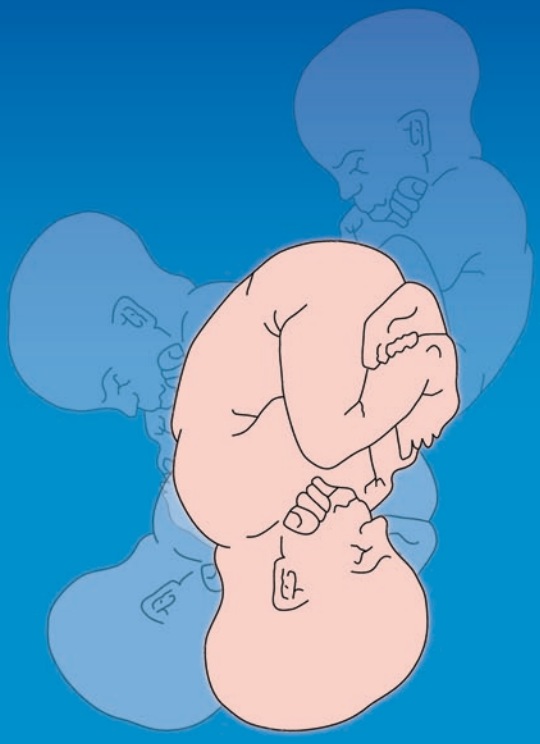
Thyroid hormone and process parameters



Simone Kuppens

Successful External Cephalic Version in Breech

Thyroid hormone and process parameters

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Successful External Cephalic Version in Breech

Thyroid hormone and process parameters

Proefschrift

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

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"Voor alles wat er gebeurt is er een uur, een tijd voor alles wat er is onder de hemel. "

Prediker 3:1

Voor mijn ouders.

Voor Maurice, Thomas en Sophie.

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General introduction

Chapter 1: General Introduction

1.1. Normal foetal presentation at term

1.1.1. Cephalic position: definition and prevalence

About 95% of all foetuses are in cephalic presentation at term. A cephalic presentation is the birth situation in which the foetus is lying in a longitudinal position with his head in the pelvic channel. The most common form of cephalic presentation (i.e., 95% of all cases) is the vertex presentation where the head is flexed sharply so that the chin is in contact with the thorax. As a result the occiput fontanel is the presenting part, and, hence, this presentation is referred to as vertex or occiput presentation. A much less common form of cephalic presentation is referred to as face presentation. This type of birth presentation is characterized by a pronounced extention of the foetal neck, so that the occiput touches the spine, and the face enters first in the birth canal.[1]

1.1.2. Physiology of cephalic presentation

Several hypotheses have been postulated to explain cephalic presentation at term.

1) The width of the uterine fundus and the relative narrowness of the pelvic segment has led to the notion that foetal kicking enables the foetus to move into cephalic position.[2,3]

2) Labour itself may also have an effect on presentation at term.[4-6] As such one may argue that Braxton Hicks contractions in the second half of pregnancy contribute to the rotation of the foetus into cephalic position.

3) It has also been suggested that moving into cephalic position may function as a "reward" for the foetus in terms of a less noisy foetal environment. In breech, for instance, the greater amount of amniotic fluid surrounding the head may facilitate the transmission of sound to the foetal skull, thereby creating uncomfortable loudness levels.[7]

4) From 24-35 weeks onwards, foetal maturation produces a constant change of lie and presentation. This maturation process is in caudiocranial direction and mediated by the interplay between inhibitory and stimulatory influences of the reticular nuclei and cerebellum. Lower extremity antigravity movements including sudden leg extensions, kicking and body rolling are prominent in this process. In the cephalic position, the foetus is allowed an uncompromised posture in the caudal parts of the body segments along gravity.[8] For example: paraplegic and tetraplegic pregnant females, who spend their pregnancy in horizontal supination or close to it, have a high percentage of non-cephalic presentations at term.[9,10]

1.2. Breech presentation

1.2.1. Definition of breech

In the breech presentation the foetus enters the birth canal with the buttocks or feet first as opposed to the normal head first presentation. There are three types of breech presentation: (1) frank breech where the foetus' legs are extended up to its head; (2) complete breech where the foetus' legs are flexed back to the bottom; (3) breech where one or both legs are extended below the foetus' bottom.[11]

1.2.2. Epidemiology

In The Netherlands, about 6000 live term singleton breech births occur every year.[12] The incidence of breech presentation decreases with increasing gestational age from approximately 16% at 32 weeks to 3-5% of all pregnancies at term.[4,13]

1.2.3. Spontaneous course of breech presentation

Until 24 weeks gestation there is no tendency towards any preferred foetal position in utero. This means that until this point in time breech presentation is a physiological presentation and that about half of the babies lie in this position.[6,14,15] When gestation proceeds, the prevalence of breech position gradually decreases. Boos et al.[16] found foetal position tends to stabilize from the 32nd week onwards. An explanation for this observation could be that the uterine space available for the foetus to move decreases between 30 and 37 weeks (as measured by the AFI/EFW ratio = amniotic fluid index/ estimated foetal weight ratio).[17] Furthermore, it has also been stated that the amount of foetal leg movements decreases during the third trimester. This decrease in leg movement may be indicative of progressive neurobehavioral maturation.[17]
Some authors state that spontaneous version cannot be expected after the 37th week of gestation[14], whereas others, in contrast, found an incidence of spontaneous version at 37 weeks of 25% (28% multiparae / 8% nulliparae).[18]

1.2.4. Consequences of breech presentation

1.2.4.1. Impact on foetal development

Foetal heart rate patterns in breech presenting foetuses show more fluctuations in (behavioral) state compared with cephalic presenting foetuses.[19] This suggests that, although breech foetuses move for similar total lengths of time as their cephalic counterparts, there are shorter periods of sustained movement and they spend a shorter time in any one behavioural state and that breech foetuses are neurologically different from their cephalic counterparts. Foetal eye movement patterns in utero are also different in breech presenting versus cephalic presenting babies.[20] Foetuses in breech position show atypical

movement responses to vibroacoustic (fewer movements) and airborne sound (more movements) stimuli.[7] Probably the greater amount of amniotic fluid surrounding their head facilitates the transmission of sound to their skull resulting in greater experienced sound intensity levels in breech babies versus cephalic babies. These differences in sensory experiences may affect the development of neural networks during the perinatal period.[7] A study on lateralized head-position in near term babies showed that the development of a lateralized head-position preference was less pronounced in breech foetuses than in cephalic foetuses. Furthermore, as cephalic foetuses showed a preference for a right-sided head position, breech foetuses did not have a clear preference for left or right.[21] Since breech foetuses have more freedom of head movement than cephalic foetuses, this could lead to a less pronounced difference in stimulation between the left and the right otoliths, and thus to a weaker manifestation of lateralization. This would converge with Previc's left-otolithic dominance theory.[21]
Foetuses in breech position show a clear preference for an extended leg position, whereas cephalic foetuses show more leg crossing.[22]
Finally, less spontaneous wrist flexion has been found in breech presenting babies of 36-38 weeks gestational age, and was attributed to their less restricted intrauterine environment.[21]

1.2.4.2. Obstetrical outcome in breech

Breech foetuses are more susceptible to the burden of stress during labour than cephalic foetuses.[23] Furthermore, vaginal breech delivery in breech presenting babies is frequently accompanied by asphyxia from cord compression or cord prolapse. Finally, breech presenting babies are at increased risk for traumatic injury associated with the delivery of head and shoulders during the final stage of expulsion.[24] Breech position in most western countries, therefore, is one of the most common reasons to perform elective primary Caesarean Section.

1.2.4.3. Neonatal aspects of breech

Breech babies tend to be smaller and this difference in weight has been shown to disappear at about 14 months of age.[25]
Breech babies are known to have a typical side-to-side flattening of the skull, known as the "Breech Head".[26,27] This altered head shape is the likely reflection of intrauterine environmental factors. Once this constraint is relieved post-natally, the altered head shape has the potential for complete resolution.
On examination on the second and fourth day of life, newborns delivered in breech presentation have a significantly lower score on all active movement measurements. In particular, the popliteal angle in these neonates is significantly increased, whereas the extension in their hip joints is decreased.[28]
Furthermore, over the course of the first 6 postnatal weeks, significantly less hip extension and more hip flexion has been reported in babies delivered in breech

position.[29] These motor problems do not seem to disappear with age as indicated by findings showing lower limb, reflex and posture problems in breech-delivered infants up until the age of 12-18 months.[30]
Finally, breech presentation is known to be a major risk factor for the development of hip dysplasia. This increased risk of hip dysplasia is unrelated to method of delivery and is higher in frank breech than in complete breech positions.[31]
Infants delivered in breech compared to cephalic position are at increased risk for adverse perinatal outcome, and score lower on neurological tests of development.[19,32] Impaired neurological outcome was found to be unrelated to delivery mode [33], suggesting that the in utero neurological impairment found in breech presenting foetuses may indeed be contributory to the foetal malpresentation. However, whether atypical foetal position leads to in utero neurological impairment (through alterations in proprioceptive feedback mechanisms) or whether in utero neurological impairment contributes to breech presentation is presently unclear.[7]
Finally, because breech presentation is associated with adverse obstetric and neonatal outcomes, it is often difficult to determine the causal relationships between poor outcome on the one hand and intrinsic foetal condition and/or birth mechanics on the other.[33]

1.2.4.4. Long term aspects of breech

Breech presentation constitutes a significant risk for cerebral palsy (CP), especially among singletons born by vaginal breech delivery at term.[34]
In school-aged children, lower vestibular reactions after thermic and rotational balance test were found in children born in breech position compared to children born in cephalic position.[35]
Substantially more hyperkinesia, learning disability, speech and language disorders were found among 8-15 year old children born in breech compared to born in cephalic presentation. Especially boys born in breech exhibit hyperkinesia.[36]
Autism spectrum disorders occur more frequently among children born in breech position, even after correcting for other complications such as foetal distress.[37] Probably there is a shared aetiology and not a causal relationship (as complications such as foetal distress were eliminated).
Finally, adult cognitive outcomes in follow-up studies of infants delivered in breech presentation are ambiguous. Some studies show no difference in intellectual performance between breech and cephalic born adults.[38,39] However, in a Danish study, young men delivered in breech presentation had lower cognitive outcomes, independent of delivery mode.[40]

1.2.5. Etiologic aspects of breech presentation

Ultrasound observations of foetal movement patterns have shown that the foetus turns from breech to cephalic presentation through active whole body movements such as kicking.[41] Foetal kicking near term enables the foetus to move into the cephalic position.[2,3,14,42]

In a normal term pregnancy, a foetus with normal motility will likely present in the cephalic position. Factors within the foetus affecting its motility will therefore enhance the chances of a baby presenting in breech position (foetal factors). Likewise, external factors affecting foetal mobility may also increase the risk of breech presentation (environmental factors). In spite of this, however, only in 15% of breech cases, risk factors can be identified.[16,43]

1.2.5.1. Foetal factors

Compromised foetal motor abilities resulting in decreased kicking near term may prevent the foetus from moving into the vertex position.[3] Foetal neuromuscular dysfunction is, thus, an established risk factor for breech presentation. Similarly, malformations of the central nervous system and chromosome anomalies are associated with breech presentation.[44]

Cigarette smoking may decrease foetal muscle tone which, in turn, may affect foetal mobility. Maternal smoking, therefore, is clearly associated with breech presentation.[3,42,45,46] In a similar way are alcohol abuse and anticonvulsant therapy related with breech presentation.[47]

Reduced foetal mobility has also been observed in diabetic pregnancies[48], and, as such, maternal diabetes constitutes a risk factor for breech presentation.[42]

Spontaneous foetal version is depending on normal neuromotor development. Foetal size and body symmetry in pregnancy are associated with infant neuromotor development: higher foetal weight was found to be beneficial to infant neurodevelopment.[49] Therefore, as breech babies tend to be smaller for gestational age[5,18,42-44,46,50-52] impaired neuromotor development could be the underlying cause of breech pregnancy. Furthermore, less vigorous foetal movements may also result from low birth weight, thereby reducing the chances of spontaneous foetal version.[53]

It has earlier been suggested that foetal leg extension is a significant aetiological factor in breech presentation because leg extension may prevent the infant from kicking himself round.[2,54] Interestingly, female sex is another factor associated with breech presentation[17,52,55,56]: female babies tend to be less active and smaller in size.[17,56] Also the shape of the foetal female pelvis and hips could play a role.[55]

Both maternal and paternal histories of breech delivery have been found to increase the risk of breech delivery in first born offspring.[43] Recurrence of breech delivery between generations suggests that one or more genetic factors may be passed on from parents to foetus.[57]

1.2.5.2. Environmental factors

Decreased amniotic fluid is associated with a reduction in space available to the foetus and, thus, constitutes a risk factor for breech presentation.[3,50]

Umbilical cord length (UCL) has repeatedly been found to be shorter in breech than in cephalic presentation.[46,58-62] Since UCL is a marker of foetal mobility[63-65], this finding strengthens the notion that foetal motility plays an important role in the pathogenesis of breech presentation. Whether short umbilical cord is a cause or a consequence of breech presentation remains to be established.

In the literature correlations between breech presentation and primiparity[3,5,18,42,44,52], older maternal age[5,42], fundal position of the placenta[3] and ethnicity[42] have been reported.

Primiparity restricts foetal mobility: i.e., there is a combination of less intrauterine space and a tense abdominal muscular wall. The amount of uterine malformations due to scars or myomas increases with age. Therefore, older maternal age is associated with increased risk for breech presentation.[5,42]

Breech presentation in a previous pregnancy significantly reduces the chances of spontaneous version to vertex. This is probably due to special characteristics of the uterus and/or abdominal cavity. Mechanical factors such as a contracted pelvis and uterine abnormalities are rare causes of term breech presentation.[4,44,50]

In case of obvious placental abnormalities, such as placenta previa, cornual placenta, the risk of persisting breech presentation is enhanced.

The significance of the location of the placenta for foetal presentation is debatable. No association between spontaneous cephalic version and placental position was found in the study of Westgren[18], whereas others found a fundal position of the placenta to be a causal factor for breech presentation.[3,46,66]

Afro American and Filipino women have a decreased risk of breech presentation compared to white Caucasian women.[42,67] Breech presentation is most frequent in urban (non-rural) areas.[5,36]

In certain cases, a combination of factors enhances the risk of breech presentation. This is, for instance, the case in frank breech presentation. Primiparity and frank breech (extended legs) are closely associated (because the increased tone in the abdominal wall in primiparae could predispose to extended legs). Therefore, it is difficult to determine if extended legs are a primary or a secondary factor in the aetiology of breech presentation.[18]

1.3. Thyroid and breech presentation

Much attention has been paid on the consequences of breech presentation and on strategies to minimize the negative consequences of breech presentation for both mother and child. Much less attention, however, has been focused on why some foetuses present in breech.[57] A better understanding of the causes of breech presentation would promote research into preventive measures.[42]

Further research into the underlying mechanisms of breech presentation is, thus, important.[57]

Thyroid hormone is an important factor in the development of the foetal central nervous system[68], and maternal-foetal transfer of thyroxine accounts for up to 50% of the foetal serum thyroxine level at term.[69] Therefore, one might speculate about the possibility that maternal thyroid status affects foetal mobility and future psychomotor development. Today, several studies have shown that even subtle maternal thyroid problems (e.g., elevated TSH or thyroid stimulating hormone levels, lower free thyroid hormone (FT4) levels or elevated thyroid peroxidase antibody (TPO-Ab) titers are associated with impaired psychomotor development of the offspring at the age of 3 weeks[70], 10 months[71], 1-2 years[72], 18 months[73], 23-30 months[74], 5 years[75], 7-9 years[76]. Other studies, however, deny such an association.[77]

Maternal thyroid hormone (high-normal TSH) during late gestation has been associated with abnormal cephalic foetal position at birth.[78]

A population-based cohort study from Finland recently demonstrated that noncephalic presentation at birth was more common among Thyroidglobulin antibody (TG-Ab) positive mothers.[79] Because Finland has an active policy with regard to external cephalic version, this may have affected the rate of noncephalic presentations in this study.

To date only one study, albeit with low epidemiological power, showed a relation between maternal thyroid function and breech presentation.[80]

Motor skills in children with congenital hypothyroidism were reported to be significantly worse in children with high TSH or low T4-values on newborn screening compared to those with normal TSH values.[81,82] Suboptimal maternal thyroid hormone supply has also been related to neonatal motor deficits.[70-76]

Since breech presentation has also been linked to motor impairment, one may suggest that - if suboptimal maternal thyroid function is related to breech - the neonatal consequences of breech presentation could be explained via the thyroid hormone pathway.

Moreover, since suboptimal maternal thyroid hormone supply has been related to behavioural problems such as autism and ADHD[83,84], and breech presentation has also been linked to autism and ADHD[5,36,37], it might be suggested that the common link between behavioural problems and breech presentation could be explained in terms of thyroid hormone dysfunction.

Therefore the first aim of this thesis was to investigate a possible relationship between maternal thyroid function and breech presentation. Furthermore, we investigated a possible relationship between maternal and neonatal thyroid function.

1.4. Attitude towards breech presentation

1.4.1. Caesarean Section (CS)

In the Netherlands, vaginal delivery in case of breech presentation used to be common practice: roughly 25% of all term breeches were delivered by planned CS, 25% by CS after a trial of labour and 50% were delivered vaginally. After publication of one randomized trial "Term Breech Trial" (TBT) in 2000 a dramatic policy change occurred. In this study it was concluded that planned CS was better than planned vaginal birth for the term breech foetus, while serious maternal complications were similar between both birth groups.[85]

Within 2 months following publication of the TBT the total CS rate for term breeches increased from 50 to 80%, all of this as a direct result of an increase in planned elective CS from 20-50%.[86] International guidelines concluded that "planned vaginal delivery of a term singleton breech may no longer be appropriate" and that external cephalic version should be attempted "whenever possible".[87] In 2004 a follow-up study of the TBT birth cohort found no differences in maternal and infant outcomes of the planned CS group versus the vaginal delivered group, 2 years after delivery.[88] The TBT has, since, been criticized. In 2006, the ACOG revised their guidelines to incorporate the new findings, recommending that "the decision regarding mode of delivery should depend on the experience of the health care provider, while continuing to endorse external cephalic version whenever possible".[89]

Also the Dutch and Canadian societies of obstetricians and gynaecologists currently state that with careful case selection and labour management of breech deliveries, a level of safety similar to elective CS may be achieved.[24,90]

1.4.2. External Cephalic Version

External cephalic version (ECV) is the manipulation of the foetus, through the maternal abdomen, into a cephalic presentation.

1.4.2.1. History

ECV has been practiced since the time of Hippocrates.[91] ECV almost became extinct in the 1960s after several reports suggested high foetal complication rates associated with version maneuvers. In these studies general anesthesia was used, and preterm infants were included to improve the chances of success.[92] In 1974 Salinger and Müller-Holve suggested that ECV be performed under tocolysis after 37 weeks gestation and after screening with ultrasound and foetal cardiotocography (CTG).[93] Subsequent studies from the 1980s showed that successful ECV could be achieved in a substantial proportion of term breech pregnancies with a low risk of complications. Recent randomized controlled trials demonstrate that ECV at or near term effectively reduces the risk of noncephalic births and caesarean delivery for malpresentation.[11] Consequently,

ECV has now become common practice. Publication of the Term Breech Trial[85] increased the popularity of ECV substantially.

1.4.2.2. Procedure

Various ECV procedures have been reported but have not been compared in randomized trials. In general terms, the procedure is as follows: clinical examination and ultrasound examination is performed to confirm the presentation, type of breech, placenta location and to assess the amniotic fluid index, and, preferably, to rule out the presence of a cord around the neck. Patients are usually asked to empty their bladder before the ECV.
Prior and immediately after the procedure, foetal heart rate monitoring (CTG) is performed to confirm foetal well-being. The patient is placed in Trendelenburg position (bed tilted in 20 degrees head down position). Usually, only one operator performs the ECV and he/she stands on the side of the patient in the direction of version of the foetal head. Gel or powder is spread on the abdomen to facilitate hand movement and to be gentler to the skin. The breech is first disengaged by gentle pressure on both sides of the presenting part with the palm of the hand.[94] Tocolysis to relax the uterus may or may not be administered. Slight back-and-forth movement between the two hands may help promote foetal movement. Generally, a forward roll is used to rotate the baby. A backward flip may be indicated if the spine lies directly anterior.[95] Simultaneously with the ECV, the foetal heart rate is registered intermittently, leading to interruption of the procedure if bradycardia occurs. In general, the procedure takes up to 5 minutes per attempt, with a maximum of 3-4 attempts in one session. Anti-D immune globulin (1000 IE) is administered to Rh(D)-negative women who undergo ECV.

1.4.2.3. Inclusion and exclusion criteria of ECV

All women with a singleton term breech pregnancy should be offered ECV.[90,96,97] There are, however, a few important contra-indications, such as ante partum hemorrhage within the last 7 days, abnormal foetal heart rate pattern, if caesarean delivery is indicated irrespective of foetal presentation, major uterine anomaly, ruptured membranes, multiple pregnancy, severe maternal hypertension, or the mother carries the Human Immunodeficiency Virus.
Some contra-indications may in fact be 'relative' contra-indications, and the risks and benefits of ECV should be individualized. These cases are small-for-gestational age foetuses (less than 10th percentile), oligohydramnios, mild maternal hypertension, scarred uterus, and in case of major foetal anomalies.

1.4.2.4. Safety

-Foetomaternal hemorrhage

Obstetric invasive procedures can lead to foetomaternal hemorrhage (FMH). A systematic review reported a 3.7% incidence of FMH after ECV.[98] A recent

prospective observational study in which a Kleihauer-Betke test was done in 1311 women before and after ECV showed an FMH incidence of 2.4%, with a 0.8% incidence of FMH greater than 1.0 ml and a 0.1% incidence of FMH greater than 30 ml of foetal blood. The risk of FMH was not influenced by parity, gestational age, body mass index, number of version attempts, placental location or amniotic fluid index. Furthermore, the occurrence of FMH was not related to foetal heart decelerations during the procedure.[99]

-Other complications

Complications after ECV, such as placental abruption, cord prolapse, foetal heart rate abnormalities and stillbirths are well-recognized but uncommon. A systematic review revealed the following incidence figures: transient abnormal heart rate patterns (5.7%), persistent pathological CTG (0.37%), vaginal bleeding (0.47%), placental abruption (0.12%), emergency caesarean sections (0.4%) and perinatal mortality (0.1%).[98] A recent meta-analysis confirmed that serious complications are rare and not related to foetal position after ECV.[100] Therefore, ECV is stated as a safe procedure.

-Caesarean scar

Previous caesarean delivery (CD) is considered as a relative contra-indication for an ECV attempt despite the absence of serious complications or risks.[11] The risk of uterine rupture in patients with previous CD has not been determined. In a review of 5 studies investigating ECV after previous CD (n=166), 76% of the cases had favourable foetal and maternal outcomes. The results of ECV after a previous CD are, therefore, encouraging with a substantial success rate and a high probability of future normal vaginal delivery in more than 85% of cases.*[101]*

1.4.2.5. Success rates and Effectiveness of ECV

-Success rates

Success rates for ECV range between 30 and 80%.[97] Success rate figures from Dutch studies vary between 25 and 42%.[102-107] These differences in success rates can partially be explained by differences in ethnicity (i.e., tendency to postpone breech engagement in the pelvic brim in Africo Americans) and selection bias (i.e., pre-selection of "favorable" ECV attempts).

