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Carpal tunnel syndrome during pregnancy and the postpartum period and the effect of mechanical traction treatment

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Chapter 1

General introduction

GENERAL INTRODUCTION

Carpal tunnel syndrome (CTS) is a neuropathy in which the median nerve is compressed at the level of the carpal tunnel.[1,2] The carpal tunnel is an anatomical space in the wrist, surrounded by the carpal bones and the transverse carpal ligament.[3] The compression of the median nerve within this tunnel leads to the typical symptoms of numbness, paresthesia and sometimes pain in the patient's hand. The symptoms are usually sensed in the first three fingers and the radial side of the ring finger, because these areas are innervated by the median nerve.[2] Severity of the symptoms can range from mild and annoying to very painful, and they can be unilateral or bilateral. Initially, the symptoms present at night and awaken patients from sleep.[3] When the condition progresses, the symptoms persist during the day and may be aggravated by (heavy) activities involving the hand or wrist. When the nerve is compressed for a longer period of time, nerve degeneration and thenar atrophy may occur.[2]

CTS is very common; the prevalence in the general population in the United States is 5%,[4] and in Netherlands about 0.6% in men and between 5.8 and 9.2% in women.[5-7] In general, it is more prevalent in women compared to men, and although CTS can occur at any age, it most commonly arises between 40 and 60 years.[1]

Pathophysiology and clinical neurophysiology

CTS can be either idiopathic (spontaneous) or secondary to another disorder. Several theories have been proposed, but the common belief is that idiopathic CTS is caused by mechanical compression and subsequent ischemia. Long-term, this results in demyelination, inflammation and fibrosis. The median nerve and flexor tendons run through the carpal tunnel parallel to each other, affecting the other's dynamics. Wear and degeneration of the tendons with age possibly cause edema and fibrosis. This increases the tissue volume within the carpal tunnel, compressing the median nerve.[8] Nerve compression leads to microvascular dysfunction and subsequent endoneurial edema, demyelination, inflammation, distal axonal degeneration, fibrosis, growth of new axons, remyelination, and thickening of the perineurium and endothelium.[9]

The diagnosis of CTS is primarily based on history and patient-reported clinical signs and symptoms.[3,8] Patients commonly report the typical symptoms of numbness, paresthesia and pain in the distribution of the median nerve.[3] More severe cases may also present with persisting sensory symptoms, weakness and thenar muscle atrophy. Several clinical tests are used to support the diagnosis of CTS (such as Tinel's sign and Phalen test), but they have major limitations in sensitivity and specificity.[10] Electrodiagnostic testing (EDT) is used as an objective measure to support the diagnosis.[11] EDT is considered the 'gold standard' among the diagnostic tests.[12] Compression of the median nerve leads to damage and dysfunction of the myelin sheath, which results in slowed conduction velocity. Nerve conduction velocity can be measured using EDT. The nerve is stimulated by an electrical impulse through the skin, resulting in an action potential in the nerve. The wave of depolarization is then detected over a certain distance by a recording electrode.

Latency times of the median nerve across the wrist are recorded and compared to a reference value or latency time of another nerve segment which does not pass through the carpal tunnel. There are universal criteria for the diagnostic values of EDT.[11] However, EDT also has its limitations: false positives and false negatives are not uncommon.[1,13] Another promising diagnostic technique is ultrasonography of the median nerve.[14,15] With this technique, the cross-sectional area of the median nerve can be measured, which is enlarged in CTS patients. Contrary to EDT, sonography is painless and can detect possible underlying (anatomical) abnormalities. Although sonography has several advantages over EDT, it is not yet widely used in clinical practice.

Risk factors: CTS during pregnancy

In most cases, CTS is idiopathic.[3,14] However, some conditions are known to predispose to CTS. Mass lesions and anatomical variants can cause an increase in tissue volume within the carpal tunnel or a decrease in size of the carpal tunnel itself. Obesity is a known risk factor for CTS, especially in younger patients.[16,17] Specific diseases that affect the synovium and can cause secondary CTS include diabetes mellitus, rheumatoid arthritis, tenosynovitis and hypothyroidism.[8,14,18] The prevalence of CTS among hypothyroid patients is over 30%.[19,20] It is suspected that CTS has a genetic component, although the supportive evidence is sparse.[21] Another frequently reported risk factor for CTS is pregnancy. Pregnancy-related CTS (PRCTS) is more often bilateral[22-24] and typically occurs during the third trimester,[22,25] although the onset can be as early as the first trimester in some cases. The true prevalence of PRCTS is unclear. According to a systematic review by Padua *et al*., the prevalence of electrophysiologically confirmed PRCTS ranges from 7 to 43%, while the prevalence of clinically diagnosed PRCTS ranges from 31 to 62%.[26] The reason for this variation is probably the different methods and diagnostic criteria. Several causes of PRCTS have been suggested, including hormonal and musculoskeletal changes.[25,27] The predominant belief, however, is that PRCTS is caused by local edema in the carpal tunnel during pregnancy.[22,24,28]

As stated above, hypothyroidism is a risk factor for CTS in the general population. Hypothyroidism is an endocrine disorder characterized by low levels of free thyroid hormone called thyroxine (FT4). Thyroid hormone plays an important role in the regulation of metabolism.[29] In hypothyroid patients, CTS is most likely caused by (myxo)edema in the carpal tunnel and subsequent neuropathy.[30] During pregnancy, FT4 levels decrease towards end of term as a natural physiological phenomenon.[31] Moreover, obesity is a risk factor for developing CTS in the non-pregnant population. Pop *et al*.[29] showed that FT4 and BMI were negatively correlated during pregnancy. They also found a significant association between inappropriate weight gain and lower FT4 levels during pregnancy. Whether the weight gain can be attributed to the metabolic effects of lower FT4 or an effect of lower FT4 on fluid retention or edema during pregnancy remains to be clarified. Altogether, it does suggest a possible relation between thyroid function and CTS during pregnancy, although the nature of this relationship has not been investigated yet.

CTS is possibly an under recognized problem during pregnancy, as reflected by poor insight in the true prevalence and it is often overlooked by both pregnant women and health care

providers.[32] Moreover, the clinical implications of PRCTS are unclear. Even though symptoms are generally mild compared to the non-pregnant population,[23] 34-75% report impairment of hand function and the symptoms may also contribute to sleep problems during pregnancy.[32,33] The best 'solution' for pregnancy-related CTS is delivery. The symptom severity quickly reduces in the first weeks postpartum[22] and symptoms are believed to resolve completely in time,[34] but clear figures on persisting CTS symptoms postpartum are hardly available. Between 4% and 54% of women report persisting symptoms at one year postpartum.[26,27,34,35] Padua *et al*.[35] suggested that women with onset of symptoms earlier in pregnancy are more likely to have persisting symptoms postpartum.

We conducted a large prospective cohort study among pregnant women: the HAPPY study (Holistic Approach to Pregnancy and the first Postpartum Year). Psychological and physiological data were collected to investigate determinants that may interfere with maternal and child well-being during pregnancy and postpartum. In this thesis, we focused on the prevalence and nature of CTS symptoms, and possible predictors and negative effects of these symptoms during pregnancy and postpartum. Emotional status is another possible predictor that needs to be considered when assessing self-reported sensory symptoms. Depression, for example, can influence the subjective experience of pain,[36] also in pregnant women.[37] People with chronic pain (>3 months) reported more psychological problems, including depression, compared to healthy controls.[38] Depression was also a predictor of symptom severity in CTS patients.[39,40] Therefore, it is important to consider depressive symptoms when assessing self-reported CTS symptoms.

Current treatment options for CTS

Treatment options for CTS can be divided into surgical and non-surgical. Non-surgical, less invasive treatment options are often offered as initial treatment for patients with mild to moderate symptoms or a short duration of symptoms. The most common non-surgical interventions are wrist splinting and steroid injections at the inlet of the carpal tunnel. A wrist splint is often applied at night and stabilizes the wrist in a neutral position because the pressure on the median nerve increases during wrist flexion and extension, and is lowest in a neutral position.[41] Steroid injections are used to reduce inflammation-induced swelling in the carpal tunnel, and thereby relieving pressure on the median nerve. Both splinting and steroid injections are effective short-term, but there is little evidence for their effectiveness long-term.[41-44] Local steroid injections seem to primarily suppress the symptoms because the treatment effect often diminishes over time.[43,45] However, patients with an electrodiagnostically mild case of CTS may benefit from steroid injections long-term.[46] Other (less traditional) forms of non-surgical treatment include non-steroidal drugs, exercise and mobilization interventions, therapeutic ultrasound, yoga, carpal bone mobilization, vitamins, magnet therapy, laser acupuncture and chiropractic care.[47,48] Most of the evidence for these interventions is very limited or of low quality.

To this date, surgery is the only known treatment option for CTS that is effective at long-term.[49] The principle of the procedure, called carpal tunnel release, is to cleave the transverse carpal

ligament, thereby increasing the volume in the carpal tunnel and reducing pressure on the median nerve.[7] This can be accomplished using two different techniques: open or endoscopic carpal tunnel release. The procedure is usually performed unilateral and under local anesthesia. Although surgery is considered the best treatment option, especially when conservative treatment has failed, it is associated with several risks. Patients can suffer sustained surgery-related pain, hypertrophic scar, hand weakness or complications from surgery, such as wound infection.[50] Between 20 and 30% of patients are unsatisfied with the surgery outcome.[6,8,51-53] They experience persistence or recurrence of symptoms or suffer from surgery-related complications.[8,52] Up to 12% of patients require re-operation.[52]

To the best of our knowledge, there are no randomized controlled trials comparing carpal tunnel release surgery to no treatment or sham surgery. A small number of RCTs have compared surgery to conservative treatment.[49,54,55] Hui *et al.*[55] randomly assigned 50 patients with electrophysiologically confirmed idiopathic CTS to surgery or a single steroid injection. Surgery resulted in greater symptom reduction than steroid injection at 20 weeks follow-up. Contrary, Ly-Pen *et al*.[56] showed a greater treatment benefit from steroid injection compared to surgery at three months follow-up and no difference at one year follow-up in an RCT with 163 wrists with clinically and electrophysiologically confirmed CTS. Surgery led to significantly lower self-reported symptom severity than non-surgical treatment (anti-inflammatory) drugs, hand therapy and ultrasound therapy at six months follow-up in an RCT by Jarvik *et al.*[49] However, they reported that the clinical relevance of the difference was only modest. Gerritsen *et al.*[5] found that surgery was more effective than splinting at three and 18 months follow-up. In their study, 67% of patients had adverse effects after surgery, although they were generally mild and short of duration. Two of 54 patients, however, had severe pillar pain and one patient had reflex sympathetic dystrophy, which can be considered to be severe adverse effects.

Mechanical traction

A promising and relatively new non-invasive treatment for CTS is mechanical wrist traction. During this treatment, repeated traction movements are applied to the wrist in different positions using gravitational force. The treatment comprises a series of treatment sessions, with one or two sessions per week. A session takes 10 to 15 minutes per affected hand. Figure 1 presents and image of the traction device that was used, the Phystrac.

Mechanical traction has several advantages. First, it is non-invasive: in general, patients do not experience any pain or discomfort from the treatment and they are able to continue their work and other daily activities for the duration of the treatment. Secondly, patients with bilateral symptoms can be treated on both hands during the same session. Thirdly, the treatment can be tailored to individual patients: the weight of the gravitational force and the number of treatments can vary depending on individual needs. Finally, if the treatment fails, there is still an option for surgery without any difference in outcome.

Figure 1 The Phystrac traction device provides repeated mechanical traction to the wrist using gravitational force. *From: www.phystrac.com*

Brunarski *et al*.[57] described four case studies using mechanical traction that showed promising results. In an observational study in the Netherlands among 78 CTS patients in a practice for physical therapy, treatment with mechanical traction resulted in a post-treatment success rate of 70%,[58] and 60% after two years follow-up.[59] Symptom severity scores and functional scores decreased significantly after treatment, especially in patients with a shorter duration of complaints. However, no randomized controlled trial had been performed to provide clinical evidence for the effectiveness of mechanical traction compared to other (non-)surgical interventions. We therefore conducted an RCT comparing 12 sessions of mechanical traction to care as usual in an outpatient neurology clinic in the Netherlands.

How to measure treatment outcome in CTS patients

Electrodiagnostic testing (EDT) is a useful tool to support a clinical diagnosis of CTS, but is less valuable as an outcome measurement for treatment effect. It is time-consuming, relatively expensive and can create temporary discomfort for the patient. Moreover, the only meaningful measure of treatment effect in CTS patients is the patient-reported improvement in symptoms.[51] In 1993, Levine *et al*.[60] published a new self-administered questionnaire for the assessment of CTS symptoms: the Boston Carpal Tunnel Questionnaire (BCTQ). Six critical domains were identified: pain, paresthesia, numbness, weakness, nocturnal symptoms and functional status. Two different subscales were therefore developed: the Symptom Severity Scale (SSS) and the Functional Status Scale (FSS). The SSS comprises 11 questions about symptom severity, including pain and paresthesia during the day and at night, numbness and weakness. The FSS comprises eight daily activities which are rated on degree of difficulty. All activities are common and performed by a large variety of people, including young adults to elderly. Levine *et al*.[60] tested the reproducibility, internal consistency and responsiveness to clinical change, which was later confirmed in a systematic review by De Carvalho Leite *et al*.[61] in 2006. It is an easy, quick, standardized, patient-centered, user-friendly and inexpensive measure that can be compared across studies. The BCTQ is therefore widely used in studies concerning treatment effect in CTS patients, although sometimes under a different name. The BCTQ is also referred to as Levine scale, Carpal

Tunnel Questionnaire or Carpal Tunnel Syndrome Instrument.[61] We have used a Dutch version of the BCTQ for all the chapters of this thesis. The Dutch version has previously been used in other studies.[6,43]

Aims and outlines of this thesis

This thesis focusses on the prevalence, determinants and possible consequences of CTS during pregnancy, based on data of the HAPPY study. Moreover, the design and outcomes of a randomized controlled trial involving mechanical traction, a non-invasive treatment option for CTS, in an outpatient (non-pregnant) neurologic CTS population are described.

Pregnancy is a known risk factor for CTS, but prevalence rates of CTS during pregnancy vary between 1 and 62% in the current literature due to methodological flaws. Therefore, in **Chapter 2**, we investigated the prevalence of CTS symptoms during pregnancy in a large sample of healthy pregnant women.

Hypothyroidism is another known risk factor for CTS in the non-pregnant population, but the relation between thyroid function and CTS has not been investigated in pregnancy. In **Chapter 3**, we investigated the relationship between thyroid function and CTS symptoms during pregnancy.

In Chapter 2, we describe that the one in three women report CTS symptoms during pregnancy, but the possible negative effects of these symptoms on the well-being of mother and child are unknown. Therefore, we describe the possible impact of CTS symptoms during late pregnancy on breastfeeding initiation in **Chapter 4**.

CTS symptoms in pregnancy are believed to quickly resolve after birth. However, some women may experience persisting CTS symptoms postpartum. In **Chapter 5**, we report the prevalence of persisting pregnancy-related CTS symptoms in our cohort of pregnant women. Possible predictors of CTS at 12 months postpartum were also investigated.

Carpal tunnel release surgery is the only known long-term effective treatment, but it is invasive and up to 30% of patients report recurrence or persistence of symptoms or suffer from post-surgical complications. A promising non-surgical treatment for CTS is mechanical wrist traction. In **Chapter 6**, we describe the design of a randomized controlled trial in a non-pregnant outpatient neurologic population investigating the effectiveness of mechanical wrist traction as a non-surgical treatment compared to care as usual in CTS patients. **Chapter 7** describes the results of this trial.

Finally, the main results of this thesis are summarized in **Chapter 8**, and clinical implications of the results and suggestions for future research are discussed.

An overview of the used samples

Between January 2013 and September 2014, a total of 2,221 pregnant women were included in the HAPPY study. These women were followed during pregnancy up to one year postpartum. They filled out questionnaires at 12, 22 and 32 weeks' gestation and at 1 week, 6 weeks, 4, 8 and 12 months postpartum. Figure 2 presents a flow chart of the available CTS-related data at the different time points. The samples presented in Figure 2 were used in Chapters 2 to 5. CTS

symptoms were assessed using the BCTQ at 32 weeks' gestation and postpartum. Moreover, thyroid parameters were assessed at 12 and 32 weeks' gestation. Table 1 provides an overview of the measurements and time points.

For the RCT investigating the effectiveness of mechanical traction, we recruited adult patients (men and women) with electrophysiologically confirmed CTS from an outpatient neurology clinic in the Netherlands. A total of 181 patients were randomly assigned to the intervention group (mechanical traction) or the control group (care as usual). Participants in the intervention group received 12 treatments with mechanical traction during six consecutive weeks. They completed questionnaires at baseline and 3, 6 and 12 months follow-up. Figure 3 provides a flow chart of the inclusions.

The sample presented in Figure 3 was used in Chapter 7.

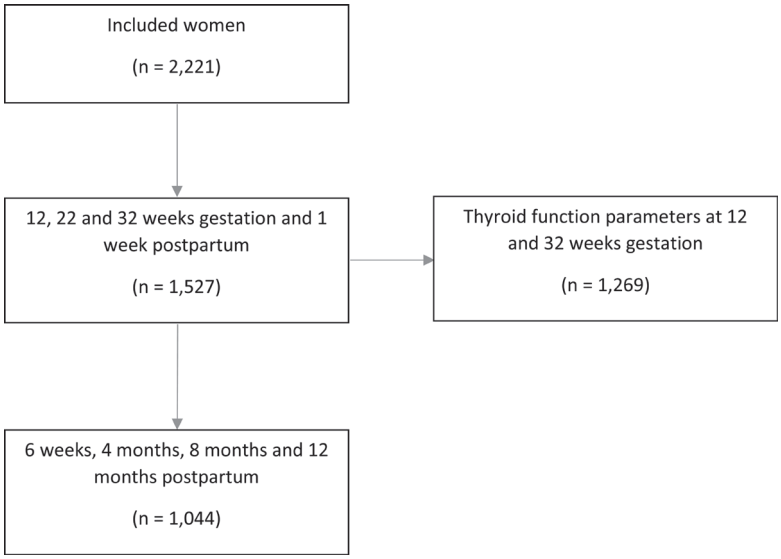

Figure 2 Flow chart for the CTS-related data of the HAPPY study.

Table 1 Time points of CTS(-related) assessments during pregnancy up to 12 months postpartum.

	Pregnancy			Postpartum				
	12 wks	22 wks	32 wks	1 wk	6 wks	4 mnths	8 mnths	12 mnths
Presence of CTS symptoms			X	X	X	X	X	X
BCTQ[a]			X	X				
Depression (EDS[b])	X	X	X	X	X	X	X	X
Thyroid function parameters	X		X					

[a] Boston Carpal Tunnel Questionnaire, only in women with CTS symptoms. [b] Edinburgh Depression Scale.

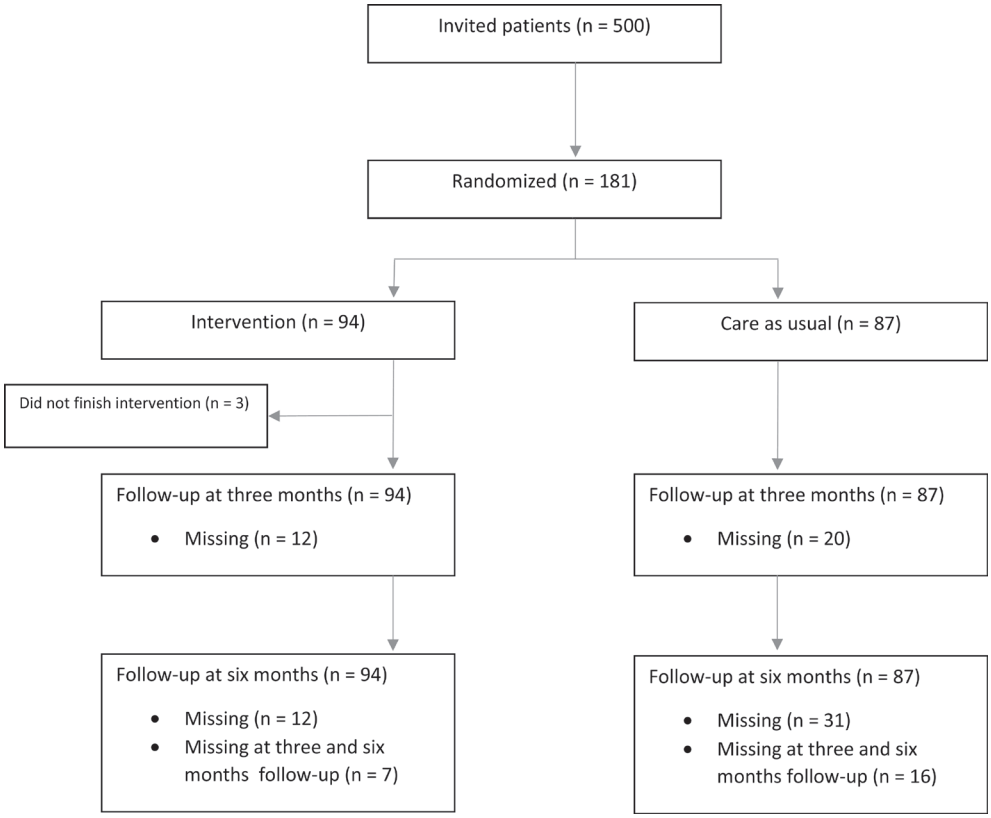

Figure 3 Flow chart of inclusions of the RCT investigating mechanical traction as treatment for CTS.

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Chapter 2

Prevalence, course and determinants of carpal tunnel syndrome symptoms during pregnancy: a prospective study

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ABSTRACT

Objective: To investigate the prevalence, severity and relation to fluid retention of self-reported pregnancy-related carpal tunnel syndrome (CTS) symptoms in a large sample of pregnant women.

Design: A prospective longitudinal cohort study.

Setting: Dutch women who became pregnant between January 2013 and January 2014 in the southeast of the Netherlands.

Population or Sample: A total of 639 Dutch pregnant women.

Methods: Baseline characteristics were assessed at 12 weeks' gestation. CTS symptoms were assessed using the Boston Carpal Tunnel Questionnaire (BCTQ) at 32 weeks and during the first postpartum week regarding the last weeks of pregnancy. Fluid retention, sleeping problems and depressive symptoms (using the Edinburgh Depression Scale) were assessed at several time points during pregnancy.

Main Outcome Measures: BCTQ scores, fluid retention and sleeping problems.

Results: Of the 639 women, 219 (34%) reported CTS symptoms during pregnancy. Total mean scores on the BCTQ were significantly higher after 32 weeks than up to 32 weeks' gestation. Most women experienced mild to moderate symptoms. Pregnant women with CTS symptoms reported significantly higher levels of fluid retention during gestation compared to pregnant women without CTS symptoms ($F = 60.6$, df {1, 598}, $p < .001$), adjusted for body mass index (BMI) age, parity and depression scores. Higher scores on fluid retention throughout the pregnancy were significantly related to CTS (OR = 1.8, 95% CI [1.5-2.1], $p < .001$). Finally, the occurrence of CTS was independently related to sleeping problems.

Conclusions: Although the severity of symptoms and functional impairment of CTS were relatively mild, health care professionals should be aware of the high prevalence. The occurrence of CTS symptoms is significantly higher in women who report fluid retention during gestation and it can contribute to sleeping problems.

INTRODUCTION

In patients with carpal tunnel syndrome (CTS) the median nerve is compressed in the carpal tunnel, leading to the key symptoms of tingling, pain and a numb feeling in the first three fingers and the radial side of the fourth finger.[1,2] CTS occurs in 4% of the general population[3] and 10% of the working population.[4] Risk factors for CTS are obesity, diabetes mellitus and rheumatoid arthritis.[2] In general, CTS is objectively diagnosed by means of electrodiagnostic testing (EDT). Compression of the median nerve leads to a slowed conduction velocity at the carpal tunnel due to dysfunction of the myelin sheath, which can be measured using EDT.[5]

CTS occurs frequently during pregnancy: pregnancy-related CTS (PRCTS). PRCTS is often bilateral[6-8] and mostly present in the third trimester.[7,9,10] Although the true cause of PRCTS is unknown, it is believed that the symptoms are caused by local edema in the carpal tunnel due to hormonal changes.[6,7,10,11] Reported prevalence rates of PRCTS vary between <1% up to 62%.[8-11] According to a recent systematic review by Padua *et al* [12], the prevalence of PRCTS based on clinical symptoms ranges between 31% and 62%, whereas electrophysiologically confirmed PRCTS ranges between 7% and 43%. This variety is explained partly by methodological aspects of assessing PRCTS, but the most important reason is patient- and doctor-delay: women do not report symptoms and physicians do not ask for them.[13] This means that figures based on patient record forms in general result in underestimation of PRCTS.

