A novel technique combining transcutaneous electrical nerve stimulation with external tocography for personalized automated labor pain control

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A NOVEL TECHNIQUE COMBINING TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION WITH EXTERNAL TOCOGRAPHY FOR PERSONALIZED AUTOMATED LABOR PAIN CONTROL

BY
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DENMARK

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PHD THESIS

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Dissertation submitted

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CV

Kenoja Thuvarakan received a BSc degree in Medicine with Industrial Specialization in 2014 and subsequently attained MSc degree in 2016 with a specialty in Translational Medicine. She later joined Viewcare A/S in 2017 and worked primarily with clinical study protocol writing and clinical evaluation of a medical device. Viewcare team has been developing a device, Centaflow, to diagnose fetal growth restriction.

Later in 2017, Kenoja developed an idea of creating an additional feature to the device. She suggested that combining CentaFlow with transcutaneous electrical nerve stimulation might create a new impact on the device by adding a pain-relieving function to the additional features of the device. She applied for an Industrial PhD program with Innovation Fund Denmark and successively received the grant. She started her PhD program in March 2018.

During the PhD period, Kenoja published her first full-text paper, wrote a clinical study protocol, and established collaboration with the Department of Gynecology and Obstetrics at Gødstrup Hospital. In 2019, she went for an externship in the Clinical Research Laboratory of Dr. Siobhan Schabrun at Neuroscience Research Australia, Centre for Pain Discovery and Translation, Sydney, Australia. Further, she presented posters at international conferences and peer-reviewed for an acknowledged journal.

After a brief break in late 2019 to mid-2020 to pursue the new role of mother to her son, Mithraan, she completed two clinical pilot studies in the labor ward at Gødstrup Hospital, submitted two full-text papers, and finally completed the dissertation.

ENGLISH SUMMARY

Transcutaneous electrical nerve stimulation (TENS) has been used for labor pain management for several decades, though it is not routinely used in intrapartum care. Some of the reasons include the preferred use of neuraxial anesthesia (e.g., epidural) and no systematic reviews showing significant effects of TENS for labor pain control. Neuraxial anesthesia is associated with several side effects leading to less maternal satisfaction, even though it effectively manages labor pain. The efficacy of TENS is unclear due to the included studies with inadequate methodological considerations, including randomization, allocation concealment, and blinding. Neither has it been clear what stimulation pattern is optimal for labor pain management, including frequency, pulse pattern, and pulse duration. However, high maternal satisfaction with the use of TENS is reported, but it is unclear if it is due to the effect of TENS or the maternal use of TENS, that provides a distraction from the anxiety of labor and prompts the sense of self-control of pain for the women in labor.

Therefore, the present thesis aimed to investigate TENS for labor pain control through three coherent studies. First, a systematic review and meta-analysis were conducted to evaluate the efficacy of TENS for labor pain control (Study I). Next, a pilot study investigated the optimal varying frequencies for labor pain control (Study II). Finally, a feasibility study aimed to develop a novel technique of combining TENS with tocodynamometer (TOCO) for automated stimulation during uterine contractions (Study III).

Study I showed a small but significant efficacy of TENS for labor pain reduction compared to control treatments, i.e., sham-TENS, routine care, no treatment, and oxytocin administration. Further, this was supported with the outcomes including the duration of labor, additional analgesia, and Apgar scores, which tend to favor TENS, except for satisfaction using TENS. Even though the latest included studies showed an improvement in methodological quality, prior studies suffered from poor quality. The significant efficacy was also affected by the high heterogeneity in the meta-analysis. Hereby, it is not possible to conclude if the efficacy of TENS was actual or influenced by bias. Study II showed that varying frequencies of low-to-high frequencies (4/100 Hz) tend to reduce labor pain compared to high-frequencies (80/100 Hz) and sham-TENS (placebo). Even though a high maternal satisfaction was seen, the results were inhibited in the interpretation due to the low sample size. Study III showed a feasible model of TENS-TOCO combination for automated labor pain control that increases current intensity during uterine contraction and lowers back to basic stimulation between uterine contractions using 4/100 Hz.

In interpretation, this thesis presented data from three studies showing a trend of possible effects of TENS on labor pain. Especially considering the findings from Study I with significantly reduced pain intensity, while in Study II, a non-significant

decrease of pain intensity was seen for 4/100 Hz TENS, and a high maternal satisfaction was observed. These findings suggest TENS as an alternative treatment approach for labor pain control in intrapartum care, especially in the latent phase. The use of TENS might be improved with the introduction of a new technology (TENS-TOCO combination), which needs to be assessed for efficacy and safety in future clinical studies based on Study III.

DANSK RESUME

I adskillige årtier har transkutan elektrisk nerve stimulering (TENS) været anvendt som smertelindrende metode under fødslen, selvom det ikke benyttes rutinemæssigt. Blandt årsagerne ligger den foretrukne brug af anæstesi bag (f.eks. epidural) samt uklarheder i litteraturstudier, der ikke kan påvise en effekt af TENS som smertelindrende metode under fødslen. Anæstesi anvendt under fødslen er forbundet med flere bivirkninger og derfor mindre tilfredshed hos de fødende, selvom det effektivt virker på fødselssmerterne. Effekten af TENS er uklart i literaturstudierne dels på grund af utilstrækkelige metodiske overvejelser, herunder randomisering, allokering og blinding. Det er heller ikke klart, hvilket stimuleringsmønster, der er optimalt i forhold til behandling af fødselssmerte, herunder frekvens, pulsmønster og pulsvarighed. Der rapporteres dog en stor tilfredshed ved brug af TENS blandt fødende, men det er uklart, om det skyldes effekten af TENS eller den fødendes kontrol ved brug af TENS, der distraherer fokusset fra angsten af fødslen og giver fornemmelsen af kontrol over smerten.

Formålet med afhandlingen var derfor at undersøge virkningen af TENS på fødselssmerter igennem tre sammenhængende studier. Først blev effekten af TENS for smertekontrol under fødslen undersøgt i et litteraturstudie og meta-analyse (studie I). Dernæst blev varierende frekvenser undersøgt for optimal smertekontrol under fødslen i et pilotforsøg (studie II). Til sidst blev der udviklet og afprøvet en ny teknik, der kombinerer TENS med tokodynamometer (TOCO) for automatiseret stimulering under veerne (studie III).

Studie I viste, at TENS havde en lille men signifikant effekt på smertereduceringen under fødslen sammenlignet med en kontrol behandling, dvs. sham-TENS, rutinemæssig pleje, ingen behandling, samt administration af oxytocin. Dette blev yderligere understøttet med en tendens af virkning af TENS på følgende udfald, herunder varigheden af fødslen, yderligere brug af smertelindringsmetoder og Apgar score, dog undtaget tilfredshed af TENS. Selvom de seneste inkluderede studier viste en forbedring af kvaliteten af forsøgsmetoder, var der stadig et stort antal studier med ikke tilstrækkelig kvalitet. Den signifikante effekt blev også påvirket af den høje heterogenitet i meta-analysen. Herved er det ikke muligt at konkludere, om effekten af TENS var reel eller påvirket af bias. Studie II viste, at varierende frekvenser fra lav-til-høj (4/100 Hz) har en tendens til at reducere smerte sammenlignet med høje frekvenser (80/100 Hz) og sham-TENS (placebo). Selvom der var en stor tilfredshed blandt de fødende, var der ikke en tilstrækkelig stor gruppe af fødende rekrutteret i studiet, som derfor påvirker validiteten af resultaterne. Studie III viste en forsøgsmodel af kombineringen af TENS-TOCO for automatiseret kontrol af fødselsrelateret smerter ved at stimulere med øget intensitet under livmoderkontraktioner og sænke tilbage til den basale stimulering mellem livmoderkontraktionerne ved brug af 4/100 Hz.