-Effectiveness

ECV reduces both the number of breech presentation in labor (RR=0.42, 95%CI 0.35-0.50) and the number of caesarean sections (RR=0.52, 95%CI 0.39-0.71).[11] These favourable statistics have led the American College of Obstetricians and Gynecologists (ACOG), the Royal College of Obstetricians and Gynaecologists (RCOG), the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) and the Dutch association of Obstetricians and Gynaecologists (NVOG) to recommend ECV as the best method to reduce the number of breech presentations and breech deliveries at term.[90,96,97,108]

The application of ECV leads to considerable cost savings in the management of breech presentation at term.[95,109,110]

-Spontaneous version after (un)successful ECV

Spontaneous version rates for nulliparous women of less than 5 % are reported both for unsuccessful [98,111,112] and successful ECV attempts.[112,113]

The same factors thought to affect spontaneous version can potentially impede successful ECV treatment. The reported spontaneous version rates after (un)successful ECV, therefore, are higher (up to 12,5%) in multiparous women and in women with abundant amniotic fluid.[114]

1.4.2.6. Determinants of success of ECV

Several factors have been associated with successful ECV outcome including multiparity, non-frank breech, non tense uterus, non-anterior placenta location, higher birth weight, non–Caucasian ethnicity, amniotic fluid index > 7cm, normal body mass index, palpable foetal head, non-posteriorly located spine and non-engagement of the breech.[104,115-118]

Several prognostic models or scoring systems have been proposed, but, so far, none of these models/systems have proven to be satisfactory due to their limited clinical impact.[116,119-121]

-Influence of gestational age

Non-engagement of the breech is an important clinical factor interfering with ECV success. Therefore, ECV between 34 to 35 weeks gestation may have some advantage over ECV at 37 weeks or later, especially in nulliparous women. A multicentre randomized controlled trial (n = 233) included nulliparous women with any breech presentation and multiparous women with a frank breech presentation. ECV was initiated between 34 weeks and 36 weeks in the early group (n = 117); and between 37 weeks and 38 weeks in the delayed group (n = 116).[122] Although not statistically significant, a 9.5% higher decrease in the rate of breech presentation at birth, and a 7% higher decrease in the caesarean section rate was found in the early ECV group compared with the delayed ECV group.[122,123] Clearly, replication studies with adequate sample sizes are needed to further determine the possible benefit of initiating ECV prior to term. One international multicentre trial is currently in progress: The Early ECV2Trial, Canada (www.utoronto.ca/miru/eecv2).[123]

-Influence of tocolytics

The Cochrane database states that the use of tocolytics (beta-adrenergic drugs) in ECV reduces the failure rate of ECV. Whether tocolysis should be used routinely, or selectively in case of ECV failure, has as yet not been adequately addressed.[124]

*Beta-adrenergic drugs

The most widely used tocolytics are beta-adrenergic drugs such as salbutamol, ritodrine, hexoprenaline or terbutaline. These drugs are given intravenously or by inhalation. Because of the sometimes troublesome side-effects for mother and baby (i.e., tachycardia, tremor, anxiety, palpitations, sweating, retrosternal pain) and because of the inavailability of the drugs (e.g., ritodrine) in some

countries[125], other tocolytic drugs are often used such as nitroglycerine, nifedipine and atosiban.

*Nitroglycerine

The Cochrane review states that nitroglycerine should not be used for ECV because of increased side-effects, no evidence of effectiveness compared with placebo, and a trend towards lower effectiveness than with beta-stimulants.[124] However, a recent randomized controlled trial in 126 women showed higher ECV success rates in nulliparous women when using nitroglycerine intravenously titrated.[125] It is, thus, possible that titration of this drug on an individual basis may yield superior results compared to a standard dose of nitroglycerin.

*Nifedipine

Three randomized controlled trials comparing the effect of oral nifedipine and beta-mimetics reported comparable ECV success rates for both drugs, albeit with fewer side effects for nifedipine.[126-128] However, use of oral nifedipine in a randomized, double-blind, placebo-controlled trial in 310 women did not improve the success rate in ECV.[102]

*Atosiban

Experience with the use of atosiban (oxytocin antagonist) in ECV is limited to one small retrospective study in 38 women. The success rates were similar to data reported in the literature, but maternal side effects were less compared to other commonly used drugs.[129]

-Influence of regional anesthesia

Previous standard protocol dictated that no anesthesia should be employed for ECV, as pain is a reason to discontinue the attempt.[44] Also Neiger et al. discouraged the use of neuraxial techniques out of fear of injuring the foetus by applying too much force.[130] Other potential adverse effects of regional analgesia include a fall in blood pressure and headache.[131]

In recent years however, there has been a renewed interest in the use of regional anesthesia to facilitate ECV. A meta-analysis showed that regional anesthesia can improve the success rate of ECV (RR=1.5, 95% CI 1.12-1.98).[132] A prospective randomized controlled trial in 70 women confirmed these results.[133]

Despite these favorable results, it is difficult to draw definite conclusions regarding the use of regional anesthesia because of differences in study design and patient population in the various randomized control trials.[131]

-Influence of experience

Some authors have suggested that ECV success is not dependent on experience and clinical skills of the practitioner[134-137], whereas others claim the opposite.[104,138,139] There is certainly a learning process associated with performing ECV. Analysis of 80 consecutive ECV cases performed by one obstetrician without previous ECV experience showed that at first the learning curve for ECV is sharp, and then levels off after the first 20 cases.[94]

According to the Australian and British guidelines ECV should be performed by suitably trained health professionals.[97,140] Furthermore, accumulating ECV experience allows the practitioner to optimize the procedure through introducing new features and techniques.

The second aim of this thesis was, therefore, to evaluate the determinants/potential prognostic variables affecting the outcome of ECV in breech presentation.
The third aim of this thesis was to investigate whether the ECV protocol/procedure could be improved, by implementing a number of process policy guidelines.

-Influence of umbilical cord length

Umbilical cord length (UCL) is a marker of foetal mobility.[63-65] Since UCL is shorter in breech than in cephalic presentation[46,58-62], it might be hypothesised that UCL, in turn, may affect ECV outcome.
Furthermore, the literature shows that after successful ECV with cephalic presentation at delivery, the rate of vaginal delivery is substantially lower compared to women with cephalic presentation at birth without a history of breech.[141-145] Therefore, it might also be hypothesised that UCL could affect delivery mode, even after successful ECV.

-Influence of maternal thyroid function

Maternal thyroid function has an impact on foetal motility[146] and placental growth[147], both determinants of successful ECV. Therefore, it could be hypothesized that ECV outcome is influenced by thyroid function.
Until now, no studies have been published addressing the possible effects of maternal thyroid function on ECV outcome.

Therefore a fourth aim of this thesis was to investigate whether women with suboptimal thyroid function are more prone to failed ECV.

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Chapter
2

Outline of the thesis

Chapter 2: Outline of the thesis

II.1. Questions

The aim of this thesis was to address two different types of questions.
Firstly, with regard to maternal thyroid function during pregnancy:

- *The effect on foetal presentation*
- *The effect on neonatal thyroid function assessed at screening*

Secondly, with regard to ECV outcome:

- *Which determinants affect ECV outcome?*
- *What is the impact of ECV- performed according to a standardized protocol in an outpatient clinic- on delivery mode?*
- *What is the effect of implementing a number of process policy guidelines (protocol), on ECV success rate?*
- *Is there a relationship between maternal thyroid function during gestation and successful ECV?*

II.2. Study design

II.2.1. The Kempen study

A prospective follow-up study throughout pregnancy in healthy Dutch Caucasian pregnant women was performed from 12 weeks gestation onwards, until term (≥ 37 weeks) delivery. This study was approved by the Medical Ethical Committee of Máxima Medical Centre Eindhoven/Veldhoven, The Netherlands. All women who booked for antenatal control at 12 weeks gestation in five community midwife practices were invited for maternal thyroid function screening. Women who consented to participate were followed at 24 and 36 weeks gestation to assess thyroid function, obstetrical parameters and foetal presentation by ultrasound (36 weeks).
The primary outcome measure was the relationship between maternal thyroid function at each pregnancy trimester and foetal presentation at 36 weeks gestation. A secondary outcome measure was the relationship between maternal thyroid function at each pregnancy trimester and neonatal screening results.

II.2.2. Retrospective ECV and Prospective EBIS (Eindhoven Breech Intervention Study)

In 2003 a standardized ECV protocol was developed for the outpatient obstetric clinic at the Catharina Hospital in Eindhoven, The Netherlands. A retrospective study design was used to analyze all ECV's performed from January 2004 until July 2006. The aim of the study was to identify the determinants affecting ECV outcome in breech presentation, and to evaluate the impact of ECV performed according to a standardized protocol on delivery mode.
Over this 3-year period a standardized ECV protocol was developed, evaluated, and further optimized/modified/adapted. The changes in the original protocol

could be summarized according to the four R's: regularity, routine, release and relaxation. ECV was regularly performed (every week at fixed dates) by two clinicians from a team of 4 experienced obstetricians, who were released from other obstetrical/ medical activities. Tocolysis (Atosiban, 6,75 mg. intravenously) was administered routinely. After implementing this modified protocol as "process policy guidelines", the effect on ECV success rate was prospectively evaluated from the 1st of January 2007 to the 31st of July 2008.
This prospective study was approved by the Medical Ethical Committee of the Catharina Hospital.
Finally, to investigate whether maternal thyroid function is related to ECV outcome, a prospective study in ECV patients was performed. This prospective study was approved by the Medical Ethical Committee of the Catharina Hospital.

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Chapter
3

Maternal thyroid function during gestation is related to breech presentation at term

Abstract

Objective
To study the relationship between suboptimal maternal thyroid function during gestation and breech presentation at term.

Design
Prospective follow-up study during three trimesters of gestation.

Patients: A total of 1058 Dutch Caucasian healthy pregnant women were prospectively followed from 12 weeks gestation until term (> 37 weeks) delivery.

Measurements: Maternal thyroid parameters (TSH, FT4 and TPO-Ab) were assessed at 12, 24 and 36 weeks gestation as well as foetal presentation at term.

Results
At term, 58 women (5.5%) presented in breech. Compared with women with foetuses in the cephalic position, those women who presented in breech at term had significantly higher TSH concentrations, but only at 36 weeks gestation ($p = 0.007$). No between group differences were obtained for FT4 level at any assessment. The prevalence of breech presentation in the subgroup of women with TSH ≥ 2.5 mIU/l (90^{th} percentile) at 36 weeks gestation was 11%, compared to 4.8% in the women with TSH < 2.5 mIU/l ($p = 0.006$). Women with TSH below the 5^{th} percentile had no breech presentations. Breech position was significantly and independently related to high-normal maternal TSH concentration (≥ 2.5 mIU/l) at 36 weeks gestation (OR: 2.23, 95% CI: 1.14 - 4.39), but not at 12 and 24 weeks gestation.

Conclusion
Women with TSH levels above 2.5 mIU/l during end gestation are at risk for breech presentation, and as such for obstetric complications.

Introduction

Breech presentation at term is the most common abnormal foetal presentation and is associated with neonatal and maternal morbidity and mortality. The incidence of breech presentation decreases with term of gestation from approximately 16% at 32 weeks to 3-5% at 40 weeks gestation.[1] Many aetiological factors associated with breech presentation have been described previously, including, among others, prematurity, low birth weight, primiparity and smoking during pregnancy.[2-5] As these factors explain only 15 % of the variance of breech presentation,[6,7] further research into the mechanisms of breech presentation is needed.[8]

Ample evidence suggests a relationship between (sub)clinical thyroid dysfunction during gestation and impaired obstetrical outcome.[9-15] However, these studies mostly refer to overall impaired obstetric outcome with little emphasis on specifics including foetal presentation at term. A previous study of our group suggested a relationship between low maternal FT4 at 12 weeks gestation and breech presentation.[16] The number of breech cases, however, was very low due to the small sample size, and the sample was highly selected according to first trimester FT4 levels, which prevented us from looking at other thyroid parameters such as TSH.

The current study examines whether maternal thyroid hormone function during gestation is related to foetal position in a large sample of pregnant women from the general population, who were prospectively followed during gestation. The primary outcome measure was the relationship between maternal thyroid function and breech presentation at term.

Methods

Subjects

Over a period of 2 years, 1507 Dutch Caucasian pregnant women in five community midwifery practices, living in and around the city of Eindhoven (The Netherlands), were invited to participate at the time of their first antenatal visit at 12 weeks gestation. Seventy-nine percent (n = 1190) of the women consented to participate. Non-responders did not differ from the responders with regard to age, parity, or educational level. Women on thyroid medication (n = 10), those with known clinical hyperthyroidism (n = 8) or hypothyroidism (n = 2) at screening, those who became pregnant after hormonal stimulation (n = 8), those with multiple pregnancy (n = 8), as well as women with Type 1 diabetes (n = 5) were excluded.

Therefore, 1149 women were eligible for further participation and were followed up at 24 and 36 weeks gestation. Because spontaneous change of foetal position at term was an outcome measure, four cases with successful external cephalic version were excluded. Moreover, 11 women whose data were incomplete and an additional four mothers whose babies were born with severe congenital abnormalities (a possible determinant of abnormal foetal position)

were excluded. Of the remaining 1130 women, 72 delivered prior to 37 weeks gestation. Because breech position before term is not regarded as an abnormal foetal position, these women were excluded. Consequently, data analyses in the current study refer to a final sample of 1058 women who delivered at term (i.e., > 37 weeks gestation), and in whom thyroid function was assessed in all three trimesters. None of these women were treated for thyroid disease during gestation. Eight of the 1058 women (0.8%) developed gestational diabetes.
This study was approved by the Medical Ethics Committee of Máxima Medical Centre in Eindhoven/Veldhoven, The Netherlands.

Assessments
Term was assessed in two ways: from the date of the last menstrual period and from an ultrasound scan in the first trimester. If there was a discrepancy of more than 7 days between these two measurements, a second ultrasound was performed within 2 weeks to re-assess gestational age. Gestational age was expressed in weeks and days. Foetal position at birth was classified as cephalic or breech (i.e., complete/incomplete or frank breech). Possible confounders such as previous obstetrical history (parity, previous Caesarean section) demographic features and life style habits (smoking, alcohol intake, BMI) were carefully assessed during follow-up.

Thyroid parameters
Thyrotrophin (TSH), free thyroxine (FT4) and auto-antibodies to thyroid peroxidase (TPO-Ab) were assessed at 12, 24 and 36 weeks gestation. TSH was measured using a solid-phase, two-site chemiluminescent enzyme immunometric assay (IMMULITE Third generation TSH, Diagnostic Products Corporation, Los Angeles, USA). The inter-assay coefficients of variation were 5.0% and 4.4% at concentrations 0.22 mIU/l and 2.9 mIU/l, respectively. FT4 concentration was also measured by means of a solid-phase immunometric assay (IMMULITE FT4). 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. Reference ranges for TSH and FT4 were: 0.4 - 4.0 mIU/l and 10 - 24 pmol/l, respectively. The IMMULITE TPO-Ab kit was used for the determination of antibodies against thyroid peroxidase (TPO). The inter-assay coefficients of variation for this analysis were 9% and 9.5% for concentrations of 40 kU/l and 526 kU/l, respectively. The anti-TPO assay was standardized in terms of the International Reference Preparation for anti-TPO MRC 66/387. Women with TPO-Ab concentrations higher than 35 kU/l at 12 weeks gestation were regarded as antibody positive.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences Version 16.0. (SPSS). Initial analyses described the sample using means, standard deviations and frequencies. Kolmogorov-Smirnov tests revealed a non-normal distribution of FT4 and TSH in the sample at all assessments. Therefore, FT4 and TSH were compared in the breech versus cephalic presentation groups using Mann-Whitney U-tests. Associations between the prevalence of elevated maternal thyroid antibodies (TPO-Ab >35) and foetal presentation at term were analysed using chi-square tests. Differences in the prevalence of breech presentation were also examined using chi-square tests to compare groups based on TSH cutoffs and/or gestation. Determinants of breech presentation were analysed using single and multiple logistic regression analysis (OR, 95% CI).

Results

Throughout gestation, a decrease in mean FT4 was paralleled by an increase in mean TSH (table 1). The number of women with elevated TPO-Ab concentrations decreased towards term. Table 2 shows the differences in thyroid parameters between the 58 women (5.5%) who presented in breech position at term versus the remaining 1000 women who presented in cephalic position. At 36 weeks gestation, women with foetuses in breech position had significantly higher TSH concentrations compared to those with foetuses in cephalic position (Mann-Whitney U-test, $Z = 2.7$, $p = 0.007$) whereas there were no differences in TSH concentrations at 12 and 24 weeks gestation. FT4 was not significantly related to breech presentation at any trimester.

Similarly, groups did not differ in terms of prevalence of women with elevated TPO-Ab concentrations (data not shown).

In the absence of accepted reference values of normal thyroid function during pregnancy, the 5^{th}, 10^{th}, 90^{th} and 95^{th} percentiles cutoff points for TSH concentration at 36 weeks gestation were calculated. These values were: less than the 5^{th} (< 0.51 mIU/l), n = 54; for the 5 - 10^{th} percentiles (0.51 - 0.71 mIU/l), n = 54; for the 90 - 95^{th} (2.50 - 2.89 mIU/l), n = 49; and for the 95^{th} percentile (> 2.89 mIU/l), n = 59. Figure 1 shows the percentage of women who presented in breech presentation at delivery for each of the four percentile groups.

Table 1: ***Characteristics of 1058 term (≥ 37 weeks gestation) pregnant women in whom thyroid parameters were assessed in all three trimesters.***

		Mean	(SD)	N	(%)
Demographic features					
Age (19 - 43)		30.6	(3.5)		
Marital status					
	With partner			1037	(98)
	Single			21	(2)
Educational level					
	Low			85	(8)
	Middle			476	(45)
	High			402	(38)
	Academic			95	(9)
Life style habits					
	Smoking			127	(12)
	Alcohol intake			137	(13)
Body mass index					
	<20			741	(7)
	Between 20 and 25			636	(60)
	Between 26 and 30			234	(22)
	>30			117	(11)
Obstetrical features					
Parity					
	Primiparity			508	(48)
	Multiparity			550	(52)
Previous miscarriage in life				212	(20)
Term of gestation in weeks (37.0 - 42.9)		39.9	(1.2)		
Foetal presentation at delivery					
Cephalic				1000	(94.5)
Breech				58	(5.5)
Mode of delivery					
Spontaneously				699	(66)
After stimulation				148	(14)
Ventouse				95	(9)
Primary Caesarean section				53	(5)
Secondary Caesarean section				63	(6)
Neonatal outcome					
Male sex				550	(52)
Birth weight in grams (1940 - 5170)		3528	(482)		
Thyroid parameters					
12 weeks					
	FT4 pmol/l (9.4 - 26)	16.1	(2.5)		
	TSH mIU/l (0.01 - 9.25)	1.2	(0.8)		
	TPO-Ab >35 kU/l			91	(9)
24 weeks	FT4 pmol/l (8.4 -23)	13.8	(2.0)		
	TSH mIU/l (0.01- 6.2)	1.4	(0.7)		
	TPO-Ab >35 kU/l			79	(8)
36 weeks					
	FT4 pmol/l(7.2 - 21)	13.3	(2.0)		
	TSH mIU/l (0.5 - 5.4)	1.5	(0.7)		
	TPO-Ab >35 kU/l			70	(7)

Table 2: ***Median and range of FT4 and TSH in 58 women with breech presentation compared to 1000 women with cephalic presentation at term***

	FT4 (pmol/l)				TSH (mIU/l)			
	cephalic		breech		cephalic		breech	
12 weeks	15.9	9.1 - 27.9	15.8	12 - 21.1	1.09	0.01 - 6.20	1.06	0.39 - 5.10
24 weeks	13.8	8.4 - 23.0	13.5	9.0 - 18.4	1.19	0.01 - 5.70	1.29	0.40 - 3.50
36 weeks	13.2	7.2 - 24.6	13.3	9.8 - 17.5	1.30	0.05 - 5.01	1.60	0.58 - 5.40 *

* = significantly different, Mann-Whitney U-test, p = 0.007

With regard to the 90th and 95th percentile TSH groups at 36 weeks gestation, 11% and 14% of the women presented in foetal breech position at delivery, while there were no cases of breech presentation in the lowest 5th percentile TSH group ($\chi 2$ [3]: 9.7, p = 0.02). The prevalence of breech presentation in the subgroup of women with TSH ≥ 2.5 mIU/l (> 90th percentile) was 11% (12/108), compared to 4.8% (46/950) in the women with TSH < 2.5 mIU/l ($\chi 2$ [1]: 7.5, p = 0.006). When similar cutoff categories were made for FT4, no relation between FT4 and breech presentation was found.

Figure 1. ***Percentage of breech presentation at term, according to different percentile categories of maternal TSH at 36 weeks' gestation***

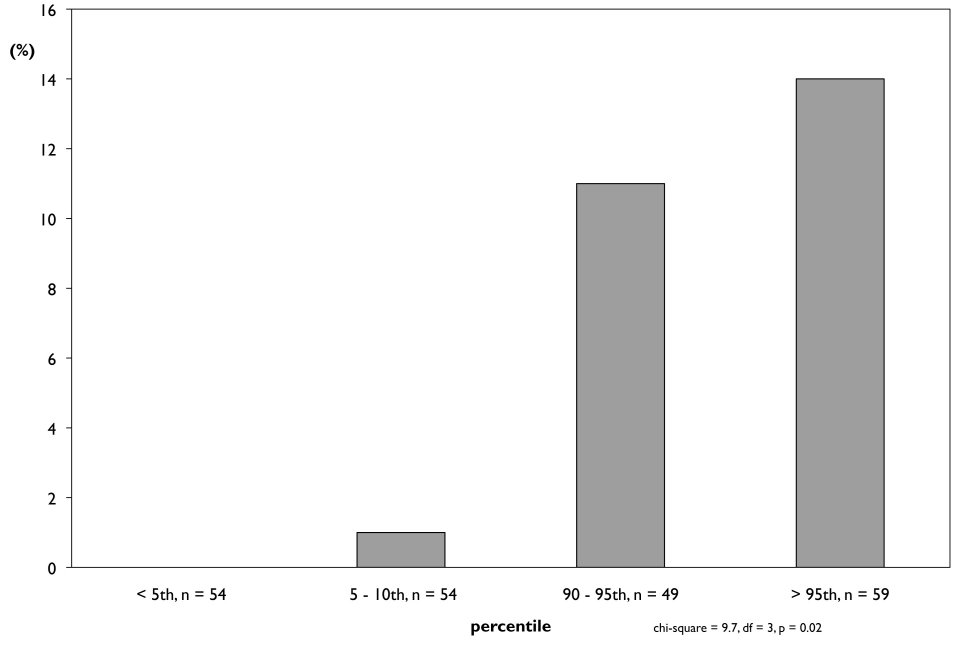

Table 3A shows the unadjusted odds ratios using logistic regression (OR, 95% CI) with breech position at birth as the dependent variable: nulliparity, birth weight and high-normal TSH (≥ 2.5 mIU/l) at 36 weeks gestation were all significantly related to breech presentation. Table 3B shows the adjusted

oddsratios using multiple logistic regression analysis, again with breech presentation at birth as the dependent variable. High-normal TSH levels at 36 weeks gestation, nulliparity, birth weight and smoking, were all significantly related to breech presentation.

Elevated TPO-Ab concentrations at 36 weeks gestation were not related to breech presentation. Of the 108 women with high-normal TSH levels at 36 weeks gestation, 17 (16%) had a history of parental thyroid disease, compared to 66 women (6.6%) in the group with low TSH levels ($\chi 2$ [1]: 10.4, $p = 0.001$). Similarly, of the 108 women with high-normal TSH at 36 weeks gestation, 20 (18%) had elevated TPO-Ab at 12 weeks gestation, compared with 66 (7%) in those with TSH < 2.5 mIU/l ($\chi 2$ [1]: 15.1, $p < 0.001$).

Finally, of the 83 women with a history of parental thyroid disease, 20% had elevated TPO-Ab at 12 weeks gestation, compared to 8% of the women with no family history of thyroid disease ($\chi 2$ [1]: 14.3, $p < 0.001$). None of the women with gestational diabetes had an elevated TSH concentration at 36 weeks gestation.

Table 3: ***Logistic regression analysis (dependent variable: breech presentation at term).***

	OR	95% CI
3A. Unadjusted oddsratios		
Nulliparity	2.38	1.12 - 4.34
Smoking during gestation	1.88	0.67 - 5.55
Alcohol intake	1.25	0.60 - 2.61
High BMI	0.99	0.94 - 1.05
High birth weight	0.93	0.92 - 0.96
High maternal age	1.03	0.96 - 1.11
Female sex	0.92	0.54 - 1.56
Low educational level	1.05	0.84 - 1.32
TPO-Ab > 35 kU/l at 36 wks	1.45	0.78 - 2.20
High-normal TSH (≥ 2.5 mIU/ml) at 36 wks	1.55	1.14 - 2.10
3B. Adjusted oddsratios		
Nulliparity	2.71	1.17 - 5.50
Smoking during gestation	2.97	1.23 - 7.69
Alcohol intake	1.22	0.77 - 2.82
High BMI	1.04	0.92 - 1.07
High birth weight	0.97	0.93 - 0.99
High maternal age	1.04	0.96 - 1.13
Female sex	0.83	0.39 - 1.78
Low educational level	1.05	0.78 - 1.40
TPO-Ab > 35 kU/l at 36 wks	1.85	0.88 - 3.21
High-normal TSH (≥ 2.5 mIU/ml) at 36 wks	2.23	1.14 - 4.39

Discussion

In the current study, breech position at birth was found to be related to maternal thyroid hormone status during late pregnancy. Not only was breech delivery almost 2.5 times more common in women with TSH levels at or above 2.5 mIU/l, regression analyses also confirmed elevated maternal TSH concentrations at 36 weeks gestation as a key predictor for breech presentation. High TSH levels were significantly associated with increased TPO-Ab concentrations as well as a history of thyroid disease in the parents. None of the women with TSH levels below the 5th percentile presented in breech position at term.