When assessing physical health problems in general, and in pregnant women in particular, it is important to be aware of mental health problems. Pregnant women are particularly at risk for depression: up to 10-15% of them suffer from depression, which is often not recognized.[14] It is well known from clinical experience and scientific research that patients with undiagnosed (and hence not properly treated) depression often report a substantial amount of somatic symptoms, including various pain symptoms.

The primary aim of the present prospective study was to study the prevalence of self-reported CTS symptoms in a large sample of pregnant women. The secondary outcome was the nature and severity of symptoms and functional impairment. The tertiary outcome was to investigate the possible relation between self-reported fluid retention and CTS complaints, adjusted for the occurrence of depression. Finally, a possible negative effect of CTS symptoms on the sleeping patterns during gestation was evaluated.

METHODS

Participants

From January 2013 to January 2014, Dutch-speaking Caucasian pregnant women were recruited from 17 community midwife practices in the region of Eindhoven, the southeast of the Netherlands, during their first prenatal visit. Women with multifetal pregnancy, previously diagnosed

endocrine disorders, severe psychiatric disease, HIV, or drug or alcohol addiction were excluded from the study. The full study protocol has been approved by the Psychology Ethics Committee of the School of Social and Behavioral Sciences of Tilburg University. All participating pregnant women (and their partners) received written and oral information and signed written informed consent.

Because the prevalence of PRCTS ranges so widely in the literature, sample size was calculated using a conservative estimated prevalence of 2.5% to increase precision. A total of 600 women needed to be included. The characteristics of the participants are shown in Table 1. As can be seen in Table 1, the number of primiparous women was similar to multiparous women and nearly 90% of the women were <35 years of age. Pregnant women with CTS symptoms did not

Table 1 Characteristics of the 639 pregnant women included in the study.

Characteristic		n (%)	Mean	SD
Demographic features				
Age (in years)			30	3.5
	<25	25 (3.9)		
	25-29	237 (37.1)		
	30-34	308 (48.2)		
	35-39	63 (9.9)		
	>40	6 (0.9)		
Educational level				
	high	443 (69.3)		
	low	196 (30.7)		
Marital status				
	With partner	632 (98.9)		
Job		594 (93.0)		
Obstetric features				
Parity				
	Primiparous	316 (49.5)		
Previous abortion		146 (22.8)		
Unplanned pregnancy		33 (5.2)		
Lifestyle habits during pregnancy				
Smoking		11 (1.7)		
Alcohol		12 (1.9)		
BMI pre-pregnancy			23.8	3.8
	<18.5	19 (3.0)		
	18.5-24.9	436 (68.2		
	25.0-29.9	136 (21.3)		
	>30.0	48 (7.5)		

differ significantly from the rest of the study sample based on baseline characteristics, except BMI pre-pregnancy (p = .01).

Assessments of baseline characteristics and pregnancy-related symptoms

At 12 weeks' gestation, the participating pregnant women completed a questionnaire to assess baseline characteristics (demographic, lifestyle habits and current and previous obstetric characteristics). At 12, 22 and 32 weeks' gestation and during the first postpartum week regarding the last weeks of pregnancy, the participants completed a questionnaire containing a variety of complaints which are generally mentioned during gestation. The items were scored on a five-point Likert scale ranging from not at all (0) to very severe (4). The items "fluid retention in hands and/or feet" fluid retention in general", "problems falling asleep" and "problems continuing sleeping" were used to evaluate a possible association with CTS, the first two as a plausible explanation of CTS and the last two as a possible negative outcome of CTS. At 32 weeks' gestation, the women were asked for the three key symptoms of CTS during the previous period of gestation: "Did you suffer any of the following symptoms during pregnancy: pain, tingling sensations, or numbness in hands or wrists?". Moreover, they were asked if the symptoms were bilateral and at what term of gestation they started. Subsequently, the positive cases (excluding those who responded with "not at all" to the key question) completed the Boston Carpal Tunnel Questionnaire (BCTQ) to evaluate the severity of symptoms as well as hand function impairment. At the end of the first postpartum week the questionnaire was also used to evaluate the last weeks of pregnancy.

The Boston Carpal Tunnel Questionnaire

The BCTQ consists of two different scales: the Symptom Severity Scale (SSS, 11 items) and the Functional Status Scale (FSS, 8 items).[15,16] Both scales are answered on a five-point Likert scale. The total score on the two subscales is calculated by dividing the absolute score by the number of items: 11-55/11 for symptom severity and 8-40/8 for functional status.[16] The BCTQ is equally useful in predicting CTS as EDT,[17] providing a simple and quick measure to assess CTS symptoms. The BCTQ has previously been validated in the Netherlands.[18]

The Edinburgh Depression Scale

At 12, 22 and 32 weeks' gestation, the occurrence of depressive symptoms was evaluated by means of the Edinburgh Depression Scale (EDS). The EDS was originally developed to assess depression in the postpartum period (EPDS) and was translated and validated for use in the Netherlands.[19] It has been shown that it has adequate psychometric properties to assess depressive symptoms during pregnancy as well.[20] The EDS consists of 10 items with total score ranges from 0 to 30, with higher scores indicating more symptoms of depression. A commonly used cut-off of 11 identifies women with depression.

Statistical analyses

Data were analyzed using SPSS 20.0 (SPSS Inc., Chicago, IL). As there was very few missing data (2%), only completed cases were analyzed. Descriptive data are presented as frequencies and corresponding percentages or means and standard deviations. Differences between groups were analyzed using t-tests for continuous variables. To assess the relationship between fluid retention during pregnancy and the presence of self-reported CTS symptoms (CTS +/-), repeated measures ANOVA was used. A p-value <.05 was considered significant. The sum scores of the two items related to fluid retention (fluid retention in hands/feet and in general) were computed for all four time points (range 0-8). Subsequently, a multiple logistic regression analysis was performed, with CTS +/- as the dependent variable and the grand mean of fluid retention (at all time points) during pregnancy as independent variable, adjusted for age, parity, BMI and depression. Finally, the possible relation between sleeping problem scores and CTS was investigated at univariate level using independent t-tests and at multivariate level using linear regression analysis, adjusting for depression, age, parity and BMI. The grand mean of sleeping problems at both time points (before and after 32 weeks) was computed using the sum scores of the two items (falling asleep and continuing sleeping), and was used as dependent variable (range 0-8).

RESULTS

In the present study, 219 of 639 women (34%) reported one or more of the three key symptoms of CTS during pregnancy. Of these 219 cases, 66 (30%) reported unilateral and 153 (70%) bilateral symptoms. Only 16 women (7% of the cases) reported the onset of symptoms before 12 weeks, 30 (14%) between 12 and 20 weeks, 86 (39%) between 21 and 30 weeks, and 87 (40%) after 30 weeks.

Of the symptomatic pregnant women, 114 (52%) cases were primiparous and 105 (48%) multiparous, of whom 27 (26%) reported having suffered from CTS symptoms during a previous pregnancy. Mean scores (total mean divided by number of items) on the symptom severity scale (SSS) and function status scale (FSS) up to and after 32 weeks' gestation were compared. Up to 32 weeks, the mean score was 1.5 (0.6) for the SSS and 1.3 (0.6) for the FSS. After 32 weeks, the mean score was 1.8 (0.7) for the SSS and 1.4 (0.6) for the FSS. Significantly higher levels of symptoms and functional impairment were reported after 32 weeks' gestation than in the first two trimesters ($t = -6.335$, $p < .001$ for SSS, $t = -3.689$, $p < .001$ for FSS). Moreover, the mean levels of severity of symptoms were significantly higher than the mean levels of functional impairment ($t = 7.573$, $p < .001$ before 32 weeks, $t = 11.765$, $p < .001$ after 32 weeks). During all trimesters, the women were asked whether they looked for medical help for any reason. Only 4 women reported to have consulted their physician because of CTS symptoms. BCTQ scores were not different between multiparous women who experienced CTS symptoms in a previous pregnancy compared with multiparous women who experienced CTS symptoms for the first time (data not shown).

The nature and severity of CTS symptoms in 219 cases using the BCTQ subscales are reported in Figure 1A and 1B. In Figure 1A, the prevalence and severity of six most typical CTS symptoms are shown. As can be seen, the most prevalent symptom was tingling sensations at night (65% >32 weeks), while pain during the night was reported in 49%. Overall, the severity of symptoms increased with increasing term. Most women experienced mild to moderate symptoms; severe and very severe symptoms were hardly reported. The severity of complaints was the highest for numbness and tingling sensations during the day and at night. After 32 weeks, 20 women (9%) reported the tingling sensations during the day to be severe or very severe. All symptoms increased in severity during the last eight weeks of pregnancy.

The degree of functional impairment is presented in Figure 1B. As can be seen, very severe functional impairment was rare, but women experienced more functional impairment during the last weeks of their pregnancy than before 32 weeks. For each of the activities, more than half of the women reported never having problems. There was no difference of reported CTS symptoms (both severity as well as functional) between primiparous and multiparous women (data not shown).

At 12, 22 and 32 weeks' gestation, the number of women suffering from depression (EDS score $\geq$11) was 64 (10%), 70 (11%) and 57 (9%), respectively. Mean scores of the EDS at different trimesters were 4.4 (4.1), 5.2 (4.2) and 4.9 (4.0), respectively.

In Figure 2, mean scores on the fluid retention items during pregnancy of women with and without CTS are presented, adjusted for BMI, age, parity and depression scores on the EDS. At all four time points mean scores on self-reported fluid retention were higher in the group of women with CTS symptoms than in the group without symptoms. Repeated measures ANOVA showed that pregnant women with CTS symptoms reported significantly higher levels of fluid retention during gestation compared with pregnant women without CTS symptoms ($F = 60.6$, df {1, 598}, $p < .001$).

Subsequently, a multiple logistic regression analysis was performed with CTS +/- as dependent variable and mean fluid retention throughout pregnancy as independent variable, adjusted for age, BMI, parity and depression scores during gestation. Only higher scores of fluid retention throughout pregnancy were significantly related to CTS (OR = 1.8, 95% CI [1.5-2.1], $p < .001$). The mean scores of sleeping problems were significantly higher in the CTS group than in the non-CTS group: 3.1 (1.8) versus 2.8 (1.8), respectively ($t = -2.048$, $p = .038$). Finally, a multiple linear regression revealed that the grand mean of the BCTQ scores predicted sleeping problems ($\beta = .087$, $p = .025$) as well as higher scores of depression symptoms on the EDS during gestation ($\beta = .237$, $p < .001$). The test for overall model fit was significant ($F = 10.55$, $p < .001$).

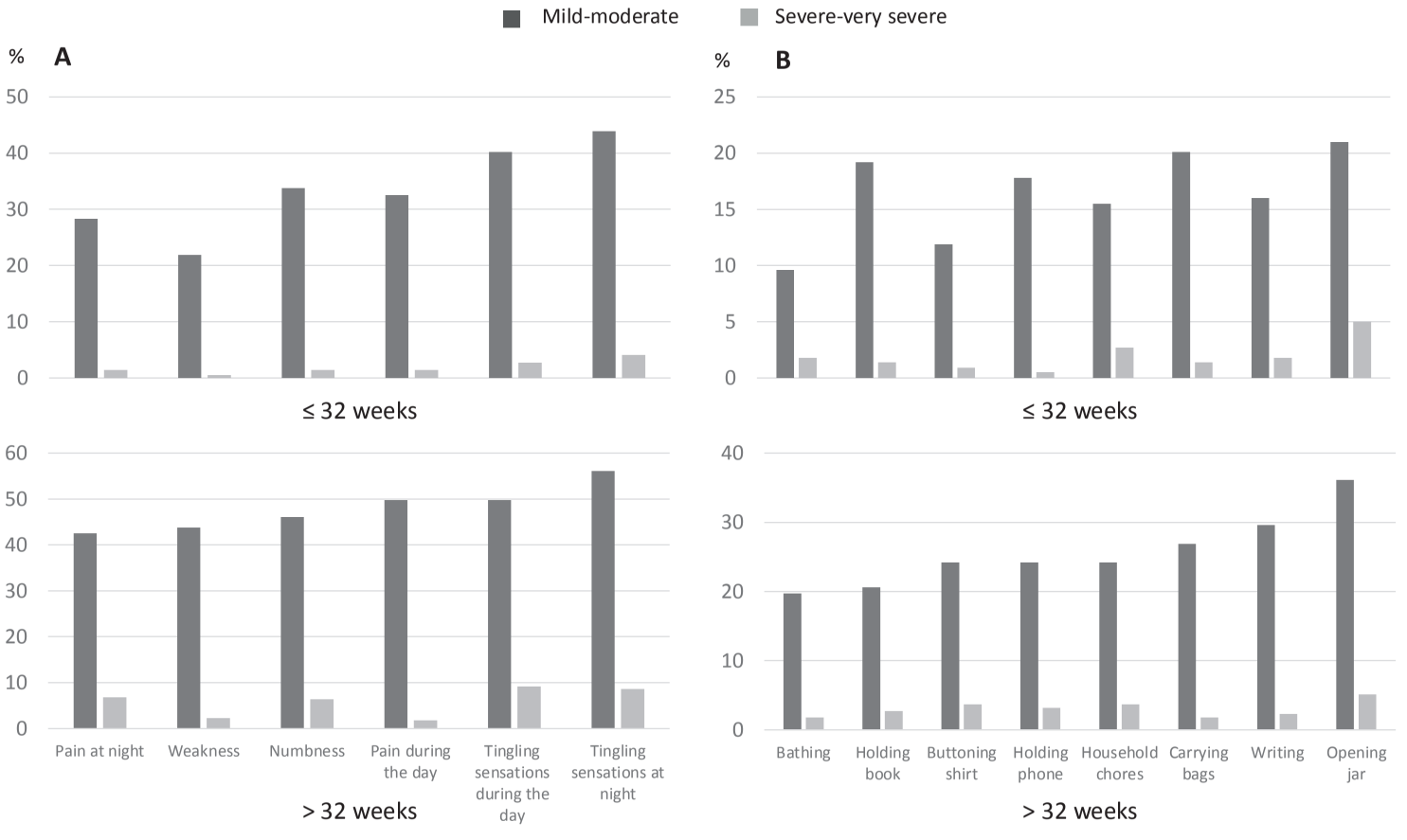

Figure 1 Nature and severity of the most common CTS symptoms (A) and functional complaints (B), measured up to and after 32 weeks' gestation.

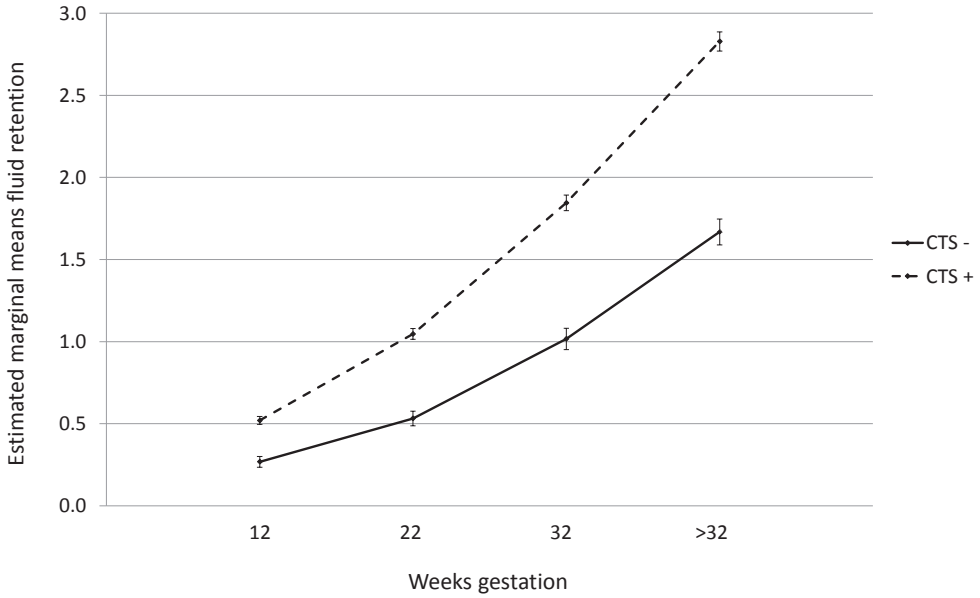

Figure 2 Estimated marginal means (repeated measures ANOVA) of the symptom fluid retention in 639 pregnant women assessed at 12, 22, 32 and after 32 weeks' gestation comparing those with CTS symptoms (CTS +, n = 219) and without CTS symptoms (CTS -, n = 420), adjusted for BMI, age, parity and depression.

DISCUSSION

Main findings

In the present study, the prevalence of self-reported carpal tunnel syndrome symptoms during pregnancy was 34%. Overall, the severity of symptoms increased with increasing term. For most women, the severity of symptoms was relatively mild and functional impairment was not frequently reported. Moreover, women with CTS symptoms reported higher levels of fluid retention during gestation compared with women without CTS symptoms. Furthermore, logistic regression results showed that for every unit increase in the mean score of self-reported fluid retention throughout pregnancy, women were almost twice as likely to report CTS symptoms. Finally, CTS had an independent negative effect on sleep during the last trimester.

Strengths and limitations

Strengths of this study are the prospective design, the repeated measurements, the adjustment for comorbid depressive symptoms and the large sample size: 639 healthy pregnant women were included in the study, providing considerable power and an accurate representation of the general population. Moreover, the study provides information about the prevalence as well as the nature, severity and course of CTS symptoms. The BCTQ assesses not only the presence

of self-reported CTS symptoms but also the severity and possible disability in hand function. The BCTQ has extensively been tested and has proved to have similar qualities as EDT.[17] This patient-friendly questionnaire made it possible to assess large samples of patients. An important finding was the increasing severity of the symptoms during the last weeks of pregnancy. This means that the last weeks of pregnancy should be taken into account when assessing CTS. Also, reported symptoms (CTS, fluid retention and sleeping problems) were corrected for depression. The study has several limitations. First, the BCTQ was completed at only two time points: at 32 weeks' gestation and during the first postpartum week. The questionnaire was not conducted at the other two time points earlier in pregnancy (12 and 22 weeks). However, it is well known that CTS rarely develops early in pregnancy.[7,9,10] Secondly, CTS was not diagnosed either clinically or using EDT. However, clinical tests such as the Tinel sign or Phalen's test have been reported to have poor sensitivity and specificity.[6,25] In clinical practice, the most important diagnostic criteria are patient reported symptoms. Concannon *et al*.[26] reported that the majority of patients with a clinical diagnosis of CTS but with a negative electrodiagnostic test benefitted from surgical release. Moreover, a questionnaire concerning the most typical CTS symptoms has been proved to have a similar sensitivity, specificity and positive predictive value as EDT.[27] As EDT is considered relatively invasive and time-consuming, the use of a questionnaire as a sensitive alternative is appropriate for pregnant women. Thirdly, only Caucasian women were included in the study, which limits the generalizability of the results. According to a recent meta-analysis, non-Caucasian people are at higher risk for CTS.[27]

Interpretation

Fluid retention increased during gestation in all women, which is consistent with the normal physiological pattern during pregnancy. The amount of weight gained between 20 and 30 weeks of pregnancy is largely attributed to an increase in maternal fat stores. After 30 weeks, an increase in extravascular fluid leads to greater weight gain.[21] This explains why CTS symptoms most commonly present after 30 weeks' gestation. In the present study, 40% of the cases reported the onset of symptoms after 30 weeks. Multiparous women with a previous history of CTS symptoms did not show a higher severity of CTS symptoms in the current pregnancy. In the current study, only (multiparous) women who reported CTS symptoms were asked for possible symptoms during earlier pregnancies. There is no evidence in the literature that the occurrence of CTS symptoms in a previous pregnancy always results in the recurrence of symptoms in a future pregnancy. However, within one woman there is a substantial individual variation of weight gain (fluid retention) between subsequent pregnancies. It is possible that a woman with a previous history of CTS during pregnancy might have had a substantially higher weight increase during that pregnancy. Unfortunately, we did not register the figures of weight gain during a previous pregnancy.

The reported prevalence of PRCTS symptoms is comparable to the prevalence range reported by Padua *et al*.[12] (31-62% clinically diagnosed PRCTS). Compared with the general population,

the prevalence of PRCTS is substantially higher. While only 4% of the general population suffers from CTS,[3] the prevalence is almost nine times higher in our study sample (pregnant women in the general population).

The severity of symptoms and functional impairment is relatively mild compared with the non-pregnant CTS population. Jarvik *et al.*[22] reported a mean score of 2.81 on the SSS and 2.32 on the FSS in their study of the general population (n = 323). These scores are considerably higher than the mean scores during the last weeks of pregnancy reported in this study (1.8 and 1.4 on the SSS and FSS, respectively). Padua *et al.*[11] also reported lower severity and impairment in pregnant women than in non-pregnant women with CTS. This is probably the main reason why PRCTS is underdiagnosed: women with mild symptoms are less likely to ask for medical care. The most commonly reported symptoms presented at night: 65% of women reported tingling sensations at night, and pain during the night was reported by 49%. As previously has been reported, these symptoms interfere with sleep.[6] The current study also shows that CTS is independently related to poorer sleeping patterns. Sleep disturbance, especially during the last trimester, interferes with quality of life and might also exhaust women, representing a possible risk of a troublesome delivery. Moreover, sleeping problems in general make people vulnerable to mental problems such as depression and anxiety. Future research could focus on the impact of CTS on the quality of life and a possible impact on mode of delivery. As CTS symptoms can be treated conservatively,[23] it is important to recognize the problem during pregnancy. Patients can wear a wrist splint, which stabilizes the wrist in a neutral position, maximizing the volume in the carpal tunnel and decreasing pressure on the nerve.[9] More than 80% of pregnant women experience considerable symptoms relief using a splint at night, thereby improving quality of sleep.[6]Moreover, steroid injections offer temporary symptom relief in most women[9]. Although serious side effects have never been reported, pregnant women do not readily accept this type of intervention. Surgery is hardly ever performed during pregnancy,[23] because many women experience symptom relief after delivery.[12] During the last decade, another non-invasive treatment has been developed for CTS: traction and rotation to the wrist using a mechanical traction device. This is a patient-friendly method that is currently being researched (described in detail elsewhere).[29] If proven effective, health care professionals will have another non-invasive treatment especially suitable for pregnant women with CTS. Ultimately, the best treatment is delivery. The fact that women with PRCTS symptoms reported significantly more severe fluid retention supports the attribution of PRCTS symptoms to local edema in the carpal tunnel due to hormonal changes.[6,7,10,11]

The trimester-specific prevalence ranges as well as the mean scores on the EDS are similar to other studies using the EDS.[20,24] It has repeatedly been reported that the number of women with depression (EDS $\geq$11) as well as the means scores decrease towards end term, which was also the case in the current study.[14] The fact that women with CTS reported higher scores of fluid retention independently of depression scores means that reporting CTS is unlikely to be related to depressed mood. To the best of our knowledge, there are no reports in the literature of stud-

ies investigating the possible effect of depression on reporting CTS symptoms in the general non-pregnant population. However, as it is well known that depression influences reporting symptoms of pain, we considered it appropriate to control for depression. The current design showed that depression scores did not interfere with the relation between CTS and fluid retention. This further supports a physiological explanation for CTS.

Conclusion

Although the severity of PRCTS is relatively mild, the prevalence of self-reported CTS symptoms during pregnancy is high, and the severity and functional impairment can easily be assessed by means of a self-rating questionnaire. CTS is strongly related to the presence of fluid retention. Severe functional impairment due to CTS symptoms is not frequently reported during pregnancy, but many women experience tingling sensations in their hands or wrists, especially at night, contributing to sleeping problems. Health care professionals should be aware of the high prevalence and the increase of symptom severity of CTS with increasing term, as symptoms can be treated effectively with conservative treatment during pregnancy.

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Chapter 3

Thyroid function and carpal tunnel syndrome symptoms during pregnancy

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Submitted

ABSTRACT

Objective: To investigate the relationship between thyroid function, fluid retention and CTS in pregnant women.

Methods: Dutch women who had their first antenatal visit at one of 17 participating community midwife offices in the Netherlands were included in this prospective longitudinal cohort study, with inclusion period from January 2013 till September 2014. A sample of 1,269 women were followed during pregnancy up until the first postpartum week. Thyroid hormone levels (TSH, FT4 and TPO-antibodies) were measured at 12 and 32 weeks. Fluid retention and CTS symptoms were measured using self-report at 12, 22 and 32 weeks' gestation, and one week postpartum regarding the last weeks of pregnancy.