Denne afhandling præsenterede data, som indikerer en mulig effekt af TENS på fødselsrelateret smerter. Især taget i betragtning af resultaterne fra studie I med en signifikant reduceret smerteintensitet, mens der i studie II var en lille reduktion af smerteintensitet for 4/100 Hz TENS, samt en stor tilfredshed ved anvendelse af TENS blev observeret blandt fødende kvinder. Disse resultater tyder på, at TENS kan anvendes som en smertelindrende metode under fødslen, især i den latente fase. Brugen af TENS kan muligvis forbedres med introduktion af en ny teknologi, TENS-TOCO, som skal vurderes for effektivitet og sikkerhed i fremtidige kliniske undersøgelser baseret på studie III.

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Foremost, I would like to express my sincere gratitude to my company supervisor Henrik Zimmermann (MSc), Head of Medical Device Engineering, Viewcare A/S, and co-supervisor Morten Kold Mikkelsen (MSc), CTO of Viewcare A/S, for accepting and approving my industrial PhD project proposal and for your great support throughout. Especially Zimmermann has shared immense knowledge on the technical part that I always will value and appreciate.

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Kenoja Thuvarakan, December 2021

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LIST OF ABBREVIATIONS

BMI: body mass index

CTG: cardiotocography

CI: confidence interval

GRADE: the grades of recommendation, assessment, development, and evaluation

I^2: inconsistency (heterogeneity)

L1: lumbar 1 spinal nerves

NICE: National Institute of Health and Clinical Science

NI-DAQ: National Instruments data acquisition card

PI: principal investigator

PC: personal computer

PPT: pressure pain threshold

RCTs: randomized controlled trials

RR: risk ratio

S2-S4: sacral 2-4 spinal nerves

SD: standard deviation

TENS: transcutaneous electrical nerve stimulation

TOCO: tocodynamometer

T10: thoracic 10 spinal nerves

VAS: visual analogue scale

CHAPTER 1. INTRODUCTION

Labor pain is inevitably an excessive burden for the parturients during childbirth. Indeed, labor pain management is crucial for women, as unmanaged labor pain is associated with deleterious effects affecting the well-being of the parturient, fetus, and the labor progress (1). Mainly, neuraxial anesthesia (e.g., epidural) has progressively been used to block the spinal transmission of labor pain stimuli to the brain (2). Even though neuraxial anesthesia is associated with reduced labor pain, several women report lower satisfaction with the use (3). This is mainly linked to several side effects and cascade of interventions complicating the childbirth experience (2). Therefore, the need for alternative non-pharmacological pain management is highly coveted to manage labor pain effectively (4).

Transcutaneous electrical nerve stimulation (TENS), a non-invasive and non-pharmacological electrophysical modality, has been used for labor pain management since the late 1970s (5). Even though the parturients reported high satisfaction using self-controlled TENS, it has not been routinely used in intrapartum care due to uncertain evidence, including systematic reviews reporting no evidence of clinical efficacy of TENS in labor pain. This led to the National Institute of Health and Clinical Science (NICE) guideline not recommending TENS for women in labor (6–9). Furthermore, the efficacy of TENS in labor is unclear due to a lack of methodological considerations in the available studies of TENS, including randomization, allocation concealment, and blinding. Likewise, it is unclear what frequency, pulse pattern, and pulse duration are optimal for labor pain management. The eventual data showed a tendency to reduce labor pain scores. In the end, it is unclear if it is due to the antinociceptive mechanism of TENS or the self-controlled use of TENS, providing a distraction from the anxiety of labor and enhancing the sense of self-control for the women in labor (6).

The present thesis focused on investigating TENS for labor pain control and developing novel technology to empower the use of TENS for labor pain management in intrapartum care by testing an automated solution of TENS combined with a tocodynamometer (TOCO). Nevertheless, introducing the TENS-TOCO combination might offer a groundbreaking therapy to achieve better quality and quantity of intrapartum pain relief.

CHAPTER 2. STATE-OF-THE-ART

2.1. LABOR PAIN

Labor is a physiologic process defined by the birth of a fetus from the uterus to the outside world. Three stages categorize the process of labor based on clinical observations by Friedman in the 1950s (10). The first stage of labor is characterized by the beginning of labor until complete cervical dilation, while the second stage continues from complete cervical dilation until delivery of the child, and lastly, the third stage is the delivery of the placenta. The first stage of labor is further divided into three phases: latent, active, and transition phases. In the latent phase of labor (up to 3-4 cm dilation), the women experience mild low-frequent uterine contractions, while the active phase (from 4-8 cm dilation) is characterized by faster and more intense contractions, which last longer and are more painful. In the end, during the transition phase (8-10 cm dilation), the uterine contractions again get more intense, frequent, and painful (11).

Bonica defined acute pain as "a *constellation of unpleasant sensory, perceptual, emotional and mental experiences with associated autonomic, psychological and behavioral responses, provoked by injury, potential injury, or acute disease*" (12). Labor pain, also known as obstetric pain, is acute pain, resulting from a unique, complex, and considerable personal significance of various physiologic and psychosocial factors on a parturient's individual interpretation of labor stimuli, and therefore different from other pathological pain conditions (13,14).

Bonica observed that 65% of laboring parturients had moderate to severe pain (14). Melzack using the McGill pain questionnaire confirmed this observation with more than 65% of women of mixed parity rated labor pain as severe or very severe. Furthermore, primiparous women tend to rate their labor pain as painful to digit amputation (14,15).

In addition to parity, other physical factors affecting the severity and duration of labor pain include maternal age, history of previous pain or dysmenorrhea, maternal fatigue, size and position of the fetus, and size and condition of the birth canal. Typically, older nulliparous women experience prolonged labor that is more painful compared to younger nulliparous women. The increased size and abnormal position of the fetus are associated with increased labor pain. Further, the cervixes of multiparous women soften earlier at the onset of labor compared to nulliparous women (16). Psychological factors, such as anxiety, stress, previous and present experiences, motivation (prepared childbirth training), education, and cultural factors, also affect the women's coping ability of labor pain (15–17).

The high inter-individual variability between the parturients is also reflected in the spatial distribution of the pain (18). For example, Melzack showed 75% of the parturients experienced episodes of low back pain while 33% experienced continuous low back pain (19). The former result was later confirmed in another study (20). Further, some women experience abdominal pain during uterine contractions, while others experience widespread and diffuse or specific and localized pain (1).

Although the mechanism of pain during labor is yet not known precisely, based on clinical observations, it is deduced that pain correlates with increasing frequency and duration of the uterine contractions and greater cervical dilation, characterized by tissue distension, stretching, and tearing (18,21–23). Especially during each uterine contraction, blood vessels in the uterine wall are compressed, causing ischemia of the myometrium, leading to cellular breakdown and release of 'pain-producing substances (e.g., bradykinin, histamine, serotonin, acetylcholine, and potassium ions) that activate nociceptors (24,25).