The current paper is among the first in which a possible relationship between maternal thyroid function and foetal position at birth was investigated. Our research group previously found breech presentation at term to be related to FT4 at 12 weeks gestation[16] in a smaller study using a highly selected sample of women (i.e., those with FT4 levels below the 10th percentile matched to those with an FT4 between the 50-90th percentile). However, a relation between breech position and TSH could not be examined in that sample, because the women were selected on the basis of FT4. In contrast, the current study used a much larger, unselected sample drawn from the general population, and we found high-normal elevated maternal TSH rather than low maternal FT4 to be the key predictor for breech presentation. In this unselected sample, 18% of the women with FT4 below the 10th percentile at 12 weeks gestation had TSH above the 90th percentile at 36 weeks gestation, compared to 6% of the women with an FT4 between 50-90th percentile (i.e., cutoff used in previous study). It is possible that the low first trimester FT4 in the previous study actually reflected high-normal TSH in late gestation. A recent paper, however, reports that free T4 immunoassays during gestation are less reliable compared to non-pregnant situations.[17] Future research is needed to detect the most appropriate tool for screening of maternal thyroid function during gestation.

The current findings are consistent with data of a large retrospective study in which elevated TSH (and not low FT4) was related to poor obstetric outcome.[14] The cutoff used in the current study to define high-normal TSH (≥ 90th percentile, 2.5 mIU/l) at 36 weeks gestation, was even lower than the cutoff of 3.0 mIU/l as recently recommended by the American Endocrine Society in pregnant women with hypothyroidism who are treated with thyroid hormone (in the absence of evidence-based reference ranges for TSH throughout gestation).[18]

Consequently, it may well be that even women with TSH levels ≥ 2.5 mIU/l are already at risk for obstetrical complications. The increase of TSH during late gestation is generally explained by physiological adaptation mechanisms during pregnancy - mainly based on an increased iodine need - as summarized elsewhere.[19] It is well known, that women with elevated TPO-Ab concentrations are at risk for high-normal TSH. This was also shown in the

current study, whereas a direct link between TPO-Ab and breech presentation could not be demonstrated. Moreover, the T3/T4 ratio might be changed, resulting in FT3 changes with a possible effect on TSH. Unfortunately, FT3 was not assessed in the current study.

How can the observed relationship between maternal TSH and foetal breech presentation be explained? The TSH receptor (TSHR) is expressed not only in the thyroid, but also in adipose tissue, brain, orbital tissue, lymphocytes and bone.[20] Evidence is accumulating for direct effects of TSH via the TSHR on these tissues.[21] However, until now, no TSHR has been described in the uterus. One could argue that elevated maternal TSH exerts an effect on uterine contractions. Empirical evidence regarding such a direct effect is, however, scarce. Only two studies were found, one showing reduced responsiveness to uterine agonists in hypothyroid rats,[22] and another concluding that this might be caused by a reduction in uterine myometrial Ca2+ channel function.[23] Uterine contractions are important for final cephalic presentation at term as has been suggested by a large Norwegian study including over 45,000 breech cases.[3] The finding in the current study that none of the women with TSH levels within the lowest 5th percentile presented in breech position may also be interpreted as indicative of a direct impact of maternal TSH on uterine contractions and, hence, on breech presentation. Such a presumed relationship would be consistent with recent findings by Casey et al. who showed that women with sub-clinical hyperthyroidism (TSH < 2.5th percentile and FT4 within normal range) did not show an increased risk for obstetric problems in general.[24]

Other factors in the current study, which were found to be related to breech presentation, have been described previously, such as nulliparity, birth weight (interfering with gestational weight) and smoking (affecting foetal muscle tone and in utero foetal motility).[2-5] Several limitations of the study need to be mentioned. First, although a large sample of over 1000 women was followed throughout gestation, the ultimate number of breech presentations was still relatively low. Another issue relates to the fact that other possible determinants of breech presentation such as umbilical cord length and amniotic fluid volume were not evaluated.

Major strengths of the study include the rather strict time frame of thyroid hormone assessments and the careful follow-up of all women by one midwife (HW) who was kept blinded to thyroid hormone status.

In conclusion, this study shows that in otherwise healthy women, high-normal levels of maternal TSH during late gestation are associated with breech presentation at term. Future strategies for minimizing breech presentation should, therefore, consider the role of maternal thyroid (dys)function, including T4 substitution during gestation in women with high-normal TSH.

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Chapter 4

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

Abstract

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

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

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

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

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

Conclusions
Women with high-normal TSH at end term are at risk for breech presentation. Substantial evidence for a relation between breech presentation and neurodevelopmental delay exists. Since high TSH during gestation has also been linked to poor neurodevelopment, the relation between breech presentation and poor neurodevelopment might be thyroid-related.

Introduction

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

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

Methods

Subjects

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

In both samples, women with twin pregnancies, on thyroid hormone replacement therapy, those with known auto-immune disorders (e.g., diabetes-I), or those who became pregnant after hormonal stimulation, were excluded, as well as women with preterm birth (study 1). To avoid potential language problems only women of Dutch Caucasian background were included. This resulted in a total of 121 women who were excluded from the first sample and 20 women from the second sample.

The study was approved by the Medical Ethical Committee of the Catharina Hospital Eindhoven.

Assessments

Foetal presentation was assessed by ultrasound in study one by one researcher (HW) who was blind to the thyroid hormone status, and in study two prior to

the ECV attempt. Breech position was categorized into complete, incomplete and frank breech. In all women a careful obstetrical history was taken.

Thyroid parameters
Thyroid parameters, free thyroid hormone (FT4), thyrotrophin (TSH) and thyroid peroxidase antibodies (TPO-Ab) were in the first sample assessed during the ultrasound visit at 35 - 38 weeks gestation, and in the second sample during the visit at the obstetrical outpatient clinic just before the ECV attempt. Only the third trimester TSH/FT4 assessments at 35 - 38 weeks in the first sample were taken into account and compared with the thyroid parameters of the women with a similar term seen in the ECV outpatient clinic.
TSH was measured using a solid-phase, two-site chemiluminescent enzyme immunometric assay (IMMULITE Third generation TSH, Diagnostic Products Corporation, Los Angeles USA). FT4 (concentration was also measured by means of a solid-phase immunometric assay (IMMULITE Free T4). The IMMULITE Anti-TPO Ab kit was used for the determination of antibodies against thyroid peroxidase (TPO). The anti-TPO assay was standardized in terms of the International Reference Preparation for anti-TPO MRC 66/387. TPO-Ab concentrations higher than 35 kU/l were regarded as antibody positive.

Statistical analysis
Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 17.0). First, a power calculation was performed. The TSH numbers at 36 weeks gestation of study one were log transformed and the difference (delta) in means between the women presenting in breech versus those presenting in cephalic position was calculated. With an alpha of 0.05 and a power of 0.8, it was calculated that the size of the breech group in the current study needed to be at least 148 women.
Kolmogorov-Smirnov tests revealed a non-normal distribution of FT4 and TSH in the current sample. Therefore, group comparisons on FT4 and TSH used Mann-Whitney U-tests. T-tests (two-tailed) and chi-square tests were used for other group comparisons. Subsequently, we looked at different cutoffs for maternal TSH with regard to breech position, and performed chi-squares to test associations.

Results
The characteristics of breech women in sample one (n = 58) and those in sample two (n = 131) were compared (table 1). As can be seen, there were no significant differences between the groups.

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

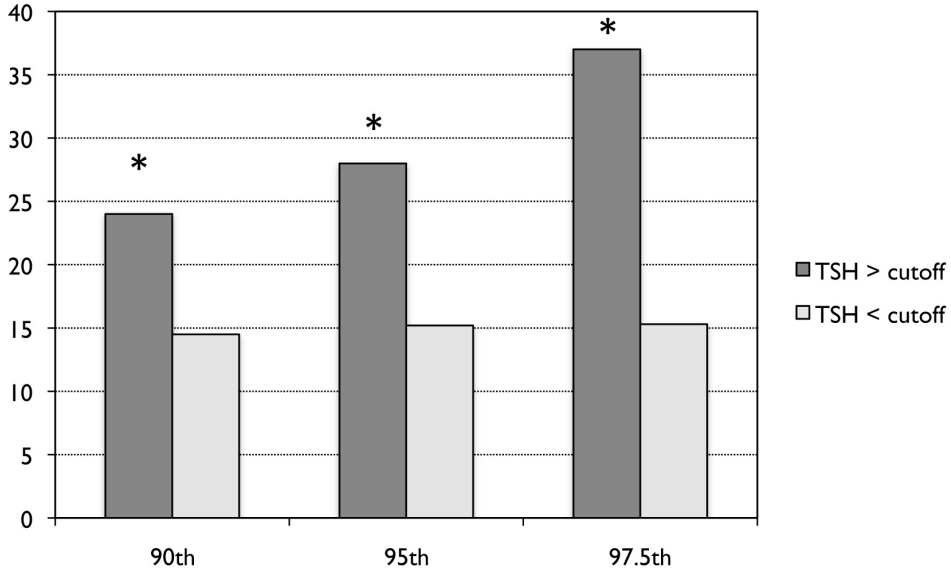
	Breech women of general population sample N = 58					Breech women presentation of outpatient ECV clinic N = 131					P		
	Mn	**(SD)**	**n**	**(%)**	**Median (range)**	**Mn**	**(SD)**	**n**	**(%)**	**Median (range)**	**t-test**	**$\chi 2$**	**MW-U**
Age	31.2	(3.7)				31.6	(4.1)				0.6		
Life style habits													
Smoking (yes/no)			6	(11)				8	(6)			0.3	
Any alcohol use			10	(18)				12	(9)			0.1	
Obstetrical features													
Parity													
Primiparity			33	(57)				87	(66)				
Multiparity			25	(43)				44	(34)			0.2	
one child			21	(37)									
two children			5	(9)									
> two children			1	(2)									
Miscarriage earlier in life			11	(19)				44	(34)			0.5	
Foetal characteristics													
Boy			34	(59)				62	(48)				
Girl			24	(41)				68	(52)				
Birth weight (grams)	3180	(464)				3293	(438)				0.1		
Placental weight (grams)	583	(128)				607	(132)				0.2		
Thyroid function parameters													
Family history of thyroid disease			5	(8)				13	(10)			0.8	
TSH (mIU/l)					1.60 (0.58-5.4)					1.59 (0.51– 9.7)			0.6
FT4 (pmol/l)					13.3 (9.8-17.5)					13.2 (9.6–18.2)			0.7

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

	Breech women N = 189					Cephalic women N = 1000					P		
	Mn	**(SD)**	**n**	**(%)**	**Median (range)**	**Mn**	**(SD)**	**n**	**(%)**	**Median (range)**	**t-test**	**$\chi 2$**	**MW-U**
Age	31.7	(3.9)				32.3	(3.6)				0.6		
Life style habits													
Smoking (yes/no)			13	(7)				120	(12)				
Any alcohol use			23	(12)				130	(13)				
Obstetrical features													
Parity													
Primiparity			120	(64)				480	(48)				
Multiparity			69	(36)				520	(52)			0.003	
Miscarriage earlier in life			51	(27)				190	(19)				
Fetal characteristics													
Boy			96	(51)				520	(52)				
Girl			93	(49)				480	(48)				
Birth weight (grams)	3299	(440)				3530	(485)				<0.001		
Placental weight (grams)	612	(109)				623	(113)						
Thyroid function parameters													
Family history of thyroid disease			2	(12)				170	(17)				
TSH (mIU/l)					1.61 (0.48-9.7)					1.30 (0.05-5.1)			0.003
FT4 (pmol/l)					13.3 (9.6-18.2)					13.2 (7.2-24.6)			
TPO-Ab > 35 (kU/l)			15	(8)				60	(6)				

Table 2 shows the characteristics of the total group of breech women (58 + 131 = 189) versus the women of sample one who presented in cephalic position (n = 1000). In the latter group, TSH and FT4 reference ranges were calculated (between the 2.5th and 97.5th percentiles) at 36 weeks gestation for those women who were TPO-Ab negative at 12 weeks gestation (n = 916). These ranges were: 0.42 - 3.2 mIU/l for TSH and 9.4 - 17.1 pmol/l for FT4. As can be seen in table 2, the women who presented in breech had significantly higher TSH levels compared to those who presented in cephalic position (Mann-Whitney U, p = 0.003), while no between group differences were found for FT4 (Mann-Whitney U, p = 0.62).

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



Significantly more primiparous women were found among the breech-presenting women versus the cephalic-presenting women. Groups did not differ in terms of the prevalence of women with elevated TPO-Ab. Subsequently, for the overall group (n = 1189) different TSH cutoff values were defined in the TPO-Ab negative women with cephalic presentation: the highest 90th (> 2.4 mIU/l, n =149), 95th (> 2.7 mIU/l, n = 77) and 97.5th (> 3.2 mIU/l, n = 37) percentiles. Comparing prevalence rates above and below these cutoffs of TSH categories, breech-presenting women were significantly more prevalent than cephalic-presenting women (25% versus 14%, 27% versus 15% and 35% versus 15%, p < 0.01, figure 1). The number of women with elevated TPO-Ab in the group with TSH > 90th, the 95th and the 97.5th percentile was significantly higher compared to the number of women below these cutoffs: 14% versus 4.5%, 17% versus 5% and 18% versus 5.2%. The mean FT4 values between groups did not differ: 13.2

pmol/l (in TSH > 3.2 mIU/l) versus 13.3 pmol/l (TSH <3.2mIU/l) or 13.4 pmol/l in women with a TSH < 50th percentile.

When high TSH (> 97.5th percentile) and parity were entered into a logistic regression analysis, both were found to be significantly related to breech presentation (dependent variable): OR: 2.3, 95% CI: 1.2 - 4.9 and OR: 5.1, 95% CI: 3.4 - 7.5, respectively. The 37 women with a TSH > 97.5th percentile (> 3.2 mIU/l) had a median TSH of 3.7 mIU/L with a range between 3.3 - 10 mIU/L, and 13 presented in breech. Finally, women with a TSH > 90th percentile (> 2.4 mIU/l) already had a 1.82 increased risk of breech presentation (RR: 1.82, 95% CI: 1.30 - 2.56).

Discussion

The current study combined the data sets of two studies in which the relationship between maternal thyroid status and foetal breech position was investigated. The present combined results obtained in 189 breech versus 1000 cephalic cases were clear in showing that high-normal maternal TSH during pregnancy is related to increased rates of breech position. It is unlikely that this relationship has arisen by chance, given the 189 breech cases in this study which was substantially higher than the minimum group size of 148 suggested by the power calculations. In line with the literature, primiparity was significantly more prevalent in breech cases compared to cephalic cases.[3]

In a recent large retrospective study elevated maternal TSH levels in both the first and second trimesters were not related to adverse obstetrical outcome.[5] In contrast, another large retrospective study did report a relation between increased TSH and poor obstetrical outcome (without detailed reports on foetal position), with TSH being assessed between 12 and 24 weeks gestation.[6]

How can the relation between high maternal TSH and breech position be explained? As discussed in a previous paper, one might speculate that TSH directly acts to modulate uterine contractility.[4] Another (more indirect) explanation might be that high-normal maternal TSH reflects suboptimal maternal thyroid function, which, in turn, would affect maternal-foetal T4 transfer, with impaired foetal neuromotor outcome as a final consequence. The finding that women with elevated TPO-Ab levels are especially at risk for high-normal TSH levels does suggest that high-normal maternal TSH in these women is pathologic rather than physiologic (the latter, for example, to compensate for high T4 turnover by deiodinase activity of the placenta).

In view of this latter explanation, several examples of delayed foetal neural maturation in breech pregnancies are worth addressing. First, the foetus, from 24-35 weeks onwards changes position through sudden leg extensions and active whole body movements (kicking).[7] These changes are caused through excitation of antigravity muscles, i.e. extensors of the body axis.[8] This excitation is a result of the interplay between inhibitory and stimulatory influences generated in the reticular nuclei, cerebellum and motor cortex. One may

speculate that sub-optimal maternal thyroid function (reflected by high TSH) might affect the neural processes involved in changes of foetal position. Secondly, foetuses in breech position show different sensory experiences compared to those presenting in cephalic position.[9] Although this was explained in terms of more amniotic fluid surrounding the head in breech, also this effect might have been due to suboptimal maternal-foetal thyroid hormone supply. In another study the development of lateralized head-position preference was found to be less pronounced in breech foetuses than in cephalic foetuses.[10] Although this may have been related to a smaller difference in stimulation between the left and right otoliths, inadequate thyroid hormone supply for development of the cochlear system might have been involved.[11]

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

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

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

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Chapter
5

Neonatal thyroid screening results are related to gestational maternal thyroid function

Abstract

Context
Overt maternal thyroid dysfunction during gestation is associated with poor neonatal thyroid function. However, research on the relationship between suboptimal maternal thyroid function (assessed at 3 trimesters) and neonatal thyroid screening outcome is scarce.

Objective
To study the relationship between maternal thyroid function at each pregnancy trimester and neonatal screening results.

Design
Prospective follow-up study during three trimesters of gestation in 886 Dutch Caucasian healthy pregnant women followed from 12 weeks gestation until term delivery (≥ 37 weeks) and their neonates.

Main outcome measure
The relation between neonatal data from the Congenital Hypothyroidism (CH) screening and maternal thyroid determinants (TSH, FT4 and TPO-Ab) assessed at 12, 24 and 36 weeks gestation.

Results
Boys have lower screening TT4 levels and their mothers have higher TSH levels at 24 and 36 weeks gestation. Lower screening TT4 levels are independently related to high-normal maternal TSH levels (> 97.5th percentile, as defined in 810 women without TPO-Ab at 12 weeks) at one or more times during pregnancy (OR: 2.15, 95% CI: 1.11 - 3.99) and lower gestational age (OR: 0.81, 95% CI: 0.70 - 0.94).

Conclusions
Maternal thyroid function during gestation is related to neonatal TT4 at screening. Future research should also link TSH-based neonatal screening results to maternal thyroid function, assessed throughout pregnancy. The finding of both lower neonatal TT4 levels in boys and higher TSH levels in mothers carrying boys is worthy of further investigation, as both observations may be meaningfully related.

Introduction

The foetus is totally dependent on maternal thyroid hormone supply during the first half of gestation. This dependency decreases during the second half of gestation when the ongoing maturation of the foetal hypothalamus-pituitary-thyroid axis (HPT axis) results in increased foetal T4 production.[1,2]

Evidence on whether poor neonatal thyroid screening results are dependent on (sub)clinical maternal thyroid dysfunction during gestation is limited. In iodine deficient areas, some studies found higher mean cord TSH levels compared to mean maternal TSH levels during different trimesters of gestation and at delivery.[3,4,5] Another study revealed a positive correlation between maternal FT4 and cord rT3 and between maternal rT3 and cord T3.[6] A recent study failed to demonstrate a relation between maternal thyroid function and neonatal screening results.[7] Conclusions based on these studies, however, cannot be definitive as they share a similar shortcoming: assessments of maternal thyroid function were done at a single, variable time point (12 - 24 weeks gestation), while the effect of maternal thyroid function on foetal thyroid development might be trimester-specific.[8,9]

This study reports on the neonatal thyroid screening outcome of a large group of healthy term born (≥ 37 weeks) neonates (n = 886), whose healthy mothers were followed at each trimester until delivery. Primary outcome was the relation between maternal thyroid function at each trimester and neonatal total T4 (TT4) screening results, after adjustment for other determinants of screening results.

Methods

Subjects

Over a 2-year period, 1190 out of 1507 Dutch Caucasian pregnant women living in the Eindhoven city area consented to participate in a follow-up study at their first antenatal control visit at 12 weeks gestation. For various reasons (e.g., thyroid medication, overt hyperthyroidism/hypothyroidism at screening, severe congenital malformations, hormone induced pregnancy, diabetes-I, missing data) 56 women were excluded. The remaining 1134 women were followed throughout pregnancy. Seventy-two of them delivered prior to 37 weeks gestation. Of the remaining 1062 women, 886 (83%) mothers gave written consent to access Congenital Hypothyroidism (CH) screening data. The Medical Ethical Committee of Máxima Medical Centre in Eindhoven/Veldhoven approved the study.

Assessments

Free thyroxine (FT4), thyrotropin (TSH) and auto-antibodies to thyroid peroxidase (TPO-Ab) were assessed at 12, 24 and 36 weeks gestation. TSH was measured using a solid-phase, two-site chemiluminescent enzyme immunometric

assay (IMMULITE Third generation TSH, Diagnostic Products Corporation, Los Angeles, USA). FT4 concentration was measured by means of a solid-phase immunometric assay (IMMULITE Free T4). The IMMULITE TPO-Ab kit was used for the determination of antibodies against thyroid peroxidase (TPO). Women with TPO-Ab concentrations > 35 kU/l at 12 weeks gestation were regarded as antibody positive. In The Netherlands, neonatal CH screening is performed by primarily assessing TT4 in heel puncture blood samples collected on filter paper. The TT4 concentration was compared with the mean TT4 of all neonates assessed that day in the screening laboratory. Babies with a TT4 ≥ 0.8 SD below the daily mean receive a TSH assessment: by definition this is around 20% of all neonates.[10]

Statistical analysis

To evaluate whether neonatal TT4 was related to maternal and neonatal parameters, we performed Pearson correlations (two-tailed), t-tests (two-tailed) and analysis of variance (ANOVA). Subsequently, different cutoffs for maternal TSH and FT4 were calculated, and chi-squares (χ^2) were used to test associations with neonatal TT4. Determinants of low neonatal screening TT4 (defined as ≥ 0.8 SD below the mean of the total study sample) were analyzed using multiple logistic regression analysis (OR, 95% CI).

Results

Mothers carrying male foetuses (table 1) had significantly higher mean TSH levels at 24 and 36 weeks gestation compared to mothers carrying girls, while mean FT4 did not differ. The number of women with elevated TPO-Ab titers did not differ as a function of foetal sex. Heel punctures for CH screening were performed at a mean age of 5.2 days (SD = 0.56). As shown in Table 1, mean overall neonatal TT4 at screening was 179 nmol/l (SD = 38 nmol/l). Boys had significantly lower mean TT4 levels compared to girls (t = 3.1, p = 0.002). Neonates born at 37 - 38 weeks gestation had significantly lower mean TT4 levels compared to those who were born ≥ 38 weeks gestation (F = 5.6, p < 0.001). This was also true for boys born at 37 - 38 weeks versus boys born ≥ 38 weeks gestation (F = 3.8, p = 0.002), while in girls this difference was only significant at the 90% level (F = 2.0, p = 0.07).

In the 810 women who were TPO-Ab negative at 12 weeks gestation, TSH and FT4 were defined as low and high using the lowest 2.5th and upper 97.5th percentiles as cutoffs (i.e., to denote the 5% extremes of the general population; Table 2). Mean TT4 was the lowest in the TSH > 97.5th percentile at 12 and 36 weeks gestation. Moreover, the percentage of neonates with low TT4 was the highest in the group with a TSH > 97.5th percentile, especially at 12 weeks (p = 0.03), and to a lesser degree at 36 weeks (p = 0.08). No differences in neonatal TT4 level among the maternal FT4 percentile groups were found for any of the three trimesters (Table 2).

Table 1. ***Maternal thyroid function during gestation and heel TT4 values assessed between 3 - 5th postpartum day in 886 at term born neonates (> 37 weeks).***

		Total n = 886 Mn (SD)	**Boys n = 464** Mn (SD)	**Girls n = 422** Mn (SD)	**t**	**p**
Maternal thyroid function						
12 weeks gestation	TSH	1.23 (0.79)	1.27 (0.81)	1.19 (0.77)	1.5	0.13
	FT4	16.1 (2.51)	16.2 (2.50)	16.1 (2.49)	0.5	0.58
24 weeks gestation	TSH	1.35 (0.67)	1.40 (0.74)	1.29 (1.59)	2.5	0.01
	FT4	13.9 (2.07)	14.0 (2.13)	13.8 (1.92)	1.6	0.14
36 weeks gestation	TSH	1.51 (0.78)	1.56 (0.79)	1.45 (0.69)	2.2	0.03
	FT4	13.3 (2.16)	13.4 (2.11)	13.2 (2.25)	0.6	0.5
Neonatal Heel results						
TT4 overall		179 (38)	176 (36)	184 (39)	3.1	0.002
37 weeks		n = 52, 164 (39)	n = 35, 160 (38)	n = 17, 172 (39)		
38 weeks		n = 122, 170 (37)	n = 70, 167 (37)	n = 52, 174 (36)		
39 weeks		n = 226, 177 (40)	n = 115, 173 (39)	n = 111, 181 (41)		
40 weeks		n = 260, 184 (36)	n = 125, 182 (33)	n = 135, 186 (39)		
41 weeks		n = 174, 186 (35)	n = 91, 183 (34)	n = 83, 188 (36)		
> 41weeks		n = 52 188 (40)	n = 28, 180 (37)	n = 24, 197 (42)		

Subsequently, women with a TSH > 97.5th percentile at least once during gestation were designated as the high-normal TSH group (n = 62 [7%] of total sample) of whom 21 (34%) had elevated TPO-Ab. Multiple logistic regression showed that high-normal maternal TSH (> 97.5th percentile) during gestation (OR: 2.15, 95% CI: 1.11 - 3.99) and gestational age ≥ 37 weeks (OR: 0.81, 95% CI: 0.70 - 0.94) were independently related to low heel TT4 (≥ 0.8 SD below the mean = 149 nmol/l) while alcohol use and smoking during gestation, maternal age, BMI, FT4 and TPO, female sex and weight of the newborn were not.