Results: In the present study, 452 of 1,269 women (36%) reported CTS symptoms during pregnancy. Of the thyroid parameters, FT4 at 12 and 32 weeks' gestation were significantly related to CTS. Multiple logistic regression analysis showed that lower levels of FT4 (OR = 0.88, 95% CI [0.80-0.97]), higher fluid retention scores throughout pregnancy (OR = 1.78, 95% CI [1.57-2.02]) and higher depression scores (OR = 1.05, 95% CI [1.01-1.09]) were significantly related to CTS. Moreover, within the group of women who reported CTS symptoms, the intensity of the symptoms were significantly correlated with thyroid hormone levels at 32 weeks and fluid retention scores.

Conclusions: Lower levels of FT4 are associated with a higher prevalence of CTS. The association between FT4 and CTS was independent of fluid retention. These results indicate that thyroid function in the lower reference range contributes to CTS during pregnancy.

INTRODUCTION

Carpal tunnel syndrome (CTS) is the second most common musculoskeletal condition during pregnancy.[1] The median nerve may become compressed at the level of the carpal tunnel, leading to tingling, paresthesia and pain in the median nerve distribution.[2,3] CTS is much more common in pregnant women compared to the non-pregnant female population[4] but the prevalence rates vary substantially in the literature (1-62%).[5-8] We have recently reported a prevalence of 34% in a large sample of pregnant women.[9] CTS often presents in the later stages of pregnancy, specifically during the third trimester.[5,8,10] It has repeatedly been suggested that the high prevalence during pregnancy is related to fluid retention with increasing term.[1,7-10]

Thyroid function, especially overt hypothyroidism, has been related to CTS.[11-13] The prevalence of CTS among hypothyroid patients is over 30%,[11,13] while only 4% of the general population suffers from CTS.[14] Because the time delay between the onset of hypothyroid function and the diagnosis of hypothyroidism in general is substantial, it is hypothesized that, due to (myxo) edema in the carpal tunnel, compression of the median nerve occurs resulting in neuropathy and as a consequence CTS symptoms.[1,10] In pregnancy, thyroid hormone levels decrease during gestation.[15] However, the role of thyroid function in relation to pregnancy-related CTS has never been investigated.

In the current study, we investigated a relation between maternal thyroid hormone parameters during gestation and the occurrence of CTS symptoms. Secondly, we investigated whether the relationship between thyroid function and CTS symptoms was independent of fluid retention.

METHODS

Participants

From January 2013 to September 2014, pregnant women who had their first antenatal appointment at one of the 17 participating community midwife offices in the southeast of the Netherlands were invited for thyroid function screening as part of the Holistic Approach to Pregnancy and the first Postpartum Year (HAPPY) study, the design of which has been described in detail elsewhere.[16] In general, 86% of pregnant women in the Netherlands register at community midwife offices, the other 14% start antenatal care in a hospital.[17] During the 20 months of inclusion, about 4,150 women visited the participating midwife offices. Since most outcomes were assessed using questionnaires, only Dutch-speaking Caucasian women (N = 3,475) were invited to participate, in order to avoid language problems. Moreover, the following NHANES (National Health and Nutrition Examination Survey)[18] exclusion criteria were used: a known history of previous thyroid dysfunction (Hashimoto thyroiditis or Graves' disease, either on hormone replacement therapy or not); a known history of autoimmune disease (e.g. diabetes-I, rheumatoid arthritis); and the use of drugs that might interfere with thyroid function (e.g. use

of lithium in bipolar patients). Women with multiple pregnancies, women using psychotropic drugs, or women with a diagnosis of severe mental illness were also excluded. This resulted in 3,159 eligible women of whom 2,275 (response rate = 72%) agreed to participate. Of these women, complete data up until the first postpartum week were available for 1,269 women. This sample size is large enough to evaluate the research questions with sufficient statistical power. Characteristics of the sample population are presented in Table 1.

Table 1 Characteristics of the 1,269 pregnant women included in the study.

	Total (N = 1,269)		CTS (+) (n = 452)		CTS (-) (n = 817)		p	
	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	t	χ^2
Demographic features								
Age (in years)	30.4 (3.5)		30.3 (3.7)		30.5 (3.4)		.147	
Educational level								
Low		414 (32.6)		172 (38.1)		242 (29.6)		.002
High[a]		855 (67.4)		280 (61.9)		575 (70.4)		
Marital status								
With partner		1257 (99.1)		449 (99.3)		808 (98.9)		.440
Obstetric features								
Parity								
Primiparous		632 (49.8)		249 (55.1)		383 (46.9)		.005
Previous abortion or miscarriage		321 (25.3)		103 (22.8)		218 (26.7)		.126
Unplanned pregnancy		65 (5.1)		26 (5.8)		39 (4.8)		.449
Lifestyle habits during pregnancy								
Smoking		47 (3.7)		17 (3.8)		30 (3.7)		.936
Alcohol intake		43 (3.4)		14 (3.1)		29 (3.5)		.670
BMI pre-pregnancy	23.8 (3.9)		24.6 (4.0)		23.4 (3.7)		<.001*	
Somatic complaints								
Mean fluid retention score (range 0-8)[b]	1.1 (1.1)		1.6 (1.4)		0.8 (0.9)		<.001*	
Psychological well-being								
EDS score	4.7 (3.4)		5.2 (3.6)		4.4 (3.4)		<.001*	

[a] Bachelor or Master's degree [b] Mean of the four time points *significance level p <.05

Standard Protocol Approvals, Registrations and Patient Consents

The study was approved by the Medical Ethical Committee of the Máxima Medical Center, Veldhoven and the Psychological Ethics Committee of Tilburg University (protocol number EC-2012.25). All participants signed a written informed consent form.

Procedure

CTS assessment

At 32 weeks' gestation, women were asked for the three key symptoms of CTS during the previous weeks: "Did you suffer any of the following symptoms during the last trimester of pregnancy: pain, tingling sensations or numbness in hands or wrists? Yes / no". Subsequently, the positive cases completed the Boston Carpal Tunnel Questionnaire (BCTQ) to evaluate the severity of symptoms and functional impairment. The BCTQ consists of two different scales measuring symptom severity (11 items) and functional status (8 items) on a five-point Likert scale.[19,20] Both scales result in mean scores between 1 and 5, where greater symptom severity or functional impairment is represented by higher scores. The total BCTQ score was calculated as the mean of all the items. The BCTQ has been validated in the Netherlands.[21] At the end of the first week postpartum the BCTQ was also used to evaluate the occurrence of symptoms during the last weeks of pregnancy.

Biological assays

Thyroid stimulating hormone (TSH), free thyroxine (FT4) and Thyroperoxidase antibodies (TPO-Abs) were determined at 12 and 32 weeks' gestation in Li-heparin plasma using electrochemoluminescence assays (Cobas® e 601, Roche Diagnostics, Mannheim Germany). The non-pregnant reference ranges of TSH are 0.40-4.0 mU/L, of FT4 10.0-24.0 pmol/L and of TPO-Abs <35 IU/L.

Covariates

Depression

Depression has been associated with heightened pain experience,[22] also in pregnant women.[23] Therefore, when assessing CTS symptoms during pregnancy, it is important to adjust for depression. The Dutch version of the Edinburgh Depression Scale (EDS)[24] was used to measure symptoms of depression at 12, 22 and 32 weeks' gestation. The EDS consists of ten items and has been validated in the Netherlands among the pregnancy trimesters.[25] The total score ranges from 0 to 30, with higher scores indicating more symptoms of depression. The EDS has shown to be a reliable instrument to detect women with syndromal depression.[25]

Assessment of fluid retention and pain

At 12, 22 and 32 weeks' gestation and during the first postpartum week regarding the last weeks of pregnancy, the participants completed a questionnaire containing a variety of complaints which are generally mentioned during gestation, including questions related to fluid retention. The items were scored on a five-point Likert scale ranging from not at all (0) to very severe (4). The sum scores on the items "fluid retention in hands and/or feet" and "fluid retention in general" were used to create a two-item subscale on fluid retention with a range of 0-8. In order to control for pain-related reporting bias in women with CTS symptoms, thyroid hormone levels were compared between women who suffered from another frequently reported pain symptom during

gestation (headache) and women who did not. Moreover, at 12 weeks' gestation, the participating pregnant women completed a questionnaire to assess baseline characteristics (demographics, lifestyle habits including BMI, smoking habits and alcohol intake, and current and previous obstetric characteristics). Information about parity was obtained from the obstetric records.

Statistical analyses

Data are presented as mean (SD) or number of participants (n) and percentages. We performed t-tests comparing the means (SD) between CTS + and CTS - women for continuous variables and χ^2-tests for categorical variables. FT4 values were normally distributed, but TSH values were not. Therefore, TSH values were log transformed. The effect sizes of significant differences between groups were evaluated according using Cohen's *d* for t-tests and Cramer's *V* for χ^2-tests.[26] For Cohen's *d,* .2, .5 and .8 are considered small, medium and large effect sizes, respectively. For Cramer's *V,* .1, .3 and .5 are considered small, medium and large effect sizes, respectively, for df = 1, and .06, .17 and .29, respectively, for df = 3. Single logistic regression analyses were used to investigate the relationship between the different thyroid parameters and CTS symptoms. We checked for a non-linear effect, which was not found. We calculated FT4 quartiles at 32 weeks' gestation and performed repeated measures ANOVA comparing mean scores of fluid retention symptoms between different quartiles, adjusting for parity, age, BMI and depression scores with Bonferroni correction for multiple testing. Finally, a multiple logistic regression analysis was performed, with CTS +/- as the dependent variable and FT4 levels as independent continuous variables, adjusted for fluid retention scores (grand mean of four time points), depression (EDS scores), age, parity and BMI. A p-value <.05 was considered significant. Statistical analyses were performed using the Statistical Package of Social Science (SPSS, 21.0).

RESULTS

Baseline data were available for 2,221 women and complete data up until the first postpartum week were available of 1,269 women. We compared baseline characteristics between women with (n = 952) and without (n = 1,269) missing data at one week postpartum. Women with missing data were less high educated (57% vs. 67%, χ^2 (1, N = 2,125) = 25.7, p <.001, *V* = .11) and less often had a partner (98% vs. 99%, χ^2 (1, N = 2,133) = 5.64, p = .018, *V* = .05). Age and parity did not differ between women with and without missing data.

In the present study, 452 of 1,269 women (36%) reported at least one of the three key symptoms of carpal tunnel syndrome during pregnancy. Of these 452 cases, 140 (23%) cases reported unilateral and 312 (69%) bilateral CTS symptoms. As shown in Table 1, women who reported CTS symptoms were more often primiparous (p = .005, *V* = .08), lower educated (p = .002, *V* = .09) and had significantly higher mean scores on fluid retention (p <.001, *d* = .68), higher BMI (p <.001, *d* = .31) and higher levels of depressive symptoms (p <.001, *d* = .23).

Association between thyroid hormone and carpal tunnel syndrome symptoms

Single logistic regression analyses results of thyroid fuction parameters and CTS are shown in Table 2. Women with higher mean FT4 levels at 12 and 32 weeks had a significantly lower likelihood of having CTS symptoms (OR = 0.93, 95% CI [0.88-0.99] and OR = 0.80, 95% CI [0.73-0.87], respectively). Because the effect size at 12 weeks was low and CTS mostly occurs later in pregnancy, FT4 levels at 32 weeks were used for further analyses. Within the groups of women with CTS symptoms, FT4 levels at 32 weeks did not relate to unilateral or bilateral symptoms (data not shown). For comparison purposes, we also examined associations between thyroid hormone levels and a non-CTS pain symptom (headache) and found no differences in FT4 levels between women with (n = 491) and without (n = 778) headache symptoms (OR = 0.95, 95% CI [0.87-1.03]).
To further assess the relation between FT4 and CTS, the FT4 levels at 32 weeks' gestation were divided in quartiles (<10.86 pmol/L, 10.86-11.77 pmol/L, 11.78-12.68 pmol/L and >12.68 pmol/L, respectively). The percentage of women reporting CTS per FT4 quartile is presented in Figure 1. Women with FT4 levels in the lowest quartile reported significantly more often CTS symptoms (χ^2 (3, N = 1,269) = 30.9, p <.001).
In Figure 2, mean scores on the fluid retention subscale during pregnancy of pregnant women in relation to FT4 quartiles at 32 weeks are presented, adjusted for BMI, age, parity and depression scores. Repeated measures ANOVA showed that the lower the quartile of FT4, the higher the scores of fluid retention during gestation ($F_{3,1261}$ = 20.5, p <.001 after Bonferroni correction).
To examine whether the association between FT4 and CTS was independent of fluid retention and depressive symptoms, a multiple logistic regression analysis was performed with CTS +/- as dependent variable and FT4 levels at 32 weeks as independent continuous variable, adjusted for fluid retention, depressive symptoms, BMI, parity and age. The results are presented in Table 3. FT4 (OR = 0.88, 95% CI [0.80-0.97]), higher fluid retention scores throughout pregnancy (OR = 1.78, 95% CI [1.57-2.02]) and higher EDS scores (OR = 1.05, 95% CI [1.01-1.09]) were significantly related to CTS, whereas other variables were not.

Table 2 Single logistic regression analyses in 1,269 pregnant women with CTS +/- as dependent variable and different thyroid parameters at 12 and 32 weeks' gestation as independent variables.

		CI		
Variable	**OR**	**Lower**	**Upper**	**p**
TPO-Abs >35 IU/l at 12 weeks	0.90	0.59	1.36	.604
FT4 at 12 weeks pmol/L	0.93	0.88	0.99	.038*
logTSH at 12 weeks	1.26	0.90	1.78	.184
FT4 32 at weeks (pmol/L)	0.80	0.73	0.87	<.001*
logTSH at 32 weeks	1.13	0.69	1.86	.635

*significance level p <.05

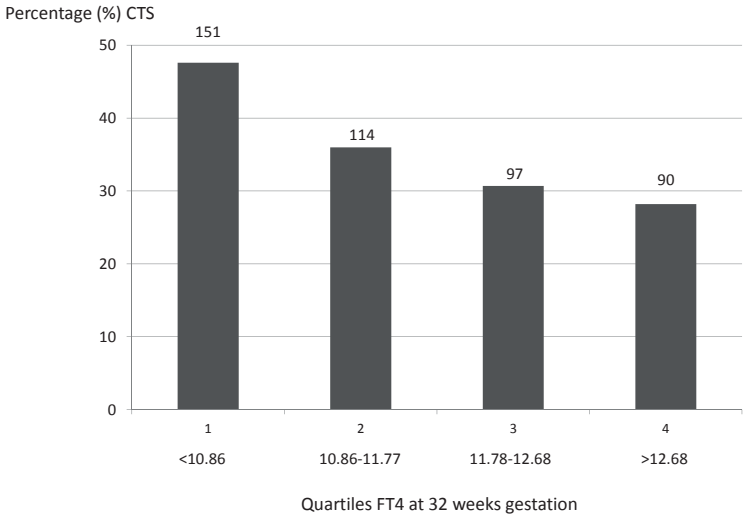

Figure 1 Percentage of women with CTS during pregnancy presented per quartile FT4 at 32 weeks' gestation. χ^2 (3, N = 1,269) = 30.9, p <.001.

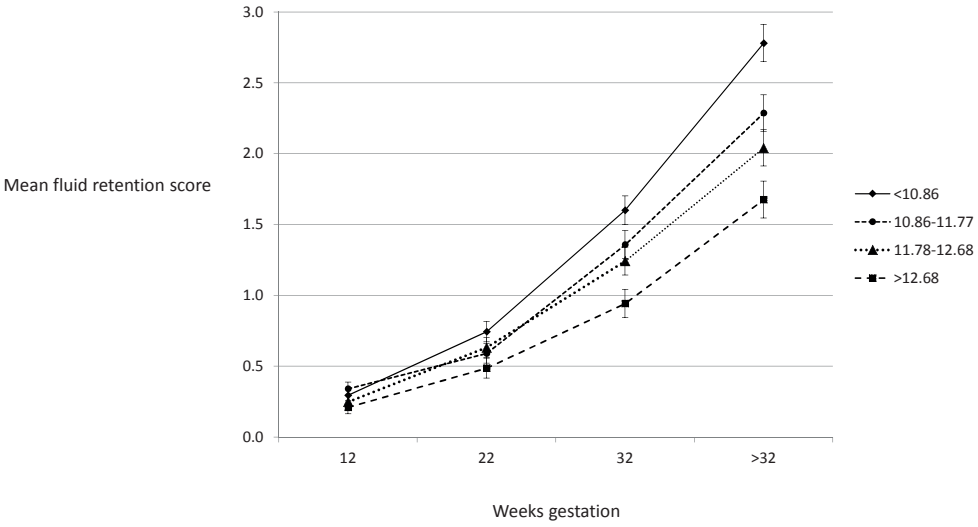

Figure 2 Relation between the symptom "fluid retention" at four time points during pregnancy and FT4 quartiles at 32 weeks' gestation, adjusted for age, parity, BMI and depression.

Finally, within the group of women who reported CTS (n = 452), the intensity of CTS symptoms (mean of total BCTQ scores at 32 weeks and during the last weeks of pregnancy) was correlated with thyroid hormone levels at week 32 and mean fluid retention scores. Women with higher symptoms intensity also reported higher mean levels of fluid retention (r_s = 0.46, p <.001, medium to large effect size according to Cohen[26]) and had lower FT4 levels at 32 weeks' gestation (r_s = -0.15, p = .002, low effect size).

Table 3 Multiple logistic regression analysis results with CTS +/- as dependent variable.

		CI		
Variable	**OR**	**Lower**	**Upper**	**p**
Higher FT4 at 32 weeks of gestation	0.88	0.80	0.97	.005*
Higher fluid retention score during pregnancy	1.78	1.57	2.02	<.001*
Higher BMI pre-pregnancy	1.03	1.00	1.06	.088
Multiparity	0.80	0.61	1.03	.086
Higher age	0.99	0.96	1.03	.705
Higher EDS score	1.05	1.01	1.09	.010*

*significance level p <.05

DISCUSSION

This study showed that women with FT4 levels in the lower quartiles reported CTS symptoms significantly more often than women with higher FT4 levels. Women with lower FT4 levels also reported significantly higher levels of fluid retention during gestation, adjusted for BMI, age, parity and depression. However, fluid retention did not account for the observed association between low thyroid levels and CTS.

CTS is a highly prevalent (30%) condition among hypothyroid patients.[11,13] The underlying physiological mechanism remains unclear. It has been hypothesized that a combination of compression and physiological changes of the median nerve lead to the typical CTS symptoms in hypothyroid patients[27] but evidence is still lacking. To date, a possible relationship between CTS and thyroid function during pregnancy has never been investigated. It is known, however, that FT4 levels decrease during gestation, partly because the substantial increase of extracellular volume, partly because of the increasing fetal demands of maternal FT4.[15] We previously showed a significant relation between inappropriate weight gain and lower FT4 levels during gestation.[28] It is not clear yet whether this increase is related to the possible metabolic effect of lower FT4 or to a possible effect of FT4 on fluid retention. In the current study, we showed that lower FT4 levels are related to a higher prevalence of CTS. Self-reported symptoms of fluid retention increased with increasing term (Figure 2), which is a normal physiological phenomenon during pregnancy. In the last trimester, the increase in weight can mostly be attributed to an increase in extravascular fluid.[29] This explains why CTS symptoms most commonly present at a later stage during pregnancy.[9] We also found that lower levels of FT4 were significantly related to higher levels of self-reported fluid retention symptoms. Moreover, within the group of women with CTS symptoms, higher levels of fluid retention were significantly related to higher levels of CTS symptom severity and functional impairment. Current theories about the pathophysiology of entrapment neuropathies are mainly based on experimental (animal) studies.[30] The biologic response to compression seems to be a cascade comprising endoneurial edema, demyelination,

inflammation, distal axonal degeneration, fibrosis, growth of new axons, remyelination and thickening of the perineurium and endothelium.[30,31] However, the pathophysiological effect of fluid retention on the median nerve as occurs in pregnancy is unclear. Fluid retention in the synovial tissue in the carpal tunnel may lead to pressure on the median nerve. On the other hand, fluid retention can also cause endoneurial edema and thickening of the perineurium causing the nerve itself to enlarge or result in metabolic changes in the nerve, resulting in impaired nerve function without nerve enlargement.[32] To distinguish between these mechanisms, further studies should focus on the use of ultrasonography of the carpal tunnel, which is non-invasive and therefore suitable for pregnant women.[33]

Reported symptoms, such as tingling, paresthesia and pain in particular, are a complex, conscious, unpleasant somatic experience with cognitive, emotional and sensory features.[34] This subjective experience can be influenced by mood and emotional state. Psychological variables are increasingly important in explaining models of reporting somatic symptoms.[35] There is abundant evidence in the literature for the significant impact of cognitive and affective variables on pain experience.[22,35] Depression, for example, has been associated with heightened pain experience,[22] also in pregnant women.[23] Therefore, when assessing CTS symptoms during pregnancy, it is important to adjust for the emotional status, especially depression. Multivariable analyses showed that the observed inverse association between FT4 levels and CTS was affected by depressed mood.

This study has several strengths, including the prospective longitudinal design with repeated measurements, the adjustment for comorbid depressive symptoms and the large sample size. One of the limitations is that CTS was not diagnosed either clinically or using electrodiagnostic tests (EDT). However, the diagnosis of CTS in general is based on patient-reported key symptoms: pain, tingling sensations or numbness in hands or wrists.[9,36,37] Clinical tests of CTS (Tinel and Phalen) have poor predictive value of accurately diagnosing CTS.[38] Moreover, it has repeatedly been demonstrated that the diagnostic validity of reporting these key symptoms is similar to electrodiagnostic techniques.[37] A questionnaire referring to the most typical CTS symptoms has a similar sensitivity, specificity and positive predictive value as EDT.[39] EDT is relatively invasive and time-consuming; the use of a questionnaire is therefore an appropriate alternative for pregnant women. Another limitation is the generalizability of the results; only white Caucasian women were included and the educational level was relatively high. Moreover, of the 2,221 women with baseline data, 1,269 women with complete data up to one week postpartum were included in the analyses. Women with and without missing data significantly differed based on education and marital status, though effect sizes were small, suggesting little if any clinical relevance. The missing data at one week postpartum were mostly due to practical reasons because midwives did not always inform in time when a woman gave birth. Missing data were therefore mostly at random, decreasing the likelihood of bias. Furthermore, the design of this study was prospective, with repeated measurements of CTS and thyroid function during pregnancy. However, the stron-

gest associations were found at the end of pregnancy (at 32 weeks), and these cross-sectional associations do not allow conclusions about causal inference.

In conclusion, lower levels of free T4 are related to a higher prevalence of CTS and higher levels of fluid retention. The results of this study contribute to the understanding of possible mechanisms related to CTS symptoms during pregnancy, which affects one out of three women.

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Chapter 4

Carpal tunnel syndrome symptoms during late pregnancy may negatively affect breastfeeding initiation

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Submitted

ABSTRACT

Objective: To investigate the relation between carpal tunnel syndrome (CTS) symptoms and the initiation of breastfeeding.

Design: A prospective longitudinal cohort study with inclusion period from January 2013 till September 2014.

Setting: Dutch women who had their first antenatal visit at one of 17 participating community midwife offices in the Netherlands were included in this project.

Participants: A sample of 1,530 pregnant women who were followed up until the first postpartum week.

Measurements: Boston Carpal Tunnel Questionnaire to assess the severity of CTS symptoms.

Findings: 1,121 of 1,530 women (73%) initiated breastfeeding their newborn and 423 of 1,530 women (28%) reported CTS symptoms during their last weeks of pregnancy. There was no difference in the prevalence of CTS between women who did or did not initiate breastfeeding. Within the group of women with CTS, mild CTS symptoms (OR = 1.93, 95% CI [1.10-3.36]), higher education (OR = 2.10, 95% CI [1.34-3.29]) and multiparity (OR = 0.61, 95% CI [0.38-0.97]) were independently related to breastfeeding initiation.

Key conclusions: Women with mild CTS symptoms seem to be more likely to initiate breastfeeding compared to women with more severe CTS symptoms.

Implications for practice: Midwives and obstetricians should ask for the presence of CTS symptoms and could offer women non-invasive treatment for symptom relief.