Eventually, two components describe the pain mechanism during labor: visceral pain involving nociceptive afferents innervating the endocervix and the lower segments passing via the uterine, pelvic, and hypogastric plexuses in the sympathetic nerves to the spinal cord at thoracic 10 (T10) to lumbar 1 (L1) spinal nerves; while somatic pain arrives from afferents innervating the vaginal surface of the cervix, perineum, and vagina of the pelvic floor through sacral 2-4 (S2-S4) spinal nerves. Visceral pain predominates in the early first stage, usually via small-diameter type IV unmyelinated C fibers, traveling at 0.5-2 m/s, and the second stage of labor. Somatic pain arises in the late first stage and second stage of labor via pudendal nerve fibers of small-diameter type III myelinated Aδ fibers traveling at 10-40 m/s (21,22,24,26).

These fibers terminate primarily in the substantia gelatinosa (laminae II) of the dorsal horn, where they are processed and transmitted via the spinothalamic tract to the thalamus and further to the somatosensory cortex to analyze the spatial and temporal distribution to create sharp, intense, and localized pain (Aδ fibers) followed by dull, aching, and spreading pain (C fibers). The transmission also collaterals to the hypothalamus and limbic system to elicit autonomic and emotional responses associated with pain, respectively. Further, the transmission through the spinoreticular tract to the reticular formation facilitates motor, autonomic, and sensory functions related to pain perception. Eventually, there is no single 'pain center' but a matrix of cerebral structures that process noxious information from different dimensions. Another essential aspect includes modulation of the nociceptive impulse in substantia gelationosa through activation of several complex inhibitory systems at the supraspinal level (25,27). Later in subsubsection 2.3.1, one well-known descending inhibitory system will be addressed.

2.2. CONCERNS ASSOCIATED WITH NEURAXIAL ANESTHESIA

It is undeniable that unmanaged labor pain is associated with deleterious effects of the parturient, fetus, and the labor progress. Potential consequences include maternal hyperventilation resulting in hypocarbia and respiratory alkalosis, while maternal stress comprises a cascade of the release of catecholamines and cortisol, which causes increased peripheral vascular resistance, and further decreased placental perfusion. Both effects lead to reduced oxygen to the fetus and fetal metabolic acidosis. It is, therefore, crucial to manage labor pain properly (1,21,22,28).

Nowadays, several methods are available to relieve labor pain, including pharmacological pain management (e.g., epidural, spinal, combined spinal-epidural, and inhaled analgesia, opioids, and non-opioid drugs), and non-pharmacological pain management (e.g., hot bath, breathing techniques, intracutaneous sterile water injection, massage, acupuncture, and TENS) (2,29).

Predominantly, neuraxial anesthesia has been progressively used especially epidural anesthesia. Epidural is considered the gold standard for labor pain management (30). In a cross-sectional study from 2020, epidural anesthesia was administered in nulliparous parturients in 79% of the cases in the United States, 40% in Denmark, and 19% in England (31).

A Cochrane review evaluated labor pain management, and the authors suggested that neuraxial and inhaled analgesia effectively manage labor pain but equivalently give rise to adverse effects (2). Pharmacological pain management in labor modifies the outcome of the childbirth, including higher chances of instrumental vaginal delivery and elevated labor duration, significantly complicating the labor situation for high-risk pregnancies (32). Compared to other forms of intrapartum analgesia, epidural use is associated with fetal distress, maternal fever, maternal hypotension, maternal motor blocks (hindering leg movement), and maternal urine retention (2,32). In addition, the use of epidural analgesia during labor may result in a cascade of other interventions, including intermittent or continuous monitoring of the laboring woman and fetus, parental administration of fluids, oxytocin administration, and risk of instrumental vaginal delivery (2,32).

Even though the use of epidural is associated with analgesic satisfaction of 88% of cases, parturients who underwent epidural procedures have reported lower satisfaction with their childbirth experience despite lower pain intensity (3,33). This may suggest insufficient information on adverse events associated with the use of epidural (34).

Despite the many advances, little has emerged in understanding labor pain. Parturients primarily receive neuraxial anesthesia to block the spinal transmission of pain-related afferents. Considering the limited satisfaction of neuraxial anesthesia, alternative approaches are needed to achieve a better quality of intrapartum pain relief (14).

2.3. TENS FOR LABOR PAIN MANAGEMENT

Even though electroanalgesia was discovered in the archives of ancient Egypt, c. 2500 BC, with stone carvings of electric fish used to treat ailments, actual attention was generated after introducing the Gate control theory in 1965 (27). This reawakened clinical interest in treating acute and chronic pain and opened several new opportunities for therapy, including TENS (35,36). Long et al. (1974) used TENS as a stand-alone treatment for different pain conditions, including chronic pain, postoperative pain, and cancer pain (27,35). Later, Augustinsson et al. (1977) reported the use of TENS in labor pain (27,37).

TENS has been used in intrapartum care since the 1970s, prominently in Scandinavia, the United Kingdom, and parts of Canada (5,38). TENS is a non-invasive and electro-physical modality used extensively to reduce pain and hyperalgesia by cutaneous application of low-intensity electrical current (39–41). In addition, it is an inexpensive, easy-applicable, and safe tool to produce analgesic effects with limited potential for inducing toxicity or overdose (42). Further, the use of TENS has been associated with shorter first and second labor stages, higher rates of spontaneous delivery, and delayed and reduced use of pharmacological analgesia (28,43).

When the Danish Association of Midwives was inquired in August 2017 about the current use of TENS in labor pain, most of the chief midwives from all hospitals in Denmark reported that they did not use TENS at all or had only used it a few times. Hospitals reporting regular use included Aalborg University Hospital, Hvidovre Hospital, and Randers Regional Hospital (44). This indicates limited use of TENS in Denmark, even though research has shown the possible benefits of using TENS to reduce labor pain. The limited use is most likely caused by a lack of knowledge about the efficacy and effectiveness of TENS (45). This is not limited to Denmark only; the use of TENS is not supported by the NICE guideline (7).

Even though TENS is non-invasive and considered safe, its clinical efficacy in labor pain is unclear due to limited high-quality evidence, including randomization, placebo control, and blinding in current available studies (2,6,40). A Cochrane Review about TENS in labor pain management evaluated 17 randomized controlled studies (n=1466). It demonstrated that women using TENS had a very small difference in pain ratings between TENS and control (sham-TENS) groups. However, women receiving TENS were less likely to report severe pain (6). The authors of the review concluded that there is some evidence of the efficacy of TENS in labor pain. Still, the evidence is neither solid nor consistent due to limited available high-quality studies (6). Similar conclusions were also consistent in other reviews evaluating the use of TENS in labor pain (8,9).

Meantime, TENS is well received by the women as they sense of self-control during labor as the women are provided with a controller to change the pattern of stimulation.

Thereby, it remains controversial if the satisfaction of TENS is associated with the efficacy of stimulation in labor pain or with the reduction of anxiety by providing distraction and thereby increasing the women's sense of control (6,46).

2.3.1. MECHANISMS OF ANTINOCICEPTIVE EFFECTS

The antinociceptive mechanisms behind TENS are not clearly known. However, mainly two fundamental theories are proposed.