Table 2. ***Mean screening TT4 (SD) and numbers (%) of neonates with low screening TT4 (≥ 0.8 SD below the mean: < 149 nmol/l) according to maternal TSH cutoffs at three different trimesters, assessed in women without TPO-Ab at 12 weeks gestation.***

	Mean TT4 (SD) Total n = 886	**Low TT4 (<149 nmol/l)** Total n = 189
12 weeks		
TSH < 2.5th percentile, < 0.16 mIU/l **+**	178 (29)	3 / 26 = 11%
TSH between 2.5th - 97.5th percentile, 0.16 - 2.9 mIU/l	181 (37)	175 / 832 = 21%
TSH > 97.5th percentile, > 2.9 mIU/l	167 (39)	11 / 28 = 39% *
24 weeks		
TSH < 2.5th percentile, < 0.41 mIU/l	171 (40)	7 / 26 = 27%
TSH between 2.5th - 97.5th percentile, 0.41 - 2.77 mIU/l	172 (37)	173 / 830 = 21%
TSH > 97.5th percentile, > 2.77 mIU/l	170 (34)	9 / 30 = 30%
36 weeks		
TSH < 2.5th percentile, < 0.42 mIU/l	173 (35)	6 / 38 = 16%
TSH between 2.5th - 97.5th percentile, 0.42 - 3.10 mIU/l	180 (38)	174 / 825 = 21%
TSH > 97.5th percentile, > 3.10 mIU/l	165 (38)	9 / 23 = 39% **

+: TSH percentiles assessed in 810 women without TPO-Ab at 12 weeks gestation;
* = χ^2 (2): 6.9, p = 0.03; ** = χ^2 (2): 5.1, p = 0.08

Discussion

Our results contrast with those of a recent study[7] in which, however, maternal thyroid function was only assessed once in the first half of pregnancy (< 22 weeks) and high TSH was defined as > 2.5 mIU/l. Because a possible impact of sub-optimal maternal thyroid function on foetal thyroid function could be trimester-specific, the current study opted for maternal thyroid function tests in each trimester.[8,9] Moreover, we used a different cutoff for high maternal TSH by defining trimester-specific upper TSH levels as > 97.5th percentile in TPO-Ab negative women (2.9 mIU/l, 2.77 mIU/l and 3.1 mIU/l respectively).

How can the link between high-normal maternal TSH during gestation and low neonatal TT4 levels at screening be explained? During the first half of gestation, foetal thyroid function is totally dependent on maternal T4 supply. After the onset of foetal thyroid function, maternal T4 transfer continues until term and represents an important proportion of thyroid hormones available to the foetus[1,2], although most of the maternal T4 supply is inactivated by deiodinase 3 (D3) into rT3. Inadequate supply of maternal T4 during gestation (reflected by high maternal TSH) may result in lower foetal T4 and T3 levels. In the current study, women in the high-normal TSH group had lower, albeit non-significant, FT4 levels at 12 and 24 weeks gestation. High-normal maternal TSH reflecting lower maternal FT4 levels at early gestation may be indicative of reduced FT4 availability for the foetus throughout pregnancy, which in turn may result in lower neonatal screening TT4 levels. Moreover, one third (37%) of the women with high-normal TSH showed elevated TPO-Ab concentrations, reflecting thyroid auto-immunity. These women are known to be at risk for impaired

maternal-foetal transfer of FT4.[11] No differences in neonatal TT4 level among the maternal FT4 percentile groups were found for any of the three trimesters. This may be due to the greater sensitivity of TSH to detect small changes in the set point of the HPT axis compared with FT4.[12] Besides, it has been reported that pregnancy FT4 assessments are less reliable than non-pregnancy assessments.[13] Alternatively, it could be that a sub-sample of pregnant women in our study may have had increased placental deiodinase activity, which would explain their increased TSH levels in order to preserve their euthyroid state. Increased placental deiodinase, as such, would then be the likely cause of decreased foetal T4 availability, and hence lower screening neonatal TT4 levels.

Our finding that maternal TSH at 24 weeks was unrelated to low neonatal TT4 is difficult to explain. One may speculate that this decreased maternal T4 dependency mirrors the mid-gestation rise in foetal T4 production. It should be realized, however, that foetal T4 availability is dependent on a complex system of currently (largely) unknown maternal, placental and foetal regulatory components.

Possible determinants related to normal TT4 (and TSH) in healthy term babies such as gestational age and foetal sex (boys) have been described earlier.[7,14,15,16,17,18] To our knowledge, this is the first report describing higher TSH levels in pregnant women carrying a male foetus. An explanation for this finding is lacking, but one may speculate that male foetuses have a more active deiodinase activity than female foetuses, given consistent reports that boys have lower neonatal TT4 (and higher cord TSH) compared to girls.[7,16,18] However, in the current study, amniotic fluid data or newborn T3 values to support this hypothesis were not available. Moreover, the question whether this finding is clinical relevant, remains unresolved. It would be interesting to study whether neonatal male TT4 levels are associated with any of the neurodevelopmental problems known to preferentially affect boys.

Several limitations of the study need to be mentioned. First, iodine excretion data in mothers and neonates were not collected. It might be argued that increased maternal TSH and lower neonatal screening TT4 reflect the same underlying mechanism: sub-optimal iodine intake. Although all participants lived in iodine sufficient areas, it is questioned whether adequate iodine intake outside pregnancy also guarantees sufficient iodine intake to meet the demands of pregnancy.[19] Second, cutoffs to define elevated TSH (and FT4) cannot be compared with trimester-specific reference ranges of TSH, because they do not exist. Using the 5% extremes of the group in TPO-Ab negative women, as is done in the general population, appears to be the most valid approach available. Third, the absence of thyroid cord blood data did not allow us to examine whether the obtained association between high maternal TSH and low neonatal screening TT4 was already present in utero. On the other hand, a major strength of the study is the rather strict time frame of thyroid hormone assessments at each trimester.

Future research should consider linking TSH-based neonatal screening results (besides TT4) to maternal thyroid function, assessed at fixed time points for each trimester of pregnancy. The finding of both lower neonatal TT4 levels in boys and higher TSH levels in mothers carrying boys is worthy of further investigation, as both observations may be meaningfully related.

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Chapter
6

Minder keizersneden wegens stuitligging dankzij geprotocolleerde uitwendige versie in een speciaal spreekuur

Samenvatting

Doel
Identificatie van factoren die de kans op een succesvolle uitwendige versie van kinderen in stuitligging beïnvloeden, en evaluatie van het effect dat poliklinische, geprotocolleerde, uitwendige versie heeft op de wijze van bevallen.

Opzet
Retrospectieve analyse.

Methode
In 2003 werd een protocol voor uitwendige versie ontwikkeld op de polikliniek Verloskunde van het Catharina-ziekenhuis te Eindhoven; dit werd getoetst in een 'versiespreekuur'. Van alle zwangeren bij wie in de periode januari 2004-juni 2006 tijdens dit spreekuur een poging tot uitwendige versie was uitgevoerd, werden obstetrische kenmerken en de partus geanalyseerd. Van de versies werd 85% uitgevoerd door dezelfde 2 personen (1 verloskundige en 1 gynaecoloog), volgens het protocol.

Resultaten
Uitwendige versie bleek succesvol bij 96 van de 209 zwangeren (46%). Bij 1 zwangere moest na de versie een spoedsectio worden verricht wegens een partiële abruptio placentae. Nulliparitеit, onvolkomen stuitligging en een laag geboortegewicht van de baby hingen in deze studie samen met een kleinere kans op een succesvolle versie. In de groep waarin de versie succesvol was, was het percentage geboorten via sectio caesarea aanmerkelijk lager (9 versus 83%; OR: 0,21; 95%-BI: 0,09-0,51).

Conclusie
Uitwendige versie die volgens een standaardprotocol werd uitgevoerd door een vast team, bestaande uit een verloskundige en een gynaecoloog, bleek effectief te zijn: door uitwendige versie nam het aantal à terme stuitliggingen af en daarmee het percentage sectio's. Dit kan leiden tot een aanzienlijke gezondheidswinst voor de moeder en een belangrijke kostenbesparing voor de gezondheidszorg in Nederland.

Bij 3-5% van de vrouwen met een à terme zwangerschap (≥ 37 weken) heeft de foetus een stuitligging. Wat het optimale obstetrische beleid is bij stuitligging, is tot op heden onderwerp van heftige discussie. In 2000 suggereerden de uitkomsten van een groot multicentrisch onderzoek, de 'Term breech trial', dat een partus langs vaginale weg bij stuitligging gepaard ging met een toegenomen neonatale morbiditeit en sterfte.[1] Als gevolg hiervan nam in Nederland het aantal sectio's wegens stuitligging bij een à terme zwangerschap drastisch toe: van 50% in 2000 tot 80% in 2006.[2,3] Bij nadere, kritische beschouwing van deze multicentrische studie, en ook bij vervolgonderzoek van de onderzoekers zelf, werd echter de validiteit van de bevindingen achteraf ernstig in twijfel getrokken.[4-6] De trend naar meer sectio's wegens stuitligging was toen al begonnen.

De nadelen van sectio's, namelijk toegenomen maternale morbiditeit en sterfte en forse toename van obstetrische complicaties bij toekomstige zwangerschappen, zijn genoegzaam bekend.[7,8]

In de obstetrie bestaat er al vele decennia een relatief veilige methode om een à terme stuitligging te voorkomen: de uitwendige versie. Uit recente internationale literatuur blijkt dat deze methode het aantal sectio's aanzienlijk doet afnemen.[9-11] Wat de determinanten van een succesvolle versie zijn, weet men nog maar ten dele.[12-15] De laatste Nederlandse cijfers over uitwendige versies dateren van 1990.[16] In het betreffende artikel werd het nut van uitwendige versie niet groot geacht omdat in die tijd een vaginale bevalling bij stuitligging de voorkeur had. Inmiddels echter is het aantal keizersneden bij stuitligging spectaculair toegenomen. Het is dus gerechtvaardigd om veel aandacht te besteden aan uitwendige versie en aan een zo efficiënt mogelijke uitvoering hiervan.

In de huidige studie beschrijven wij de resultaten van een apart opgezet polikliniscch 'versiespreekuur'. Tijdens dit spreekuur verrichtte een klein team van speciaal getrainde obstetrici (2 gynaecologen en 1 tweedelijnsverloskundige) een versie volgens een standaardprotocol. De resultaten van ruim 200 versies in de periode 2004-2006 werden geanalyseerd.

Aan de hand van deze bevindingen wordt nader ingegaan op de recent in Nederland opgelaaide discussie over de vraag waar een versie het beste kan plaatsvinden: in de eerste of in de tweede lijn (www.ziekenhuis.nl/index.php?cat=nieuws&nieuws=item&id=5242&nieuwstype=pat).[17-19]

Patiënten en methoden

Versieprotocol. Gedurende een periode van 1 jaar (2003) werd op de polikliniek Verloskunde van het Catharina-ziekenhuis te Eindhoven een versieprotocol ontwikkeld (tabel 1).

Hierbij was het streven de versies zoveel mogelijk te laten uitvoeren door een klein aantal speciaal hierin getrainde medewerkers: 1 verloskundige en 2 gynaecologen. Alle medewerkers dienden zich aan het versieprotocol te houden om een effectieve evaluatie van het beleid mogelijk te maken.
In de onderzoeksperiode werd 85% van de versies uitgevoerd door dezelfde 2 personen (1 verloskundige en 1 gynaecoloog), volgens het protocol. Hierbij duwde een van de twee de stuit uit het bekken terwijl het foetale hoofd door de ander richting bekkeningang werd geduwd. Tijdens de kering controleerde een derde medewerker echoscopisch de harttonen en de ligging van het kind. Zo nodig werd een weeënremmer toegediend na klinische beoordeling van de tonus van de uterus vóór versie.

Tabel 1. ***Protocol voor de uitwendige versie van een foetus in stuitligging, ontwikkeld op de polikliniek Verloskunde van het Catharina-ziekenhuis te Eindhoven***

1. anamnese afnemen, informeren van de patiënte over de procedure en uitsluiten van contra-indicaties
2. echoscopisch onderzoek om de ligging van de foetus, de ligging van de placenta en de vruchtwaterindex te bepalen
3. cardiotocografie om foetaal welzijn te bevestigen
4. optioneel: toediening weeënremmer (atosiban 6,75 mg i.v.)
5. uitwendige kering
6. echoscopie na de versie om de foetale ligging te bevestigen
7. cardiotocografie na de versie
8. toediening van rhesus(D)immunoglobuline als de rhesusbloedgroep van de moeder negatief is

Patiënten. Gedurende de periode 1 januari 2004-30 juni 2006 kregen alle zwangeren met een foetus in stuitligging (vastgesteld door een eerstelijnsverloskundige of een gynaecoloog bij een zwangerschapsduur van 32-34 weken) uitleg over de mogelijkheid van een uitwendige versie als onderdeel van 'good clinical practice'. Na instemming van de zwangere (n = 280) vond verwijzing plaats naar het versiespreekuur bij een zwangerschapsduur van ongeveer 35-36 weken. De poging tot versie werd onmiddellijk na de verwijzing uitgevoerd.
Bij echoscopische controle volgens het protocol bleek dat bij 62 vrouwen de foetus een hoofdligging had. Er waren 9 vrouwen met een contra-indicatie voor versie: dwarsligging van de foetus (6), oligohydramnion (1) of een afwijkend foetaal hartfrequentiepatroon (2). Deze vrouwen (71 in totaal) werden geëxcludeerd; de data-analyse betreft dus 209 casussen.
De uitkomstmaten waren het percentage succesvolle versies en het percentage vaginale bevallingen na een geslaagde versie. Een versiepoging werd als succesvol gedefinieerd als direct na de poging echoscopisch een hoofdligging werd aangetoond. Verschillende determinanten waarvan uit de literatuur bekend was dat ze konden samenhangen met de uitkomst van uitwendige versie werden

geregistreerd, zoals de zwangerschapsduur bij versie, de pariteit, het type stuitligging, de ligging van de placenta, en het neonatale geboortegewicht.

Statistische analyse. De data werden geanalyseerd met behulp van het Statistical Package for the Social Sciences (SPSS), versie 14.0 (SPSS Inc., Chicago, VS). Verschillen in prevalenties van categoriale variabelen werden onderzocht met behulp van een χ^2-toets. Verschillen in gemiddelde waarden van continue variabelen (zwangerschapsduur, gewicht, leeftijd) werden onderzocht met behulp van een tweezijdige t-toets. De samenhang tussen de afhankelijke variabele (geslaagde versie) en een set van onafhankelijke variabelen werd getoetst met een logistische-regressieanalyse.

Resultaten

In tabel 2 zijn de patiëntkenmerken en het succespercentage na uitwendige versie weergegeven, opgesplitst naar pariteit.

Uitwendige versie bleek succesvol bij 96 van de 209 zwangeren (46%). Bij multiparae was de versie statistisch significant vaker succesvol dan bij nulliparae (oddsratio (OR): 1,91; 95%-BI: 1,29-2,84). Tabel 2 laat verder zien dat er een statistisch significant verschil was tussen nulliparae (n = 121) en multiparae (n = 88) in de zwangerschapsduur bij versie.

Tabel 2. ***Obstetrische kenmerken van zwangeren vóór, tijdens en na geprotocolleerde uitwendige versie van een foetus in stuitligging, in een onderzoek naar de resultaten van een poliklinisch 'versiespreekuur'***

Obstetrische kenmerken	Totaal (n = 209)	Nulliparae (n = 121)	Multiparae (n = 88)
vóór versie			
gemiddelde leeftijd (SD)	31,2 (4,4)	30,7 (4,8)	31,8 (3,7)
gemiddelde zwangerschapsduur in weken (SD)	36,2 (1,1)	36,0 (0,9)	36,4 (1,3)*
obstetrische anamnese (huidige zwangerschap); n (%)			
diabetes gravidarum	1 (0,5)	1 (0,8)	-
IUGR	1 (0,5)	1 (0,8)	-
ligging placenta; n (%)			
anterieur	76 (36)	39 (32)	37 (42)
posterieur	84 (40)	54 (45)	30 (34)
lateraal	15 (7)	9 (7)	6 (7)
fundaal	8 (4)	5 (4)	3 (3)
overig	26 (12)	14 (12)	12 (14)
type stuitligging; n (%)			
volkomen	51 (24)	29 (24)	22 (25)
onvolkomen	135 (65)	80 (66)	55 (62)
overig	23 (11)	12 (10)	11 (13)
complicaties tijdens versie; n (%)			
abnormaal cardiotocogram	3 (1,4)	2 (1,7)	1 (1)
PPROM	1 (0,5)	1 (0,8)	-
vaginaal bloedverlies	1 (0,5)	1 (0,8)	-
partiële abruptio placentae die spoedsectio nodig maakte	1 (0,5)	1 (0,8)	-
hoofdligging na versie; n (%)	96 (46)	44 (36)	52 (59)†

IUGR = intra-uteriene groeiretardatie; PPROM = 'preterm premature rupture of membranes'.
*Uitkomst statistisch significant verschillend van die bij nulliparae; tweezijdige t-toets, $p < 0,05$.
†Uitkomst statistisch significant verschillend van die bij nulliparae; χ^2-toets, $p < 0,01$.

Er was geen noemenswaardig verschil tussen nulliparae en multiparae wat betreft andere obstetrische factoren die een uitwendige versie kunnen beïnvloeden (zie tabel 2). Bij 1 nullipara (0,5% van het totale aantal zwangeren) moest na de versie een spoedsectio worden verricht wegens een partiële abruptio placentae; het kind werd in goede conditie geboren.

Tabel 3. ***Resultaten van een logistische-regressieanalyse waarin de invloed van obstetrische kenmerken op het succes van geprotocolleerde uitwendige versie van een foetus in stuitligging is onderzocht***

obstetrische kenmerken	univariate analyse		multivariate analyse	
	OR	95%-BI	OR	95%-BI
leeftijd zwangere	1,05	0,98-1,12	1,03	0,96-1,10
zwangerschapsduur bij versie	1,23	0,96-1,58	1,14	0,87-1,49
nulliparitеit	0,40*	0,23-0,71	0,42†	0,23-0,78
onvolkomen stuitligging	0,41*	0,23-0,74	0,48†	0,25-0,89
laag placentagewicht‡	0,33*	0,12-0,93	0,61	0,31-1,23
anterieure ligging placenta	0,62	0,34-1,10	0,59	0,31-1,11
laag geboortegewicht baby§	0,35*	0,12-0,98	0,33†	0,15-0,72

*Significant minder succesvolle versies als dit kenmerk aanwezig was (univariate logistische- regressieanalyse).
†Significant minder succesvolle versies als dit kenmerk aanwezig was (multivariate logistische-regressieanalyse).
‡Placentagewicht < P10 (< 486 g).
§Geboortegewicht < P10 (< 2637 g).

Tabel 3 geeft de resultaten van een univariate logistische-regressieanalyse weer, waarbij de uitkomst van de versie (succesvol/niet succesvol) de afhankelijke variabele was. De leeftijd werd gerekend in jaren, de zwangerschapsduur in weken. Nulliparitеit is hierbij vergeleken met multipariteit (die laatste term geeft aan dat een vrouw 1 of meerdere partussen heeft doorgemaakt); onvolkomen stuitligging is vergeleken met volkomen stuitligging. De volgende variabelen bleken een statistisch significante invloed te hebben op het succes van de poging tot versie: nulliparitеit, onvolkomen stuitligging, laag placentagewicht (< P10) en laag geboortegewicht van het kind (< P10).
Tabel 3 geeft ook de resultaten van een multivariate logistische-regressieanalyse weer, waarbij de uitkomst van de versie opnieuw de afhankelijke variabele was. Bij nulliparitеit, onvolkomen stuitligging en laag geboortegewicht bleek in deze cohort de kans op een succesvolle versie kleiner te zijn.
In tabel 4 zijn de obstetrische kenmerken van de partus weergegeven. Het gemiddelde geboortegewicht van de baby's was bij multiparae hoger dan bij nulliparae. Voor de hele groep (n = 209) was het aantal sectio's na een succesvolle versie statistisch significant kleiner dan bij een persisterende stuitligging: 9 versus 83% (OR: 0,21; 95%-BI: 0,09-0,51).
Dit gold ook voor nulli- en multiparae afzonderlijk.

Tabel 4. ***Kenmerken van de partus bij zwangeren die een geprotocolleerde uitwendige versie van een foetus in stuitligging hadden ondergaan***

Kenmerken van de partus	Totaal (n = 209)	Nulliparae (n = 121)	Multiparae (n = 88)	p
gemiddelde zwangerschapsduur in weken (SD)	39,2 (2,5)	39,0 (3,1)	39,6 (1,3)	
gemiddeld geboortegewicht in g (SD)	3 288 (504)	3 213 (510)	3 389 (481)*	0,005
wijze van bevallen (totaal); n (%)				
vaginaal in hoofdligging	90 (43)	36 (30)	54 (61)†	< 0,001
vaginaal in stuitligging	16 (8)	7 (6)	9 (10)	
primaire sectio bij stuitligging	81 (39)	59 (49)	22 (25)†	0,001
secundaire sectio bij hoofdligging	9 (4)	8 (7)	1 (1)	
secundaire sectio bij stuitligging	13 (6)	11 (9)	2 (2)†	0,04
na succesvolle versie; n (%)	96	44	52	
vaginale partus	87 (91)	36 (82)	51 (98)†	0,006
secundaire sectio caesarea	9 (9)	8 (18)	1 (2)†	0,006
na niet succesvolle versie; n (%)	113	77	36	
vaginale partus hoofd‡	3 (3)	0	3 (8)	
vaginale partus stuit	16 (14)	7 (9)	9 (25)†	0,02
primaire sectio caesarea	81 (71)	59 (77)	22 (61)	
secundaire sectio caesarea	13 (12)	11 (14)	2 (6)	

*Uitkomst statistisch significant verschillend van die bij nulliparae; tweezijdige t-toets.
†Uitkomst statistisch significant verschillend van die bij nulliparae; χ^2-toets.
‡Na een niet succesvolle uitwendige versie hadden 3 multiparae een spontane versie.

Beschouwing

Het opzetten van een spreekuur voor uitwendige versie, waarbij een vast team van specialisten (verloskundigen en gynaecologen) volgens een standaardprotocol werkt, lijkt erg efficiënt. Uitwendige versie bleek succesvol bij 96 van de 209 zwangeren (46%).

In de literatuur wordt voor uitwendige versie een succespercentage van 35-86 beschreven.[12] In een enquête onder de Nederlandse gynaecologen bleek dat er in slechts 19% van de maatschappen een formele registratie plaatsvond van het aantal versiepogingen en de slagingspercentages. Het slagingspercentage van de niet-geregistreerde pogingen werd ruwweg op 36 geschat; het slagingspercentage van de wél geregistreerde versiepogingen was hoger: 44.[20] Ons slagingspercentage van 46 komt hiermee overeen. In ons onderzoek blijken nulliparitеit, onvolkomen stuitligging en laag geboortegewicht de belangrijkste factoren te zijn die de succeskans bij een versiepoging verkleinen, conform de literatuur.[12,21]

Uit een cochrane-review blijkt dat versie een statistisch significante en klinisch relevante afname bewerkstelligt van het aantal sectio's (OR: 0,55; 95%-BI: 0,33-0,91).[22] Ook in onze studie nam het aantal sectio's fors af: van 83% bij persisterende stuitligging tot 9% na succesvolle versie. Uitwendige versie blijkt - in een klinische setting - ook een veilige methode te zijn. Er werden kortdurende foetale bradycardieën en tijdelijke veranderingen op het

cardiotocogram (CTG) geconstateerd, maar er trad bij slechts 1 zwangere (0,5%) een ernstige complicatie op, namelijk een partiële abruptio placentae waarvoor een spoedsectio binnen een half uur noodzakelijk was. Dit lage percentage complicaties komt overeen met gegevens uit de literatuur.[23-25]

Versie in de eerste lijn of in de kliniek.