INTRODUCTION

Breastfeeding is the preferred form of feeding for newborns: the World Health Organization recommends exclusive breastfeeding during the first six months of the infant's life.[1] In 2001, 75% of mothers started to breastfeed their newborns in the US.[2] In 2011, this number increased to 79%.[3] In the Netherlands, around 75% of mothers initiate breastfeeding their infant.[4,5] Characteristics that have been related to the initiation of breastfeeding are higher education, not smoking and primiparity.[4-7] There is some evidence that women who delivered at home are more likely to initiate breastfeeding.[5] Previous studies report contradictory results on the effect of mode of delivery on breastfeeding. Leung *et al.*[6] state cesarean delivery as a risk factor for not initiating breastfeeding, while Patel *et al.*[8] did not find this relation. Moreover, spontaneous labor may increase the likelihood of breastfeeding initiation. Women who do not go into spontaneous labor often receive synthetic oxytocin, which desensitizes the oxytocin receptors and therefore negatively affects milk production and ejection.[9,10] The effect of gestational depression on breastfeeding is also unclear. Some studies suggest that women who are depressed are less likely to initiate breastfeeding,[11,12] while others report a relation between depression and breastfeeding intention[13] or duration,[14] but not initiation.

Carpal tunnel syndrome (CTS) is a very common musculoskeletal condition during pregnancy.[15] Typical symptoms are tingling, paresthesia and pain in the hand, as a consequence of the compression of the median nerve at the level of the carpal tunnel.[16,17] CTS is much more common in pregnant women compared to the non-pregnant female population.[18,19] CTS often presents in the later stages of pregnancy, specifically during the third trimester.[18,20-22] Symptom severity reduces rapidly in the first postpartum week,[15,21] but up to 30% of women report symptom persistence three years after delivery.[19,23]

Symptoms of CTS may interfere with a woman's decision to initiate breastfeeding. The sensory problems in the fingers may challenge women during breastfeeding, especially during the night time feedings when symptoms are typically worse. Even though the prevalence of CTS among pregnant women is high, the possible impact on the initiation of breastfeeding has never been investigated. Therefore, the aim of the current study is to investigate whether the prevalence or severity of CTS symptoms is related to the initiation of breastfeeding. We hypothesize that women with more severe CTS symptoms are less likely to initiate breastfeeding.

METHODS

Participants

This study is part of the Holistic Approach to Pregnancy and the first Postpartum Year (HAPPY) study (described in detail elsewhere[24]). Pregnant women who had their first antenatal visit between January 2013 and September 2014 at one of the 17 participating community midwife

practices in the southeast of the Netherlands were invited to participate in the study. In general, 85% of pregnant women in the Netherlands register at community midwife offices, the other 15% start antenatal care in a hospital.[25] During the 20 months of inclusion, about 4,150 women visited the participating midwife offices. Since most outcomes were assessed using questionnaires, only Dutch-speaking Caucasian women (N = 3,475) were invited to participate, in order to avoid language problems. Women with multiple pregnancies, thyroid dysfunction, autoimmune disease, women using psychotropic drugs and with a diagnosis of severe mental illness were excluded. This resulted in 3,159 eligible women of whom 2,275 (response rate = 72%) signed a written informed consent to participate. Only women who delivered at term (≥37 weeks' gestation) were included in the current study's analyses (n = 1,530). This sample size is large enough to evaluate the research questions with sufficient epidemiologic power. Characteristics of the sample population are presented in Table 1. The study was approved by the Psychology Ethics Committee of Tilburg University (protocol number EC-2012.25) and additionally evaluated by the Medical Ethical Committee of the Máxima Medical Center in Veldhoven.

Procedure

Women completed questionnaires at 12, 22 and 32 weeks' gestation and one week postpartum. One week postpartum, women were asked how they were currently feeding their baby. Women who were exclusively breastfeeding, who started breastfeeding but had stopped and women who combined breastfeeding and bottle feeding were considered to have initiated breastfeeding.

CTS assessment

During the first postpartum week, women were asked for the three key symptoms of CTS during the last weeks of pregnancy: "Did you suffer any of the following symptoms during pregnancy: pain, tingling sensations or numbness in hands or wrists? Yes / no". Subsequently, the positive cases completed the Boston Carpal Tunnel Questionnaire (BCTQ) to evaluate the severity of symptoms and functional impairment. The BCTQ consists of two different scales: the Symptom Severity Scale (SSS; 11 items) and the Functional Status Scale (FSS; 8 items). The items are scores on a five-point Likert scale.[26,27] The total score on the two subscales is calculated by averaging the scores on all individual items. Higher scores on the two subscales reflected more severe symptoms and more functional impairment and there is no cut-off score. The BCTQ has been validated in the Netherlands.[28]

Covariates

Baseline variables were collected at 12 weeks' gestation (BMI pre-pregnancy, education, smoking behavior, etc.). Obstetric data (birth weight, parity, home birth, spontaneous labor) were obtained from the obstetric records.

The Dutch version of the Edinburgh Depression Scale (EDS)[29] was used to measure symptoms of depression at 12, 22 and 32 weeks. The EDS consists of ten items and has been validated in the

Table 1 Characteristics of 1,530 pregnant women who gave birth ≥37 weeks' gestation.

Variable		Total (n = 1,530)		Breastfeeding initiation (n = 1,121)		No breastfeeding initiation (n = 409)		p-value	
		Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	t	χ^2
CTS during last weeks of pregnancy			423 (27.6)		296(26.4)		127 (31.1)		.072
Demographic features									
Age (in years)		30.5 (3.5)		30.5 (3.4)		30.4 (3.8)		.416	
Educational level									
	High[a]		1024 (66.9)		814 (72.6)		210 (51.3)		<.001*
	Lower		506 (33.1)		307 (27.4)		199 (48.7)		
Marital status									
	With partner		1517 (99.2)		1111 (99.1)		406 (99.3)		.765
Obstetric features									
Parity									
	Primiparous		749 (49.0)		581 (51.8)		168 (41.1)		<.001*
Birth weight (gr)		3512.8 (477.6)		3515.4 (467.0)		3505.6 (506.1)		.722	
Home birth			233 (15.2)		190 (16.9)		43 (10.5)		.002*
Spontaneous labor			1231 (80.5)		911 (81.3)		320 (78.2)		.186
Lifestyle habits during pregnancy									
Smoking			68 (4.4)		37 (3.3)		31 (7.6)		<.001*
BMI pre-pregnancy		23.8 (4.0)		23.6 (3.8)		24.4 (4.3)		<.001*	
EDS score grand mean		4.7 (3.4)		4.7 (3.5)		4.8 (3.3)		.547	

[a] Bachelor or Master's degree *significance level p <.05

Netherlands among the pregnancy trimesters.[30] The total score ranges from 0 to 30, with higher scores indicating more severe symptoms of depression. The EDS has shown to be a reliable instrument to detect women with syndromal depression.[30] We computed a grand mean score of the EDS of the scores on the three different time points.

Statistical analyses

Statistical analyses were performed using the Statistical Package of Social Science (SPSS, 22.0). Data are presented as mean (SD) or percentages. We performed t-tests comparing the means (SD) between breastfeeding initiation yes/no for continuous variables and χ^2-tests for categorical variables. The effect sizes of significant differences between groups were evaluated according using Cohen's *d* for t-tests and Cramer's *V* for χ^2-tests.[31] For Cohen's *d,* .2, .5 and .8 are considered small, medium and large effect sizes, respectively. For Cramer's *V,* .1, .3 and .5 are considered small, medium and large effect sizes, respectively, for df = 1. Within the group of women with CTS symptoms, multiple logistic regression analysis was performed, with breastfeeding initiation (yes/no) as the dependent variable and mild CTS symptoms as independent variable, adjusted for BMI, educational level, smoking, parity, home birth, spontaneous labor and depressive symptoms during pregnancy.

FINDINGS

Baseline data were available for 2,221 women and complete data up until the first postpartum week were available of 1,563 women. We compared baseline characteristics between women with (n = 658) and without (n = 1,563) missing data at one week postpartum. Women with missing data were younger (30.0 vs. 30.5, t = 2.66, p = .008, *d* = .13), less high educated (52% vs. 67%, χ^2 (1, N = 2,125) = 40.1, p <.001, *V* = .14) and less often had a partner (97% vs. 99%, χ^2 (1, N = 2,133) = 15.8, p <.001, *V* = .09). Parity did not differ between women with and without missing data. Although the differences between completers and drop-out were statistically significant (due to the large sample sizes), the effect sizes were rather low, suggesting little if any clinical relevance. Only women who delivered at term (≥37 weeks' gestation) were included in further analyses (n = 1,530).

In the present study, 1,121 of 1,530 women (73%) initiated breastfeeding and 423 of 1,530 women (28%) reported CTS symptoms during their last weeks of pregnancy, with a mean BCTQ score of 1.70 (0.62), mean SSS score of 1.92 (0.68) and mean FSS score of 1.49 (0.64). There was no statistically significant difference between the prevalence of CTS during the last weeks of pregnancy among women who initiated breastfeeding compared to women who did not (Table 1). Women who initiated breastfeeding were more often higher educated (χ^2 (1, N = 1,530) = 61.2, p <.001, *V* = .20), primiparous (χ^2 (1, N = 1,530) = 13.9, p <.001, *V* = .10), non-smokers (χ^2 (1, N = 1,530) = 12.9, p <.001, *V* = .09) and more often gave birth at home (χ^2 (1, N = 1,530) = 9.61,

p = .002, *V* = .08) (Table1). Women who initiated breastfeeding also had lower BMIs (t = 3.73, p <.001, *d* = .20).

We subsequently looked within the group of women who reported CTS symptoms (n = 423). There were significantly more primiparous women in the CTS group compared to the group of women without CTS (57% vs. 46%, respectively, χ^2 (1, N = 1,530) = 16.9, p <.001, *V* = .11). Moreover, women with CTS less often gave birth at home (12% vs. 16%, χ^2 (1, N = 1,530) = 3.90, p = .048, *V* = .05), less often had spontaneous labor (76% vs. 82%, χ^2 (1, N = 1,530) = 7.77, p = .005, *V* = .07) and had a higher BMI (24.6 vs. 23.5, t = 4.96, p <.001, *d* = .28). The other characteristics as presented in Table 1 were similar in this CTS subgroup (data not shown). Within the group who reported CTS symptoms, different quartiles were calculated according to symptom severity scores, with higher quartiles reflecting more severe symptoms. As can be seen in Figure 1, in the group of women with symptom severity scores in the lowest quartile, up to 79% initiated breastfeeding while in the other quartiles this figure was between 64 and 69% (χ^2 (3, n = 423) = 6.34, p = .096). There is a clear difference in breastfeeding initiation rate between the lowest quartile and the upper three quartiles. Therefore, based on Figure 1, mild CTS symptoms was defined using the 25th percentile (SSS score = 1.38) as cut-off.

Finally, a multiple logistic regression analysis was performed with breastfeeding initiation yes/no as dependent variable and mild CTS symptoms as independent variable, adjusting for BMI, educational level, smoking, parity, home birth, spontaneous labor and depressive symptoms

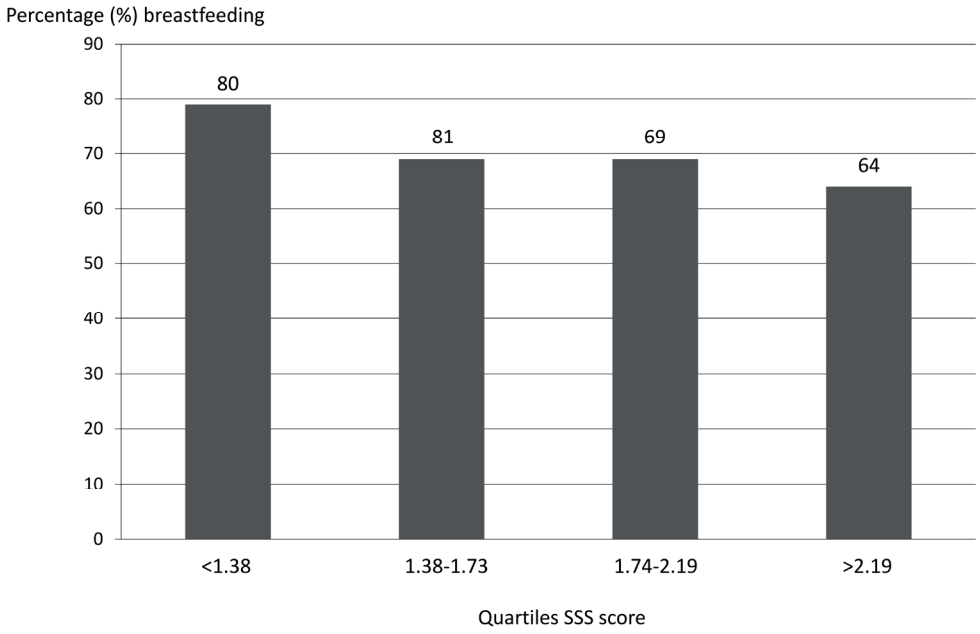

Figure 1 Percentage of women with carpal tunnel syndrome (CTS) who initiated breastfeeding presented per quartile mean Symptom Severity Scale (SSS) score. χ^2 (3, n = 423) = 6.34, p = .096.

during pregnancy. The results are presented in Table 2. Mild CTS symptoms (OR = 1.93, 95% CI [1.10-3.36]), higher education (OR = 2.10, 95% CI [1.34-3.29]) and multiparity (OR = 0.61, 95% CI [0.38-0.97]) were independently related to breastfeeding initiation. When we repeated the multiple regression analysis with the SSS as a continuous variable similar results were found (data not shown). Moreover, similar analyses with the FSS did not lead to significant results (data not shown).

Table 2 Multiple logistic regression analysis with initation of breastfeeding as dependent variable within 423 women reporting carpal tunnel syndrome (CTS) symptoms.

		CI		
Variable	**OR**	**Lower**	**Upper**	**p**
Mild CTS symptoms[a]	1.93	1.10	3.36	.021*
High education[b]	2.10	1.34	3.29	.001*
Higher BMI	1.00	0.95	1.05	.918
Smoking	0.41	0.14	1.20	.106
Multiparity	0.61	0.38	0.97	.035*
Home birth	1.99	0.92	4.30	.079
Spontaneous labor	0.92	0.54	1.57	.759
Higher EDS score	1.02	0.96	1.09	.574

[a] cut-off CTS symptoms <25th percentile (mean BCTQ <1.38) [b] Bachelor or Master's degree *significance level p <.05

DISCUSSION

In the current study, 73% of the women initiated breastfeeding and 28% reported CTS symptoms during their last weeks of pregnancy. The prevalence of breastfeeding initiation was not significantly different between women with or without CTS symptoms. However, within the group of women who reported CTS, women with mild CTS symptoms were more likely to initiate breastfeeding.

In 2013, 75% of women in the Netherlands initiated breastfeeding their newborn,[25] compared to 73% in our study. Breastfeeding initiation rates vary greatly across Europe, with over 95% in Norway[32] and about 55% in Ireland.[33] Compared to the US, breastfeeding initiation rates are similar in the Netherlands.[3]

The prevalence of CTS symptoms in our sample of pregnant women (28%) is lower compared to the 35% we have previously reported.[18] In this earlier study, we looked at CTS symptoms during the whole pregnancy, but in the current study only the last weeks of pregnancy were taken into account. We believe that symptoms earlier on in pregnancy which disappear during the last weeks of pregnancy are unlikely to influence the initiation of breastfeeding due to functional hand problems. Breastfeeding initiation rates were not lower among women who reported CTS symptoms. As we have previously shown, symptom severity and functional impairment is rela-

tively mild in the pregnant population.[18] In the current literature there are no pregnancy-specific cut-off scores for the severity of CTS. In our study, the 25th percentile of the SSS score was used as a cut-off point reflecting mild scores, and women with lower SSS scores were more likely to initiate breastfeeding.

The likelihood of breastfeeding was higher in women with higher educational level, and women who breastfed less often smoked, had a lower BMI, were more often primiparous and more often gave birth at home, which corresponds to results of previous studies.[4-7] The mean score on the EDS was 4.7, which corresponds to the mean score (4.5) of another sample of Dutch pregnant women of Bergink *et al.*[30] In the current study, the mean EDS score during pregnancy did not differ between women who initiated breastfeeding and women who exclusively bottle fed their newborn. The results are in agreement with the studies from Dias *et al.*[14] and Fairlie *et al.*[13], who conclude that depressive symptoms do not influence breastfeeding initiation. Mathews *et al.*[12] did find a relation between depressive symptoms during pregnancy and breastfeeding initiation, but they only included primiparous women in their study.

Spontaneous labor did not affect breastfeeding initiation in the current study. Home birth was associated with breastfeeding initiation in the study by Lanting *et al.*[5] but not in the current study at a multivariate level. Before 2005, however, the prevalence of home births was higher (30%)[5] compared to the current study (15%): recent annual figures of home birth in the Netherlands vary between 5-15% (with lower home births in large cities) and are declining gradually over the last decade.[25]

This study has several strengths, including the prospective design, the large sample size and the adjustment for several possible important determinants of breastfeeding initiation (educational level, parity and depression). Characteristics of the current study sample are similar to the general pregnant population in the Netherlands, based on age, parity and breastfeeding initiation rates.[25] Several limitations of the current study need to be mentioned. First, CTS was not diagnosed either clinically or using electrodiagnostic tests (EDT). However, the diagnosis of CTS in general is based on patient-reported key symptoms: pain, tingling sensations or numbness in hands or wrists.[18,34,35] Clinical tests of CTS (Tinel and Phalen) have poor predictive value of accurately diagnosing CTS.[36] Another limitation is the generalizability of the results. First, of the 2,221 women with baseline data, 1,563 women with complete data up to one week postpartum were included in the analyses. Women with and without missing data significantly differed based on age, education and marital status, though effect sizes were small. The missing data at one week postpartum was mostly due to practical reasons because midwives did not always inform us in time when a woman gave birth. Missing data was therefore mostly at random, decreasing the likelihood of bias. Secondly, only Caucasian women were included and the educational level was relatively high; 65% of the women in the current study were highly educated compared to 52% of the general Dutch female population of similar age.[37] However, the southeast of Brabant, where recruitment took place, is a relatively highly educated region in

the Netherlands. Moreover, non-Caucasian women were not included in the study, and they are generally less high educated.[38]

CTS affects at least one in four pregnant women during late pregnancy. In general, CTS during pregnancy is underdiagnosed: women often do not report complaints and health professionals do not ask for them.[39] Since severe CTS symptoms might interfere with a woman's decision to start breastfeeding, it is important for health professionals to recognize the problem. CTS symptoms can easily be treated conservatively.[40] Women can wear a wrist splint at night, which stabilizes the wrist in a neutral position, reducing pressure on the median nerve.[20] In four out of five women, a wrist splint is effective in reducing the CTS symptoms.[15] Steroid injections in the carpal tunnel can also provide symptom relief,[20] but is often not the preferred intervention for pregnant women. Since CTS symptoms mostly disappear in the weeks following delivery,[19] surgery is hardly ever performed during pregnancy.[40] Another non-invasive and patient-friendly treatment for CTS is currently under research: traction and rotation to the wrist using a mechanical traction device (described in detail elsewhere[41]). If proven effective, health care professionals will have another non-invasive treatment especially suitable for pregnant women with CTS.

In conclusion, women with mild CTS symptoms seem to be more likely to initiate breastfeeding compared to women with more severe CTS symptoms. Midwives and obstetricians should ask for the presence of CTS symptoms and could offer women non-invasive treatment for symptom relief.

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Chapter 5

Follow-up of pregnancy-related carpal tunnel syndrome symptoms at 12 months postpartum: a prospective study

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Submitted

ABSTRACT

Objective: To study the persistence and predictors of pregnancy-related carpal tunnel syndrome (CTS) symptoms in the first postpartum year.

Design: A prospective longitudinal cohort study.

Setting: Dutch women who became pregnant between January 2013 and September 2014 in the southeast of the Netherlands and who were followed until 12 months postpartum.

Population or Sample: A total of 1,044 Dutch pregnant women.

Methods: The prevalence of CTS symptoms was assessed during the last trimester of pregnancy. In the positive cases, the severity of CTS was assessed using the Boston Carpal Tunnel Questionnaire (BCTQ). Subsequently, the persistence of CTS symptoms was evaluated until 12 months postpartum.

Main Outcome Measures: Persistence and predictors of CTS symptoms during postpartum.

Results: Of the 1,044 women, 354 (34%) reported CTS symptoms during pregnancy. Of these 354 cases, 54 (15%) still reported these key symptoms at 12 months postpartum. Within these 354 women, early onset of CTS symptoms during pregnancy (OR = 2.88, 95% CI [1.45-5.72]), higher severity of CTS during the last trimester (OR = 1.93, 95% CI [1.08-3.45]) and higher mean depression scores on the Edinburgh Depression Scale (EDS) postpartum (OR = 1.11, 95% CI [1.03-1.19]) were significantly related to the persistence of CTS at 12 months postpartum.

Conclusions: One third of pregnant women report CTS symptoms of whom 15% (5% of the total pregnant population) still complain of CTS at 12 months follow-up. Early onset of CTS symptoms during pregnancy and higher severity of symptoms during the last trimester as well as depressive symptoms during postpartum are independently related to long-lasting CTS symptoms.

INTRODUCTION

Carpal tunnel syndrome (CTS) is a common condition among pregnant women. We found a prevalence of 34% during the last trimester in a large cohort of pregnant women.[1] Severity of CTS symptoms generally decreases quickly after childbirth[2] and symptoms are believed to resolve completely in the postpartum period.[3] In some women, however, symptoms may persist in the postpartum period. Only few studies have investigated persisting pregnancy-related CTS symptoms in the postpartum period and they report a great variation in persisting symptoms. According to the current literature, 4% to 54% of women with CTS symptoms during pregnancy still report symptoms at one year postpartum[4,5], and 30% at three years.[3] This wide range is mainly to be explained by methodological flaws. The studies had small sample sizes including only 37 to 46 women with CTS symptoms during pregnancy. One study[3] only included women with an electrophysiologically confirmed diagnosis of CTS but electrodiagnostic tests can lead to false negative results.[6] Insight into possible predictors of long-lasting CTS symptoms is even scarcer. Padua *et al*.[4] found that earlier onset of symptoms during pregnancy was a predictive factor for persistent CTS symptoms at follow-up.

It is reasonable to suggest that severity of CTS symptoms during pregnancy might also predict the long-lasting persistence of CTS postpartum, but evidence to support this hypothesis is lacking. Another possible predictor which needs to be considered when assessing sensory symptoms, but has never been reported, is emotional status during postpartum, including postpartum depression. Pain is a subjective experience which can largely be influenced by emotional distress such as depression,[7] also in pregnant women.[8] In a recent meta-analysis, people with chronic pain (>3 months) reported more problems in several psychological domains, including depression, compared to healthy control.[9] Depression was also a predictor of symptom severity in CTS patients.[10,11] Therefore, when assessing CTS symptoms during pregnancy and postpartum, it is important to adjust for depression.

The primary aim of the present prospective study was to investigate the persistence of pregnancy-related CTS symptoms in the first postpartum year in a large sample of healthy pregnant women. The secondary aim was to study possible predictors of CTS symptoms at 12 months postpartum.

METHODS

Participants and procedure

Criteria for participation and the procedure for this study were described in detail elsewhere.[1] In sum, healthy pregnant women who had their first antenatal visit between January 2013 and September 2014 at one of the 17 participating community midwife practices in the southeast of the Netherlands were invited to participate in the study. The presence of CTS symptoms was

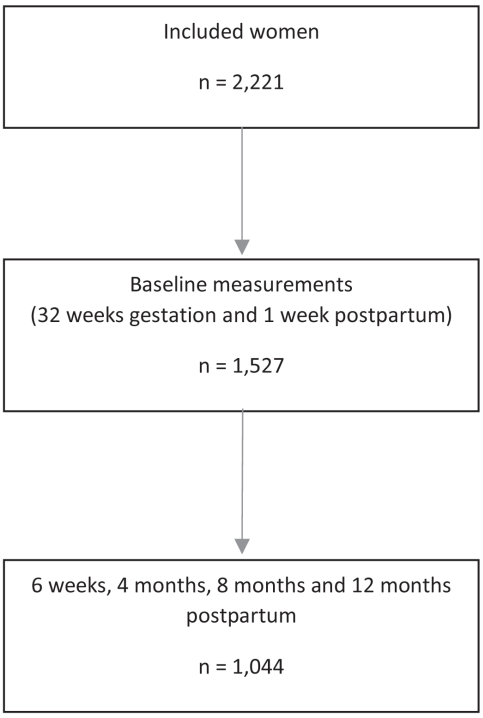

Figure 1 Flow chart of inclusions for the current study.

assessed at 32 weeks in 1,527 pregnant women and complete data up to 12 months postpartum were available for 1,044 of these women. Figure 1 presents a flow chart of the inclusions for the current study.