2.3.1.1 Gate control theory

As mentioned in subchapter 2.1, one modulation mechanism occurring at the level of substantia gelatinosa in the spinal cord explains the Gate control theory. Melzack and Wall proposed this groundbreaking theory in 1965, prompting the use of electroanalgesia for acute and chronic pain conditions. The theory explains two pathways: one pain-mediating ('gate open') pathway, while the other is a pain-relieving ('gate close') pathway. The pain mediating pathway is the system where activation of pain-mediating afferents (i.e., C and Aδ fibers) are transmitted to substantia gelatinosa. The fibers lead to the firing of the projection neuron, while the inhibitory neuron is inhibited indirectly by this activity. As a result of this, the pain gate is open, and the brain perceives pain. The pain-relieving pathway is activated by stimulating low-threshold large-diameter group II myelinated Aβ afferents (traveling with a velocity of 33-75 m/s) by electrical or mechanical stimulation that triggers the inhibitory neuron, which eventually inhibits the function of the projection neuron to fire, and the gate transmission of C and Aδ fibers close. Ultimately, these pathways lead to less pain perception to the brain (27,47–49) (see Figure 2-1). In 1967, Wall and Sweet confirmed this by stimulating Aβ fibers using needles inserted through the skin to deliver high-frequency, non-painful electrical currents percutaneously. As a result, they found that patients reported relief from their chronic neurogenic pain (27,50).

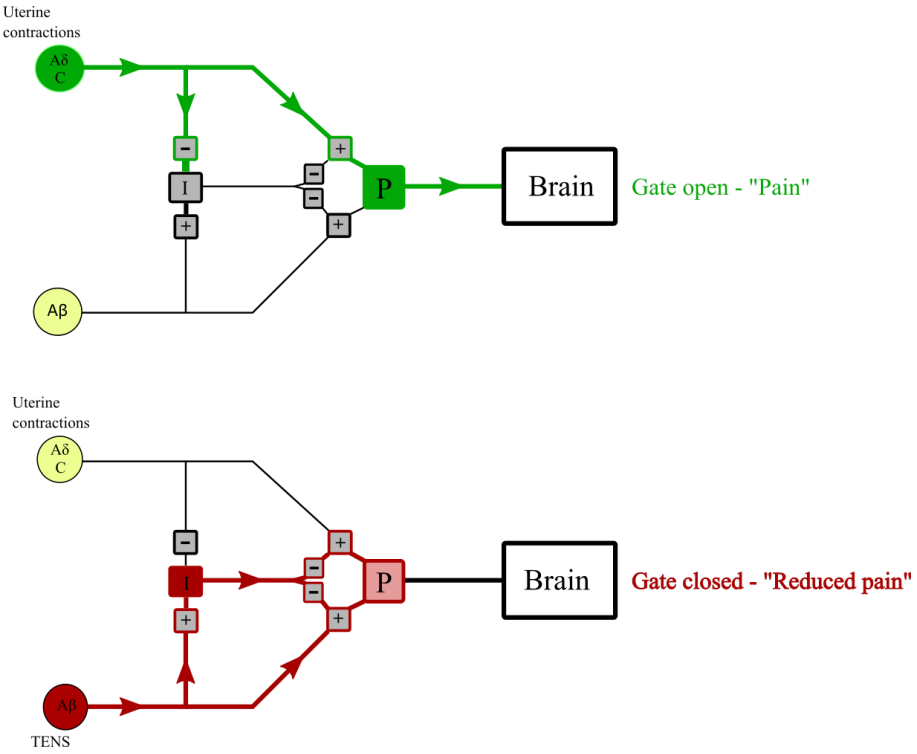

Figure 2-1. The gate control theory illustrated in two diagrams. On top, the diagram shows the activation of Aδ and C fibers through uterine contractions, leading to inhibition of the inhibitory neuron (I) and activation of the projection neuron (P), causing the gate to open to sense pain. At the bottom, the activation of Aβ fibers by transcutaneous electrical nerve stimulation (TENS) leads to activation of the inhibitory neuron and thereby inhibition of the projection neuron. Finally, the gate closes, and reduced pain will be sensed. Adapted from Melzack & Wall (1965) (47).

2.3.1.2 Endogenous opioid theory

It is also suggested that the endogenous opioid system, including μ-opioids and δ-opioids, mediate pain relief. The endogenous ligands involved in analgesic actions of TENS include norepinephrine, gamma-aminobutyric acid (GABA), and serotonin through activation of the descending inhibitory pathways in response to afferent activity in the Aδ fibers (49,51–53).

Through animal studies, Kalra et al. (2001) found that low-frequency TENS activates μ-opioid receptors and high-frequency TENS activates δ-opioid receptors (40,54). Confirming these results, Sluka et al. (1999) blocked μ-opioid receptors using naloxone. They found a significantly reduced antihyperalgesic effect of low-

frequency TENS, while the effect of high-frequency was reduced by blocking δ-opioid receptors in arthritic rats (55). Though, these facts were already revealed in Han et al.'s study (1991) (56).

2.3.2. TENS TECHNIQUES AND THEIR PARAMETERS

The basic biophysical mechanism of TENS involves the electric current of TENS flowing out of the cathode with negatively charged electrons. These electrons excite the axonal membrane, causing depolarization of the axonal membrane, leading to an action potential that changes the negative electrons to positive. These positively charged current flows towards the anode, causing hyperpolarization and blocking nerve transmission (27,49). The cutaneous application of electrodes can stimulate nerves within about four centimeters below the skin's surface (57).

Despite several years of research of TENS for pain relief, there is still no agreement on selecting TENS parameters for therapeutic applications, including intensity, frequency, pulse duration and pattern, and electrode placement within the literature (52).

However, a set of standard parameter combinations referred to as "TENS modes" have been introduced (52). These modes include conventional TENS (high frequency, low intensity), acupuncture-like TENS (AL-TENS) (low frequency, high intensity), and intense TENS (high frequency, high intensity) (27,52,58,59). Conventional TENS is traditionally associated with the Gate control theory with blocked nociception at the spinal level. Therefore, the electrodes should be placed within the same dermatomal segment, around the area of the pain (52). AL-TENS is associated with endogenous opiates, and electrodes should be placed on motor, trigger, or acupuncture points or in distant and contralateral areas to achieve effective stimulation (52). Both conventional and AL-TENS excite Aβ fibers (60). Intense TENS stimulates the small-diameter high threshold cutaneous Aδ afferents by blocking the transmission of nociception of the peripheral nerves and electrodes are ideally placed on the remote body site (58,61).

2.3.2.1 Intensity

One of the critical parameters in TENS outcome is the intensity, also known as pulse amplitude (62). Intensity refers to the magnitude of current, measured in milliampere (mA), that activates the nerve axon (27). Previous studies have shown that the degree of analgesia correlates with the intensity of TENS stimulation (63). Indeed, intensity should constantly be adjusted during treatment to achieve the optimal analgesic effect

(63). For labor pain, several studies have been using individually adjusted intensity preferred between sensory detection and pain threshold (39,64–66).

2.3.2.2 Frequency

Frequency is the number of pulses per second (pps) during stimulation and is measured in units of hertz (Hz) (67). As already mentioned, frequency is usually separated into low (< 10 Hz) and high frequencies (> 50 Hz). However, Chen and Han's study (1992) showed that alternating frequency would mediate the differential release of met-enkephalin and dynorphins (endogenous opioids) in the spinal cord as low and high frequencies produce analgesia through two separate mechanisms (68–70). One recent study used alternating frequencies that showed better pain relief compared to high frequency (64).

2.3.2.3 Pulse duration

Pulse duration is the period of a single pulse and is usually classified into short (< 200 μs) and long durations (> 200 μs). It is not clear if a varying pulse duration affects the degree of hypoalgesia (49). Gopalkrishnan and Sluka (2000) showed that pulse duration does not affect the degree of hypoalgesia in rats produced by high-frequency TENS (71). No studies have investigated the effect of pulse duration for TENS in labor pain.