Recent is er in Nederland discussie ontstaan over de plaats waar een uitwendige versie kan plaatsvinden, nu de Koninklijke Nederlandse Organisatie van Verloskundigen met de zorgverzekeraars afspraken heeft gemaakt om versies buiten de kliniek uit te laten voeren onder verantwoordelijkheid van de eerstelijnsverloskundigen (www.ziekenhuis.nl/index.php?cat=nieuws&nieuws=item&id=5242&nieuwstype=pat).[17-19] Deze aanpak strookt niet met Amerikaanse en Engelse richtlijnen, noch met de richtlijn van de Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG); in die richtlijnen wordt gesteld dat continue registratie van de foetale hartfrequentie (CTG) bij versie een absolute voorwaarde is en dat een klinische setting strikt noodzakelijk is omdat daar - indien nodig - snel een spoedsectio kan worden uitgevoerd.[12,26,27]

Bovendien wordt het succespercentage mogelijk beperkt door een aantal mechanische factoren. In sommige gevallen biedt het toedienen van een weeënremmer hierbij uitkomst, maar dit valt niet onder de bevoegdheid van de eerstelijnsverloskundige.[28]

Naar onze mening is het routinematig uitvoeren van uitwendige versies een eerste vereiste voor goede expertise. In een verloskundige normpraktijk doen zich per jaar 3-5 stuitliggingen voor.[29] Op basis van dit kleine aantal kan men geen goede expertise opbouwen; dat geldt overigens eveneens voor verloskundigen in de tweede lijn. Een gynaecoloog die incidenteel een versie uitvoert, zal ook niet genoeg handigheid opbouwen. Daarom pleiten wij voor het opzetten van een polikliniek voor uitwendige versie met een vast team van getrainde obstetrici (verloskundigen of gynaecologen).

Relevantie voor de gezondheidszorg.

De implementatie van een versiespreekuur leidt niet alleen tot afname van maternale morbiditeit, maar ook tot een aanzienlijke kostenbesparing voor de gezondheidszorg.[30-32] In een artikel in *Medisch Contact* uit 2006 zijn de kosten in Nederland van een sectio caesarea vergeleken met die van een instrumentele partus. De sectio kostte € 5594,11 euro en de partus € 993,86 (een verschil van € 4600,00).[3]

Op de huidige studie zou de volgende kostenanalyse van toepassing kunnen zijn. Van de groep vrouwen bij wie de uitwendige versie niet succesvol was, kreeg 71% een primaire sectio. Laten we aannemen dat dit percentage hetzelfde zou zijn geweest bij de succesvol behandelde groep (n = 96) als er geen versiepoging had plaatsgevonden. Dan waren in deze groep zonder versiepoging ongeveer 68

primaire sectio's te verwachten geweest. Dit suggereert dat uitwendige versie in een groep van 209 zwangeren met een kind in stuitligging een kostenbesparing oplevert van ruim € 300.000 (68 × € 4600). Op een landelijke schaal van 8000 stuitliggingen per jaar zou dit een aanzienlijke besparing betekenen.
Deze voorlopige schattingen rechtvaardigen nader onderzoek naar de kosteneffectiviteit van gestructureerde versie bij stuitligging. Een voorwaarde hierbij is dat zorgverleners uit de eerste en tweede lijn de zwangeren met een kind in stuitligging zoveel mogelijk verwijzen naar een versiespreekuur.

Conclusie
Uitwendige versie bij stuitligging is een goede methode om het aantal à terme stuitliggingen te verkleinen en het percentage sectio's fors te laten dalen. De methode lijkt naast aanzienlijke gezondheidswinst voor de moeder een belangrijke kostenbesparing op te leveren.
Elke zwangere met een kind in stuitligging moet, bij afwezigheid van contra-indicaties, de mogelijkheid aangeboden krijgen van een versie door getrainde obstetrici (verloskundigen of gynaecologen) op een speciaal hiertoe ingericht poliklinisch versiespreekuur.
Vanwege de noodzaak van foetale bewaking tijdens en na de versie, de mogelijkheid dat weeënremmers moeten worden toegediend en de, overigens zeer kleine, kans op een spoedsectio dient een versiepoging in de tweede lijn plaats te vinden.

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Chapter
7

Minder stuitbevallingen na invoering van beleidsprotocol voor versie

Samenvatting

Doel
Het effect onderzoeken van het doorvoeren van een aantal procesmatige beleidsregels, het zogenaamde procesprotocol, op het succespercentage van uitwendige versie bij stuitligging.

Opzet
Prospectief onderzoek.

Methode
Gedurende een periode van 3 jaar (2004-2006) werd een standaardprotocol voor een spreekuur voor uitwendige versie ontwikkeld, getoetst en aangepast. Vervolgens werd na invoering van het procesprotocol het effect ervan op het percentage succesvolle versies prospectief gevolgd gedurende de periode januari 2007-31 juli 2008. Een versie werd als succesvol gedefinieerd als direct na de poging echoscopisch een hoofdligging werd aangetoond. Secundaire uitkomstmaat was een mogelijke verandering van het aantal primaire sectio's bij stuitligging.

Resultaten
Het succespercentage van uitwendige versie was in de periode januari 2007-juli 2008 significant hoger dan in de periode januari 2004-december 2006, namelijk 61% (85/139 zwangeren) versus 47% (110/236; p = 0,006). De patiëntkarakteristieken waren in beide groepen gelijk, met uitzondering van 2 subgroepen bij de termijn van versie. De stijging was vooral aantoonbaar bij nulliparae en multiparae met een onvolkomen stuitligging. Nulliparitеit, onvolkomen stuitligging, placenta anterior en laag geboortegewicht van de baby waren gerelateerd aan een lagere succeskans bij versie. De termijn waarbij de versie plaatsvond bleek niet van invloed te zijn op het succespercentage.
Na invoering van een procesprotocol steeg het aantal hoofdliggingen bij de partus en daalde het aantal primaire keizersneden voor stuitligging van 39 naar 27% (p = 0,03). Het 'number needed to treat' om 1 sectio te voorkomen door middel van uitwendige versie volgens het procesprotocol, bedroeg 8.

Conclusie
Na invoering van een procesprotocol vond een aanzienlijke toename plaats van het succespercentage van uitwendige versie. Hierdoor daalde het aantal primaire sectio's wegens stuitligging verder. Deze bevindingen pleiten voor het oprichten van verschillende, in uitwendige versie gespecialiseerde centra in Nederland.

Uitwendige versie is de meest efficiënte methode om het aantal keizersneden bij stuitligging te verminderen. Het succespercentage van versie varieert in de internationale literatuur van 30-80%. Cijfers uit Nederlands onderzoek variëren echter van 25 - 41%.[2-7] Deze verschillen kunnen deels verklaard worden door verschillen in etniciteit in de onderzoeksgroepen - bij negroïde vrouwen daalt het ongeboren kind in stuitligging later in het maternale bekken in - en selectiebias, waarbij te verwachten moeilijke casussen niet meegenomen werden in de analyse. Veelal ontbreekt deze laatste informatie in de literatuur.
Vanaf 2004 werd in het Catharina-ziekenhuis te Eindhoven uitwendige versie volgens een standaardprotocol uitgevoerd door 2 obstetrici. Eén van hen was een lid uit een team van 3 ervaren versiespecialisten. De ander werd gerekruteerd uit een grote groep wisselende medewerkers, zoals arts-assistenten en verloskundigen, die geen specifieke training hadden gehad in uitwendige versie of er ervaring in hadden opgebouwd. Recentelijk beschreven wij in dit tijdschrift de uitkomsten na invoering van het standaardprotocol: over de periode januari 2004 - juni 2006 bedroeg het succespercentage van de verrichte versies 46%.[8]
Vanaf 2007 werkten wij dit standaardprotocol nader uit door het invoeren van een aantal procesmatige beleidsregels, hierna 'procesprotocol' genoemd. Deze wijzigingen waren samen te vatten onder de 4 R's: regelmaat, routine, relaxatie en rust. 'Regelmaat' betekende: iedere week, op een vast tijdstip, een versiespreekuur. Met 'routine' bedoelden wij dat het team dat de versies uitvoerde bestond uit 4 ervaren obstetrici, namelijk 2 gynaecologen en 2 verloskundigen. Iedere versie werd standaard door 2 leden uit dit team uitgevoerd. Om relaxatie van de uterus zoveel mogelijk te bevorderen, werd bij iedere versie altijd een weeënremmer gegeven. 'Rust' tenslotte, impliceerde dat deze vaste groep van ervaren medewerkers tijdens het versiespreekuur zoveel mogelijk van andere taken binnen de afdeling obstetrie werd vrijgesteld. De aanwezigheid van een doktersassistente bevorderde de accuraatheid van registratie van relevante data rondom een versie.
Het huidige onderzoek betreft een eerste evaluatie van het nieuw gevoerde beleid vanaf 2007. Hierbij luidde de vraagstelling: is het mogelijk om na invoering van procesmatige beleidsregels het succespercentage van uitwendige versie te verhogen en het percentage sectio caesarea bij stuitligging verder te verminderen?

Patiënten en methoden

In de periode januari 2007 - juli 2008 kregen alle zwangeren, bij wie de foetus bij een zwangerschapsduur van 32-34 weken in stuitligging lag, vastgesteld door een eerstelijnsverloskundige uit de regio Eindhoven en omstreken of een gynaecoloog uit het Catharina-ziekenhuis, uitleg over de mogelijkheid van een uitwendige versie. Na instemming van de zwangere vond bij een zwangerschapsduur van ongeveer 35-36 weken verwijzing plaats naar het

versiespreekuur. De poging tot versie werd onmiddellijk na de verwijzing uitgevoerd.
Verschillende determinanten, waarvan uit de literatuur bekend was dat ze mogelijk samenhangen met een succesvolle uitwendige versie, werden ten tijde van de versie geregistreerd, zoals de zwangerschapsduur bij versie, de pariteit, het type stuitligging en de ligging van de placenta. Bij de partus werd het geboortegewicht geregistreerd. De primaire uitkomstparameter van het onderzoek was het percentage succesvolle versies. Een versiepoging werd als succesvol gedefinieerd indien direct na de poging echoscopisch een hoofdligging werd aangetoond. Secundaire uitkomstmaat was een mogelijke verandering van het aantal primaire sectio's bij stuitligging. Hierbij werd het percentage electieve sectio's wegens stuitligging voor het doorvoeren van het procesprotocol berekend en vergeleken met het percentage electieve sectio's na invoering. Vervolgens werd de reductie van het absolute risico op een electieve sectio door een geslaagde uitwendige versie na het doorvoeren van het procesprotocol berekend.

Statistische analyse
De data werden geanalyseerd met behulp van de Statistical Package for the Social Sciences (SPSS), versie 16.0 (SPSS Inc., Chicago, VS). Verschillen in prevalenties van categorische variabelen werden onderzocht met behulp van een χ2-toets. Verschillen in gemiddelde waarden van continue variabelen (termijn, gewicht, leeftijd) werden onderzocht met behulp van een tweezijdige t-toets.
Bij de bestudering van de succespercentages van de verschillende jaren werd separaat gekeken naar de verdeling van de 2 belangrijkste voorspellers voor niet-succesvolle versie: primipariteit en onvolkomen stuitligging. Op deze manier kon worden nagegaan of een eventuele toename van het percentage geslaagde versies toe te schrijven was aan het voorkomen van relatief eenvoudigere casussen die zich in de periode van het vervolgonderzoek aandienden op het spreekuur.
Tenslotte werd het logistische regressiemodel gebruikt (odds ratio (OR), 95%-BI) om de samenhang tussen de afhankelijke variabele (al dan niet geslaagde versie) en de onafhankelijke variabele (procesprotocol) te beschrijven. Hiervoor werden alle versiepogingen over de periode 2004-2008 bij elkaar gevoegd, waarbij werd gedichotomiseerd in een versiepoging verricht volgens een procesprotocol of volgens een standaardprotocol (als referentie). Dit betekende in de praktijk: versiepoging voor of na 2006. De gecorrigeerde OR van succesvolle versie werden uitgerekend met het multiple logistische-regressiemodel. Hierbij werd de lokalisatie van de placenta gedichotomiseerd in: anterior of niet anterior; het type stuit in: onvolkomen of overige types stuit; en het termijn bij versie in: voor of na 37 weken. Het geboortegewicht en het gewicht van de placenta werden gedichotomiseerd in: boven of onder het 10de

percentiel van de totale groep. De leeftijd van de zwangere werd als een continue variabele ingevoerd.

Resultaten

In de periode januari 2007-juli 2008 werd aan alle patiënten, bij wie bij een termijn vanaf 32 weken een stuitligging werd vastgesteld, de mogelijkheid van een uitwendige versie voorgelegd. Na instemming van de zwangere (n = 208) vond verwijzing plaats naar het versiespreekuur vanaf een termijn van 35 weken.

Tabel 1: ***Effect van het doorvoeren van een procesprotocol op het succes van uitwendige versie bij stuitligging. Karakteristieken van een patiëntengroep uit de periode 2004-2006 (standaardprotocol, n=236) en een patiëntengroep uit 2007-2008 (procesprotocol, n=139).***

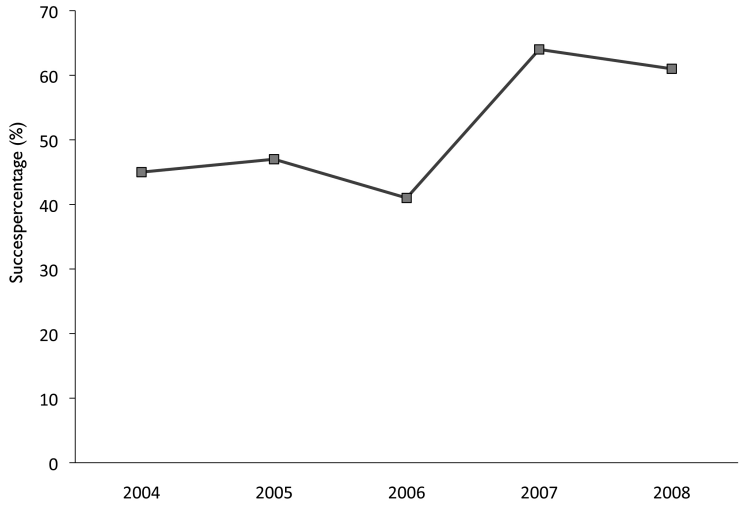
	2004-2006 n = 236	**2007-2008** n = 139	**Totaal** n = 375
leeftijd in jaren, gemiddelde (SD)	31(4,4)	31(4,5)	31(4,4)
pariteit, n (%)			
nullipara	139(59)	86(62)	225(60)
multipara	97(41)	53(38)	150(40)
type stuit, n (%)			
volkomen	53(23)	36(26)	89(24)
onvolkomen	157(66)	93(67)	250(66)
half onvolkomen	26(11)	10(7)	36(10)
termijn bij versie			
gemiddelde, in weken plus dagen (SD, in dagen)	36+3(1,1)	36+4(1,2)	36+3(1,2)
range in weken	35 - 39	35 - 39	35 - 39
< 36 weken, n(%)*	109(46)	46(33)	155(41)
36-37 weken, n(%)**	70(30)	65(47)	135(36)
37-38 weken, n(%)	34(14)	14(10)	48(13)
>38 weken, n(%)	23(10)	14(10)	37(10)
placentaligging bij versie, n(%)			
posterior	94(40)	62(45)	156(42)
anterior	90(38)	55(40)	145(38)
lateraal	52(22)	22(15)	74(20)
obstetrische kenmerken bij partus			
termijn in weken plus dagen, gemiddelde (SD, in dagen)	39+4(1,4)	39+4(1,7)	39+4(1,5)
placentagewicht in g, gemiddelde (SD)	622(117)	605(116)	616(117)
geboortegewicht in g, gemiddelde (SD)	3305(497)	3257(488)	3287(494)
primaire sectio wegens stuitligging, n(%) ***	92(39)	38(27)	130(35)

*: Significant verschillend bij χ^2-toets; 1 vrijheidsgraad; 95%-BI: 1,06 - 2,51; p=0,013
**: Significant verschillend bij χ^2-toets; 1 vrijheidsgraad; 95%-BI: 0,31 - 0,74; p=0,001
***: Significant verschillend bij χ^2-toets; 1 vrijheidsgraad; 95%-BI: 1,08 - 2,36; p=0,03.

Bij 62 patiënten bleek er bij echoscopische controle al sprake te zijn van een hoofdligging van de foetus; 2 patiënten zagen bij nader inzien af van een versiepoging; 3 patiënten werden uit de analyse geëxcludeerd vanwege

dwarsligging van de foetus; en 2 hadden een contra-indicatie voor versie vanwege oligohydramnion.
De uitkomsten van versie bij de overige 139 vrouwen werden geanalyseerd en vergeleken met de uitkomsten van de groep uit de periode 2004-2006 (n = 236), de periode voordat de procesmatige veranderingen werden doorgevoerd. De obstetrische kenmerken van deze 2 groepen staan weergegeven in tabel 1. Hieruit blijkt dat de patiëntkarakteristieken voor de groep 2004-2006 vrijwel identiek waren aan die van de groep 2007-2008, met uitzondering van 2 subgroepen bij de termijn bij versie. In de periode 2007-2008 werden er namelijk significant meer versies verricht bij een termijn van 36-37 weken dan in de periode 2004-2006 en significant minder versies verricht voor een termijn van 36 weken.
In de totale groep (n = 375) kwamen 17 spontane versies voor. Dit betrof bij 9 patiënten, na mislukte versie, een spontane versie van stuit naar hoofdligging bij de partus (4 nulliparae en 5 multiparae). Bij 8 patiënten betrof dit, na geslaagde versie, een spontane versie van hoofd naar stuitligging bij de partus (5 nulliparae en 3 multiparae).

Figuur 1. ***Percentages succesvolle uitwendige versies bij stuitligging na oprichting van een speciaal versiecentrum in 2004, en het doorvoeren van een aantal procesmatige beleidsregels in 2007.***



In de figuur is het succespercentage van de versies per jaar weergegeven. Het succespercentage over de jaren 2004, 2005 en 2006 verschilde nauwelijks, respectievelijk 45, 48 en 41%, maar nam in 2007 abrupt toe (62%), waarna in 2008 geen verdere stijging waarneembaar was (60%). In tabel 2 is het percentage succesvolle versies in de perioden 2004-2006 en 2007-2008 weergegeven, voor zowel de groep als geheel, als uitgesplitst naar pariteit en type stuit, en worden deze onderling vergeleken. Hieruit blijkt een hoger succespercentage in de periode 2007-2008 voor de gehele groep patiënten (61%), alsook voor

nulliparae en multiparae afzonderlijk, ten opzichte van de periode 2004-2006. Verder blijkt dat deze stijging vooral bij de onvolkomen stuit (moeilijke versies) werd teruggevonden. Zo nam bij nulliparae met een onvolkomen type stuit het succespercentage significant toe van 27 naar 46%, terwijl bij volkomen stuit een geringe stijging te zien was van 57 naar 65%. Bij multiparae was er een vergelijkbare stijging van het succespercentage bij de onvolkomen stuit van 58 naar 77%, en een geringe stijging bij de volkomen stuit van 66 naar 78%.

Tabel 2: ***Overzicht van succesvolle uitwendige versies bij stuitligging, vóór (2004-2006) en na (2007-2008) invoering van een procesprotocol, zowel van de patiëntengroep in zijn geheel, als opgesplitst naar pariteit en moeilijkheidsgraad.***

	Totaal N = 375	**2004-2006 N = 236**	**2007-2008 N = 139**	**p-waarde**	**95%-BI**
hoofdligging na versie	195 (52)	110 (47)	85 (61)	0,006	1,17 - 2,73
n (%) totaal					
nullipara	95/225 (42)	51/139 (37)	44/86 (51)	0,03	1,09 - 3,01
moeilijke versie (onvolkomen stuit)	55/158 (35)	26/95 (27)	29/63 (46)	0,01	1,11 - 3,91
makkelijke versie (volkomen stuit)	40/67 (60)	25/44 (57)	15/23 (65)	0,5	0,57 - 4,11
multipara	100/150 (67)	59/97(61)	41/53(77)	0,04	1,06 - 4,08
moeilijke versie (onvolkomen stuit)	59/92 (64)	36/62 (58)	23/30 (77)	0,08	0,96 - 8,07
makkelijke versie (volkomen stuit)	41/58 (71)	23/35 (66)	18/23 (78)	0,3	0,68 -4,59

De ruwe OR van het doorvoeren van het procesprotocol op succesvolle versie bedroeg 1,61 (95%-BI: 1,03-2,61). In tabel 3 staan de gecorrigeerde OR's weergegeven van geslaagde versie (afhankelijke variabele) bij 375 zwangeren met een stuitligging, met het doorvoeren van het procesprotocol als onafhankelijke variabele. Daarbij werd gecorrigeerd voor een aantal uit de literatuur bekende factoren. Hieruit blijkt dat bij nulliparitеit, onvolkomen stuitligging, een placenta anterior lokalisatie en een laag geboortegewicht de kans op een succesvolle versie afnam, terwijl na implementatie van het procesprotocol deze kans toenam. Tevens blijkt uit tabel 3, dat de termijn bij versie, dat wil zeggen voor of na 37 weken, niet van invloed was op het succespercentage.

Tabel 3: ***Effect van het invoeren van een procesprotocol voor uitwendige versie bij 375 zwangeren met een stuitligging, weergegeven als gecorrigeerde oddsratio's (OR), met het doorvoeren van het procesprotocol als onafhankelijke variabele multipele logistische-regressiemodel***

	gecorrigeerde OR	95% - BI
procesprotocol	1,71	1,12 – 2,87
leeftijd zwangere	0,98	0,94 – 1,04
lermijn bij versie: vóór of na 37 weken	0,94	0,57 – 1,52
nulliparíteit	0,35	0,22 – 0,56
onvolkomen stuit	0,48	0,30 – 0,77
placenta anterior	0,64	0,41 – 0,98
laag placentagewicht*	1,01	0,45 – 2,29
laag geboortegewicht kind**	0,38	0,16 – 0,89

*: Laag placentagewicht: gewicht < 10de percentiel (< 479 gram) van de totale groep
**: Laag geboortegewicht: gewicht < 10de percentiel (< 2674 gram) van de totale groep

Over de gehele periode (2004-2008) nam het percentage sectio's na een succesvolle versie af met een factor 6,5: van 79% naar 12%. Het percentage primaire sectio's wegens stuitligging à terme nam na de invoering van het procesprotocol significant af: van 39% in de periode 2004-2006 naar 27% in de periode 2007-2008 (95%-BI: 1,08-2,36; p = 0,03, zie tabel 1). Dit betekent, dat het 'number needed to treat' om 1 sectio te voorkomen door middel van uitwendige versie volgens het procesprotocol, 8 bedraagt. De reductie van het absolute risico op een electieve sectio door een geslaagde uitwendige versie na het doorvoeren van het procesprotocol bedroeg 12% (95%-BI: 1,7-21,0).

Beschouwing

Na invoering van een procesprotocol in het versiespreekuur nam het succespercentage van uitwendige versie significant toe van 47 naar 61%. Dit resulteerde in een daling van het percentage primaire sectio's wegens stuitligging met 12%. Het blijkt dat vooral een hoger succespercentage werd behaald bij zwangeren bij wie de baby in onvolkomen stuit lag. Deze stijging was niet het gevolg van een verandering van de samenstelling van de patiëntenpopulatie.

Invloed van wijzigingen op procesniveau

In de periode 2004-2006 bleek al vrij snel dat in een grote perifere opleidingskliniek slechts een beperkt aantal obstetrici routine kunnen krijgen in het verrichten van uitwendige versies. Door vanaf 2007 een vast team van versiespecialisten te formeren en deze op een vast tijdstip in de week vrij te plannen van andere taken binnen de dagelijkse praktijk, werd een hoger rendement behaald bij uitwendige versies.