At 32 weeks' gestation and one week postpartum (regarding the last weeks of pregnancy), women were asked for the three key symptoms of CTS during the previous period of gestation: "Did you suffer from any of the following symptoms during pregnancy: pain, tingling sensations or numbness in hands or wrists?". Moreover, they were asked if the symptoms were bilateral and at what term of gestation they started. Positive cases subsequently completed the Boston Carpal Tunnel Questionnaire (BCTQ), a disease specific questionnaire to evaluate the severity of symptoms and hand function impairment. The BCTQ consists of two different scales: the Symptom Severity Scale (SSS, 11 items) and the Functional Status Scale (FSS, 8 items), both scales result in a mean score from 1 to 5.[12,13] In addition to the questionnaires during pregnancy, women filled out questionnaires at 6 weeks, 4 months, 8 months and 12 months postpartum. At every time point, they were asked: "Do you still suffer any of the following symptoms: pain, tingling sensations or numbness in hands or wrists?". Women also filled out the Edinburgh Depression Scale (EDS) to evaluate depressive symptoms. The EDS is the most widely worldwide used self-rating scale to assess depressive symptoms during the postpartum period and has also been validated in Dutch postpartum women.[14] The EDS consists of 10 items with total score ranges from 0 to 30, with higher scores indicating more symptoms of depression.[15] The reliability values of the EDS indicated by Cronbach's alpha-coefficient during the postpartum period varied between 0.82 and 0.84.

Statistical analyses

Data were analyzed using SPSS 22.0 (SPSS Inc., Chicago, IL). Descriptive data are presented as frequencies and corresponding percentages or means and standard deviations. Differences between groups were analyzed using t-tests for continuous variables and χ^2-tests for categorical variables. A p-value <.05 was considered significant. Effect sizes were evaluated using Cohen's *d* for t-tests and Cramer's *V* for χ^2-tests.[16] For Cohen's *d,* .2, .5 and .8 are considered small, medium and large effect sizes, respectively. For Cramer's *V,* .1, .3 and .5 are considered small, medium

and large effect sizes, respectively, for df = 1. Subsequently, within the group of women who reported CTS symptoms during pregnancy, a multiple logistic regression analysis was performed, with persistence of CTS at 12 months postpartum as the dependent variable and BCTQ scores during pregnancy as independent variable, adjusted for bilateral symptoms, early onset of symptoms, parity, age and mean depression scores postpartum. Postpartum depression scores were calculated as the grand mean EDS scores of 6 weeks, 4, 8 and 12 months postpartum, to correct for incidental high or low scores.

Table 1 Baseline characteristics of the 1,044 women included in the 12 months follow-up study.

Characteristic		n (%)	Mean	SD
Demographic features				
Age (in years)			30.5	3.5
	<25	35 (3.3)		
	25-29	376 (36.0)		
	30-34	506 (48.5)		
	35-39	120 (11.5)		
	>40	7 (0.7)		
Educational level				
	high	752 (72.0)		
	low	292 (28.0)		
Marital status				
	With partner	1039 (99.5)		
Job		994 (95.2)		
Obstetric features				
Parity				
	Primiparous	521 (49.9)		
Previous abortion		252 (24.1)		
Unplanned pregnancy		42 (4.0)		
BMI pre-pregnancy			23.8	3.8
	<18.5	31 (3.0)		
	18.5-24.9	725 (69.4)		
	25.0-29.9	205 (19.6)		
	>30.0	83 (8.0)		

RESULTS

Baseline BCTQ and general characteristics data were available of 1,527 women and complete data up until 12 months postpartum were available of 1,044 women (68%). We compared baseline characteristics between women with (n = 483) and without (n = 1,044) missing data at 12

months postpartum. Women with missing data were less highly educated (57% vs. 72%, χ^2 (1, N = 1,527) = 33.3, p <.001, *V* = .15), more often multiparous (58% vs. 50%, χ^2 (1, N = 1,527) = 9.1, p = .003, *V* = .08), less often had a partner (99% vs. 100%, χ^2 (1, N = 1,527) = 4.0, p = .046, *V* = .08) and had a higher mean EDS score during pregnancy (5.2 vs. 4.5, p = .001, *d* = .19). These differences, although significantly different, showed low effect sizes. Age and BMI did not differ between women with and without missing data. Within women with CTS symptoms, mean BCTQ scores during pregnancy did not differ between women with and without missing data at 12 months postpartum.

In the present study, 354 of 1,044 women (34%) reported one or more of the three key symptoms of CTS during pregnancy. Of these 354 cases, 163 (46%) developed symptoms before the third trimester and they had a total mean BCTQ score of 1.65 (0.63), mean SSS score of 1.77 (0.67) and mean FSS score of 1.48 (0.63). Moreover, 54 (15%) still reported these key symptoms at 12 months postpartum. BCTQ scores during pregnancy were compared between women who reported persisting CTS symptoms at 12 months postpartum (n = 54) and those who did not (n = 300). Scores of women with persisting symptoms were significantly higher on the BCTQ (1.65 (0.63) vs. 1.44 (0.44), p = .026), SSS (1.77 (0.67) vs. 1.55 (0.45), p = .025) and FSS (1.48 (0.63) vs. 1.29 (0.43), p = .040). The prevalence and persistence of CTS symptoms during the first postpartum year is presented in Figure 2.

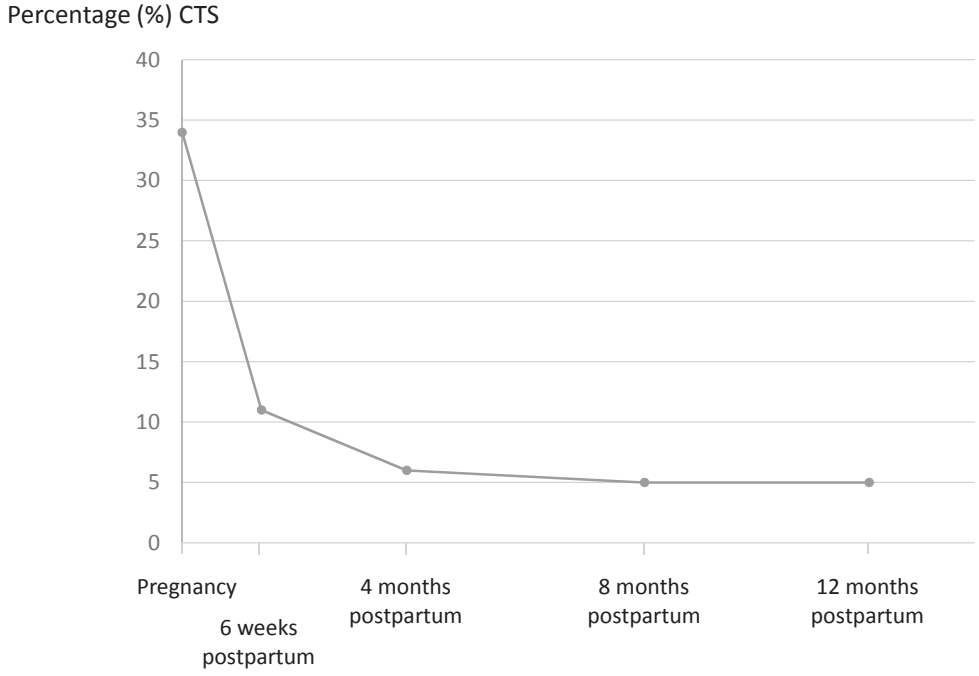

Figure 2 Percentage of women who reported CTS during pregnancy up to 12 months postpartum.

As can be seen, 35% of women reported CTS symptoms during pregnancy, which dropped to 11% at 6 weeks postpartum and further to 6% at 4 months postpartum, to remain more or less stable until 12 months postpartum: 5% of the total sample (n = 1,044) still reported CTS symptoms at 12 months postpartum, which is 15% of women who reported CTS symptoms during pregnancy (n = 354). Subsequently, within the group of women who reported CTS symptoms during pregnancy, a multiple logistic regression analysis was performed with persistence of CTS at 12 months postpartum as dependent variable and mean BCTQ score during pregnancy as independent variable, adjusted for confounders as bilateral symptoms, onset of symptoms during pregnancy, parity, age and mean depression scores on the EDS postpartum. Higher BCTQ scores during pregnancy (OR = 1.93, 95% CI [1.08-3.45]), early onset of symptoms during pregnancy (OR = 2.88, 95% CI [1.45-5.72]) and higher mean EDS scores postpartum (OR = 1.11, 95% CI [1.03-1.19]) were significantly related to persistence of CTS at 12 months postpartum.

Table 2 Multiple logistic regression analysis results with the persistence of CTS as dependent variable within the group of women who reported CTS symptoms during pregnancy (n = 354).

		CI		
Variable	**OR**	**Lower**	**Upper**	**p**
BCTQ score during pregnancy	1.93	1.08	3.45	.028*
Bilateral CTS symptoms	0.90	0.44	1.83	.762
Early onset of CTS symptoms[a]	2.88	1.45	5.72	.003*
Multiparity	1.45	0.76	2.77	.258
Age	0.96	0.88	1.05	.341
Mean EDS score postpartum	1.11	1.03	1.19	.009*

[a] Before third trimester of pregnancy * p-value <.05.

DISCUSSION

Main findings

In the present study, the prevalence of self-reported carpal tunnel syndrome symptoms during pregnancy was 34%, of whom 15% reported persisting symptoms at 12 months postpartum. Higher BCTQ scores during pregnancy, early onset CTS of symptoms during pregnancy and depression symptoms postpartum increase the likelihood of persisting CTS symptoms at 12 months postpartum.

Strengths and weaknesses

Strengths of this study are the prospective design, the repeated measurements, the adjustment for comorbid depressive symptoms and the large sample size: 1,044 healthy pregnant women were included in the study, of whom 354 reported CTS symptoms during pregnancy, providing

considerable power and an accurate representation of the general population. The study also has several limitations. First, CTS was not diagnosed either clinically or using electrodiagnostic testing. However, the most important diagnostic criteria in clinical practice are patient reported symptoms. Tests such as the Tinel sign or Phalen's test have poor sensitivity and specificity.[17,18] Moreover, the majority of patients with clinical CTS but a negative electrodiagnostic test benefit from treatment, including surgery.[19] Secondly, it is unclear whether the CTS symptoms were already present before pregnancy. The prevalence of CTS in women between 18 and 40 years is unknown. However, women in general are at risk for CTS and in the general population CTS is reported to develop especially between 40 and 60 years,[20] reducing the likelihood in the current study that CTS symptoms were present before pregnancy. Thirdly, one third of the women dropped out at 12 months postpartum and some baseline characteristics of these women were significantly different from the completers. However, the absolute differences and effect sizes were small, decreasing the likelihood of bias. Moreover, 68% completion in a large sample during 12 months follow-up can be regarded as acceptable. We also compared the characteristics of the current study sample (n = 1,044) with those of our previous study (n = 639).[1] There were no significant differences between the two samples based on all baseline characteristics (data not shown).

Interpretation

The sample of women in the current study was similar to other studies based on age and BMI.[3,4,21] The sample from Turgut *et al*.[5] was slightly younger, while Padua *et al*.[21] reported more primiparous women. In line with the study by Padua *et al*.[4], earlier onset of symptoms was a predictive factor for persistent CTS symptoms at follow-up. However, their reported prevalence of persisting CTS symptoms at 12 months postpartum was much higher (54% vs. 15% in the current study), but their sample size was much smaller (n = 37) compared to the current study and they did not report the time of onset of symptoms in their sample. Moreover, at one year follow-up, they re-evaluated 37 women (78%) of the 47 who had CTS symptoms during pregnancy. They did not report how women were selected for re-evaluation and only compared characteristics to the original sample based on age and CTS data, so selection bias was not eliminated. Compared to the current study, Turgut *et al*.[5] reported a very small prevalence of pregnancy-related CTS at one year postpartum (4%). Their sample size of women with pregnancy-related CTS was also much smaller (n = 46). Moreover, many women in their sample developed CTS in the third trimester (85%, compared to 54% in the current study) and we showed that women who develop CTS in the third trimester are more likely be asymptomatic at 12 months postpartum. Moreover, the initial evaluation for CTS during pregnancy was based on patient-reported symptoms at the time of delivery. However, they did not specify when these women were asked about CTS symptoms and baseline characteristics of the participants (such as education) were not reported.

Higher postpartum depression scores on the EDS were also a predictor for CTS symptoms at 12 months postpartum. It is well known that patients with depression in general report higher

levels of somatic symptoms. Especially patients who report chronic pain also experience problems in a range of psychological domains, such as depression, anxiety and general emotional functioning.[9] Therefore, in women with long lasting CTS symptoms, the existence of depression should be considered. These women should be offered a depression screening tool and – if positive – offered an intervention, given the known negative impact of maternal depression on child development.[22]

Conclusion

Pregnancy-related CTS symptoms do not resolve in all women who report symptoms during pregnancy: one out of six women with CTS symptoms during pregnancy still report symptoms at 12 months postpartum, especially women with early onset of symptoms and more severe symptoms during pregnancy, as well as women with higher depression scores postpartum.

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Chapter 6

Effectiveness of mechanical traction as a non-surgical treatment for carpal tunnel syndrome compared to care as usual: study protocol for a randomized controlled trial

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ABSTRACT

Background: Carpal tunnel syndrome (CTS) is a common condition (prevalence of 4%) where the median nerve is compressed within the carpal tunnel resulting in numbness, tingling and pain in the hand. Current non-surgical treatment options (oral medication, corticosteroid injections, splinting, exercise and mobilization) show limited effects, especially in the long-term. carpal tunnel release (CTR) surgery is effective in 70 to 75% of patients, but is relatively invasive and can be accompanied by complications. In an observational study, mechanical traction proved to be effective in up to 70% of patients directly after treatment and in 60% after two years follow-up. This randomized controlled trial (RCT) will examine the effectiveness of mechanical traction compared to care as usual in CTS.

Methods/Design: Patients diagnosed with CTS will be recruited from an outpatient neurology clinic and randomly assigned to the intervention group (mechanical traction) or the control group (care as usual). Participants in the intervention group will receive 12 treatments with mechanical traction during six consecutive weeks. Primary outcome is symptom severity and functional status, which are measured with the Boston Carpel Tunnel Questionnaire (BCTQ). Secondary outcomes are quality of life (WHOQOL-BREF), health related resource utilization and absenteeism from work. Outcomes will be assessed at baseline, and at 3, 6 and 12 months after inclusion.

Linear mixed effect models will be used to determine the change from baseline at 12 months on the BCTQ, WHOQOL-BREF, absenteeism from work and health related resource utilization. The baseline measurement, change from baseline at three and six months, as well as duration of symptoms until inclusion, age, gender and co-morbidity will be included as covariates. The Pearson's correlation coefficient will be generated to assess the correlation between depression and anxiety and treatment outcome.

Discussion: Since current non-surgical treatment options are not effective long-term and CTR is relatively invasive, there is a need for an effective and non-invasive treatment option. Mechanical traction is a safe treatment option that may provide a good alternative for the usual care. Considering the prevalence of CTS, the study is of great clinical value to a large patient population.

Trial registration: Clinical Trials NL44692.008.13 (registered on September 19, 2013).

BACKGROUND

Carpal tunnel syndrome (CTS) is a common compressive neuropathy in which the median nerve is compressed at the level of the carpal tunnel.[1,2] CTS can occur in one or both hands and is either idiopathic (spontaneous) or dynamic (only during certain movements). The compression leads to numbness and tingling in the first three fingers and the radial side of the ring finger, paresthesia, pain and (in severe cases) weakness. The symptoms are often worse at night or after use of the hand.[2] Prevalence is estimated to be about 4% in the general population[3] and up to 10% in the working population.[4] Although CTS can occur at any age, it most commonly occurs between 40-60 years and its prevalence is higher in women compared to men.[1] Obesity, diabetes mellitus and alcohol abuse are risk factors for developing CTS.[1] Occupation has been identified as an environmental risk factor: vibration, hand force and repetition are associated with increased risk for developing CTS.[5] Furthermore, there is a psychological component to the experience of CTS symptoms: depression has been reported as a predictor of pain in CTS patients.[6]

CTS can be diagnosed using electromyography (EMG). Compression of the median nerve can lead to damage and dysfunction of the myelin sheath, resulting in slowed conduction velocity, which can be detected using EMG.[7] Treatment options to reduce the compression and relieve symptoms can be roughly divided into surgical and non-surgical procedures. Non-surgical, less invasive treatment options are numerous, including oral medication, corticosteroid injections, splinting, exercise and mobilization interventions.[8-12] However, there is only short-term or limited evidence of benefit for these interventions. Many (nonsteroidal) drugs did not prove to be significantly superior compared to placebo.[12] There is only limited evidence for the effectiveness of splinting, exercise and mobilization interventions.[10,11] Local corticosteroid injections provide considerable symptom relief and therefore show the best results of the nonsurgical treatments.[8,9] However, corticosteroids seem to merely suppress CTS symptoms and the positive effects do not last.[8,13] The treatment effect diminishes over time and half of patients who receive corticosteroid injections experience recurrence of symptoms within a year.[13]

Compared to non-surgical treatment, surgery is the only known treatment option that shows long-term positive effects.[14] The principle of the procedure, called carpal tunnel release (CTR), is to decompress the nerve by dividing the transverse carpal ligament.[15] Evidence suggests that CTR is a more effective treatment for CTS than splinting or oral medication, especially long-term.[15] However, up to 30% of patients who underwent CTR experience persistence or recurrence of CTS symptoms in the long-term or suffer from complications.[16,17] Therefore, there is still a clear need for an alternative non-invasive therapy, possibly making surgery redundant for a sub-category of patients.

Another promising non-surgical treatment for CTS is mechanical wrist traction using the Phystrac traction device. The Phystrac applies repeated traction movements to the wrist in different positions using gravitational force. Brunarski *et al.*[18] described four case studies using mechanical traction that showed promising results. In an observational study, physical therapists reported a

success rate of 70% with mechanical traction immediately post-treatment,[19] and 60% after two years follow-up.[20] However, until now, no randomized controlled trial (RCT) has been performed to show clinical evidence for the effectiveness of mechanical traction as compared to care as usual (surgical and non-surgical intervention).

Hypothesis and objectives

The purpose of this study is to evaluate the effectiveness of mechanical traction in alleviating symptoms and improving hand function in patients with CTS compared to care as usual. The primary outcome is the change from baseline in symptom severity and functional status at 12 months, which is measured using the Boston Carpal Tunnel Questionnaire (BCTQ). Change from baseline in functional status and symptom severity at three and six months will be used as covariates. As secondary outcomes, we will assess quality of life, health related resource utilization and absenteeism from work. Tertiary outcome is the impact of psychological distress on treatment outcome.

We hypothesize that hand function and symptom severity will significantly improve more in CTS patients receiving 12 treatments with mechanical traction compared to CTS patients who receive care as usual after 12 months. Moreover, 12 treatments with mechanical traction will result in less absenteeism from work, a higher quality of life, and less health related resource utilization compared to care as usual in CTS patients after 12 months follow-up. Furthermore, a higher degree of depression and anxiety at baseline will result in a lower treatment effect in CTS patients.

METHODS / DESIGN

Study design

This study is designed as an RCT. Eligible patients diagnosed with CTS will be recruited from the outpatient neurology clinic of VieCuri Medical Center in Venlo, the Netherlands. They will be randomly allocated to the intervention (mechanical traction) or control (care as usual) group. The intervention group will receive 12 treatments with mechanical traction using the Phystrac traction device. The control group will receive care as usual, which may involve an expectant strategy, splinting, drug therapy, local corticosteroid injections or CTR.

Eligibility

Adult men and women (aged 18 to 80 years) who have been diagnosed with CTS by means of a positive EMG will be invited to participate in our study. They have to be physically able to visit the outpatient clinic twice a week and sit in an upright position for at least 20 minutes. Patients with a previous history of CTS surgery will be excluded as well as those with insufficient understanding of the Dutch language. In addition, patients who have been diagnosed with another

known (rare) cause of neuropathy, or who are suffering from a severe psychiatric disorder, such as personality disorder, schizophrenia or bipolar disorder will also be excluded.

Recruitment, screening process and enrolment

Neurologists will select eligible patients based on the in- and exclusion criteria. During the visit to the outpatient clinic, the neurologist will inform patients about the study. In addition, the patients will receive an information letter. Two weeks after their visit to the outpatient clinic they will be phoned by the researcher and asked whether they are interested to participate in the study. Eligible patients who are willing to participate will be invited for an intake visit at the hospital. During this intake, the eligibility of the patients will be double-checked and there will be an opportunity for the patients to ask additional questions about the study. Full written informed consent will be obtained from each participating patient. Subsequently, the patients will receive an interview and complete a set of questionnaires, which will result in the baseline measurement.

Ethical approval

The study protocol was approved by the Medical Ethical Committee of the St. Elisabeth Hospital in Tilburg, the Netherlands in August 2013 (reference number P1340). The RCT has been registered under the trial number: NL44692.008.13.

Randomization

After inclusion, every patient will be randomly assigned to either the intervention or the care as usual group. Before the start of the study, a list of 200 random numbers of 1 (intervention) or 2 (care as usual) will be created using SPSS, version 21 (SPSS Inc., Chicago, IL, USA). The random numbers will be uniformly distributed. The list will be kept at the secretary's office of the outpatient neurology clinic. At the end of the intake, a participant number will be assigned to the patient. The secretary will refer to the generated random list and inform the researcher to which group the patient is allocated. The random list cannot be edited and is concealed from the researcher. The above described process of randomization will ensure objectivity of the researcher and will eliminate bias in the participants' group allocation.

Blinding

Blinding of patients or practitioners is not possible due to the current study design. As described previously, group allocation will not be known to both the patient and researcher during the intake. This allows for an objective baseline measurement.

Intervention: Phystrac mechanical traction therapy

Patients in the intervention group will receive 12 treatments (twice a week for a period of six weeks) with the Phystrac mechanical traction device (type GR 10). The Phystrac provides me-

chanical traction to the wrist using weights between 1 and 18 kg. One treatment takes 10 to 15 minutes per diseased hand. The patient will be seated beside the traction device on a seat that is adjustable in height. The patient will put his arm on the arm support of the device and will be secured with two Velcro straps; one above and one below the elbow. Another Velcro strap which is attached to the weights will be fastened around the wrist with the palm of the hand upwards. The weight is set at 5 kg for women and 7 kg for men during the first treatment session. Every following treatment session, the weight is increased with 1 kg for women and 2 kg for men until 10 kg for women or 13 kg for men, or until the mechanical traction becomes painful or uncomfortable for the patient. When the patient is fitted correctly, the weight will be lowered and provides a pulling force on the wrist. After eight seconds the weight is lifted, providing a rest period of four seconds. This cycle will be repeated ten times. After 10 traction movements, the device stops and the researcher will rotate the wrist straps 30 degrees supination, after which another 10 traction movements will be provided. After that, a third set of 10 traction movements will be provided in 30 degrees pronation position. In total, 30 traction movements will be applied during each treatment. During the six weeks of treatment, patients will not receive other forms of treatment. After the six weeks of treatment, patients are allowed to receive usual CTS care when mechanical traction was not sufficient.

Control group: 'care as usual'

The control group will receive 'care as usual', which means they will receive regular treatment from their usual health care provider. Patients may adopt an expectant approach or receive treatment in the form of a wrist splint, local corticosteroid injections or CTR. Forms of treatment received in both groups will be documented during the full length of the study using questionnaires and medical records.

Outcome measurements

Measurement time points and questionnaires used are shown in Table 1. Data collection will take place at baseline (before the start of the intervention) and at 3, 6 and 12 months after baseline in both groups. Additional data of the intervention group will be collected at two other time points: at 3 weeks (after 6 treatments) and at 6 weeks (after 12 treatments = immediately post treatment). Information about patient attendance and drop-out will be recorded continuously. Patients of both groups will receive the follow-up questionnaires at 3, 6 and 12 months via internet or a paper-and-pencil version with an addressed return envelope, depending on the participant's preference.

Primary outcome measure

Functional status and symptom severity

Self-reported functional status and symptom severity will be measured using the Boston Carpal Tunnel Questionnaire (BCTQ).[21,22] The BCTQ is a disease-specific questionnaire referring to a

Table 1 Measurements and time points.