2.3.2.4 Pulse pattern

Tonic and burst modes are commonly used pulse patterns in TENS. Tonic stimulation is a consistent stimulation of one set of frequency, pulse duration, and amplitude. On the other side, burst stimulation is a novel stimulation developed to mimic the firing of the thalamic cells, as they fire both in tonic and burst modes (72). Burst patterns consist of trains of pulses with different settings, including one carrier frequency and one internal frequency, e.g., a high-frequency current applied at a much lower frequency, for instance, 100 Hz with a burst frequency of 2 Hz (27,73). Several recent studies have been using the latter example (74–76).

2.3.2.5 Waveform

A waveform is the shape of one cycle of current flow and is represented by plotting amplitude against time, as shown in Figure 2-2. TENS currents flow in single polarity (monophasic pattern) or anode and cathode polarity in each wave phase (biphasic pattern). Biphasic waveforms are primarily used in TENS devices as monophasic waveforms may cause reactions in the underlying tissue of the electrode as an accumulation of ions could result in polar concentration (27). A study reported that the subjects preferred the symmetrical biphasic waveform to the asymmetrical biphasic waveform for neuromuscular electrical stimulation (49,77). In addition, a conference abstract showed that biphasic symmetrical TENS might produce better clinical results than monophasic in cold-induced pain (78). Therefore, the symmetrical biphasic waveform is suggested compared to asymmetrical, as the latter acts more like a monophasic waveform (27).

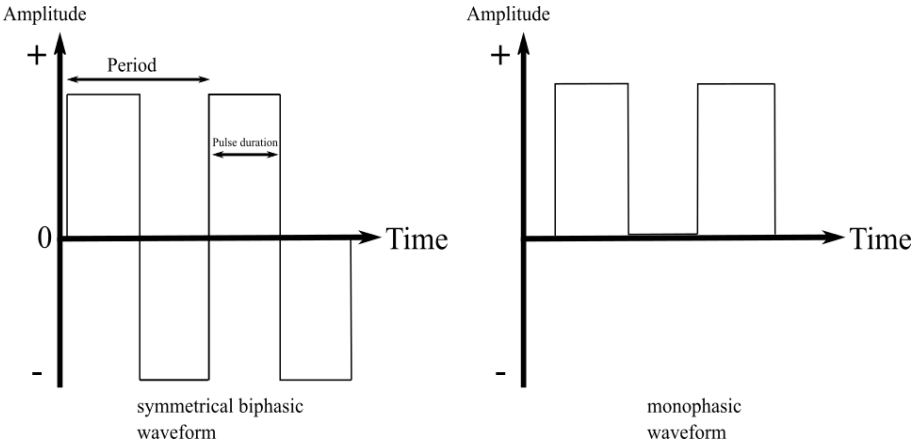

Figure 2-2. Diagrams of symmetrical biphasic and monophasic waveforms. The period (one cycle) and pulse duration are indicated in the left diagram. Frequency is calculated as seconds per period. Adapted from Johnson (2014) (27).

2.3.2.6 Electrode placement

Another critical factor in TENS outcome is the stimulation site, as it is suggested that ineffective electrode placement may cause negative findings (62,79). TENS is considered most successful when the electrodes are applied close to the site of pain, such as directly over the painful area or over the main nerve bundle arising from the painful site (80). However, it is also claimed that TENS is successful when applied distant to the pain, such as spinal nerve roots (paravertebrally), contralateral,

myotomal placement over muscles, acupuncture points, and transcranially (80). Conversely, studies also show that distant and contralateral positions are ineffective (80,81).

Classically, two pairs of electrodes are placed at T10-L1 and S2-S4 spinal segments for labor pain management as these segments are involved in mediating pain in the first and second stages, respectively (37).

Table 2-1. Summary table of standard TENS parameters used for labor pain management

CHARACTERISTIC	COMMON SPECIFICATIONS
Intensity	Individually adjusted
Frequency	Low (< 10 Hz), high (> 50 Hz), or alternating
Pulse duration	Long (> 200 μs) or short (< 200 μs)
Pulse pattern	Tonic or burst
Waveform	Symmetrical biphasic
Electrode placement	T10-L1 and S2-S4 (spinal level)

2.3.2.7 Sham-TENS

The use of an adequate authentic placebo in TENS studies, providing sufficient blinding of the parturient and investigator, has been a core problem in the previous studies (82). Several studies used inactive devices either turned off or emitting light and sound like active devices (17,64,83–89). This method limits the blinding of the parturient and investigator, leading to expectation, investigator, and observer bias (90). A few studies used an active sham-TENS, stimulating below 5 mA (73,74).

2.3.2.8 Safety aspects of TENS

In the literature, there are no reports of serious adverse events caused by the use of TENS (17,27,64,87,88,91–93). Generally, TENS are considered a safe modality if the precautions and extra cautions are followed according to ACPWH (Association of Chartered Physiotherapists in Women's Health) (94). Precautions include pacemaker

and other electric implants, an allergic response to electrodes, and use of other fetal monitoring systems as electrical interferences have been reported. Extra cautions include epilepsy and irritable uterus (94).

The research about teratogenic and effects on fetal heart conduction has not been evolving in the last few decades (94). Bundsen et al. (1982) evaluated the fetal heart rate patterns when using TENS and showed no differences between the basal heart rate and decelerations even if the intensity was up to 30-40 mA (95). In precaution for fetal heart conduction, keeping the current density low is recommended (94). Though, the current density is most likely less by the time it reaches the uterus as a result of dispersal within the conducting tissues (94).

Acupuncture points San Yin Jiao (SP6) and He Gu (LI4) have been associated with the induction of uterine contraction. However, as the evidence of these techniques is limited, it is inconclusive (94). However, several studies have used these acupuncture points with no reports of side effects or induction of contractions (73–75,96).

Commonly reported side effects are due to the electrodes, including skin irritation and redness. Though, currently available electrodes are biocompatibility safe, and side effects reported are minimal (61).

2.4. UTERINE ACTIVITY MONITORING

In intrapartum care, when the parturient is associated with prenatal or antenatal risk factors, she will be monitored with conventional cardiotocography (CTG) intermittently or continuously dependent on the list of risk factors (e.g., diabetes mellitus is monitored intermittently, while polyhydramnios is continually monitored). External CTG is a non-invasive electronic fetal monitoring system consisting of a Doppler ultrasound transducer measuring the fetal heart rate and a pressure transducer, tocodynamometer, measuring the uterine contractions (97,98).

The tocodynamometer, TOCO, is placed on the anterior abdominal wall over the fundus of the uterus by a stretchy elastic band to indirectly record the pressure wave of the uterine contractions based on changes in the shape and tone of the anterior abdominal wall. With this, the pressure wave does not reflect the strength of the uterine contractions. In addition, the changes in positions may influence the abdominal wall's shape and tone, and therefore the recording does not always represent uterine activity (10,97).

The combination of TOCO with other technology in an automated loop has been less investigated. Thus, an automatic infusion system combined with TOCO for labor induction in a closed-loop was proposed by Arulkumaran et al. (1986) (99).

The system of combining TENS with TOCO in an automated open-loop to control the duration and intensity of the stimulation during and between uterine contractions has not been reported in the literature ahead.

2.5. SUMMARY OF STATE-OF-THE-ART

Even though the parturients experience labor pain reduction while using epidural, which is considered the gold standard for labor pain management, they are not satisfied as they experience several side effects associated with the use. Therefore, an alternative approach without side effects is needed. TENS is a non-pharmacological modality used for labor pain relief. Parturients are highly satisfied with TENS, but no systematic reviews report TENS' clinical efficacy. This is mainly due to the lack of methodological considerations of included studies in the reviews. It is also unclear what frequency, pulse patterns, or pulse duration are optimal for labor pain management. The effect of TENS is uncertain, while the use of TENS has been limited. Hence, a new approach combining TENS with TOCO for automated and optimal pain relief during uterine contractions is proposed.