Invloed van weeënremming

In 2004 werd in ons ziekenhuis als weeënremmer ritodrine (voorheen bekend als Prepar) 10 mg intramusculair gebruikt. Vanwege de vervelende, veelal

cardiale bijwerkingen zoals maternale hartkloppingen, werd ritodrine in februari 2005 vervangen door atosiban 6,75 mg intraveneus. Tot nog toe is alleen de effectiviteit van ritodrine bij versie evidence-based bewezen.[9] Echter, een kleine retrospectieve analyse waarin 17 patiënten ritodrine kregen toegediend en 21 patiënten atosiban, liet zien dat beide middelen even effectief lijken.[10]
Onze eerste ervaringen met atosiban deden wij op in 2005, toen dit middel steeds vaker werd toegediend op het versiespreekuur. Omdat het consequent toepassen van atosiban in het nieuwe protocol mogelijk een verklaring zou kunnen zijn voor de toename van het succespercentage, werden de data over de periode van 2004-2006 nader geëvalueerd. Hieruit bleek dat in 2004 bij 40% van de vrouwen tocolyse was toegediend, in 2005 bij 75% en in 2006 bij 97%. Uit de figuur blijkt dat het succespercentage gedurende die jaren niet veranderde. Dit maakt het onwaarschijnlijk dat een toename van het succespercentage van versie na deze periode toe te schrijven is aan het standaard toedienen van tocolyse. Uiteraard is alleen een gerandomiseerde klinische trial in staat om het onafhankelijk effect van tocolyse op het succespercentage aan te tonen.

Effectiviteit en veiligheid
Uitwendige versie in een klinische setting is een zeer efficiënte manier om het percentage keizersneden bij stuitligging te reduceren.[11] Ook in onze studie nam het aantal sectio's fors af, namelijk met een factor 6,5: van 79% bij niet succesvolle versie tegen 12% na succesvolle versie. Daarnaast is het ook een veilige methode om het aantal keizersneden bij stuitligging te doen dalen.[12-15] In onze studie trad er gedurende de gehele periode 2004-2008 1 ernstige complicatie op, namelijk een partiële abruptio placentae. Na een spoedsectio werd een gezond kind geboren, met een apgarscore van 9 en 9 na respectievelijk 1 en 5 min. Deze ernstige complicatie impliceert dat een versie in een klinische setting dient plaats te vinden.[1,16-18]

Beperkingen van het onderzoek
Een beperking van de huidige studie is dat het een niet-gerandomiseerd onderzoek betreft, maar deels een retrospectieve (2004-2006), deels een prospectieve (2007-2008) studie. Het is echter de vraag of - met de huidige gegevens voorhanden - het ethisch nog verantwoord is om een uitwendige versie aan te bieden anders dan volgens een strak omlijnd protocol.
Een andere beperking is het aantal deelnemers in de prospectieve studie: door het nog relatief geringe aantal is analyse bij subgroepen, zoals verschillen in de termijn bij versie, niet altijd mogelijk. In de literatuur is de invloed van de termijn bij versie op het succespercentage nog niet duidelijk.[19-20] Op dit moment loopt er een gerandomiseerde multicenter studie naar het effect van de termijn op de uitkomst van een uitwendige versie, waarvan de resultaten in de loop van 2009 te verwachten zijn (http://www.utoronto.ca/miru/eecv2).

Tenslotte zijn sommige parameters, waarvan uit de literatuur bekend is dat deze een versie kunnen beïnvloeden, zoals de hoeveelheid vruchtwater en de mate van indaling van de stuit in het bekken, niet meegenomen, zodat hun onafhankelijk effect op het succespercentage binnen het huidige model niet kan worden geschat.

Implicaties voor de organisatie van zorg

Concentratie van zorg komt de kwaliteit ten goede. Zoals de Inspectie voor de Gezondheidszorg voorstelt, moeten er binnen het ziekenhuiswezen regionale specialistische centra komen voor specifieke ingrepen.[21] Het huidige onderzoek laat zien dat dit niet alleen geldt voor technisch ingewikkelde operaties, maar ook voor relatief eenvoudige handelingen zoals uitwendige versie, waarbij een strakke organisatie, gekoppeld aan brede ervaring, in belangrijke mate bijdraagt aan het succes van de interventie, met alle positieve gevolgen voor moeder en kind. Ook buitenlandse richtlijnen bevelen een gespecialiseerd versiecentrum aan.[1,18]

Conclusie

Na het oprichten van een obstetrisch centrum gespecialiseerd in uitwendige versies bij stuitligging, waarbij ook op procesniveau beleidsregels werden doorgevoerd, was er een sterke toename van het percentage geslaagde versies. Dit resulteerde in een aanzienlijke verlaging van het aantal primaire keizersneden wegens stuitligging.

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Chapter
8

External cephalic version policy in case of breech presentation: a matter of patient-centred good clinical practice

In The Netherlands, there is a current controversy regarding the policy of external cephalic version (ECV) in case of breech presentation in term pregnancies. [1]

The question of where to perform ECV involves aspects of safety, success rate, competence, training and cost-effectiveness. In The Netherlands, a woman can deliver at home with a community midwife (30%), in hospital with a community midwife (10%), or - after referral to an obstetrician - with a hospital midwife (10%) or with an obstetrician (50%).[2] ECV is an intervention which is experienced as an unpleasant and stressful event by the mother.[3] A community midwife in The Netherlands deals with only 3 to 5 pregnancies complicated by breech presentation per year [4], a number which is by far too small to build up sufficient experience for performing ECV. Immediate referral to a hospital for getting an ECV would also provide a partial solution to the problem as often only part of the obstetrical staff members and residents in the Dutch hospitals are experienced in performing ECV.

ECV is a relatively safe procedure, with a rare chance of serious complications, resulting in emergency Caesarean section in up to 0.4% of cases. [5] International guidelines, therefore, recommend that cardiotocographic monitoring is required and that ECV should be attempted only in settings in which Caesarean delivery services are available.[6,7] The argument by the Royal Dutch Society of Midwives favouring current clinical practice regarding ECV is based on a retrospective cohort analysis of 958 ECV's showing a similar incidence of emergency Caesarean section as in usual obstetric care.[4] This can be regarded as a typical example of 'health professional centred' thinking: how to convince a woman who needs an emergency Caesarean section after ECV that ECV in a community setting is nevertheless a safe intervention?

The success rate of ECV varies between 35 - 86%.[7] Tocolysis is associated with successful ECV [8], although its precise role within a standard protocol remains to be addressed. Administration of (intravenous) tocolytics during ECV, however, is not within the routine care of community midwives.

There is no debate as to whether or not ECV can easily be performed by a midwife specifically trained in ECV. Between January 2004 and July 2006, 209 ECV's were performed (120 primipara and 89 multipara) according to a standardized protocol at the Catharina Hospital (Eindhoven) with the aid of one trained hospital midwife and one trained obstetrician. Ninety-six (46%) women had a successful ECV: 44 primipara (37%), and 52 (60%) multipara. One emergency Caesarean (0.5%) was performed because of placental abruption. All women with successful ECV were referred back to the community midwife who delivered 45 (46%) of them. After failed ECV, the number of total Caesarean sections was 93 (83%) compared to 9 (9%) in women after successful ECV, implicating a nine fold reduction, and thus suggesting high cost/effectiveness. The number of participants of this follow-up of standardized ECV is clearly too small to generalize. The much needed randomised clinical trials (including tocolysis) to

provide evidence based data are currently underway. It is nevertheless believed that our study indicates that ECV is a safe and highly effective procedure which, when performed by trained healthcare professionals, meets the patients' right for optimal obstetrical care. In our perception, this creates a win-win situation as the following objectives are met: the community midwife's policy to deliver as many women as possible; the obstetricians' objective to reduce the number of technical interventions, and the health insurer's wish to achieve optimal care at minimal costs.

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Chapter
9

Maternal thyroid function is related to the outcome of external cephalic version in breech presentation

Abstract

Objective
To investigate the relation between maternal thyroid function and the outcome of external cephalic version (ECV) in breech presentation.

Design
Prospective cohort study in 141 women (≥ 35 weeks gestation) with a singleton foetus in breech. Blood samples for assessing thyroid function were taken prior to ECV. Main outcome measure was the relation between maternal thyroid function and ECV outcome indicated by post ECV ultrasound.

Results
ECV success rate was 77/141 (55%), 41/48 (85%) in multipara and 36/93 (39%) in primipara. Women with a failed ECV attempt had significantly higher TSH concentrations than women with a successful ECV ($p < 0.001$). Multiple logistic regression showed that TSH (OR: 0.52, 95% CI: 0.30-0.90), nulliparity (OR: 0.11, 95% CI: 0.03-0.36), frank breech (OR: 0.30, 95% CI: 0.10-0.93) and placenta anterior (OR: 0.31, 95% CI: 0.11-0.85) were independently related to ECV success.

Conclusion
Higher TSH levels increase the risk of ECV failure.

Introduction

The incidence of breech presentation decreases with increasing gestational age from approximately 16% at 32 weeks to 3-5% of all pregnancies at term.[1] External cephalic version (ECV) is recommended by the American College of Obstetricians and Gynecologists (ACOG) [2] and the Royal College of Obstetricians and Gynaecologists (RCOG) [3] as the best method to reduce the number of breech presentations and breech deliveries at term. Reported success rates vary widely from 30-80%.[3] Several factors have been associated with successful ECV outcome including parity, type of breech, placenta location, amniotic fluid index, and engagement of the breech.[4-6]

Recently, our research group showed that at 36 weeks gestation women with TSH levels above 2.5 mIU/l are at risk for breech presentation.[7] It is stated that foetal movements and mobility are a prerequisite for spontaneous version into the cephalic position.[8] Since maternal thyroid function is related to the probability of spontaneous version, it may be hypothesized that TSH may, in turn, affect ECV outcome.

To the best of our knowledge, this is the first prospective study to examine the relationship between maternal thyroid hormone status and ECV success.

Methods

Subjects

Over a period of two years, 194 women seen in a specialized ECV clinic were invited to participate when they presented at ≥ 35 weeks gestation with a foetus in breech presentation. Only Caucasian patients with sufficient knowledge of the Dutch language were eligible (n = 169). Nineteen patients declined to participate, while four patients with a transverse lie and five patients with known thyroid disease were excluded. Data analysis, therefore, included the remaining 141 participants (see table 1), all of whom gave written informed consent.

This study was approved by the Medical Ethical Committee of the Catharina Hospital in Eindhoven, The Netherlands.

Assessments

At intake, demographic features (maternal age, BMI, tobacco/alcohol use) and obstetrical parameters (parity, previous obstetrical history) were recorded. Prior to ECV, ultrasound was performed to determine type of breech, amniotic fluid index and placental location. Ultrasound was repeated post-ECV in order to confirm success. At birth, foetal presentation, placental and birth weight were carefully assessed.

Table 1: ***Characteristics of 141 women who had an ECV attempt and in whom thyroid parameters were assessed.***

	Mean (SD)	N (%)
Demographic features		
Maternal age (years)	31.6 (4.2)	
Range (23-46)		
Any tobacco use		11(8)
Any alcohol use		12(8.5)
Body mass index (BMI)		
Range (17-47)	23.7 (4.2)	
BMI <25		112 (79.5)
BMI between 25 and 30		17 (12)
BMI > 30		12 (8.5)
Previous miscarriage in life		31(22)
Obstetrical features		
Parity		
Nulliparity		93 (66)
Multiparity		48 (34)
Gestational age at ECV (weeks, days)	36.1 (0.9)	
Range (35.0-39.9)		
Type of breech		
Frank		93 (66)
Complete		36 (25.5)
Incomplete		12 (8.5)
Placenta location		
Anterior		55 (39)
Posterior		56 (39.7)
Lateral		30 (21.3)
Cephalic presentation after ECV		77 (55)
Cephalic presentation at delivery		79 (56)
Placental weight (grams)	615 (127)	
Range (295-1000)		
Birth weight (grams)	3344 (447)	
Range (1765-4576)		
Thyroid parameters		
TSH mIU/l		
Median	1.48	
Range (0.02-10.0)		
FT4 pmol/l		
Median	10.0	
Range (7.1-14.0)		
TPO-Ab >35 kU/l		9 (6)

ECV intervention

Cardiotocography was performed routinely before and after the procedure. Before ECV, all women had a full bladder and were routinely given a tocolytic drug (Atosiban, 6.75 mg. intravenously). Anti-D (1000 IE) was given prophylactically to all Rhesus negative women. ECV (monitored by ongoing ultrasound) was performed by two experienced obstetricians working in unison: the hands of one staff member concentrated on the breech, while the other's concentrated on the foetal head, with manipulation being consecutive rather than simultaneous. While a "forward somersault" was the preferred method to achieve cephalic position, a "backward flip" was an alternative strategy for nulliparous patients with a frank breech presentation. ECV was defined as

successful when cephalic position was demonstrated on the post-ECV ultrasound.

Thyroid parameters

Blood samples were taken prior to administration of the tocolytic drug and subsequently stored for assessing the following thyroid parameters: thyroxine (FT4), thyrotrophin (TSH) and thyroid peroxidase antibodies (TPO-Ab). TSH was measured using a solid-phase, two-site chemiluminescent enzyme immunometric assay (IMMULITE Third generation TSH, Diagnostic Products Corporation, Los Angeles USA). The inter-assay coefficients of variation were 5.0% and 4.4% at concentrations 0.22 mIU/l and 2.9 mIU/l, respectively. FT4 concentration was also measured by means of a solid-phase immunometric assay (IMMULITE Free T4). The inter-assay coefficients of variation for this technique were 6.7% and 4.4% at concentrations of 11.6 pmol/l and 31.5 pmol/l, respectively. Reference ranges for non-pregnant women for TSH and FT4 were: 0.4 - 4.0 mIU/l and 10 - 24 pmol/l, respectively. The IMMULITE TPO-Ab kit was used for the determination of antibodies against thyroid peroxidase (TPO). The inter-assay coefficients of variation for this analysis were 9% and 9.5% for concentrations of 40 kU/l and 526 kU/l, respectively. The anti-TPO assay was standardized in terms of the International Reference Preparation for anti-TPO MRC 66/387. TPO-Ab concentrations >35 kU/l at 36 weeks gestation were regarded as antibody positive.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 17.0). Initial analyses described the sample using means, standard deviations and frequencies. The distributions of FT4 and TSH were non-Gaussian (Kolmogorov-Smirnov tests); therefore, Mann-Whitney U-tests were used to examine FT4 and TSH for group comparisons and ECV success. Associations among elevated maternal thyroid antibodies (TPO-Ab > 35 kU/l) and ECV outcome were analyzed using chi-square tests. Prevalence of successful ECV stratified according to quartiles of TSH was also examined using a chi-square test. Single and multiple logistic regression analysis (odds ratios and 95% CI's) were performed to calculate un-adjusted and adjusted OR's for successful ECV (dependent variable). The independent variable was TSH. For the multiple logistic regression analysis, age (continuous), body mass index (continuous), parity (dichotomized in nulliparous and parous), type of breech (frank breech versus the rest), gestational age at version (continuous), placental position (dichotomized in anterior versus other), placental weight (continuous), birth weight (continuous) and amniotic fluid index (dichotomized using 10 cm as a cutoff) were also controlled for.

Results

The overall ECV success rate, indicated by the post-procedure ultrasound results, was 55% (77/141), and was significantly lower in nulliparous women (39%: 36/93) than in multiparous women (85%: 41/48; χ^2 = 27, df = 1, p < 0.001). In one patient prolonged post-ECV foetal bradycardia occurred which necessitated emergency cesarean section. Transient heart rate abnormalities were observed in 3 patients. Spontaneous version into cephalic position at birth after failed ECV occurred in 2 (nulliparous) women. Spontaneous version back into breech after successful ECV did not occur.

The median TSH level for the whole study sample was 1.48 mIU/l (range: 0.02 - 10 mIU/l). Table 2 shows the distribution of FT4 and TSH values in relation to ECV outcome. Women with failed ECV's had significantly higher TSH levels than those with successful ECV's (Mann-Whitney U, p < 0.001), but corresponding FT4 levels did not differ between groups (Mann-Whitney U, p = 0.88). The correlation between FT4 and TSH was 0.18, (p = 0.034). Also, the prevalence of elevated TPO-Ab (> 35 kU/l) did not differ between groups (9% versus 4%, p = 0.18) with regard to ECV outcome.

Table 2: ***Median and range of FT4, TSH and number of elevated TPO-Ab titres in 141 breech women in relation to ECV outcome***

	Success ECV N=77	Failed ECV N=64	P Mann-Whitney U	P χ^2
Median TSH mIU/l	1.20	1.90	<0.001	
Range	0.02-10.0	0.60-9.20		
Median FT4 pmol/l	10.0	10.0	0.88	
Range	7.2-14.0	7.1-14.2		
TPO-Ab > 35 kU/l	3 (4%)	6 (9%)		0.18

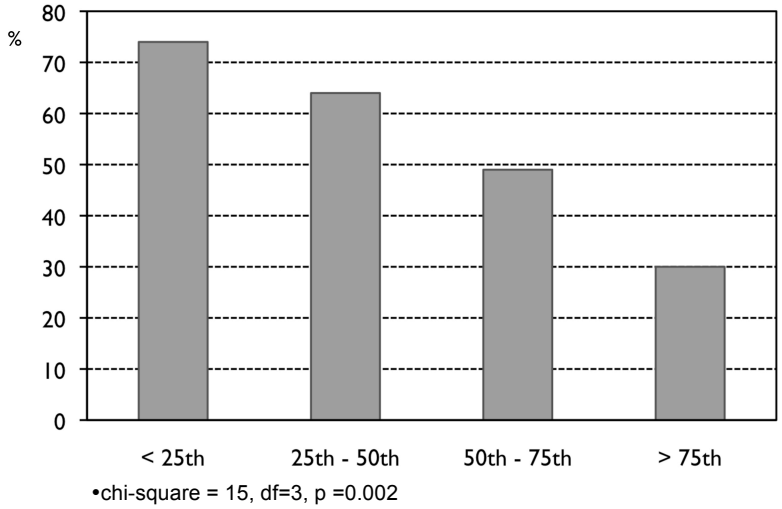
Figure 1 shows the prevalence of successful ECV according to different TSH quartiles (25th percentile: < 0.99 mIU/l, 25th - 50th percentile: 0.99 - 1.48 mIU/l, 50th - 75th percentile: 1.49 - 2.0 mIU/l and > 75th percentile: > 2.0 mIU/l). Clearly, the percentage of ECV success significantly decreased with increasing TSH quartile (74% to 30%, χ^2 = 15, df = 3, p = 0.002).

In table 3a, single logistic regression is shown with successful ECV as the dependent variable. TSH, parity, type of breech and placenta anterior location were all significantly related to successful ECV outcome. In table 3b, adjusted OR's are shown with TSH as independent variable and successful ECV as dependent variable using multiple logistic regression analysis. TSH (OR: 0.52, 95% CI: 0.30-0.90), nulliparity (OR: 0.11, 95% CI: 0.03-0.36), frank breech (OR: 0.30, 95% CI: 0.10-0.93) and placenta anterior (OR: 0.31, 95% CI: 0.11-0.85) were all significantly and independently related to ECV success.

In healthy pregnant women (without elevated concentrations of TPO-Ab and with proven sufficient iodine intake) trimester specific cutoffs for elevated TSH are still lacking. A frequently used upper TSH reference level in pregnancy

is ≥ 2.5 mIU/l.[9] In the current study 20 women had a TSH above this level. Of these 20 women 5 (25%) underwent successful ECV, compared to 72 successful ECVs from the sample of 121 women (60%) with TSH levels below the cutoff of 2.5 mIU/l (χ^2 = 8.2, df = 1, p = 0.004). The RR of women in breech with TSH above 2.5 mIU/l for failed ECV was 2.4, (95% CI = 1.1 - 5.3).

Figure 1: ***percentage of ECV success in relation to TSH quartiles (mIU/l) in 141 women with breech presentation ≥ 35 weeks gestation ****



Discussion

In the current study, successful ECV outcome was independently related to maternal TSH: women with unsuccessful ECV had significantly higher TSH levels. The ECV success rate of 55% in the current study is comparable to others reported in the literature.[2,3] While our data support earlier observations showing that factors affecting ECV success include parity, type of breech and placenta location [4-6], to our knowledge, this is the first study reporting on a possible relationship between maternal thyroid function and ECV outcome.

We recently showed in a large sample of over 1000 pregnant women from the general population that higher levels of TSH constitutes a risk factor for breech presentation.[7] The median TSH of breech-presenting women (n = 58) in that sample was 1.47 mIU/l which is remarkably similar to the median TSH value of 1.48 mIU/l obtained in the current sample of 141 women presenting in breech.

How can the observed relationship between maternal TSH and ECV outcome be explained? Several mechanisms might be suggested. First, one could argue that elevated maternal TSH directly impacts uterine relaxation, thereby negatively affecting ECV outcome. Empirical evidence regarding such a direct effect is, however, scarce. TSH receptors have been shown in other non-thyroid tissues such as bone, heart and brain tissue, but so far no studies on human uterine samples have been published.[10,11] Also, in patients with subclinical

hypothyroidism (reflected by high TSH), the myocytes of the smooth muscle cells of the aorta are dysfunctional, leading to increased arterial stiffness and impaired diastolic function.[12] The mechanism behind is a reduced activity of the sarcoplasmatic reticulum CA-ATPase which controls the efficient concentration of calcium in the cytoplasm. Another study in sub-clinical hypothyroid women showed a beneficial effect of thyroxine replacement on arterial stiffness.[13] It is known from earlier studies that thyroid hormone (T3) has a direct relaxation effect on vascular smooth muscle cells.[14] It might be hypothesized that a similar relation between TSH and uterine myocytes does exist. Inappropriate relaxation of uterine smooth muscle vessels in women with high TSH might hinder ECV.

Table 3: ***Unadjusted (A) and adjusted OR's (B) for successful outcome of ECV (dependent variable), n = 141***

A	**OR**	**95% CI**
Maternal age	1.05	0.97-1.14
Body Mass Index	0.93	0.86-1.02
Gestation at version	1.05	0.73-1.50
Nulliparity	0.12	0.05-0.29
Frank breech	0.37	0.18-0.78
Amniotic fluid > 10 cm	1.33	0.67-2.65
Placenta anterior	0.36	0.18-0.74
Placental weight	1.00	0.99-1.01
Birth weight	1.001	1.00-1.002
TSH	0.59	0.41-0.88
FT4	1.03	0.83-1.29
B	**OR**	**95% CI**
Maternal age	1.02	0.91-1.14
Body Mass Index	0.88	0.76-1.01
Gestation at version	0.91	0.53-1.56
Nulliparity	0.11	0.03-0.36
Frank breech	0.30	0.10-0.93
Amniotic fluid index > 10	1.21	0.51-2.34
Placenta anterior	0.31	0.11-0.85
Placental weight	0.99	0.98-1.01
Birth weight	1.001	1.000-1.002
TSH	0.52	0.30-0.90
FT4	1.15	0.82-1.61

Another candidate mechanism might relate to foetal motility and its ability to facilitate spontaneous version. High maternal TSH during gestation has been associated with impaired neonatal motor function.[15] One may argue that higher levels of maternal TSH could conceivably reflect low circulating foetal T4 levels. Shortage of foetal T4 compromises foetal neural maturation and, in turn, foetal motility through its effects on muscle tone and reflexes.[16] Furthermore, breech babies tend to be smaller[17], have lower scores on neuromotor tests[18,19], and are balanced-impaired until the age of 12-18 months.[20] Their impaired neuromotor development could in fact hinder ECV outcome. The current study findings did

not reveal differences in FT4 level between the successful versus the unsuccessful ECV groups. This may have been due to the greater sensitivity of TSH - compared to FT4 - to detect small changes in the set point of the hypothalamus-pituitary-thyroid axis.[21] Moreover, it has been reported that pregnancy FT4 assessments are less reliable than non-pregnancy assessments.[22] Also in this study a weak correlation ($r = 0.18$, $p = 0.34$) was found between FT4 and TSH, but in the opposite direction of what would be expected: normally there is an inverse correlation between TSH and FT4.

Despite growing insight into the prognostic factors of successful ECV, no scoring system that accurately predicts success exists.[23-26] A recent study shows that if the estimated probability of success is less than 32%, an ECV attempt is not cost effective with poorer quality-adjusted life-years (QALYs) for the patient when compared to a caesarean section.[27] It may well be that the inclusion of maternal TSH in improved cost-effectiveness analyses would lead to enhanced probability-of-ECV success estimates.

A limitation of the current study relates to the fact that iodine excretion data in mothers and neonates were not assessed. This made it impossible to relate higher TSH levels to inadequate iodine intake during gestation. A major strength of the current study was its relatively large sample size and the fact that ECV was performed in one obstetric department by a small team of trained experts following the same protocol and blind to the thyroid status of the patients.

In conclusion, the current study is among the first to report a possible relationship between maternal thyroid function and ECV outcome. While the study suggests that higher levels of TSH are independently related to ECV outcome, the precise mechanism behind this finding remains to be determined.

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Chapter
10

General Discussion

This thesis focuses on the interrelated topics of breech presentation, maternal and neonatal thyroid function and determinants of successful ECV.