Measure	Questionnaire	Measurement time points					
		T0	V1	V2	T1	T2	T3
Patients' background (demographics, clinical)	-	X			X	X	X
CTS symptom severity and functional status	BCTQ	X	X	X	X	X	X
Quality of life	WHOQOL-BREF	X		X	X	X	X
Depression and anxiety	PHQ-4	X	X	X	X	X	X
Health related resource utilization	Non-standardized	X					X
Absenteeism from work	Non-standardized	X			X	X	X

T0 = baseline, V1 = 3 weeks (only intervention group), V2 = 6 weeks (only invention group), T1 = 3 months, T2 = 6 months, T3 = 12 months, BCTQ = Boston Carpal Tunnel Questionnaire, WHOQOL-BREF = World Health Organization Quality of Life questionnaire abbreviated version, PHQ-4 = Patient Health Questionnaire-4

typical 24 hour period in the past two weeks. It consists of two different scales: the Symptom Severity Scale (SSS) and the Functional Status Scale (FSS). The SSS comprises 11 questions about symptom severity, while the FSS consists of 8 daily activities which are rated based on degree of difficulty. The SSS and the FSS will be rated on a five-point scale. Both scales result in mean scores between 1 and 5, where greater impairment is represented by higher scores. The BCTQ is responsive to clinically relevant change and therefore an appropriate measure for treatment outcome.[21] It has been validated and is used in multiple studies to assess improvement in CTS symptoms over time [14], also in the Netherlands.[13,23]

Secondary outcome measures

Quality of life

As a secondary outcome measure, self-reported quality of life will be measured using the abbreviated Dutch version of the World Health Organization Quality of Life (WHOQOL-BREF).[24,25] The WHOQOL-BREF measures quality of life in four domains: physical health, psychological health, social relationships and environment. In addition, it includes one facet on overall quality of life and general health. The WHOQOL-BREF consists of 26 items referring to the past two weeks, and which can be scored on a five-point scale, where a higher score represents a better quality of life. The WHOQOL-BREF has been proven to be a valid and reliable instrument.[24,25]

Absenteeism from work

The number of days off work of each patient will be collected using a non-standardized questionnaire. Furthermore, participants will be asked whether they are on sick leave or have been because of their CTS complaints.

Health care related resource utilization

Patients will be asked how many times they visited a professional caregiver (general practitioner, physiotherapist, psychologist, specialist or other health care providers) in the past 12 months, if they spent time in the hospital or used medication via a non-standardized questionnaire.

Tertiary outcome measures

Depression and anxiety

The four-item Patient Health Questionnaire (PHQ-4) will be used to measure self-reported depression and anxiety. The questionnaire consists of two items on depression and two on anxiety, referring to the past two weeks. A higher score represents a higher level of anxiety and depression. The PHQ-4 is a reliable instrument that has been validated in a general population.[26]

Demographic and clinical variables

Demographic variables will be collected during the intake interview. Information about age, education, job status, nationality, residence and marital status will be documented. Also, BMI and life style habits (smoking, alcohol intake, physical activity) will be documented at baseline. Finally, clinical variables including medication and the existence of co-morbidity (for example, diabetes, cardiovascular disease, COPD) will be verified from the patient's medical record forms after obtaining written informed consent.

Statistical analysis

Sample size and power calculation

The sample size calculation is based on a clinically relevant improvement from baseline on the functional and symptom severity scores of the BCTQ after 12 months follow-up. Sixty-four patients need to be included per treatment arm to statistically detect a minimum effect size of $d = 0.5$ between mean BCTQ scores of both groups with a power of 0.8 and a two-sided alpha of 0.05. A total of 200 patients will be included (100 patients per treatment arm), taking into account possible drop-out.

The following outcomes are defined. A completer is a patient who participated in at least 70% of the intervention sessions and the assessments. A responder is a patient who will have a reduction of 0.74 of the mean score (minimal clinical important difference) on the BCTQ compared to baseline.[21] A drop-out is a patient with less than 70% of the intervention or the follow-up data.

Planned analyses

The baseline characteristics of those who complete and will drop out during follow-up will be compared by means of an independent t-test for continuous data and by χ^2-tests for categorical data. All analyses will be based on the intention-to-treat principle. Linear mixed effect models will be used to compare the change from baseline at 12 months between groups on the BCTQ, WHOQOL-BREF, absenteeism from work and health related resource utilization. Linear mixed

effect models are able to adjust for missing values and are therefore used to avoid loss of information.[27] The baseline, three months and six months measurements, as well as duration of symptoms until inclusion, age, gender and co-morbidity will be included as covariates. Taking these covariates into account will adjust for differences within the groups and decrease variance. It will also adjust for possible baseline differences between groups.[28] When the data are normally distributed, Pearson's correlation coefficients will be generated to examine the relationship between treatment outcome and depression and anxiety.

DISCUSSION

This paper describes the design for an RCT with the purpose to study the effectiveness of mechanical traction as a treatment for CTS compared to care as usual. Recruitment started in October 2013 in the VieCuri Medical Center in Venlo, the Netherlands. The outpatient neurology clinic registers over 400 CTS patients annually of whom about 350 will be eligible. During a period of 12 months, these patients will be invited to participate in the RCT. For several reasons, it is realistic to predict a response rate of 60%. First, the new treatment is painless and non-invasive. Second, in case of a non-responder, the patient can always make a choice for surgery without any evidence for poorer prognosis. The predicted sample size of 200 patients will easily enable the researchers in one year to include sufficient patients into the trial with sufficient power.

The clinical relevance of this RCT is substantial. First, CTS is very common, not only in the general population (up to 4%), but especially in the working population (up to 10%). Secondly, because the prevalence in the working population is relatively high, CTS-related days of sick leave and workers' compensation lead to an economic burden. Absenteeism from work after carpal tunnel release (CTR) is on average two to seven weeks.[29,30] In the US, cumulative excess loss of earnings of 4,443 workers who filed a CTS related workers' compensation claim was estimated at $197 to $382 million over 6 years.[31] Thirdly, the long-term benefits of current treatment strategies of CTS are far from optimal. Fourth, it is well known that recovery from pain symptoms can be mediated by the patient's mental state, especially anxiety and depression. Pain is a process from nociceptive registration to a subjective experience, which can be influenced by psychological wellbeing.[32] Depression has been reported as a predictor of pain intensity in CTS patients.[6] Research into the mediator effect of emotional distress on the outcome of CTS treatment is limited. Hobby *et al.*[33] reported a significant association between BCTQ scores and scores on the depression and anxiety scales. Moreover, Lozano Calderon *et al.*[34] reported that patient dissatisfaction and perceived impairment after CTR can partly be predicted by depression.

Up until now, non-invasive CTS treatment mostly consists of splint therapy and corticosteroid injections. These treatments have not been proven to be effective in the long-term.[8-10] Invasive CTR, on the other hand, results in a positive outcome in only 70 to 75% of the patients in the long-term.[16,17] Mechanical traction using the Phystrac traction device is a promising treatment

option. It is non-invasive and has been reported to result in substantial symptom relief in 70% of the patients, and in 60% of the patients two years post-treatment.[20] However, there is no conclusive scientific evidence for the effectiveness of mechanical traction. Therefore, there is a clear need for an RCT to compare mechanical traction to regular treatment options, such as splint therapy, steroid injections and CTR.

Improvements in functional status and symptom severity will be measured using the BCTQ. This questionnaire has been proven to be a valid and reliable outcome measure.[21,22] It is widely used in clinical practice to evaluate the recovery of CTS symptoms after treatment. This means that we have an easy, user-friendly and quick measure to assess clinical outcome.

One strength of this study is the additional outcome measures. Apart from clinical measures, quality of life, absenteeism from work and health related resource utilization will be measured. Another strength of this study is the follow-up length. Many studies only include a few weeks or months follow-up, while the current study aims at a 12 months follow-up period. A possible limitation of this study is the heterogeneity of the care as usual group. The patients in this group can receive different forms of treatment or no treatment at all. However, since this represents the general practice in an outpatient neurology clinic, the results of this RCT will provide clinically relevant information.

Since the current treatment options are not effective in all patients, or only short-term, research into an alternative, long-term effective treatment option will be of great clinical value. The proposed RCT will provide possible evidence for mechanical traction as a new non-invasive treatment for CTS. Since 4% of the general population develops CTS, the results of this trial will be of benefit to a large patient population. Surgery is often considered a last resort and many patients postpone it for as long as possible, resulting in irreversible nerve damage in some cases. Furthermore, contrary to CTR, mechanical traction does not interfere with work or other daily activities. A less invasive treatment may also have a positive influence on quality of life. Therefore, mechanical traction provides a safe treatment option as an alternative to usual care.

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Chapter 7

Mechanical wrist traction as non-invasive treatment for carpal tunnel syndrome: a randomized controlled trial

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Submitted

ABSTRACT

Background: Carpal tunnel syndrome (CTS) is a common compressive nerve entrapment disorder with symptoms of numbness, paresthesia and pain. Carpal tunnel release surgery is the only known long-term effective treatment. However, surgery is invasive and up to 30% of patients report recurrence or persistence of symptoms or suffer from post-surgical complications. A promising non-surgical treatment for CTS is mechanical wrist traction. The purpose of this study was to evaluate clinical outcomes following mechanical traction in patients with CTS compared to care as usual.

Methods: Adult patients (N = 181, mean age 58.1 (13.0) years, 67% women) with electrodiagnostically confirmed CTS were recruited from an outpatient neurology clinic between October 2013 and April 2015. After baseline assessments, patients were randomized to either the intervention group (12 treatments with mechanical traction) or care as usual. The main clinical outcome measure was surgery during six months follow-up. In addition, symptom severity was measured using the Boston Carpal Tunnel Questionnaire (BCTQ) at baseline, three, and six months follow-up.

Findings: The intervention group had fewer surgeries (28%) compared to the care as usual group (43%) during follow-up (χ^2 (1, N = 181) = 4.40, p = .036). Analyses of the survival curves revealed a statistical significant difference between the groups over time (log rank χ^2 (1, N = 181) = 6.94, p = .008). At six months follow-up, symptom severity and functional status scores had significantly decreased from baseline in both groups (p <.001) and the improvements did not differ between the two groups.

Interpretation: Mechanical traction is associated with fewer surgical interventions compared to care as usual in CTS patients. Reductions in patient-reported symptoms at six months follow-up was similar in both groups. The long-term effects of mechanical traction require further evaluation.

BACKGROUND

In recent years, concerns have been raised about the large number of invasive treatments performed every year.[1] In some cases, initial conservative treatment may be more cost-effective and preferred by the patient.[2] The benefit of these invasive treatments should be critically evaluated compared to more conservative approaches. This especially applies to carpal tunnel syndrome.
Carpal tunnel syndrome (CTS) is a compressive nerve disorder in which the median nerve is compressed in the carpal tunnel.[3,4] It is very common; the prevalence of CTS in the general population in the United States is 5%,[5] and in Netherlands about 0.6% in men and between 5.8 and 9.2% in women.[6-8] CTS can occur in only one or both hands. The compression leads to numbness, paresthesia and pain, especially in the first three fingers and the radial side of the ring finger, which are innervated by the median nerve. Symptoms are typically worse at night.[3] In severe cases, the compression can cause permanent nerve damage leading to thenar atrophy and sensory disturbances in the part of the hand which is innervated by the median nerve.[3] Although CTS can occur at any age, the condition is most commonly observed between the ages of 40 – 60 years and the prevalence is higher in women compared to men.[4]
CTS can be diagnosed using electrodiagnostic testing to detect slowing of conduction velocity that results from median nerve compression-related damage and dysfunction of the myelin sheath.[9] Treatment options to relieve symptoms are either surgical or non-surgical. Non-surgical, less invasive treatment options include oral non-steroidal drugs, corticosteroids (injections), splinting, exercise and mobilization interventions.[10-14] There is only short-term or limited evidence of benefit for these interventions. Many (nonsteroidal) drugs are not significantly superior to placebo.[12] Local corticosteroid injections provide considerable symptom relief,[10,11] but seem to primarily suppress CTS symptoms and the treatment effect diminishes over time.[10,15] There is only limited evidence for the effectiveness of splinting, exercise and mobilization interventions.[13,14]
Surgery is the only known treatment option with long-term positive effects.[16] The principle of the procedure, called carpal tunnel release, is to decompress the nerve by dividing the transverse carpal ligament.[6] Evidence suggests that surgery is a more effective treatment for CTS than conservative treatment (splinting or steroid injections).[16-18] However, surgery is associated with several disadvantages: some patients suffer from sustained surgery-related pain, hand weakness or complications from surgery.[19] Patient satisfaction rates of carpal tunnel release surgery vary between 70 to 80%.[7,20-23] The remaining 20-30% report persistence or recurrence of CTS symptoms or suffer from complications.[21,22] The reported frequency of re-operation rate is between 3 and 12%.[21] Therefore, there is a clear need for an alternative, preferably non-invasive, therapy for CTS.
A promising non-surgical treatment for CTS is mechanical wrist traction. This intervention involves repeated traction movements to the wrist in different positions using gravitational force. Brunarski *et al*.[24] described four case studies using mechanical traction that showed promising

results. In an observational study among 78 CTS patients, treatment with mechanical traction resulted in a success rate of 70% immediately post-treatment,[25] and 60% after two years follow-up.[26] However, no randomized controlled trial (RCT) has been performed to show clinical evidence for the effectiveness of mechanical traction as compared to care as usual (surgical and non-surgical interventions).

The purpose of this study was to evaluate the impact of mechanical traction in patients with CTS compared to care as usual using a randomized controlled trial. The main clinical outcome of the study was surgery for carpal tunnel release during six months follow-up. We also examined differences between mechanical traction versus usual care on the decrease in symptom severity and hand function problems at follow-up.

METHODS

Participants

Patients diagnosed with CTS were recruited from the outpatient neurology clinic of VieCuri Medical Center in Venlo and Venray, the Netherlands between October 2013 and April 2015. Adult men and women (aged 18 - 80 years) who were diagnosed with CTS by means of electrodiagnostic testing were invited to participate in the study. Electrodiagnostic values were considered abnormal if there was a difference greater than 0.5 ms on distal sensory latency (DSL) between ulnar and median nerve in Digit IV or between radial and median nerve in Digit I, a distal motor latency (DML) greater than 3.7 ms across the wrist to digit I of the median nerve (measured in the Abductor Pollicis Brevis), or a difference greater than 0.4 ms in the median nerve across the wrist compared to palm to digit III. The criteria used for diagnosis were at least two abnormal measures.[9]

Patients with a previous history of CTS surgery were excluded as well as those with insufficient understanding of the Dutch language. In addition, patients who were diagnosed with another known (rare) cause of neuropathy or who suffered from a severe psychiatric disorder, such as personality disorder, schizophrenia or bipolar disorder were also excluded. During the visit to the outpatient clinic, the neurologist provided eligible patients with oral and written information about the study. Between October 2013 and April 2015, 500 eligible patients were invited of whom 181 patients agreed to participate and were randomized to the mechanical traction intervention or care as usual. Main objections to participation were lack of time and transport problems, preventing patients to visit the outpatient clinic twice a week. Patients who were willing to participate were invited for an interview at the hospital, at the start of which the eligibility of the patients was double-checked and full written informed consent was obtained. This included permission to check medical data in the patients record forms. Figure 1 presents a flow chart of participant inclusions, treatment condition and data availability.

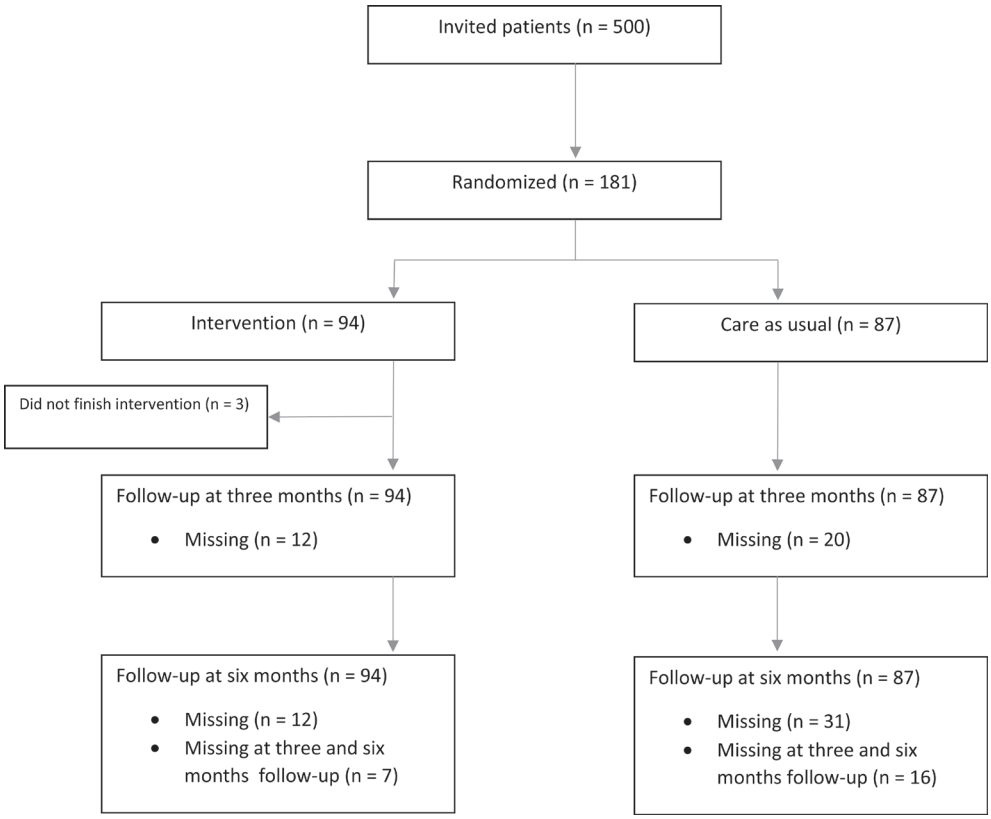

Figure 1 Flow chart of inclusions.

The study protocol was approved by the Medical Ethical Committee of the St. Elisabeth Hospital in Tilburg, the Netherlands in August 2013 (protocol #P1340). The trial was registered at Clinical Trials on September 19, 2013 (trial registration #NL44692.008.13).

Procedure

After inclusion, patients were interviewed by the research staff (MM), during which they also answered a set of paper-and-pencil questionnaires. Demographic variables (age, education, job status, nationality and marital status) were documented. Also, BMI and life style habits (smoking, alcohol intake) were assessed. Results of the electrodiagnostic test were obtained from the patient medical record forms.

After the baseline interview, the 181 patients were randomized into two groups: the traction intervention (n = 94) or care as usual (n = 87). As shown in Table 1, the groups were comparable on demographic and clinical variables and the slight imbalance in the group sizes resulted from the randomization procedure, which was based on a priori group allocation of the first 200 participants.[27] The patients filled out the Boston Carpal Tunnel Questionnaire (BCTQ) at baseline

and at three and six months after inclusion, either through an email invitation online or a paper-and-pencil version which they received at their home address. There were significantly more drop-outs in the care as usual group (36%, n = 31) compared to the intervention group (13%, n = 12: $\chi^2_1 = 13.0$, $p < .001$).

Intervention: Phystrac mechanical traction therapy

Patients in the intervention group received 12 treatment sessions (twice a week for a period of six weeks) with the Phystrac mechanical traction device (type GR 10). The Phystrac provides mechanical traction to the wrist using weights between 1 and 18 kg. One session takes 10 to 15 minutes per affected hand. The weight was set at 5 kg for women and 7 kg for men during the first session. Every following session, the weight was increased with 1 kg for women and 2 kg for men until 10 kg for women or 13 kg for men, or until the mechanical traction became uncomfortable for the patient. Twelve treatments is considered sufficient for most patients.

Control group: 'care as usual'

The control group received 'care as usual', which meant they received regular treatment from their usual health care provider. Patients adopted an expectant approach or received treatment in the form of a wrist splint, local corticosteroid injections or carpal tunnel release surgery. Forms of treatment received in both groups were documented during the full length of the study using questionnaires and checking the medical records.

Outcome measures

The main outcome variable was whether patients received surgery during follow-up, which was derived from the patient medical records. Self-reported functional status and symptom severity were measured using the Boston Carpal Tunnel Questionnaire (BCTQ), which was developed at Harvard.[28,29] The BCTQ is a disease-specific questionnaire referring to a typical 24 hour period in the past two weeks. It consists of two different scales: the Symptom Severity Scale (SSS) and the Functional Status Scale (FSS). The SSS comprises of 11 questions about symptom severity, while the FSS consists of 8 daily activities which are rated based on degree of difficulty. The SSS and the FSS were rated on a five-point scale. Both scales result in mean scores between 1 and 5, where greater impairment is represented by higher scores. The total BCTQ score was calculated as the mean of all the items. The BCTQ is responsive to clinically relevant change and therefore an appropriate measure for treatment outcome.[28] It has been validated and is used in multiple studies to assess improvement in CTS symptoms over time,[16] also in the Netherlands.[7,15]

Statistical analyses

Data are presented as mean (SD) or percentages. Independent samples t-test and χ^2-tests were used to compare baseline characteristics between groups, as well as between total eligible and included patients and between patients with missing data versus patients with complete data

at six months follow-up. Time-to-first-event (surgery) curves were displayed for the intervention and care as usual groups using Kaplan-Meier analysis. Cox proportional hazards analysis was used with group, age, sex, pre-enrolment symptom duration, dominant hand involved and baseline BCTQ score as predictor variables. The proportional hazards assumption was visually checked based on the survival curves and the log minus log survival versus log of survival time curves for the different covariates. Analyses were performed using an intention-to-treat approach: the patients remained in the group to which they were allocated at baseline, regardless of the interim treatments or drop-out during follow-up. To avoid loss of data, missing data were imputed using multiple imputation. Statistical analyses were performed using the Statistical Package of Social Science (SPSS, 22.0).

RESULTS

Baseline characteristics of the sample are presented in Table 1. The mean age was 58.1 (13.0) years, 67% was female and 25% had had CTS complaints for longer than three years. The care as usual and intervention groups did not differ based on any of the baseline characteristics. We also compared the patients included in the trial (N = 181) to all eligible patients on age, sex and affected hand. Patients who participated in the trial were older than the overall group of eligible patients (58.1 (13.0) and 54.8 (14.4), respectively; p = .011). Moreover, within the included patients, we compared baseline characteristics of the completers with those of the drop-outs at six months follow-up. The patients who dropped out were significantly younger than the completers in the whole study population (53.7 (14.9) and 59.5 (12.1), respectively; p = .010), as well as within the intervention (p = .036), but not the care as usual group (p = .157).

Effects of mechanical traction on surgery during six months follow-up

At six months follow-up, 26 (28%) patients in the intervention group had surgery, compared to 37 (43%) in the care as usual group (χ^2 (1, N = 181) = 4.40, p = .036). Kaplan-Meier survival curves showed significant group differences over time (Figure 2; log-rank χ^2 (1, N = 181) = 6.94, p = .008). Time to surgery was shorter (median = 41 days) in the care as usual group than in the intervention group (median = 90 days). The proportional hazards assumption was verified. Cox proportional hazards analysis revealed a significantly higher rate of surgery during six months follow-up in those receiving care as usual (HR = 2.27, 95% CI [1.35-3.80]), as well as in those with a symptom duration of more than three years (HR = 1.89, 95% CI [1.11-3.24]), adjusted for age, sex, dominant hand involved and BCTQ score at baseline.

Symptom status at follow-up

At six months follow-up, symptom severity and functional status scores did not differ between the intervention and care as usual group (Table 2). When comparing the change in scores from

Table 1 Baseline characteristics of the sample (N = 181).