CHAPTER 3. OBJECTIVES OF THE PHD PROJECT

Although the investigation of the use of TENS for labor pain has been noticeable in the previous literature, there is still some lack of knowledge in the methodological and technical aspects. Moreover, it has not been evolving for the last few decades. Even the latest systematic reviews evaluating the efficacy of TENS in labor pain were published back in 2011 (6,8). Several studies have investigated stimulation parameters in other pain conditions (39,100–102), while only a few have investigated the TENS parameters in labor pain (64).

Therefore, the overall objective of this PhD project was to explore new aspects of the use of TENS for labor pain management in methodological and technical aspects. The objective can subsequently be divided into three aims and corresponding hypotheses.

Study I

Aim: To investigate the current evidence of efficacy and safety of TENS in labor pain through a systematic review and meta-analysis.

Hypothesis:

a) It is anticipated that the current evidence with the latest available data of RCT studies will show a significant effect of TENS on labor pain reduction compared to sham-TENS, routine care, no treatment, and oxytocin administration.
b) It is expected that the use of TENS will result in a decreased duration of labor, reduced use of analgesics, higher maternal satisfaction, and no changes in Apgar scores.

The study has resulted in the following publication (Paper 1) (103): Thuvarakan K, Zimmermann H, Mikkelsen MK, Gazerani P. Transcutaneous electrical nerve stimulation as a pain-relieving approach in labor pain: a systematic review and meta-analysis of randomized controlled trials. Published in: Neuromodulation. 2020 Aug; 23(6):732:746. doi: 10.1111/ner.13221. Epub 2020 Jul 21.

Study II

Aim: To explore the effective alternating frequencies of TENS in labor pain through a randomized sham-controlled pilot study.

Hypothesis:

a) It is proposed that either or both low (4/100 Hz) and high (80/100 Hz) varying frequencies lead to better pain relief than sham-TENS (placebo), measured in lower visual analog scale (VAS) and higher mean pressure pain threshold (PPT) in parturients.
b) It is anticipated that increased maternal satisfaction and reduced use of supplemental analgesics will be observed for parturients using TENS compared to sham-TENS. Further, no Apgar scores and mode of delivery changes are observed in any groups.

The study has resulted in the following manuscript (Paper 2) (104): Thuvarakan K, Zimmermann H, Hammer A, Lorentzen IP, Jensen W, Gazerani P. Investigation of varying frequencies of transcutaneous electrical nerve stimulation for labor pain control: a randomized double-blinded sham-controlled pilot study. Submitted to: Danish Journal of Obstetrics and Gynaecology (under review).

Study III

Aim: To develop a technique combining TENS with TOCO for automated TENS stimulation for labor pain control through a randomized sham-controlled feasibility study.

Hypothesis:

a) The selected set of varying frequencies (based on the outcome from hypothesis a in Study II) will lead to better pain relief for women in labor using TENS with TOCO (increased current intensity of 30-40%) compared to sham-TENS, measured in lower VAS and higher mean PPT in parturients.
b) It is anticipated that increased maternal satisfaction and reduced use of analgesics will be observed for parturients using the TENS-TOCO combination compared to sham-TENS. Further, no Apgar scores and mode of delivery changes are observed in any groups.

The study has resulted in the following manuscript (Paper 3) (105): Thuvarakan K, Zimmermann H, Hammer A, Lorentzen IP, Jensen W, Gazerani P. A novel technique combining transcutaneous electrical nerve stimulation with external

tocography for automated personalized labor pain control: a feasibility study. Submitted to: Journal of Obstetrics and Gynaecology (under review).

Finally, it was also aimed to evaluate the feasibility of the protocol implementation at the labor ward in Gødstrup Hospital (Study II and Study III). In addition, it was aimed to identify and address practical issues for the study investigator, health professionals, and parturients.

CHAPTER 4. METHODS

4.1. STUDY DESIGNS

The PhD project aimed to explore new aspects of the use of TENS for labor pain management, both in methodological and technical aspects. Therefore, three fundamental studies were designed as a coherent pathway to reach the thesis's objective (see Figure 4-1). First, a systematic review and meta-analysis were conducted to investigate the current evidence of the efficacy of TENS in labor pain (Study I / Paper 1). Second, a randomized sham-controlled pilot study was conducted to investigate the optimal frequency for labor pain relief (Study II / Paper 2). Third, another randomized sham-controlled feasibility study was conducted to examine if an automated increased stimulation during uterine contraction is an optimal solution compared to sham-TENS (Study III / Paper 3).

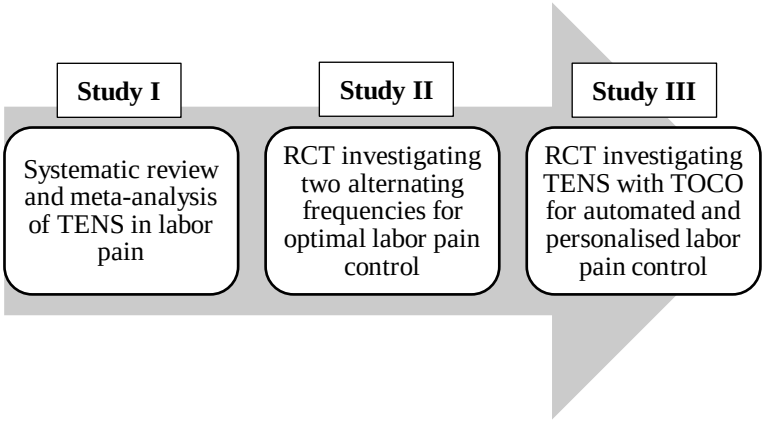

Figure 4-1. Overview of the coherent research design of each study.

4.2. METHODS OF STUDY I

Study I consisted of a comprehensive systematic review and meta-analysis followed the PRISMA checklist (106) and Cochrane guidelines (90).

4.2.1. THE SEARCH STRATEGY

A research question was formulated according to the PICO model (population, intervention, control, and outcomes) for a systematic search (107): 'Is TENS more effective than sham-TENS, no treatment, routine care, oxytocin administration, and other non-pharmacological treatment for labor pain control in women?' Based on this question, the PICO model emphasized the search strategy (see Table 4-1).

Table 4-1. PICO model for search strategy

PICO MODEL	ELEMENTS	SEARCH KEYWORDS
POPULATION	▪ Laboring women ▪ Parturient	▪ Labor ▪ Labor pain ▪ Parturition ▪ Childbirth ▪ Obstetric delivery
INTERVENTION	▪ Transcutaneous electrical nerve stimulation (TENS) ▪ Electrostimulation ▪ Electric therapy	▪ Transcutaneous electrical nerve stimulation (TENS)
COMPARATOR	▪ Sham-TENS ▪ Routine care ▪ No treatment ▪ Non-pharmacological treatment ▪ Oxytocin	
OUTCOMES	▪ Pain relief (i.e., VAS) ▪ Duration of labor ▪ Analgesic requirements ▪ Apgar scores ▪ Satisfaction of TENS	

The search strategy was further narrowed with eligibility criteria including studies about TENS for women in labor, randomized controlled trials (RCTs) comparing

TENS with sham-TENS, no treatment, routine care or other non-pharmacological treatments, English and Danish literature, and full-text papers were included.