In **chapter 3**, the relationship between suboptimal maternal thyroid function during gestation and breech presentation at term was studied. Compared to women with foetuses in the cephalic presentation, those women who presented with a foetus in breech presentation at term had significantly higher TSH concentrations, but only at 36 weeks gestation ($p = 0.007$). No between group differences were obtained for FT4 level at any assessment. Women with TSH concentrations below the 5th percentile had no breech presentations. Breech presentation was significantly and independently related to high-normal maternal TSH concentration (≥ 2.5 mIU/l) at 36 weeks gestation (OR: 2.23, 95% CI: 1.14 - 4.39), but not at 12 and 24 weeks gestation. Women with TSH levels above 2.5 mIU/l during end gestation were at risk for breech presentation, and as such for obstetric complications.

How can the observed relationship between maternal TSH and foetal breech presentation be explained? First, uterine contractions are important for final cephalic presentation at term, as was suggested by a large Norwegian study including over 45,000 breech cases.[1] Elevated maternal TSH might affect uterine contractility. In animal studies, hypothyroidism leads to impaired uterine contractility.[2,3] Second, high maternal TSH during gestation has been associated with impaired neonatal motor function.[4-6] If impaired motor development in the offspring is related to low maternal thyroid hormone concentrations during gestation, then similar motor deficits during gestation might affect foetal motility and hence interfere with spontaneous rotation from breech into cephalic presentation.

Evidence is accumulating for a direct effect of TSH (other than by increasing T4 production) in other tissues than thyroid tissue, such as bone and heart[7,8], although a TSH receptor (TSHR) in myometrium has not yet been described. Future (animal) studies are needed to evaluate the direct effect of TSH on uterus tonus and contractility.

How can high-normal TSH in women be explained? First, the finding that high-normal TSH is strongly associated with higher prevalence rates of elevated TPO-Ab concentrations suggests an auto-immune origin: women with high TSH in fact are women with high risk for auto-immune hypothyroidism. Because TSH assessment is much more sensitive than FT4 assessment to detect women with even minor thyroid dysfunction, high-normal TSH (definitely in TPO-Ab positive women) should be regarded as a high risk for inappropriate thyroid hormone production and hence sub-optimal T4 supply to the foetus. Secondly, high-normal TSH might be caused by inappropriate iodine intake during pregnancy. Iodine excretion data in mothers and neonates were not collected in the present study. Although all participants lived in iodine sufficient areas, one may question whether adequate iodine intake outside pregnancy also guarantees sufficient iodine intake during pregnancy in order to meet increased pregnancy

demands. Finally, high-normal TSH might also reflect a maternal physiological response to supply the foetus with appropriate amounts of T4. In view of this, it is important to note that a substantial part of the maternal T4 supply is inactivated in the placenta through deiodinase. This means that different placental deiodinase activity levels may interfere with T4 supply and hence with maternal TSH. Unfortunately, most of the deiodinase placental pathways are still unknown.

The reason why only high-normal TSH at 36 weeks was related to foetal presentation and not at 12 and 24 weeks gestation is intriguing but difficult to explain. During early gestation, HCG production interferes with TSH which means that at this trimester, maternal TSH levels are less reliable in predicting foetal thyroid hormone supply. Another explanation could be that the period of high-normal TSH is of importance. In this light it is interesting to note that the pattern of T4 fluctuations during gestation was directly related to neurodevelopment of the offspring.[9] Women with low T4 during early gestation but who were able to increase (spontaneously) their T4 levels towards end gestation showed no neurodevelopmental delay in the offspring while women in whom T4 levels decreased further during gestation had infants at one and two year with important neurodevelopmental delay. Future studies therefore, should also concentrate on TSH (and FT4 patterns) during gestation rather than trimester specific TSH (FT4) concentrations.

Although this is a large sample of over 1000 women, the obtained number of breech presentations is relatively low. The current study may, therefore, be criticized for having relatively low epidemiological power. Future research, therefore, awaits replication with large size prospective studies, in which thyroid parameters of pregnant women presenting in breech are compared with those of women presenting in cephalic presentation. In those studies, other possible determinants of breech presentation such as umbilical cord length and amniotic fluid volume should then also be examined.

In **chapter 4**, we investigated whether high-normal maternal TSH is related to breech presentation. Enhanced statistical power was achieved by combining two prospective studies on women from the same region using similar thyroid assessments. Overall, we compared the thyroid data of 189 women with a foetus in breech presentation at 35 - 38 weeks gestational age with those of 1000 women who presented with a foetus in cephalic presentation. Again, women with breech presentation had significantly higher mean TSH values.

Subsequently, we reviewed the literature and found multiple studies reporting a relationship between breech presentation and compromised foetal, neonatal or infant neurological development. Our finding that breech presentation and high-normal TSH are related, together with other findings showing that impaired neurological development (including autism) and suboptimal maternal thyroid function are related, suggest that the association between breech and

neurological development may, in fact, be mediated by maternal thyroid hormone (dys)function.

Our findings reported in chapter 3 and 4 may have future clinical implications. Large-scale prospective studies are necessary to investigate whether antenatal iodine supplementation and / or T4 replacement therapy could decrease the number of breech presentations at term. If this would be the case, an important argument in favor of routine maternal thyroid function screening during early gestation may be added to the debate in the literature on this topic.

In **chapter 5**, we studied the relation between newborn screening data for congenital hypothyroidism (CH) and maternal thyroid parameters (i.e., TSH, FT4 and TPO-Ab) assessed at 12, 24 and 36 weeks gestation.

Lower screening TT4 levels were independently related to both high-normal maternal TSH levels (at one or more times during pregnancy) and lower gestational age. Furthermore, boys had lower screening TT4 levels and their mothers had higher TSH levels at 24 and 36 weeks gestation.

High-normal maternal TSH reflecting lower maternal FT4 levels at early gestation may be indicative of reduced FT4 availability for the foetus throughout pregnancy, which, in turn, may result in lower neonatal screening TT4 levels. Regarding gestational age, it is known that the foetal synthesis of both T4 and TSH increases with increasing gestational age.[10] To our knowledge, this is the first report describing higher TSH levels in pregnant women carrying a male foetus. An explanation for this finding is lacking, but one may speculate that male foetuses have a more active deiodinase activity than female foetuses, given existing reports that boys have lower neonatal TT4 levels (and higher cord TSH) than girls.[11-13]

We did not analyse iodine excretion in mothers nor neonates. One may argue that increased maternal TSH levels and lower neonatal heel TT4 levels/concentrations reflect the same underlying mechanism: sub-optimal iodine intake. Second, we did not analyse thyroid cord blood concentrations, so we could not establish whether the obtained association between high-normal maternal TSH and low neonatal TT4 is already present in utero. It is important to recognize that low maternal thyroid hormone levels during gestation may not result in low foetal thyroid hormone levels per se. It is, for instance, well established that healthy individuals from iodine deficient areas (e.g., sub-optimal iodine intake) are able to provisionally increase their thyroid hormone production. Third, trimester-specific reference ranges of TSH and FT4 (taking into account iodine intake and the presence/absence of TPO-Ab) do not exist. Using the 5% extremes derived from the group of TPOAb-negative women (as done in the general population) appears to be the most valid approach currently available. Fourth, amniotic fluid data or newborn T3 values to support the hypothesis of a more active deiodinase activity in male compared to female foetuses, were not available.

Whether our finding of lower neonatal screening TT4 levels is clinically relevant in terms of a possible negative impact on infant neurodevelopment, remains unresolved. With regard to the obtained sex difference in neonatal TT4 screening levels, it would be interesting to study whether lower TT4 levels in boys are associated with increased levels of neurodevelopmental impairment commonly found in boys compared with girls. Future research should also link TSH-based neonatal screening values to maternal thyroid function during pregnancy. The finding of both lower neonatal TT4 levels in boys and higher TSH levels in mothers carrying boys is worthy of further investigation, as both observations may be meaningfully related. Similarly, relating maternal thyroid function, assessed at different trimesters, with cord blood en neonatal screening TT4, might elucidate the mechanism by which sub-optimal maternal thyroid function relates to neonatal screening TT4.

In **chapter 6**, determinants affecting the outcome of external cephalic version (ECV) in breech presentation were identified: nulliparity, frank breech presentation and low birth weight of the baby were associated with a lower ECV success rate. In the group with a successful ECV the percentage of caesarean deliveries was substantially lower. A regular team of a trained hospital midwife and a gynaecologist working according to a standardized ECV protocol proved successful: the number of term breech presentations substantially diminished and, consequently, the percentage of caesarean sections was lower in the successful ECV group. We do not know the number of women potentially suitable for ECV who were not offered an attempt of ECV. Whether selection bias occurred is, thus, not known. Because our study had a retrospective study design potential selection bias, confounding factors and data quality could not be optimally controlled for.

Introduction of regular ECV teams, working according to a standardized ECV protocol may have a significant and positive impact on health care provision in the Netherlands in terms of reduced maternal morbidity and cost savings.

ECV is a relatively easy procedure with potential serious consequences on delivery mode. ECV, therefore, should be performed by trained healthcare professionals. These professionals can be either obstetricians or midwifes. ECV is a relatively safe procedure, with a rare chance of serious complications, and a likelihood of emergency caesarean section in up to 0.4% of cases.[14,15] International guidelines recommend cardiotocographic monitoring, and that ECV should only be performed in medical settings in which caesarean delivery services are available.[16-18] Whether tocolysis should be used routinely or selectively cannot be answered from this study but only from an RCT.

In **chapter 7**, implementing process policy guidelines (PPG), resulted in a considerable increase of the ECV success rate. This increase was paralleled by an increase of cephalic presentations at delivery and a decrease in the number of elective caesarean sections for breech presentation. After implementing PPG compared to the standardized protocol, the caesarean delivery rate for breech

presentation decreased from 39 to 27%. The increase in ECV success was especially found in nulliparous and multiparous women with a frank breech presentation. Whether routine administration of tocolysis (Atosiban, 6,75 mg. intravenously) results in favorable outcome of ECV could not be answered in the current study and would require an RCT. An RCT would also be needed to establish whether the improved ECV results could be directly related to the implementation of the PPG.

Given the substantial decrease of caesarean sections and the related cost reductions, the current findings already now make a clear case for establishing specialized ECV centers in The Netherlands. ECV should be offered to each pregnant woman with breech presentation without contra-indications at end term. Local policies should be implemented to actively increase the number of women who are offered ECV. Finally, ECV should be performed in a hospital setting, in which monitoring facilities and facilities for caesarean delivery are available.

In **chapter 9**, we studied the relation between maternal thyroid function and the outcome of ECV in breech presentation.

Women with a failed ECV attempt had significantly higher TSH concentrations than women with a successful ECV, while FT4 did not differ between the groups.

As high-normal maternal TSH has been associated with a reduced likelihood of spontaneous cephalic version[19], it could also be a factor in ECV outcome. Several mechanisms might be suggested. First, one could argue that elevated maternal TSH directly impacts uterine relaxation, thereby negatively affecting ECV outcome. Empirical evidence regarding such a direct effect is, however, scarce. TSH receptors have been shown in other non-thyroid tissues such as bone, heart and brain tissue, but so far no studies on human uterine samples have been published.[7,8] Also, in patients with subclinical hypothyroidism (reflected by high TSH), the myocytes of the smooth muscle cells of the aorta are dysfunctional, leading to increased arterial stiffness and impaired diastolic function.[20] The mechanism behind is a reduced activity of the sarcoplasmatic reticulum CA-ATPase which controls the efficient concentration of calcium in the cytoplasm. Another study in sub-clinical hypothyroid women showed a beneficial effect of thyroxine replacement on arterial stiffness.[21] It is known from earlier studies that thyroid hormone (T3) has a direct relaxation effect on vascular smooth muscle cells.[22] It might be hypothesized that a similar relation between TSH and uterine myocytes does exist. Inappropriate relaxation of uterine smooth muscle vessels in women with high TSH might hinder ECV. Another candidate mechanism that may account for the obtained relationship between maternal TSH and ECV outcome might relate to foetal motility and its ability to facilitate spontaneous version. High maternal TSH during gestation has been associated with impaired neonatal motor function.[6] One may argue that

high-normal maternal TSH could also be associated with impaired foetal motor function, and hence predispose for breech presentation.
Future strategies for optimizing ECV outcome should take into account the possible role of maternal thyroid (dys)function.

In conclusion: this thesis has two major outcomes.
First, maternal thyroid function during gestation may be an important determinant of foetal presentation. RCT's are warranted to investigate the effect of (sub)optimal maternal thyroid function on foetal presentation. The question whether this should be performed by supplementing T4, iodine or both remains, however, to be resolved.
Secondly, this thesis makes a strong case for offering all pregnant women in breech presentation an ECV attempt in specialized ECV centres in which a standardized ECV protocol is applied by experienced obstetricians (MD or midwives). Serious complications, albeit rare, do occur after ECV, with emergency caesarean section as a likely consequence. ECV attempts should, thus, be performed in a hospital setting. Again, the possible role of maternal thyroid function on success outcome should be taken into account.

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Summary

Since the publication of a randomized multicenter international trial called " the Term Breech Trial" (TBT), the percentage of caesarean delivery (CD) for breech presentation has strongly increased in the Netherlands. In this study it was concluded that compared with vaginal delivery, planned CD was safer for the term breech foetus. As a result, there was a high increase in the number of CD's for breech presentation in The Netherlands in October 2000.
External cephalic version (ECV) is a method to avoid breech presentation, and hence CD.
From studies it appears that ECV is the most efficient and safe method to reduce the number of breech deliveries. International guidelines therefore advise ECV in case of breech presentation. This thesis is a research on several aspects of breech presentation and ECV. Furthermore, this thesis clarifies the consequences of suboptimal maternal thyroid function for the child, in particular the relation between maternal thyroid function and breech presentation.

In **chapter 1**, the introduction, an overview is given on three aspects which come along with breech presentation. Firstly pathophysiology, epidemiology, etiology, spontaneous course of breech presentation and the consequences of breech presentation for mother and child are described. Subsequently, the role of maternal thyroid function is illustrated and the consequences of suboptimal thyroid function for child brain development (motor, behavior and intellect) are summarized. At last, an overview of several aspects of ECV, such as history, procedure, in- and exclusion criteria, safety, effectiveness and determinants for successful outcome of ECV is given.

In **chapter 2** the study design is explained.

In **chapter 3** the relationship between suboptimal maternal thyroid function during gestation and breech presentation at term is presented. A total of 1058 Dutch Caucasian healthy pregnant women were prospectively followed from 12 weeks gestation until term (≥ 37 weeks) delivery. Maternal thyroid parameters (TSH, FT4 and TPO-Ab) were assessed at 12, 24 and 36 weeks gestation. At term, 58 women (5.5%) presented with a foetus in breech presentation. Compared to women with a foetus in cephalic presentation, those women who presented with a breech presentation at term had significantly higher TSH concentrations at 36 weeks gestation ($p = 0.007$). No between group differences were obtained for FT4 level at any assessment. The prevalence of breech presentation in the subgroup of women with TSH ≥ 2.5 mIU/l (90th percentile) at 36 weeks gestation was 11%, compared to 4.8% in the women with TSH < 2.5 mIU/l ($p = 0.006$). Women with TSH below the 5th percentile had no breech presentations. Breech presentation was significantly and independently related to nulliparity (OR: 2.71, 95% CI: 1.17 - 5.50), smoking (OR: 2.97, 95% CI: 1.23 - 7.69), birth weight (OR: 0.97, 95% CI: 0.93 - 0.99) and

high-normal maternal TSH concentration (≥ 2.5 mIU/l) at 36 weeks gestation (OR: 2.23, 95% CI: 1.14 - 4.39), but not at 12 and 24 weeks gestation. In conclusion: women with TSH levels above 2.5 mIU/l at end gestation are at risk for breech presentation, and as such for obstetric complications.

In **chapter 4** the relation between high-normal maternal TSH and breech presentation in a larger sample by combining two studies (chapter 3 and 9) is described. Therefore maternal thyroid parameters (TSH, FT4 and TPO-Ab) at term between a group of 189 women with a foetus in breech presentation and 1000 women with cephalic lying foetuses were compared. Women with breech presentation had significantly higher mean TSH levels compared to women with cephalic lying foetuses. When different cutoff levels were used to define high-normal TSH (> 90th percentile: TSH > 2.5 mIU/l, 95th percentile: TSH > 2.9 mIU/l and 97.5th percentile: TSH> 3.4 mIU/l) breech presentation occurred significantly more often above the cutoff compared to below the cutoff level. A review of the literature showed that in a substantial number of reports a relation has been shown between breech presentation and neuro-developmental delay in the offspring. Because neurodevelopmental delay is also related to high(-normal) maternal TSH during gestation, it might be suggested that sub-optimal maternal thyroid function in fact explains the relation between breech and impaired neuro-development.

Chapter 5 describes the relationship between maternal thyroid function at each pregnancy trimester and neonatal screening results. A prospective follow-up study during three trimesters of gestation in 886 Dutch Caucasian healthy pregnant women followed from 12 weeks gestation until term delivery (≥ 37 weeks) and their neonates was performed. Main outcome measure was the relation between neonatal data from the congenital hypothyroidism (CH) screening and maternal thyroid determinants (TSH, FT4 and TPO-Ab) assessed at 12, 24 and 36 weeks gestation. Results show that boys have lower screening TT4 levels and their mothers have higher TSH levels at 24 and 36 weeks gestation. Lower screening neonatal TT4 levels are independently related to high-normal maternal TSH levels (> 97.5th percentile) at one or more times during pregnancy (OR: 2.26, 95% CI: 1.20 - 4.29) and lower gestational age at delivery (OR: 0.82, 95% CI: 0.71 - 0.95). In conclusion: maternal thyroid function during gestation is related to neonatal TT4 at screening. The finding of both lower neonatal TT4 levels in boys and higher TSH levels in mothers carrying boys compared to mothers carrying girls is worthy of further investigation, as both observations may be meaningfully related.

In **chapter 6**, determinants affecting the outcome of ECV in breech presentation are identified. Also the impact of ECV - performed according to a

standardized protocol in an outpatient clinic - on the mode of delivery is evaluated.
Study design is a retrospective analysis of ECV performed in the Catharina Hospital in Eindhoven, The Netherlands. In 2003 a standardized protocol of ECV was developed; it was tested in 'version office visits'. In this standardized protocol ECV was performed by two practitioners, one of which was a member of the team of three experienced obstetricians trained in ECV. The other practitioner was recruited from the staff members of the Ob/Gyn department, not specially trained in ECV. Tocolysis was not given routinely, but only in selected cases in which difficulty was anticipated or initial attempts failed.
Obstetric characteristics of all pregnant women who underwent attempts of ECV in the clinic from January 2004 until June 2006 during these sessions, and the subsequent births, were analysed. In accordance with the protocol, 85% of all ECVs were performed by the same hospital midwife and gynaecologist. ECV was successful in 96 of 209 pregnant women (46%). In one patient a partial abruption placentae occurred resulting in an emergency caesarean section. Nulliparity, frank breech presentation and low birth weight of the baby were associated with a lower success rate of ECV in this study. In the group with a successful ECV, the percentage of caesarean deliveries was substantially lower (9 versus 83%; OR: 0.21; 95% CI: 0.09-0.51).
In conclusion: a regular team consisting of a hospital midwife and a gynaecologist working according to a standardized protocol for ECV in case of breech presentation proved successful: the number of term breech presentations substantially diminished and therefore the percentage of caesarean sections was lower in the group in which ECV had been successful. This could have considerable impact on health care in The Netherlands in terms of reduced maternal morbidity and cost savings.

In **chapter 7** the effect of implementation of a number of process policy guidelines (protocol), on the success rate of ECV for breech presentation is evaluated. The changes in the original protocol could be summarized by four R's: regularity, routine, release and relaxation.

- Regularity means that ECV is done at a regular basis every week at fixed dates.
- Routine means that ECV is performed by a fixed team of 4 experienced practitioners (2 gynaecologists and 2 midwives).
- Release means that these practitioners have been released from other activities.
- Relaxation means that tocolysis (Atosiban, 6,75 mg. intravenously) is administered routinely.

After implementing this modified protocol as 'process policy guidelines' (PPG), the effect on the rate of successful ECV was prospectively evaluated during the period 1 January 2007-31 July 2008. ECV success was defined as cephalic presentation indicated by post-ECV ultrasound. A secondary outcome measure

was the elective caesarean section rate for breech presentation. The rate of successful ECV increased significantly from 47% (110/236 pregnant women) in the period January 2004 - December 2006 to 61% (85/139, p = 0.006) in the period January 2007 - July 2008. Patient characteristics were similar in both groups, with the exception of a small difference in gestational age at ECV. The increase was preferentially found in nulliparous and multiparous women with frank breech. Nulliparity, frank breech, placenta anterior and low birth weight were factors associated with a lower success rate of ECV. After implementing PPG compared to the standardized protocol, the number of cephalic presentations at delivery increased and the CD rate for breech presentation decreased from 39 to 27% (p = 0.03). Conclusion: after implementation of the process policy guidelines, the success rate of ECV increased considerably. The rate of elective caesarean section for breech presentation declined. These findings are in favor of establishing specialized ECV centers in The Netherlands.

Chapter 8 is a comment on the question where ECV should be performed (in or outside a hospital) and who should perform it (midwife or gynaecologist). In the Netherlands, there is a controversy regarding the policy of ECV in case of breech presentation in term pregnancies.
ECV is a relatively safe procedure, with a pooled complication rate of 6.1%, resulting in emergency caesarean section in up to 0.4% of cases. International guidelines recommend that cardiotocographic monitoring is required and that ECV should be attempted only in settings in which caesarean delivery services are available. Furthermore, tocolysis is associated with higher success rates. Administration of (intravenous) tocolytics during ECV, however, is not within the routine care of Dutch community midwives. So, in conclusion, ECV should be performed in a hospital.

ECV is a relatively easy procedure but the outcome has serious impact on the mode of delivery of the woman. Therefore, ECV should only be performed by trained healthcare professionals with sufficient experience. These professionals can be either obstetricians of midwives.

Chapter 9 reports on a possible relationship between maternal thyroid function and the success of ECV. Since maternal TSH is related to the probability of breech presentation and hence spontaneous version (chapter 3), it might be hypothesised that TSH may in turn affect ECV outcome. In 141 women (≥ 35 weeks gestation) with a singleton foetus in breech, suitable for ECV, demographic, lifestyle and obstetrical parameters were assessed prospectively at intake. Blood samples for maternal thyroid parameters (TSH, FT4 and TPO-Ab) were taken prior to ECV. ECV success was defined as cephalic presentation indicated by post-ECV ultrasound. ECV success rate was overall 77/141 (55%), and was higher for multiparas 41/48 = 85% than for nulliparas 36/93 = 39%.

Women with a failed ECV attempt had significantly higher TSH concentrations than women with a successful ECV ($p< 0.001$). Multiple logistic regression showed that TSH (OR: 0.52, CI: 0.30-0.90), nulliparity (OR: 0.11, CI: 0.03-0.36), frank breech (OR: 0.30, CI: 0.10-0.93), placenta anterior (OR: 0.31, CI: 0.11-0.85) were all independently related to ECV success. We conclude that women with high-normal TSH levels are at increased risk of failed ECV. Future strategies should consider the role of maternal thyroid(dys)function.

Samenvatting

Sedert de publicatie van de Term Breech Trial in oktober 2000 is het percentage keizersneden bij stuitligging sterk gestegen. De Term Breech Trial verwijst naar een grote gerandomiseerde internationale studie die concludeerde dat voor een voldragen kind in stuitligging een geplande keizersnede veiliger is dan een vaginale baring.

Uitwendige versie is een methode om stuitligging, en dus keizersnede, te vermijden. Uit onderzoek blijkt dat uitwendige versie de meest effectieve en veilige methode is om het aantal bevallingen in stuitligging te reduceren. Internationale richtlijnen bevelen daarom uitwendige versie aan bij deze afwijkende foetale ligging. Dit proefschrift betreft een onderzoek naar diverse aspecten van stuitligging en uitwendige versie. Bovendien belicht dit proefschrift de relatie tussen een suboptimale maternale schildklierfunctie en foetale ligging en de schildklierfunctie van de neonaat.

In **hoofdstuk 1**, de inleiding, wordt een overzicht gegeven van drie aspecten die samenhangen met stuitligging. In de eerste plaats worden in deze context de pathofysiologie, epidemiologie, etiologie, spontaan beloop van een stuitligging en de gevolgen van een stuitligging voor de moeder en het kind belicht. Vervolgens wordt de rol van de maternale schildklierfunctie belicht en worden de gevolgen van een suboptimale schildklierfunctie voor de hersenontwikkeling (motoriek, gedrag, intellect) van het kind samengevat. Tenslotte wordt een overzicht gegeven van de verschillende aspecten van uitwendige versie, zoals de geschiedenis, procedure, in- en exclusie criteria, veiligheid, effectiviteit en determinanten voor een succesvolle versie.