	Total (N = 181)		Intervention (n = 94)		Care as usual (n = 87)		p	
	Mean (SD)	n (%)	Mean (SD)	n (%)	Mean (SD)	n (%)	t	χ^2
Demographic features								
Age (in years)	58.1 (13.0)		59.0 (12.4)		57.2 (13.7)		.339	
Sex								.454
male		59 (32.6)		33 (35.1)		26 (29.9)		
female		122 (67.4)		61 (64.9)		61 (70.1)		
Educational level								.809
low		149 (82.3)		78 (83.0)		71 (81.6)		
high		32 (17.7)		16 (17.0)		16 (18.4)		
Marital status								.560
with partner		138 (76.2)		70 (74.5)		68 (78.2)		
CTS related								
Duration of complaints								.212
<3 years		136 (75.1)		67 (71.3)		69 (79.3)		
>3 years		45 (24.9)		27 (28.7)		18 (20.7)		
Dominant hand involved								.950
no		35 (19.3)		19 (20.2)		16 (18.4)		
yes		53 (29.3)		27 (28.7)		26 (29.9)		
both hands		93 (51.4)		48 (51.1)		45 (51.7)		
Direct relative with CTS		54 (29.8)		28 (29.8)		26 (29.9)		.989
Paid hand labor								.605
no		113 (62.4)		57 (60.6)		56 (66.4)		
heavy		68 (37.6)		37 (39.4)		31 (35.6)		
SSS score	2.86 (0.77)		2.89 (0.80)		2.82 (0.74)		.589	
FSS score	2.34 (0.89)		2.39 (0.92)		2.28 (0.86)		.374	
BCTQ score	2.64 (0.76)		2.68 (0.79)		2.59 (0.72)		.421	
Lifestyle habits								
Smoking		29 (16.0)		16 (17.0)		13 (14.9)		.703
Alcohol		43 (23.8)		24 (25.5)		19 (21.8)		.560
BMI	28.8 (5.08)		29.2 (5.24)		28.4 (4.89)		.296	

baseline to six months follow-up (paired samples t-test) based on intention-to-treat, the BCTQ scores decreased significantly both in the intervention (p <.001) as well as the care as usual group (p <.001).

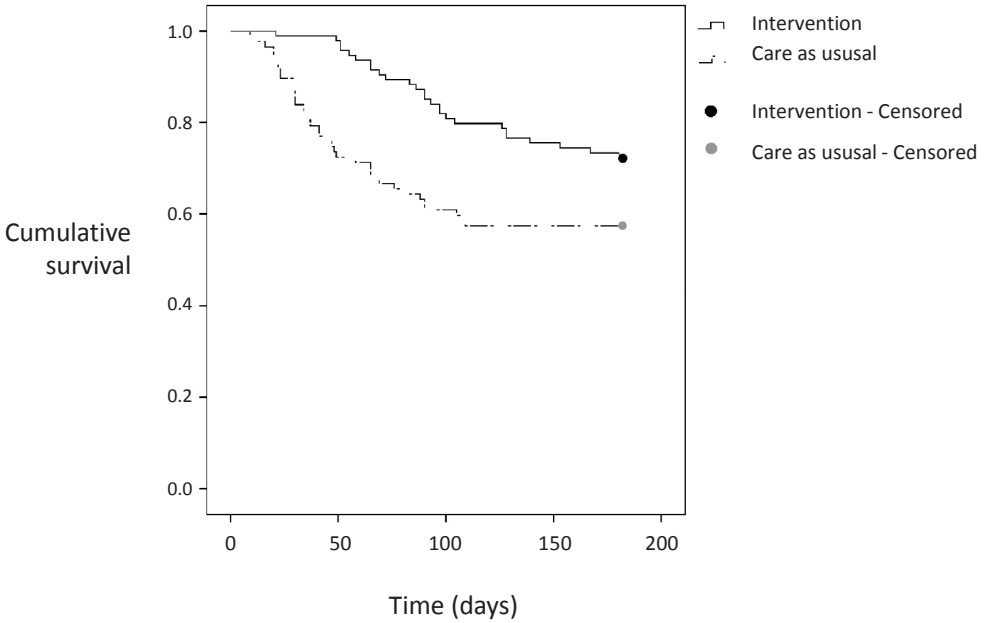

Figure 2 Kaplan-Meier survival curves for the number of days after randomization until occurrence of surgery for the intervention and care as usual groups (log-rank test: χ^2 (1, N = 181) = 6.94, p = .008).

Table 2 Comparison of CTS symptom scores at six months follow-up between the intervention and care as usual group.

	Mean (SE) score intervention group (n = 94)	Mean score (SE) care as usual group (n = 87)	t	p
SSS	1.84 (0.10)	1.89 (0.14)	-.32	.747
FSS	1.75 (0.09)	1.75 (0.09)	-.07	.947
BCTQ	1.80 (0.08)	1.84 (0.08)	-.31	.756

DISCUSSION

Patients who received care as usual had a 2.3-fold risk of receiving carpal tunnel release surgery compared to patients who were treated with mechanical traction during the follow-up period. Moreover, the symptom severity had decreased significantly from baseline to follow-up in both groups, suggesting that not having received surgery did not result in a persistence of CTS-related symptoms. To date, this is the only RCT evaluating the effectiveness of mechanical traction. In 2004, Brunarski *et al.*[24] published a series of four case studies in which patients with CTS received mechanical traction. In all four cases, symptoms improved both subjectively and objectively (measured using electrodiagnostic studies). In an observational study among 78 patients, symptoms reduced significantly after mechanical traction immediately post-treatment (p <.01).[25] After two years follow-up, 60% reported a reduction on the SSS subscale of the BCTQ compared to baseline and only 18% had

had surgery.[26] A few studies have compared other non-surgical treatments with surgery. Two RCTs comparing steroid injections to surgery reported conflicting results; one in favor of steroid injections[30] and the other in favor of surgery.[18] Jarvik *et al.*[16] compared surgery to non-surgical treatment (anti-inflammatory drugs, hand therapy and ultrasound therapy) in 116 patients. At six months follow-up, patients in the surgery group (n = 57) had significantly lower scores on the subscales SSS (-0.42) and the FSS (-0.46) of the BCTQ, compared to patients in the non-surgical treatment group (n = 59), but the clinical relevance of the difference was only modest. Surgery was more effective than splinting in a study by Gerritsen *et al*.[8] However, they did not include patients with very mild or very severe symptoms. Altogether, evidence regarding the effectiveness of non-surgical compared to surgical treatment is limited and has provided conflicting results.

In line with the current study, Baker *et al*.[31] reported that an orthosis and stretch intervention was inversely related to progression to surgery at six months. In the current study, over 35% fewer patients underwent surgery compared to the care as usual group. Many patients do not prefer surgery when there is another non-invasive treatment available. There are several reasons for patients, or physicians, to choose conservative treatment, including symptom severity, age, pregnancy, patients' perception of the efficacy of a certain treatment, insurance, patients' educational level, pregnancy (during which CTS is highly prevalent) and the presence of comorbidities.[32-35]

The median time to surgery was longer in the intervention group compared to the care as usual group, meaning surgery was delayed for approximately the duration of the intervention. Therefore, it is not likely that a substantial number of patients will have had surgery after six months in the intervention group, compared to the care as usual group. Moreover, both survival curves in Figure 2 regress to a horizontal line, which also suggests not many people receive surgery after 6 months in both groups.

The CTS patients in the present investigation is comparable to CTS population in the study by Jarvik *et al.*[16], based on age, gender and percentage of patients with bilateral symptoms. Jarvik *et al*. reported a mean score of 2.98 (0.70) on the SSS in their sample of CTS patients at an outpatient neurologic clinic (n = 116), which is very similar to the 2.86 (0.77) in the current study. Compared to the population of patients with electrodiagnostically confirmed CTS of Gerritsen *et al.*[8], our study population is slightly older (58 vs 49), we included less women (67% vs 76%) and patients with more severe symptoms (mean SSS 2.9 vs 2.5). Gerritsen *et al*., however, applied more specific exclusion criteria, excluding patients with diabetes, which could explain the difference.

Patients included in the study did not differ from eligible patients at the outpatient neurology clinic based on the distribution of gender and affected hand. However, patients in the study were slightly older compared to eligible patients who did not participate. The main objections to participation were long traveling distance to the clinic and lack of time. Older people often have more time, because they are less likely to have young children or a fulltime job. In the care as usual group, there was significantly more drop-out compared to the intervention group, which is a common limitation of randomized controlled trials: participants may be disappointed to be randomized in the control group and feel less motivated to continue.[36]

A limitation of the study is the lack of discrimination between hands in bilaterally affected patients. Other studies only included the most severely affected hand[37] or assessed both hands separately.[38] However, it is often difficult for patients to discriminate between hands when assessing symptom severity, and only including one hand in bilaterally affected patients was not preferable for ethical and practical reasons. Another limitation is that the response to intervention was based on the patients' symptoms perception, not by an objective measure, such as electrodiagnostic testing. However, electrodiagnostic testing is not sensitive enough to clinical change following treatment: after surgery, nerve conduction improves, but only moderately correlates to patient reported improvement.[39] Patient reported outcomes are considered superior in evaluating treatment effect and are used in most studies evaluating treatment effectiveness and the BCTQ is a highly validated self-reporting symptom questionnaire which is commonly used in clinical practice to evaluate changes of symptoms after treatment.[7,16,28] Lastly, complete data on other forms of treatment received by patients (other than mechanical traction or surgery) was not available. Of the 82 completers in the intervention group, three patients had received a corticosteroid injection and 14 patients used a wrist splint at follow-up. Of the 56 completers in the care as usual group, three patients had received a corticosteroid injection and 11 used a wrist splint. A strength of this study is the selection of the control group. Patients in the control group received care as usual, and hence we compared the intervention to standard care and not a specific control treatment. This design leads to more generalizable results.

In conclusion, treatment by means of mechanical traction can possibly prevent progression of symptoms requiring surgery within six months in CTS patients. Although surgery was not performed in the majority of patients receiving mechanical traction, CTS symptoms declined significantly to a similar level as seen in CTS patients who received usual care. Because up to 30% of patients who received surgery report (new) CTS symptoms at longer follow-up (one to two years), a longer period of observation is needed to compare the long-term effect of mechanical traction to care as usual (including surgery). The mechanism for the effectiveness of mechanical traction is still unclear. We expect that the traction improves blood microcirculation, reduces edema in the synovial tissue, and therefore reduces pressure in the carpal tunnel.[14,24] Future studies should focus on what the possible working mechanism is of mechanical traction. The clinical relevance of the current study is that by introducing a new non-invasive treatment of CTS, different sub-groups of CTS patients might be identified that will benefit from mechanical traction. This approach may result in a substantial reduction in the number of surgeries with similar patient-reported symptoms. Mechanical traction may prove to be a more cost-effective intervention for CTS than surgery. CTS is very common in the general population. Considering that the total cost of mechanical traction is about $420 per patient and the total cost of surgery about $2500, this would mean a substantial reduction in health care costs. Moreover, the current study contributes to the current discussion regarding the critical evaluation of the actual benefit of invasive interventions in general in comparison to more conservative approaches.

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Chapter 8

Summary and general discussion

SUMMARY AND GENERAL DISCUSSION

In this thesis, we focused on carpal tunnel syndrome (CTS) during pregnancy and the effectiveness of a non-invasive treatment option: mechanical traction. The chapters concerning pregnancy-related CTS (**Chapters 2, 3, 4 and 5**) are based on data from the HAPPY study, a large prospective longitudinal cohort study following pregnant women during their pregnancy up to the first postpartum year. **Chapters 6 and 7** focused on the design and results of a randomized controlled trial in a general, non-pregnant population investigating the effectiveness of mechanical traction.

Carpal tunnel syndrome during pregnancy

Summary and interpretation of the main findings

In **Chapter 2** we reported a prevalence of 34% of pregnancy-related CTS in our sample of 639 women. The mean scores on the Boston Carpal Tunnel Questionnaire (BCTQ) increased towards the end of gestation. Still, symptom severity was generally mild to moderate. The presence of CTS symptoms during pregnancy was significantly related to fluid retention (OR = 1.8, 95% CI [1.5-2.1]), adjusted for BMI, age, parity and depression scores. Within the group of women with CTS symptoms, mean scores on the BCTQ independently predicted sleeping problems (β = 0.087, p = .025) and higher depression scores based on the Edinburgh Depression Scale (EDS) (β = 0.237, p <.001). Fluid retention increased during gestation in all women and was related to CTS symptoms, which explains why CTS typically occurs in the third trimester: 40% of the cases reported the onset of symptoms after 30 weeks. After 30 weeks, maternal weight gain can largely be attributed to an increase in extravascular fluid.[1]

While the prevalence of CTS in the general population is only 4-5%,[2,3] the prevalence of pregnancy-related CTS symptoms seems to be substantially higher. It is therefore important to understand the underlying pathophysiology of CTS during pregnancy, which might help selecting the proper treatment. Since CTS is related to hypothyroidism in the general population[4-6] and free thyroid hormone (FT4) level decreases during pregnancy,[1,7] we hypothesized that pregnancy-related CTS was possibly associated with thyroid function. In **Chapter 3**, we found that lower FT4 levels at 12 and 32 weeks' gestation were significantly related to pregnancy-related CTS. This relation persisted at a multivariate level: FT4 levels in the lower quartiles (OR = 0.88, 95% CI [0.80-0.97]), higher fluid retention scores throughout pregnancy (OR = 1.78, 95% CI [1.57-2.02]) and higher depression scores (OR = 1.05, 95% CI [1.01-1.09]) were independently related to CTS, adjusted for BMI, age and parity. Moreover, the reported symptom severity of CTS was correlated with the level of fluid retention. Although FT4 and fluid retention were independently related to CTS, FT4 was also related to fluid retention. Therefore, the relation between FT4 and CTS is most likely partially mediated by fluid retention. However, lower FT4 levels also have a direct effect on the occurrence of the CTS, possibly as a result of physiological changes in peripheral nerve function leading to a slowed conduction. In another study, nerve conduction was significantly prolonged in women between 20 and 45 years old with newly diagnosed and untreated hypothyroidism.[8]

Thus, CTS is a highly prevalent condition among pregnant women, but symptoms are generally mild. Is it just a mild discomfort during pregnancy or does it affect maternal or child well-being? To the best of our knowledge, there have been no previous studies investigating the possible impact of pregnancy-related CTS. We hypothesized that CTS symptoms may prevent women from starting to breastfeed their newborn. Wrist extension and flexion increase the pressure on the median nerve, provoking or exacerbating symptoms of paresthesia, numbness or pain,[9] possibly making it hard for a women to hold her baby during breastfeeding. In **Chapter 4**, we provided evidence to support this hypothesis. Within women with CTS, milder symptoms were significantly related to a higher likelihood of breastfeeding initiation. Breastfeeding is the best form of nutrition for infants and is promoted worldwide among new mothers.[10] Mild CTS symptoms (OR = 1.93, 95% CI [1.10-3.36]), higher education (OR = 2.10, 95% CI [1.34-3.29]) and multiparity (OR = 0.61, 95% CI [0.38-0.97]) were predictive factors for breastfeeding initiation in women with CTS. We did not find a relationship between the presence of CTS symptoms and breastfeeding initiation in the sample as a whole, most likely because part of the women have only mild symptoms. Symptom severity and functional impairment is milder in pregnant women compared to the general non-pregnant population with CTS.[11] This was confirmed in our RCT: the mean score on the BCTQ was 1.65 (0.63) during pregnancy, compared to 2.64 (0.76) in our general outpatient population.

In **Chapter 5**, we reported that 15% of women with pregnancy-related CTS have persisting symptoms at 12 months postpartum. Within the group who reported CTS symptoms during pregnancy, higher BCTQ scores during pregnancy (OR = 1.93, 95% CI [1.08-3.45]), early onset of symptoms during pregnancy (OR = 2.88, 95% CI [1.45-5.72]) and higher mean EDS scores postpartum (OR = 1.11, 95% CI [1.03-1.19]) predicted the persistence of CTS symptoms at 12 months postpartum.

General methodological considerations

Prevalence rates of pregnancy-related CTS vary between 1 and 62% in the current literature.[11-14] The large variety in prevalence figures is likely due to variances in methodology. Stolp-Smith *et al.*[14] reported a prevalence of 0.34% among 14,579 pregnancies in 10,873 women. They retrospectively analyzed medical records and only included women with a new diagnosis of CTS at an outpatient neurology clinic during pregnancy, which most likely resulted in a substantial underestimation. In a study by Mondelli *et al.*[13], 45 (17%) of the 259 pregnant women had electrophysiologically confirmed CTS, but only women who spontaneously reported hand symptoms to their gynecologist were assessed. In our study, only 4 of 219 women with CTS symptoms consulted a physician because of their symptoms, and it is unknown how many of these were referred to a specialist. Padua *et al.*[15] conducted a systematic review investigating the prevalence of pregnancy-related CTS. After a thorough literature search, they selected only five studies and reported clinically diagnosed CTS from 31% to 62% and electrophysiologically confirmed CTS in 7% to 43% of the cases. However, most studies were possibly affected by

selection bias. In an earlier prospective cohort study, Padua *et al*.[11] found clinically diagnosed CTS in 62% of the pregnant women in their sample. However, they recruited women from an obstetrics and gynecology department and did not report any specific in- or exclusion criteria, while we clearly included only healthy pregnant women. Therefore, Padua *et al*. possibly also included women with primary hypothyroidism or other endocrine disorders, which increases the likelihood of developing CTS during pregnancy.

People with depression in general report higher levels of somatic symptoms[16], also in pregnancy.[17] In Chapter 2, however, EDS scores were not related to the presence of CTS symptoms during pregnancy in a multivariate analysis. On the other hand, the relationship was found during the postpartum period in Chapter 5. Moreover, mean EDS scores during pregnancy were a significant predictor of the BCTQ scores during pregnancy within women with CTS symptoms. From our data, it is hard to determine a causal relationship between depressive symptoms and CTS. In a recent meta-analysis of the literature, depression showed to be an important co-morbid factor in patients who suffered from chronic pain (>3 months).[18] Two previous studies have investigated the association between psychological distress and depression on self-reported symptom severity in CTS patients. Nunez *et al*.[19] found that depression predicted pain intensity in patients with CTS, while gender, age and electrodiagnostic parameters did not. Similarly, psychological disturbance (based on the hospital anxiety and depression scale) was significantly associated with BCTQ in a study by Hobby *et al*.[20] It is therefore important to take depressive symptoms into consideration when assessing CTS. To the best of our knowledge, our study is the first to adjust for depressive symptoms when investigating predictors of CTS symptoms during pregnancy.

Strengths and limitations

The HAPPY study has several strengths. One is the large sample size: a large sample size reduces the likelihood of bias and increases external validity. Other prospective cohort studies investigating CTS during pregnancy had much smaller sample sizes, from 58 to 259.[15] Another strength is the prospective design with multiple measurement time points. CTS was assessed at 32 weeks' gestation and at one week postpartum regarding the last weeks of pregnancy. Most studies assessed CTS only once during pregnancy, possibly missing women who develop it during the last few weeks. We found that 21% reported CTS symptoms before 32 weeks' gestation, which increased to 35% from 32 weeks until labor. Assessing CTS at a single time point may result in an underestimation of the prevalence.

As part of the HAPPY study, women were asked "Do you experience symptoms of tingling, numbness or pain in hands or wrist?" in the questionnaires at 32 weeks' gestation and one week postpartum regarding the last weeks of pregnancy. The questionnaires were filled out online or on paper. When they answered affirmative, they would then fill out the BCTQ. This means that women who (self) reported CTS symptoms were not clinically or electrophysiologically diagnosed by a physician. There are several clinical tests to evaluate CTS, of which the Phalen's test and Tinel sign are often used in scientific studies. In both tests, symptoms are provoked

either by holding the wrists in complete flexion (Phalen's test) of by tapping on the wrist (Tinel sign). Both tests have limited diagnostic value, especially in patients with a more advanced form of CTS.[21] The 'gold standard' in clinical practice to diagnose CTS is electrodiagnostic testing (EDT). However, it is time-consuming, expensive and uncomfortable for the patient. Therefore, in large longitudinal cohort studies (such as the HAPPY study) the use of EDT on all participants is undesirable. Moreover, the diagnosis of CTS is primarily based on the presence of patient-reported symptoms typical for CTS (pain, tingling and numbness).[22,23] Therefore, the presence of CTS symptoms was assessed using questionnaires in Chapters 2 through 5. Unfortunately, it is unclear from the data whether the CTS symptoms were present before pregnancy (and possibly exacerbated during pregnancy), or whether they developed during pregnancy. In the general population, CTS usually occurs after the age of 40. Although the exact prevalence of CTS in women between 18 and 40 years is unknown, the likelihood that CTS symptoms were present already before pregnancy is small.

There was a considerable amount of missing data in the HAPPY study, around 30% of the participants described in Chapters 3, 4 and 5. Part of these missing data can be attributed to drop-out, which is a common challenge in longitudinal studies. Another major cause of missing data was related to practical issues, especially at one week postpartum. It was not always possible to send the questionnaire at the right time because childbirth is not usually planned. Out of respect for the rest of the new mother, we also did not send reminders after sending the questionnaire. However, since these causes for missing data were partly random, the risk of bias is limited. Comparisons of baseline characteristics between women with and without missing data were significantly different for some variables, but the effect sizes were generally small, meaning they had little, if any, clinical relevance.

Many women in the HAPPY study were highly educated. On average, 70% had a Bachelor's or Master's degree, compared to 52% of the general Dutch female population in a similar age range.[24] Pregnant women were recruited in and around Eindhoven, an area with a large proportion of highly educated people. In 2011, the Eindhoven region was voted the smartest region in the world by the Intelligent Community Forum. Women with a higher education are less likely to work with their hands, possibly reducing the likelihood for them to develop CTS. There is some evidence that CTS can be work-related, especially in occupations requiring repetitive or forceful hand motions.[25] However, CTS during pregnancy occurs mostly during the last trimester, when women stop working. In Chapter 3, it was shown that women who reported CTS were less highly educated and education was also a predictor of breastfeeding initiation (which is generally seen in the literature, Chapter 4). Therefore, conclusions should be interpreted with caution for less highly educated regions in the world.

Implications and considerations for clinical practice

In our study, only 2% of the pregnant women with CTS symptoms mentioned their symptoms to a health care provider. This is partly because symptoms are mild and are known to resolve

postpartum, so they do not need special attention. However, health care providers usually do not ask for CTS symptoms,[26] which could leave the problem unrecognized. As we have shown in Chapters 2 and 4, CTS can have significant impact on the maternal well-being. Gynecologists and midwives should therefore be aware of the high prevalence. They could actively ask about CTS symptoms, especially during check-ups in the last trimester. To support a clinical diagnosis of CTS with objective measurements, ultrasonography can be used to assess the median nerve. Ultrasonography is readily available in obstetric departments and midwifery practices, it is inexpensive and non-invasive, therefore making it a more suitable diagnostic technique to use during pregnancy than EDT. When the symptoms present, appropriate treatment should be offered if necessary. Early diagnosis of CTS and subsequent treatment may prevent sleep problems and functional impairment in a later stage during pregnancy. Many pregnant women experience symptom relief with conservative treatment.[12,27,28] CTS symptoms were also related to fluid retention.

If symptoms could be relieved or reduced during pregnancy in women with more severe CTS, they may be more likely to start breastfeeding. Moreover, there are some breastfeeding positions that allow for a neutral position of the wrist.[29] Midwives, obstetric nurses and lactation specialists can help new mothers to find the right positions and be comfortable during breastfeeding.

In our study, one out of six women report persisting CTS symptoms. Timely treatment of CTS during pregnancy may also prevent symptoms to persist postpartum.

Depressive symptoms should be considered in women with persisting CTS symptoms postpartum. Women with CTS had significantly higher EDS scores in our study and higher mean EDS scores throughout the postpartum period were an independent predictor of persistence of CTS symptoms at 12 months postpartum. Women with symptoms of depression during the perinatal period are at increased risk for premature delivery and the child is at increased risk for psychological and social developmental issues.[30] Women with pregnancy-related CTS should therefore be screened for depressive symptoms and offered an appropriate intervention.

Directions for future research

In non-pregnant CTS patients, symptoms are believed to be the result of wear and degeneration of the tendons, leading to ischemia and, in later stages, demyelination, inflammation and fibrosis.[23,31] The pathophysiological role of pregnancy in the development of CTS is unclear. Fluid retention in the synovial tissue in the carpal tunnel could lead to an increase in tissue volume and therefore pressure on the median nerve. Fluid retention could also cause endoneurial edema and thickening of the perineurium. Here, the nerve itself enlarges, creating increased pressure in the carpal tunnel. Fluid retention may also lead to metabolic changes, affecting nerve function.[23] Ultrasonography is a non-invasive diagnostic technique which would be able to differentiate between these mechanisms. In future research, pregnant women with and without symptoms of CTS could be compared based on ultrasonographic parameters to investigate the pathophysiology of CTS during pregnancy.

In the current literature, an association between pregnancy-related CTS and the development of CTS later in life has not yet been investigated in a prospective study. CTS is much more common in women compared to men, suggesting the presence of female-specific risk factors. Future research could further focus on the follow-up of women with pregnancy-related CTS, to investigate whether they are at risk for CTS later in life.