The selected information sources were PubMed, Embase, Cochrane Library, and Web of Science. For identification of studies, the following headings were chosen to include numerous studies, including MeSH (Medical Subject Headings) terms in PubMed and Cochrane Library, EMTREE (Embase Medical Subject Heading) terms in Embase. Further, the text words were searched in all databases, restricted to papers in the English language was conducted in Web of Science. The keywords were entered in different syllables, including Britain and American English, and combined using the Boolean operators AND and OR. In Figure 1 in Paper 1, a PRISMA flowchart showed the process from identifying papers to screening and selection based on the eligibility criteria. The selected articles were described with a summary in Table 1 in Paper 1 (103).

4.2.2. OUTCOMES

Several outcomes were selected to investigate the studies' efficacy, safety, and quality, including primary, secondary, and quality outcomes as specified in Table 4-2. Further, in Table 2 in Paper 1, a comprehensive overview of the primary and secondary outcomes of the included studies is shown, while quality outcomes were reported in Table 3 in Paper 1.

Table 4-2. Overview of the outcomes investigated in the systematic review

Primary outcome
• Pain relief (e.g., VAS)
Secondary outcomes
• Duration of labor (min.) • Analgesic requirements • Apgar scores (1st and 5th min.) • Satisfaction of using TENS
Quality outcomes
• Randomization • Allocation concealment • Blinding • GRADE

4.2.3. STATISTICAL ANALYSIS AND QUALITY ASSESSMENT

A meta-analysis was conducted as a statistical approach to bring results from multiple studies together. For this purpose, a fixed-effects model (Mantel-Haenszel method) was applied to estimate risk ratio (RR), calculated with 95% confidence intervals (CI). A statistically significant difference from control was assumed when the 95% CI of RR did not include 1 (108). The analysis was performed using Review Manager (RevMan), version 5.3, 2014 (109).

A χ^2-based test of heterogeneity developed by Julian Higgins was performed to determine inconsistency (I^2) across studies. Based on his suggestions, the interpretation of I^2 can be described in percentages (see Table 4-3) (110):

Table 4-3. Overview presenting the heterogeneity (I^2) percentages and the corresponding descriptions.

I^2	DESCRIPTION
0 - 40%	considered less important
30 - 60%	represent moderate heterogeneity
50 - 90%	might represent substantial heterogeneity
75 - 100%	suggest strong heterogeneity

Data, including the degree of pain relief (e.g., VAS), additional analgesia, and satisfaction of TENS, were all included for statistical analysis as shown in forest plots (Figures 2, 3, and 4 in Paper 1) (103).

The Cochrane Risk of Bias Tool for RCTs using GRADE (the Grades of Recommendation, Assessment, Development, and Evaluation Working Group) was followed to assess the quality and certainty of evidence in the included studies (90). The quality level of the body of evidence is graded into four levels (see Table 4-4).

Table 4-4. Overview of the GRADE levels

GRADE	DEFINITIONS
+	very low
++	low
+++	moderate
++++	high

The quality of evidence was converted into GRADE based on the following five factors:

1. *Limitations of the study design (risk of bias)*: one downgrade if the description of methods or data were presented inadequate for either 1) randomization or allocation concealment, 2) blinding (participant/clinical staff/outcome assessor), 3) outcome data.
2. *Inconsistency of results*: one downgrade if the effect estimates were different between the groups (heterogeneity or variability), e.g., differences in sample size in each treatment group.
3. *Indirectness of evidence*: one downgrade if, e.g., inadequate selection of the population, intervention, comparator, or outcomes.
4. *Imprecision of results*: one downgrade if, e.g., low sample size.
5. *Publication bias*: one downgrade if, e.g., selective reporting of outcomes.

If the quality level was considered more serious, further two levels were downgraded (90,103).

4.3. METHODS OF STUDY II AND STUDY III

Study II and Study III had similar methodological approaches. Both were designed as double-blinded randomized sham-controlled studies and were carried out in the labor ward at the Department of Obstetrics and Gynecology (formerly known as Region Hospital West Jutland). Study II was conducted over 12 weeks between September 2019 and April 2021, while for Study III, it was a period of 6 weeks from July to August 2021. The Danish Committee System on Health Research Ethics, Capital Region of Denmark, approved the studies with H-19025662. Further, the studies were registered at ClinicalTrials.gov with NCT04894539 (Study II) and NCT04946838

(Study III) and were conducted according to the Declaration of Helsinki well as the CONSORT guidelines.

4.3.1. SCREENING

For the screening and selection of parturients, the principal investigator (PI, KT) contacted a midwife at the labor ward regarding potential candidates for recruitment. The midwife and PI screened the list of admitted women in labor based on the inclusion and exclusion criteria. Then, the midwife addressed the potential woman and asked if she might be interested in using TENS. If she agreed, the PI entered the labor room and orally presented the participation information. The parturient was included in the study if the screening was successful, and she was eligible and agreed to participate.

The PI obtained the parturient's informed consent after explaining the purpose and function of TENS, randomization of groups, risks associated with the study, and the possibility of withdrawal of consent at any point during the study without affecting their obstetric care. In addition, the PI informed the participants about possible side effects, including skin redness and irritation due to electrodes, which would most likely disappear spontaneously in a few minutes to hours (104).

Table 4-5 shows an overview of the common inclusion and exclusion criteria with specific inclusion and exclusion criteria for Study II and Study III.

Table 4-5. Overview of the common and specific inclusion- and exclusion criteria for Study II and Study III.

Common inclusion criteria

- Singleton pregnant women above age 18, giving birth at Gødstrup Hospital
- Fetus in vertex presentation
- Speak, read, and understand Danish

Common exclusion criteria

- Gestational age < 37+0 and > 41+6 weeks
- Pre-gestational BMI above 40 kg/m^2
- Use of fetal scalp-electrode during experiment
- Use of pacemakers and other electronic implants
- Severe arrhythmia
- Present muscloskeletal illnesses (including myopathy and arthritis)
- Chronic pain within last 6 months (Pelvic girdle pain (PGP) to a mild degree (VAS 0-6 cm) is accepted in the experiment. Severe degree (VAS 6-10 cm) (e.g., bedridden or difficulty walking) especially within 24 hours before labor.
- Present/previous neurologic illnesses (including epilepsy, migraine, and sclerosis)
- Present medicated mental disorders (including personality disorders, bipolar, ADHD, and anxiety)
- Dermalogical disorders (including skin allergy, tattoos, or scars on the locations of electrodes)
- Use of other long-acting pain relief before the experiment (including epidural, morphine (less than 6 hours before experiment), acupunture, paracetamol (less than 8 hours before experiment), cocktail (less than 8 hours before experiment), nitrous oxide (less than one hour before experiment), sterile water injection (less than 2 hours before experiment)
- Use of TENS 48 hours before the trial
- Drug addiction defined as the use of cannabis, opioids or other drugs
- Smokers
- Lack of ability to cooperate

Specific inclusion/exclusion criteria

- *Study II exclusion / Study III inclusion*
  - High-risk pregnancies (including risk factors: pre-eclampsia, diabetes, gestational diabetes, hypertension (above 140/90, intrauterine growth restriction (IUGR), polyhydramnious, or oligohydramnious)
- *Study III inclusion:*
  - Indication for the use of CTG (external monitoring)

4.3.2. TENS INTERVENTION

4.3.2.1 Testing of varying frequencies

In Study II, three frequency patterns were investigated, including TENS1, with low-to-high varying frequencies between 4 Hz to 100 Hz, and TENS2, with high frequencies, varying between 80 Hz and 100 Hz. Sham-TENS consisted of a frequency of 100 Hz with an intensity below 5 mA. The stimulation pattern consisted of a symmetrical biphasic waveform and a sampling interval of 200 µs. Table 1 and Figure 1 in Paper 2 showed how the pattern of each stimulation was combined and programmed using MATLAB® 2019A software (Mathworks, Natwick, Massachusetts, USA) (104).