In **hoofdstuk 2** wordt het ontwerp van de thesis verantwoord en toegelicht.

In **hoofdstuk 3** wordt het verband tussen suboptimale maternale schildklierfunctie en stuitligging op het einde van de zwangerschap onderzocht. In de eerste 20 weken van de zwangerschap is een foetus vrijwel volledig afhankelijk van de maternale schildklierfunctie. Het is bekend dat suboptimale maternale schildklierfunctie een negatieve invloed heeft op de motorische ontwikkeling van het kind na de geboorte. Wellicht dat een gebrekkig functioneren daarvan de reden is dat een kind in stuit blijft liggen. Om dit te onderzoeken werd een groep van 1058 Nederlandse gezonde zwangeren prospectief gevolgd vanaf een zwangerschapsduur van 12 weken tot aan de bevalling. Maternale schildklierfuncties (TSH, FT4 and TPO-Ab) werden bepaald bij een zwangerschapsduur van 12, 24 en 36 weken alsmede de ligging van het kind tijdens de geboorte. Tijdens de bevalling lagen 58 kinderen (5.5%) in stuitligging. Vergeleken met vrouwen met een kind in hoofdligging, hadden vrouwen met een kind in stuitligging significant hogere TSH concentraties bij een zwangerschapsduur van 36 weken ($p=0.007$). Er was geen verschil in FT4

waarden tussen vrouwen met een kind in stuit of met een kind in hoofdligging. Het voorkomen van een stuitligging in de subgroep van vrouwen met een TSH ≥ 2.5 mIU/l (90e percentiel) bij 36 weken zwangerschapsduur was 11%, vergeleken met 4.8% in de groep van vrouwen met een TSH < 2.5 mIU/l (p = 0.006). Bij vrouwen met een TSH kleiner dan de 5e percentiel was er niemand met een stuitligging. Stuitligging was significant en onafhankelijk geassocieerd met nulliparitеit (OR: 2.71, 95% CI: 1.17 - 5.50), roken (OR: 2.97, 95% CI: 1.23 - 7.69), geboortegewicht (OR: 0.97, 95% CI: 0.93 - 0.99) en met een hoge-normale maternale TSH concentratie (≥ 2.5 mIU/l) bij een zwangerschapsduur van 36 weken (OR: 2.23, 95% CI: 1.14 - 4.39), maar niet bij een zwangerschapsduur van 12 of 24 weken. Conclusie: vrouwen met een TSH concentratie van meer dan 2.5 mIU/l, gemeten aan het einde van de zwangerschap, lopen meer risico op een stuitligging en in die zin ook een groter risico op verloskundige complicaties.

Om de relatie tussen een hoog-normaal maternaal TSH en stuitligging te bevestigen in een grotere steekproefomvang, werden in **hoofdstuk 4** twee studies gecombineerd (hoofdstuk 3 en 9). À terme maternale schildklierfuncties (TSH, FT4 and TPO-Ab) in een groep van 189 vrouwen met een kind in stuitligging werden vergeleken met een groep van 1000 vrouwen met een kind in hoofdligging. Vrouwen met een baby in stuitligging hadden significant hogere gemiddelde TSH vergeleken met vrouwen met een kind in hoofdligging. Bij opsplitsing van het TSH in verschillende categorieën, bleken er meer vrouwen met een kind in stuitligging in de groepen met de hoogste waarden: 90e percentiel (TSH > 2.5 mIU/l), 95e percentiel (TSH > 2.9 mIU/l) en 97.5e percentiel (TSH > 3.4 mIU/l) vertegenwoordigd. Uit de literatuur blijkt dat een aantal artikelen een verband aantoont tussen stuitligging en motorische ontwikkelingsachterstand bij het kind. Omdat deze ontwikkelingsachterstand ook is geassocieerd met een hoge (hoog-normale) maternale TSH tijdens de zwangerschap, zou kunnen worden verondersteld dat suboptimale maternale schildklierfunctie in feite het verband verklaart tussen stuitligging en ontwikkelingsachterstand.

In **hoofdstuk 5** wordt het verband onderzocht tussen de maternale schildklierfunctie tijdens ieder trimester van de zwangerschap en het neonatale schildklierhormoon verkregen bij de hielprikscreening. Uit de literatuur blijkt dat klinisch maternaal schildklierlijden tijdens de zwangerschap is geassocieerd met een slechtere neonatale schildklierfunctie. Echter, onderzoek naar het verband tussen suboptimale maternale schildklierfunctie (bepaald tijdens ieder trimester) en de neonatale schildklierscreening is nauwelijks uitgevoerd. Derhalve werd een prospectieve observationele studie bij 886 Nederlandse gezonde kaukasische zwangeren en hun pasgeboren kinderen verricht die gevolgd werden vanaf een zwangerschapsduur van 12 weken tot en met de

bevalling (≥37 weken). De primaire uitkomstmaat was de relatie tussen de neonatale gegevens van de screening op congenitale hypothyroidie en maternale schildklierfunctie (TSH, FT4 and TPO-Ab) genomen bij een zwangerschapsduur van 12, 24 en 36 weken. Uit de resultaten bleek dat jongens lagere screening TT4 waarden hadden; hun moeders hadden hogere TSH waarden bij 24 en 36 weken zwangerschapsduur.
Lagere screening TT4 waarden bleken onafhankelijk gerelateerd aan hoog-normale maternale TSH waarden (> 97.5e percentiel) gedurende een of meerdere keren tijdens de zwangerschap (OR: 2.26, 95% CI: 1.20 - 4.29) en een kortere zwangerschapsduur bij de bevalling (OR: 0.82, 95% CI: 0.71 - 0.95). Concluderend: maternale schildklierfunctie tijdens de zwangerschap is gerelateerd aan de neonatale TT4 waarden tijdens hielprikscreening. Een opvallende bevinding hierbij was dat vrouwen met een mannelijke foetus hogere TSH waarden hadden dan vrouwen met een vrouwelijke foetus. De betekenis hiervan is nog niet duidelijk.

In **hoofdstuk 6** wordt ingegaan op de vraag welke factoren een rol spelen op succesvolle uitwendige versie bij stuitligging. Tevens wordt het effect van een poliklinische, geprotocolleerde, uitwendige versie op de wijze van bevallen beschreven.
De studie was opgezet als een retrospectieve analyse van uitwendige versies uitgevoerd in het Catharina-ziekenhuis te Eindhoven. In 2003 werd hiervoor een standaard protocol ontwikkeld, dat werd getoetst in een 'versiespreekuur'. Volgens dit standaard protocol werd uitwendige versie door 2 obstetrici tegelijkertijd verricht, waarbij één van hen deel uitmaakte van een vast team van 3 ervaren obstetrici. De andere persoon werd gerekruteerd uit de andere stafleden van de afdeling obstetrie die geen specifieke ervaring hadden met ECV. Weeënremming werd niet routinematig gegeven, maar alleen indien na klinische beoordeling van de uterus vóór versie een verhoogde tonus werd vastgesteld. Van alle zwangeren bij wie in de periode januari 2004 - juni 2006 tijdens dit spreekuur een poging tot uitwendige versie werd uitgevoerd, werden obstetrische kenmerken en de partus geanalyseerd. Van de versies werd 85% uitgevoerd door dezelfde 2 personen (1 verloskundige en 1 gynaecoloog), volgens het standaardprotocol. Uitwendige versie bleek succesvol bij 96 van de 209 zwangeren (46%). Bij 1 zwangere moest na de versie een spoedsectio worden verricht wegens een partiële abruptio placentae. Nulliparitеit, onvolkomen stuitligging en een laag geboortegewicht van de baby hingen in deze studie samen met een kleinere kans op een succesvolle versie. In de groep waarin de versie succesvol was, was het percentage geboorten via keizersnede aanmerkelijk lager (9 versus 83%; OR: 0,21; 95%-BI: 0,09-0,51).
Conclusie is dat uitwendige versie, uitgevoerd volgens een standaardprotocol door een vast team, bestaande uit een verloskundige en een gynaecoloog, effectief is: na een geslaagde versie neemt het aantal à terme stuitliggingen af en

daarmee het percentage keizersneden. Dit leidt tot een aanzienlijke gezondheidswinst voor de moeder en een belangrijke kostenbesparing voor de gezondheidszorg in Nederland.

In **hoofdstuk 7** wordt het effect onderzocht van het verder invoeren van een aantal procesmatige beleidsregels - het zogenaamde procesprotocol - op het succespercentage van uitwendige versie bij stuitligging. Gedurende een periode van 3 jaar (2004-2006) werd dit procesprotocol ontwikkeld, getoetst en aangepast. Hierbij werd een aantal procesmatige beleidsregels (procesprotocol genoemd) doorgevoerd: de 4 R's van 'regelmaat', 'routine', 'rust' en 'relaxatie'.
• 'Regelmaat' hield in: iedere week, op een vast tijdstip, een versiespreekuur.
• 'Routine' betekende dat iedere versie standaard werd uitgevoerd door twee obstetrici uit een vast team van 4 personen (2 gynaecologen en 2 verloskundigen) met specifieke ervaring op ECV gebied. Het team kon dus bestaan uit twee verloskundigen, een verloskundige en een gynaecoloog, of twee gynaecologen.
• 'Rust' betekende dat de twee ervaren obstetrici tijdens het versiespreekuur zoveel mogelijk van andere taken binnen de afdeling obstetrie werden vrijgesteld.
• 'Relaxatie' verwees naar het standaard toedienen van een weeënremmer tijdens de versiepoging.
Vervolgens werd na invoering van dit procesprotocol het effect op het percentage succesvolle versies prospectief gevolgd gedurende de periode 1 januari 2007 - 31 juli 2008. Een versie werd als succesvol gedefinieerd als direct na de poging echoscopisch een hoofdligging werd aangetoond. Secundaire uitkomstmaat was een mogelijke verandering van het aantal primaire sectio's bij stuitligging.
Na invoering van het procesprotocol (periode januari 2007 - juli 2008) bleek het succespercentage van uitwendige versie significant hoger dan in de periode van het standaardprotocol (januari 2004 - december 2006) namelijk 61% (85/139 zwangeren) versus 47% (110/236; p = 0,006). De patiëntkarakteristieken waren in beide groepen gelijk, met uitzondering van een klein verschil bij de termijn van versie. De stijging was vooral aantoonbaar bij nulliparae en multiparae met een onvolkomen stuitligging. Nulliparitеit, onvolkomen stuitligging, placenta anterior en laag geboortegewicht van de baby waren gerelateerd aan een lagere succeskans bij versie. De termijn waarbij de versie plaatsvond bleek niet van invloed te zijn op het succespercentage. Na invoering van een procesprotocol steeg het aantal hoofdliggingen bij de partus en daalde het aantal primaire keizersneden voor stuitligging van 39 naar 27% (p = 0,03). Conclusie: na invoering van een procesprotocol vond een aanzienlijke toename plaats van het succespercentage van uitwendige versie. Hierdoor daalde het aantal primaire sectio's wegens stuitligging verder. Deze bevindingen pleiten voor het installeren van centra in Nederland die zich specialiseren in uitwendige versie.

Hoofdstuk 8 bevat een commentariële publicatie over de vraag *waar* de uitwendige versie zou moeten plaatsvinden (wel of niet in een ziekenhuis) alsook de vraag wie de uitwendige versie zou moeten uitvoeren (de gynaecoloog of de verloskundige). In Nederland is er in dit verband een polemiek aangaande het beleid van uitwendige versie bij stuitligging. Onder meer in de *British Medical Journal* verscheen hierover een artikel gepubliceerd met de titel "Dutch insurers pay midwives not to refer breech presentations to hospital". In dit artikel wordt het contract besproken dat de Koninklijke Nederlandse Organisatie van Verloskundigen (KNOV) heeft afgesloten met de Nederlandse Zorgverzekeraars om uitwendige versies in de eerste lijn te houden en zo minder stuiten naar het ziekenhuis te verwijzen. Naar aanleiding hiervan worden in dit hoofdstuk aspecten van veiligheid, succeskans, competentie, training en kosteneffectiviteit besproken.

Het eerste aspect heeft betrekking op de vraag *waar* de versie zou moeten plaatsvinden. Uitwendige versie is een relatief veilige procedure, met een overall risico op complicaties van 6.1% en waarbij er in 0.4% van de gevallen een spoedkeizersnede moet plaatsvinden. Internationale richtlijnen bevelen daarom een cardiotocografische bewaking aan met indien nodig de mogelijkheid tot spoedkeizersnede. Daarnaast kan door het toedienen van een weeënremmer de succeskans verhoogd worden. Het toedienen van een (intraveneuze) weeënremmer valt niet onder de bevoegdheid van een Nederlandse eerstelijns verloskundige. Daarom dient een uitwendige versie in een ziekenhuis plaats te vinden.

Het tweede aspect heeft betrekking op het aspect van de professionele ervaring: *wie* zou de versie moeten uitvoeren, de gynaecoloog of de verloskundige? Een uitwendige versie is een relatief eenvoudige ingreep, maar met grote impact op de wijze van bevallen van de vrouw. Daarom zou een uitwendige versie alleen verricht moeten worden door getrainde professionals met voldoende ervaring. Deze professionals kunnen zowel verloskundigen als gynaecologen zijn.

In **hoofdstuk 9** wordt een mogelijk verband tussen de maternale schildklierfunctie en de succeskans van uitwendige versie onderzocht. Omdat vrouwen met een kind in stuitligging significant hogere TSH concentraties bij een zwangerschapsduur van 36 weken hebben (zie hoofdstuk 3), kan verondersteld worden dat TSH ook een invloed zou kunnen hebben op de uitkomst bij uitwendige versie. Bij 141 vrouwen (zwangerschapsduur ≥ 35 weken) met een eenling in stuitligging waarbij een versie werd verricht, werd prospectief een aantal verloskundige en demografische parameters vastgelegd. Een uitwendige versie werd als succesvol betiteld indien er direct na de versie echoscopisch een hoofdligging werd vastgesteld. Bloed voor maternale

schildklierfuncties (TSH, FT4 en TPO-Ab) werd afgenomen tijdens de versie. De succeskans bij uitwendige versie was voor de gehele groep 77/141 (55%), en deze kans was hoger voor multipare 41/48 (85%) dan voor nullipare vrouwen 36/93 (39%). Vrouwen met een niet gelukte versie hadden significant hogere TSH concentraties dan vrouwen met een gelukte versie ($p< 0.001$). Uit de multipele logistische regressie analyse bleek dat TSH (OR: 0.52, CI: 0.30-0.90), nulliparitеit (OR: 0.11, CI: 0.05-0.36), onvolkomen stuitligging (OR: 0.30, CI: 0.10-0.93) en anterieure ligging van de placenta (OR: 0.31, CI: 0.11-0.85) gerelateerd waren aan de succeskans bij versie. Wij concluderen dat vrouwen met een hoog-normale TSH waarde een verhoogd risico hebben op een mislukte versie. Toekomstige strategieën op het gebied van ECV zouden daarom de rol van maternale TSH-waarden in overweging moeten nemen, om de kans op succes van versie te verhogen.

Abbreviations

ACOG	American College of Obstetricians and Gynecologists
ADHD	Attention Deficit Hyperactivity Disorder
AFI	Amniotic Fluid Index
BI	Betrouwbaarheids Interval
BMI	Body Mass Index
CD	Caesarean Delivery
CH	Congenital Hypothyroidism
CI	Confidence Interval
CP	Cerebral Palsy
CS	Caesarean Section
CTG	Cardiotocography
D3	Deiodinase 3
EBIS	Eindhoven Breech Intervention Study
ECV	External Cephalic Version
EFW	Estimated Foetal Weight
FMH	Foetomaternal Hemorraghe
FT3	Free Triiodothyronine
FT4	Free Thyroxine
HCG	Human Chorionic Gonadotrophin
HPT-axis:	Hypothalamus-Pituitary-Thyroid axis
IUGR	Intra Uteriene Groei Retardatie
KNOV	Koninklijke Nederlandse Organisatie van Verloskundigen
MN	Mean
NVOG	Nederlandse Vereniging voor Obstetrie en Gynaecologie
OR	Odds Ratio
PPG	Process Policy Guidelines
PPROM	Preterm Premature Rupture of Membranes
QALY	Quality Adjusted Life Years
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
RCT	Randomized Controlled Trial
RCOG	Royal College of Obstetricians and Gynaecologists
RR	Relative Risk
rT3	Reverse T3
SD	Standard Deviation
SOGC	Society of Obstetricians and Gynaecologists of Canada
SPSS	Statistical Package for the Social Sciences
T3	Triiodothyronine
T4	Thyroxine
TBT	Term Breech Trial
Tg-Ab	Thyroglobulin Antibody
TPO-Ab	Thyroid Peroxidase Antibody
TSH	Thyroid Stimulating Hormone or Thyrothrophin
TSH-R	Thyroid Stimulating Hormone Receptor
TT4	Total T4
UCL	Umbilical Cord Length

Dankwoord

Dankwoord

Het onderzoek waarvan dit boek getuigt is niet het resultaat van een op voorhand geplande actie, integendeel. Om met een metafoor te spreken: er hield onverwacht een trein halt en ik meende mee te moeten reizen. Het was een spontaan initiatief. Maar goed dat je niet helemaal beseft hoe intensief de reis is waar je aan begint...

Prof. dr. V.J.M. Pop. Victor, jij was de machinist. Je was uitnodigend maar wilde verder reizen; ik moest snel kiezen of ik wilde opstappen. Je enthousiasme en liefde voor het onderzoek en onze gezamenlijke studieachtergrond in Leuven maakten voor mij de keuze om de reis te ondernemen gemakkelijker. Onze discussies hebben mij enorm geïnspireerd; onvervangbaar. Je coaching, ondersteuning en inzicht waren *conditiones sine qua non*. Een betere promotor en collega kan ik me nauwelijks wensen. We moeten nog een paar haltes en ik verheug mij op de verdere rit. Op 'Station Riethoven' wil ik nog vaak halt houden, ook voor de geweldige koffie van Bernadette.

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Curriculum Vitae

Curriculum Vitae

Simone Kuppens werd op 30 juli 1967 als oudste in een gezin van drie kinderen geboren op 30 juli 1967 in Weert. In 1985 behaalde zij haar VWO-diploma aan de Philips van Horne Scholengemeenschap te Weert. Na uitloting voor de studie geneeskunde in Nederland, kon zij nog datzelfde jaar vol enthousiasme starten aan de opleiding geneeskunde aan de Katholieke Universiteit van Leuven, België. In 1992 behaalde zij daar het artsendiploma en startte zij met de opleiding tot gynaecoloog, eveneens in Leuven. Achtereenvolgens werkte zij als arts-assistent in het Virga Jesse ziekenhuis te Hasselt, het Tygerberg Hospitaal te Stellenbosch in Zuid-Afrika, en in het universitair ziekenhuis Gasthuisberg te Leuven. In 1997 behaalde zij het diploma geneesheerspecialist in België en in datzelfde jaar werd zij ook erkend als gynaecoloog in Nederland. Na haar opleiding werkte zij nog een half jaar in het Groote Schuur Hospitaal te Kaapstad. Sedert 1998 werkt zij als gynaecoloog in het Catharina-ziekenhuis te Eindhoven. Zij is al heel wat jaren (gelukkig) getrouwd met Maurice Adams  . Samen hebben zij één tweeling van 11 jaar: Thomas en Sophie.

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Stellingen behorende bij het proefschrift:

Successful External Cephalic Version in Breech
Thyroid hormone and process parameters

1. Een uitwendige versie bij stuitligging is een must: "Nee" heb je; "Ja" kun je krijgen.

2. Zwangeren met een TSH concentratie boven 2.5 mIU/l in het derde trimester hebben 2 keer meer risico op een stuitligging en bijgevolg op verloskundige complicaties. *(dit proefschrift)*

3. De in de literatuur beschreven samenhang tussen stuitligging en ontwikkelingsstoornissen bij het kind is mogelijk schildklierhormoon gemedieerd.

4. Het succespercentage van versie neemt aanzienlijk toe door het invoeren van een aantal beleidsregels (4R's: 'regelmaat', 'routine', 'rust' en 'relaxatie'). *(dit proefschrift)*

5. De bevindingen uit dit proefschrift vormen een pleidooi voor het oprichten van 2e lijnscentra, gespecialiseerd in uitwendige versie.

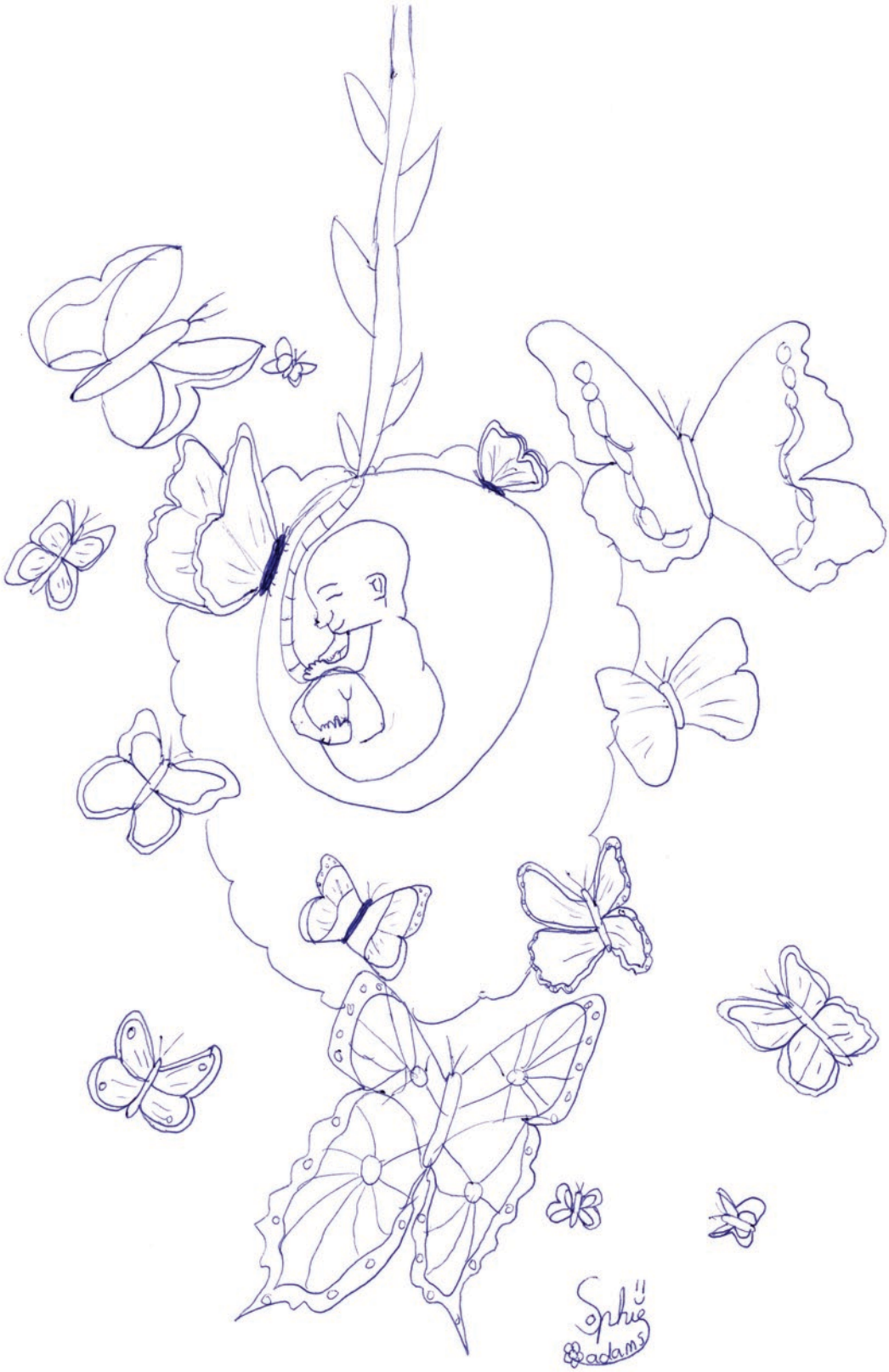
6. Zwangeren met een TSH concentratie boven 2.5 mIU/l in het derde trimester hebben 2.5 keer meer risico op een mislukte versie. *(dit proefschrift)*

7. Een foetus in hoofdligging heeft zijn eerste citotoets succesvol afgelegd.

8. Daars geen wyer draai as 'n afrikaanse draai: dis die beste plek om jou hart af te laai. *(vrij naar Steve Hofmeyr)*

9. It is better to light a lamp, than to curse the darkness. *(Father Jos Kuppens, Centre for Social Concern, Malawi).*

Simone Kuppens, augustus 2010


Sophie
adams