Mechanical traction as non-surgical treatment option

Summary and interpretation of the main findings

We described the design of an RCT to study the effectiveness of mechanical traction in **Chapter 6**. 181 adult patients from the outpatient neurology clinic of VieCuri Medical Center in Venlo, the Netherlands were included in the study. All patients were clinically and electrophysiologically diagnosed with CTS. They were randomly assigned to either 12 treatments of mechanical traction (twice a week for six weeks) or care as usual. Recruitment for this study lasted from October 2013 till May 2015. In the process of designing the study, the sample size calculation was based on a clinically relevant change from baseline on the BCTQ at follow-up. To detect a mean difference of 0.5 between BCTQ scores of the intervention and care as usual groups, a total of 128 patients needed to be included with a 1:1 distribution to either group. After 19 months, as described in **Chapter 7**, a total number of 181 patients were included. At 6 months follow-up, 24% did not return the questionnaire and were considered as drop-out. BCTQ scores were available for 138 patients, providing enough power. To minimize bias, we used multiple imputation for the missing BCTQ scores.

At six months follow-up, mean BCTQ scores had significantly decreased from baseline in the intervention and care as usual groups, but did not differ between the groups. However, in the intervention group, 28% had had surgery, compared to 43% in the care as usual group. Patients who received care as usual had a 2.3-fold risk of having surgery during follow-up.

Surgery is considered the most effective treatment option for CTS so far. Some patients, however, prefer initial conservative treatment, which may also be more cost-effective.[32] In medicine, randomized controlled trials are considered to be the golden standard to evaluate the effectiveness of a medical treatment.[33] However, only a few RCTs have been conducted to study the effectiveness of surgery versus conservative treatment.[34-36] In our study, we did not compare mechanical traction to strictly surgery, but to care as usual, which included steroid injections, wrist splints and surgery.

General methodological considerations

Only two previous reports were available evaluating mechanical traction with a similar traction device as a treatment option for CTS. Brunarski *et al.*[37] conducted a case series in which four cases were described. All four patients were women between 36 and 51 years old who received between 5 and 12 treatment sessions in three months. Symptom severity and electrophysiologic measurement improved in all patients. Kloosterman[38] conducted an observational study among 78 CTS patients who were treated with mechanical traction in a practice for physical therapy in the Neth-

erlands. The reported success rate was 70% immediately post-treatment and 60% after two year follow-up.[39] Female gender, a positive Phalen's test and shorter symptom duration (less than a year) were associated with greater improvements in symptom severity and functional status. This report, however, has not been published in a peer-reviewed scientific journal. Although mechanical traction is a promising form of treatment, it is not widely used in medical practice because evidence for treatment effectiveness was lacking so far. Therefore, we conducted a randomized controlled trial to compare mechanical traction to care as usual in an outpatient neurology clinic.

Strengths and limitations

One of the strengths of this study is the definition of the control group. We compared the intervention to care as usual, which meant they would receive the standard care for CTS from their neurologist. Many patients in the care as usual group, especially those with more severe CTS, chose to have surgery, others adopted an expectant approach or received a wrist splint. Hence, the results are generalizable to a general outpatient neurology population. Comparing the intervention strictly to surgery would have resulted in a different patient population who would be willing to participate. Patients who opt for surgery generally have a more severe form of CTS. On the other hand, comparing mechanical traction to another non-invasive treatment (for example splinting or steroid injections) would have led to a sample with milder CTS. In the current study, the included patients did not differ from eligible patients at the outpatient neurology clinic based on the distribution of gender and affected hand. However, included patients were slightly older.

We followed the design described in **Chapter 6** in conducting the RCT, with the exception of part of the statistical analyses. Initially, treatment success was defined as a significantly greater reduction in BCTQ score in the intervention group compared to the care as usual group. However, patients in the intervention group were free to have additional treatment if the 12 sessions of mechanical traction did not lead to the desired reduction in symptom severity. Consequently, 26 patients in the intervention group had received surgery at six months follow-up. Data were analyzed based on the intention-to-treat principle, resulting in no significant difference in BCTQ scores between the two groups. However, 26 (28%) patients in the intervention group had surgery, compared to 37 (43%) in the care as usual group. A reduction in the number of surgeries with a similar reduction in symptom severity would also be a favorable outcome. A non-invasive treatment is often preferred over a more invasive option by patients, such as surgery. The number of surgeries were therefore compared between both groups using Kaplan Meier survival analysis, a statistical method that is widely used in clinical trials to assess time-to-event. The log-rank test is used to compare time-to-event curves between groups.

There was a proportion of missing data at six months follow-up. Of the 181 patients who were included in the study, 138 (76%) returned the questionnaire at six months. Of the remaining 24%, missing data were imputed using multiple imputation, based on baseline characteristics and BCTQ scores. Whether a patient had surgery was checked in the medical record of the hospital. Therefore, data on carpal tunnel surgery was complete at six months follow-up.

Implications and considerations for clinical practice

In the Netherlands, patients with CTS symptoms consult their general practitioner before visiting a specialist. Only 25% of clinically diagnosed CTS patients are referred to a neurology clinic by general practitioners for electrodiagnostic testing and treatment.[40] This means that many patients, with probably milder symptoms, receive treatment by their general practitioner or no treatment at all. Mechanical traction would be especially suitable for these patients, because the treatment is non-invasive and low-risk. In our study, three patients did not finish the intervention of 12 treatment sessions, mainly because symptom severity increased during this period and mechanical traction was not effective. However, no adverse effects were reported. Therefore, patients with milder symptoms do not necessarily need a (time consuming and expensive) electrophysiologically confirmed diagnosis before starting treatment. If general practitioners would start to refer CTS patients for mechanical traction, this would lead to a more timely treatment at an earlier stage of the syndrome, possibly increasing the likelihood of success. Because mechanical traction is a non-invasive, cheap and readily accessible treatment, it could be seen as a first-line treatment option for CTS. If mechanical traction fails, surgery is still an option without any evidence for poorer prognosis.

It is interesting to note that – although not discussed in this thesis – we also explored the independent effect of depressive symptoms on CTS symptoms in the sample of patients included in the RCT. Again, depressive symptoms proved to be a strong predictor of BCTQ scores. As we have stated previously, depression is related to pain,[18] also in patients with CTS.[19,20] This suggests that, when evaluating the severity of CTS symptoms, it is always wise to investigate the co-existence of depression. It is obvious that surgery might not be the first choice of treatment for CTS patients with depression. Because depression, until now, has never been assessed at an outpatient neurology clinic of CTS patients, it might be speculated whether the poor response to surgery occurs especially in depressed patients.

Directions for future research

Several other possible positive outcomes of mechanical traction compared to care as usual have not yet been explored, such as days of sick leave from work or health care utilization. After CTS surgery, the average return to work is between two and seven weeks. During the period of treatment with mechanical traction, however, people can continue work and all other daily activities. Initial treatment with mechanical traction may therefore also be more cost-effective. In the Netherlands, about 27,500 CTS patients received carpal tunnel release surgery in 2011.[41] The introduction of mechanical traction as the primary treatment for CTS could reduce the surgery rate by roughly 35% with similar patient reported outcomes. Considering that the total cost of mechanical traction is about €360 per patient and the total cost of surgery about €2500, this would mean a possible annual saving of 14 million euros in the Netherlands alone. If similar data could be extrapolated to the US with almost 20 times more inhabitants compared to the Netherlands and a similar high standard health care system, a reduction of surgery by 35% would imply an annual saving of health

costs of 280 million euros. However, a longer follow-up time is needed to explore these outcomes. It is unknown whether the mechanical traction is also effective long-term, or merely postpones further treatment. Moreover, it is unclear who benefits most from mechanical traction. Treatment success could vary based on gender, age or symptom severity.

Connecting both studies: CTS during pregnancy and mechanical traction

CTS during pregnancy is often treated conservatively, since symptoms quickly resolve after childbirth in the majority of women. Surgery is only performed during pregnancy in very severe cases.[28] Mechanical traction would be an especially suitable non-invasive treatment option during pregnancy. Bilateral symptoms are more common during pregnancy compared to the non-pregnant CTS population. In Chapter 2, 70% of the pregnant women with CTS reported bilateral symptoms. In our non-pregnant, outpatient population, only 51% had bilateral symptoms. Mechanical traction is useful for (pregnant) patients with bilateral symptoms, because both hands can be treated during one treatment session. However, it is unknown whether the pathophysiology of CTS during pregnancy is similar to idiopathic CTS. Mechanical traction is expected to reduce pressure in the carpal tunnel by improving blood microcirculation and reducing oedema in the synovial tissue.[37,42] Whether this mechanism also applies during pregnancy remains to be investigated. Mechanical traction could therefore be less effective, or more effective in women with pregnancy-related CTS compared to a general outpatient population with idiopathic CTS. Ultrasonography could be used to examine the changes in the tissue of the carpal tunnel after treatment with mechanical traction, also in pregnancy.

In both studies, depressive symptoms at the time of diagnosis were independently related to the severity and persistence of symptoms. If depressive symptoms are also a predictor of treatment failure, outpatient clinics should consider the co-occurrence of depressive symptoms in CTS patients before surgery is offered. It might be more appropriate to first treat depression. Future research should focus on the effect of depressive symptoms on treatment outcome.

General conclusion

CTS occurs in one out of three healthy pregnant women and in one out of six of these women symptoms still persist at 12 months postpartum. Thyroid hormone changes during pregnancy are possibly related to the occurrence of CTS symptoms, most likely mediated by increased levels of fluid retention in those women with low thyroid hormone levels. Moreover, women with more severe CTS symptoms are less likely to initiate breastfeeding compared to women with milder symptoms. Mechanical traction shows beneficial effects at six months follow-up. Due to its non-invasive character, it seems to be an excellent treatment option for pregnant women with CTS. Whenever pregnant women or patients at an outpatient neurology clinic report high CTS symptom severity, the co-occurrence of depression could be considered.

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Samenvatting (summary in Dutch)

Carpaletunnelsyndroom (CTS) is een neurologische aandoening waarbij de middelste handzenuw (nervus medianus) is bekneld ter hoogte van de carpale tunnel. De carpale tunnel is een ruimte in de pols, omgeven door de handwortelbeentjes en het carpale ligament. De beknelling van de middelste handzenuw leidt tot symptomen van doofheid, tintelingen en soms pijn in de hand(en). De symptomen uiten zich voornamelijk in de eerste drie vingers van de hand en de radiale zijde van de ringvinger, het deel van de hand dat wordt geïnnerveerd door de middelste handzenuw, en ontstaan meestal 's nachts. CTS komt vaak voor: de prevalentie in de algemene populatie is ongeveer 5%. Het komt vaker voor bij mannen dan bij vrouwen en ontstaat meestal tussen de leeftijd van 40 en 60 jaar. De diagnose van CTS is voornamelijk gebaseerd op patiënt-gerapporteerde klinische symptomen. In de meeste gevallen ontstaat CTS spontaan. Er zijn echter aandoeningen die de kans op het ontstaan van CTS vergroten, waaronder overgewicht, diabetes, reuma, tenosynovitis en hypothyreoïdie. De prevalentie van CTS onder hypothyreoïdie patiënten is meer dan 30%. Zwangerschap is ook een bekende risicofactor voor CTS. Zwangerschaps-gerelateerde CTS is vaker bilateraal en ontstaat meestal in het derde trimester. De prevalentie van CTS in de zwangerschap varieert tussen 1 en 62% in de huidige literatuur.

In dit proefschrift worden de resultaten van twee verschillende studies beschreven. De eerste studie is de HAPPY studie, een observationele studie onder 2,221 vrouwen die we hebben gevolgd tijdens hun zwangerschap en het eerste jaar postpartum. Met behulp van deze data hebben we prevalentie, determinanten en mogelijke (negatieve) effecten van CTS tijdens de zwangerschap onderzocht. De tweede studie is een gerandomiseerde en gecontroleerde studie (*randomized controlled trial,* RCT) waar het effect van mechanische tractie van de pols als non-invasieve behandeling voor CTS is onderzocht onder CTS patiënten (mannen en vrouwen) van een polikliniek neurologie.

CTS komt vaak voor tijdens de zwangerschap, maar de exacte prevalentie is onduidelijk. In **Hoofdstuk 2** hebben we daarom de prevalentie van CTS symptomen onderzocht in 639 zwangere vrouwen van de HAPPY studie. De ernst van de klachten werd gemeten met de *Boston Carpal Tunnel Questionnaire* (BCTQ), een gevalideerde vragenlijst die de mate van symptomen en functionele beperking meet. 34% van deze vrouwen rapporteerde CTS klachten tijdens de zwangerschap en de ernst nam toe naar het einde van de zwangerschap. Ten opzichte van de algemene, niet-zwangere CTS patiëntenpopulatie is de ernst van de symptomen tijdens de zwangerschap relatief mild. De aanwezigheid van CTS symptomen was gerelateerd aan het vasthouden van vocht. Binnen de groep van vrouwen met CTS symptomen was de ernst van de klachten gerelateerd aan slaapproblemen en hogere depressie scores, gebaseerd op de *Edinburgh Depression Scale* (EDS). Het is belangrijk om te controleren voor de mentale gesteldheid, in het bijzonder depressie, wanneer patiënt-gerapporteerde symptomen worden gemeten is. Depressie kan van invloed zijn op de subjectieve pijnervaring.

Hypothyreoïdie, een aandoening waarbij het lichaam te weinig schildklierhormoon (thyroxine, FT4) aanmaakt, is een risicofactor voor het ontstaan van CTS. FT4 daalt tijdens de zwangerschap,

maar een relatie tussen schildklierfunctie en CTS in de zwangerschap is tot op heden niet onderzocht. In **Hoofdstuk 3** laten we zien dat lagere FT4 levels op 12 en 32 weken zwangerschap, hogere scores op zelf-gerapporteerd vocht vasthouden en hogere depressie scores onafhankelijk waren gerelateerd aan CTS.

CTS komt dus vaak voor bij zwangere vrouwen, maar de symptomen zijn relatief mild. Is het enkel een ongemak tijdens de zwangerschap, of heeft het mogelijk ook effect op het welzijn van moeder en kind? In **Hoofdstuk 4** beschrijven we dat, binnen de groep zwangere vrouwen met CTS symptomen, vrouwen met mildere symptomen vaker startten met het geven van borstvoeding na de bevalling ten opzichte van vrouwen met ernstigere symptomen. Extensie en flexie van de pols kan de druk op de middelste handzenuw vergroten, waardoor de CTS symptomen kunnen verergeren. Dit maakt het mogelijk lastig en/of pijnlijk voor een vrouw om haar baby (gedurende langere tijd) vast te houden tijdens het geven van borstvoeding.

CTS symptomen verminderen of verdwijnen vaak na de bevalling, maar een deel van de vrouwen blijft persisterende klachten houden postpartum. Van de vrouwen met CTS symptomen heeft 15% persisterende klachten tot 12 maanden postpartum, zoals gerapporteerd in **Hoofdstuk 5**. Hogere BCTQ scores tijdens de zwangerschap, het vroeg ontstaan van de symptomen en hogere depressie scores op de EDS postpartum voorspelden het persisteren van CTS symptomen tot 12 maanden postpartum.

In de algemene, niet-zwangere populatie wordt CTS conservatief of operatief behandeld. CTS wordt meestal conservatief behandeld wanneer de klachten nog maar kort bestaan of mild zijn. De meest gebruikte conservatieve behandelingen zijn een polsspalk of steroïde injectie in de carpale tunnel. Beide behandelopties zijn effectief op korte termijn, maar bewijs voor effect op de lange termijn is schaars. Een CTS operatie, waarbij het carpale ligament gekliefd wordt, is de enige behandeling die effectief is op lange termijn. Het is echter een invasieve methode en 30% van de patiënten ervaren aanhoudende symptomen, operatieve complicaties of een terugkeer van de symptomen. Mechanische tractie uitgeoefend op de pols is een veelbelovende, conservatieve behandeloptie voor CTS. Tijdens deze behandeling wordt er herhaaldelijk trekkracht uitgeoefend op de pols met behulp van een gewicht. In **Hoofdstuk 6** wordt het design van een RCT beschreven waarbij 12 behandelingen met mechanische tractie gedurende zes weken wordt vergeleken met de gebruikelijke zorg (*care as usual*). De resultaten van deze RCT worden beschreven in **Hoofstuk 7**. In totaal werden 181 volwassen CTS patiënten (mannen en vrouwen) geïncludeerd van de polikliniek Neurologie van het VieCuri Medisch Centrum in Venlo/Venray, Nederland. Alle patiënten hadden een klinische CTS diagnose, welke was bevestigd door middel van elektrofysiologisch onderzoek. Al deze patiënten werden gerandomiseerd in één van de twee groepen: interventie (mechanische tractie) of de controle groep (gebruikelijke zorg). Zij vulden vragenlijsten in bij de start van het onderzoek en na 3, 6 en 12 maanden. Na 6 maanden was de gemiddelde BCTQ score (ernst van de symptomen) significant gedaald ten opzichte van de start van het onderzoek in beide groepen, maar er was geen verschil tussen de groepen. Patiënten in de controle groep ondergingen echter vaker een operatie: In de interventie groep

was op dat moment 28% van de patiënten geopereerd, ten op zicht van 43% in de controle groep. Mechanische tractie heeft een aantal voordelen. Het is non-invasief: patiënten ervaren over het algemeen geen pijn of ongemak van de behandeling en kunnen hun dagelijkse bezigheden blijven doen. Patiënten met bilaterale symptomen kunnen behandeld worden aan beide handen tijdens dezelfde sessie en de behandeling kan door middel van de gewichten en het aantal sessies worden aangepast aan de behoefte van individuele patiënten. Wanneer mechanische tractie niet effectief is, is een operatie alsnog een optie.

Implicaties voor de praktijk

De prevalentie van CTS in de algemene populatie is ongeveer 5%, terwijl de prevalentie van CTS in de zwangerschap veel hoger ligt. Het is daarom belangrijk het probleem te onderkennen en de onderliggende pathofysiologie te begrijpen, wat mogelijk kan helpen met het kiezen van de juiste behandeloptie. Een tijdige diagnose van CTS en behandeling kan mogelijk slaapproblemen en functionele handproblemen later in de zwangerschap voorkomen. Tijdige behandeling tijdens de zwangerschap voorkomt mogelijk ook het persisteren van klachten postpartum.
In Nederland wordt ongeveer 25% van de patiënten met een klinische CTS diagnose doorverwezen door de huisarts naar een polikliniek neurologie. De overige patiënten worden behandeld door hun huisarts of krijgen geen behandeling. Mechanische tractie zou uitermate geschikt zijn voor deze patiënten omdat het non-invasief is en een laag risico met zich mee draagt. Operatieve behandeling wordt gezien als de meest effectieve optie, maar sommige patiënten geven aanvankelijk een voorkeur aan conservatieve behandeling, wat ook meer kosteneffectief kan zijn. Mechanische tractie is daarom geschikt als primaire behandeloptie, waarna patiënten die er geen baat bij hebben alsnog kunnen worden geopereerd. Mechanische tractie is mogelijk ook een geschikte behandeloptie voor CTS tijdens de zwangerschap. CTS is vaker bilateraal in zwangere vrouwen vergeleken met de algemene populatie. Het is echter nog niet bekend of de pathofysiologie van zwangerschaps-gerelateerde CTS gelijk is aan spontaan CTS.

Conclusie

Een derde van de zwangere vrouwen ervaart CTS symptomen in de zwangerschap en een zesde van deze vrouwen (5% van alle zwangere vrouwen) houdt klachten tot 12 maanden postpartum. Veranderingen in schildklierhormoon concentraties en het vast houden van vocht zijn mogelijk gerelateerd aan het ontstaan van CTS symptomen in de zwangerschap. Vrouwen met ernstigere CTS symptomen geven minder vaak borstvoeding dan vrouwen met mildere symptomen. Behandeling voor CTS met mechanische tractie resulteert in minder operaties na 6 maanden. Het is non-invasief en daarom mogelijk een zeer geschikte behandeloptie voor zwangere vrouwen met CTS symptomen.

Boston Carpal Tunnel Questionnaire

BOSTON CARPAL TUNNEL QUESTIONNAIRE (BCTQ)

Klachtenscore

1. Hoe ernstig is de *pijn* in uw hand(en) of pols(en) 's *nachts*?
   1 Ik heb geen pijn in mijn hand of pols 's nachts
   2. De pijn is mild
   3 De pijn is behoorlijk
   4 De pijn is ernstig
   5 De pijn is nauwelijks te verdragen

2. Hoe vaak wordt u wakker van de *pijn* gedurende de *nacht*?
   1 Nooit
   2 1 maal
   3 2 - 3 maal
   4 4 - 5 maal
   5 > 5 maal

3. Heeft u *overdag* ook *pijn* in uw hand(en) of pols(en)?
   1 Ik heb nooit pijn overdag
   2 Ik heb milde pijn overdag
   3 Ik heb behoorlijk veel pijn overdag
   4 Ik heb ernstige pijn overdag
   5 Ik heb nauwelijks te verdragen pijn overdag

4. Hoe vaak heeft u *pijn overdag?*
   1 Nooit
   2 1 maal
   3 2 - 3 maal
   4 4 - 5 maal
   5 > 5 maal

5. Hoe lang duurt zo'n periode met *pijn* gemiddeld *overdag*?
   1 Ik heb geen pijn
   2 < 10 min
   3 10 - 60 min
   4 > 1 uur
   5 Constant aanwezig

6. Heeft u een *doof gevoel of last van gevoelloosheid* in uw hand(en)?
   1 Nooit
   2 Een beetje
   3 Behoorlijk
   4 Ernstig
   5 Zeer ernstig

7. Heeft u *krachtsverlies* (zwakte) van de hand(en)?
   1 Nee
   2 Een beetje
   3 Behoorlijk
   4 Ernstig
   5 Ik kan er bijna niets meer mee

8. Heeft u *tintelingen of een slapend gevoel in* uw hand(en)?
   1 Nee
   2 Een beetje
   3 Behoorlijk
   4 Ernstig
   5 Zeer ernstig

9. Hoe ernstig zijn het *dove gevoel of de tintelingen 's nachts*?
   1 Geen last
   2 Nauwelijks
   3 Behoorlijk
   4 Ernstig
   5 Zeer ernstig

10. Hoe vaak wordt u wakker van een *doof gevoel of tintelingen*?
   1 Nooit
   2 1 maal
   3 2 - 3 maal
   4 4 - 5 maal
   5 > 5 maal

11. Heeft u problemen met het vastpakken van kleine voorwerpen, bijvoorbeeld sleutels of een balpen?
    1 Geen
    2 Een beetje problemen
    3 Behoorlijk wat problemen
    4 Ernstige problemen
    5 Ik kan zulke voorwerpen helemaal niet vastpakken

Functionele score

Kunt u aangeven hoeveel moeite u heeft ervaren, vanwege hand of polsklachten, bij het uitvoeren van onderstaande activiteiten op een voor u normale dag gedurende de afgelopen twee weken. Omcirkel het antwoord dat het beste weergeeft hoe u de activiteit kon uitvoeren.

	geen probleem	een beetje problemen	behoorlijk wat problemen	ernstige problemen	ik kan het helemaal niet meer
Schrijven	1	2	3	4	5
Knopen vastmaken	1	2	3	4	5
Een boek vasthouden bij het lezen	1	2	3	4	5
Een telefoon / mobieltje vasthouden	1	2	3	4	5
Een potje openmaken	1	2	3	4	5
Huishoudelijk werk verrichten	1	2	3	4	5
Tassen dragen	1	2	3	4	5
Wassen/aankleden	1	2	3	4	5

Naar: Köke AJA, Heuts PHTG, Vlaeyen JWS, Weber WEJ. Meetinstrument: Functionele Handicap Score. In: Meetinstrumenten chronische pijn Deel 1. Pijn Kennis Centrum Maastricht; 1999. p. 82-85.

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About the author

Margreet Meems was born on the 22nd of February 1991 in Venlo, the Netherlands. She completed her pre-university education at College Den Hulster in Venlo. From 2009 until 2013, she studied at Maastricht University. In these years she obtained a Bachelor's degree in Biomedical Sciences and a Master's degree in Human Movement Sciences. Margreet started her PhD research project in September 2013 at Tilburg University. She conducted the practical aspects of the project between September 2013 and May 2015 at VieCuri Medical Center in Venlo. In May 2015, she also started a part-time position as research assistant at Open Universiteit (OU), working on a study that aims to investigate the effectiveness of couple therapy in former cancer patients. Currently, Margreet combines her position at the OU with a Bachelor Occupation Therapy at PXL in Hasselt, Belgium. In the future she hopes to have the best of both worlds and combine clinical practice (occupational therapy) and research.