Based on the outcomes of Study II, TENS1 and sham-TENS were selected for further investigation in Study III. This coherent research design is simply illustrated in Figure 4-2.

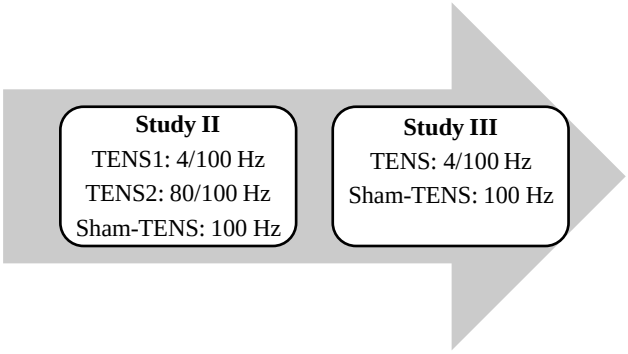

Figure 4-2. Overview of the varying frequencies used for Study II and Study III.

4.3.2.2 TENS protocol

For studies II and III, the TENS protocol was conducted similarly with minor differences. Following skin preparation by gentle rubbing with an alcohol swab (Mediq, Denmark), one set of electrodes (Valutrode® Lite rectangle electrodes (5x10 cm, Axelgaard Denmark) was applied at the S2-S4 spinal level at the lower back. The electrodes were connected to a DS5 isolated bipolar constant current stimulator (Digitimer Ltd., Hertfordshire, United Kingdom) (see Figure 2 in Paper 2) (104). This was driven by a voltage waveform generated on a data acquisition card (NI-DAQ, USB-6003, National Instruments, Austin, TX) and was controlled via custom code written in MATLAB (104,105).

In Study III, the combination of TENS and TOCO was developed and tested on parturients. Using the TOCO part of the available external CTG (SP02 fetal monitor, Sonicaid, Huntleigh Healthcare Ltd., Cardiff, United Kingdom; or STAN® monitor, Neoventa Medical, Göteborg, Sweden) at the labor ward was placed on the maternal anterior abdominal wall over the fundus uteri by a stretchy elastic band (97). The TOCO part was combined with a personal computer (PC) using a medical device galvanic isolator (USB isolator 2.0 USI-01, MESO, Mittweida, Germany) to separate the equipment electrically to protect the woman. Further, this part of the system is connected to the DS5 system through the PC. Figure 4-3 shows a block diagram of the interconnections between each technology mentioned. This whole system was also described in Figure 1 in Paper 3 for Study III (105).

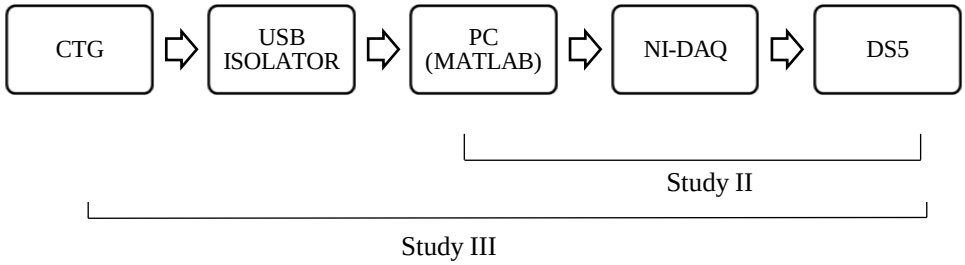

Figure 4-3. Block diagram of the open-loop system for Study II and Study III.

The TOCO registered the pressure waves created during uterine contractions, displayed with an amplitude ranging from 0% to 100%. For each pressure wave reaching above the TOCO threshold, which was set individually based on the TOCO registration between and during uterine contraction (e.g., 20%), a 'boost' function was programmed to increase the current intensity only during uterine contractions. The current intensity was multiplied by a factor (e.g., 1.3) during uterine contraction and was lowered to basic stimulation between uterine contractions. Table 1 in Paper 3 shows the values for chosen intensity threshold, the actual intensity between uterine contractions, the multiplication factor, and the intensity during uterine contractions (105).

4.3.2.3 Outcomes

In studies II and III, the primary outcomes, maternal and fetal characteristics, and satisfaction of TENS were obtained. The primary outcomes were collected three times over 30 min (baseline, 10 min, and 30 min), including pain scores evaluated on VAS (a 10-cm scale; 0 is 'no pain' and 10 is 'unimaginable level of pain') and PPT was

obtained by gradually increasing pressure (approximately 30 kPa/second) over the lower back between the spot of two electrodes until the woman pressed on the stop-button on the patient response unit when the pressure turned into pain (111,112).

Maternal and fetal characteristics were collected from screening questionnaires after childbirth using the patient journal, accessed by a midwife. The included data were maternal age, maternal BMI, cervical dilation, parity, gestational age, mode of delivery, supplemental analgesia, while fetal characteristics included Apgar scores, umbilical cord pH, and birthweight. Right after ended TENS stimulation, the parturient completed a satisfaction questionnaire. Satisfaction with TENS was rated on a scale from 0 to 10, corresponding to 0 as 'no satisfaction' and 10 as 'total satisfaction'. Further, data collection included whether the parturient would use TENS again or recommend this to others. In Figure 3 of Paper 2, an overview of the timeline of each procedure with data collection is shown (104).

4.3.3. POWER CALCULATION AND STATISTICAL ANALYSIS

The sample size was determined based on a review by Dowswell et al. (2011) by estimating the difference in the effect of the two interventions, (Δ), i.e., TENS and sham-TENS, and the standard deviations (σ), which is specified to 0.67 and 1.08 in the mentioned review, respectively (6). z_{α} is read by the table in the review to 1.96 (two-tailed) as well as $z_{(1-\beta)}$ is 0.8416 (6,113,114). The significant level was considered P<0.05 and was accepted as the significant level with a study power of 80%.

The sample size was calculated using the following formula (113):

$$n = \frac{2\left(z_{\alpha} + z_{1-\beta}\right)^2 \sigma^2}{\Delta^2} = \frac{2(1.96 + 0.8416)^2 (1.08)^2}{(0.67)^2} = 40.78$$

A drop-out rate of 10% was calculated based on the vulnerability of the group of laboring women (113). Hence, 22 subjects would be a sufficient number pr. group to determine the efficacy of TENS for labor pain control for the main clinical trial. Based on this power calculation, the selected number of subjects for the pilot study was considered to be at least 10% of the numbers (115). Therefore, it was decided to include 12 women, with 4 women pr. arm in each study (Study II and Study III).

The statistical analysis of differences between the groups was analyzed by a linear mixed model analysis, including VAS and PPT. The model had treatment (TENS1, TENS2, and sham-TENS) and timepoints (baseline, 15 min, and 30 min) as fixed factors, while a random intercept for the parturient variable was included. Analysis of groups for other outcomes included multivariate analysis of variance (MANOVA) for

continuous variables. The Fisher's Exact Test was used for categorical variables (104).

For Study III, the recruitment of parturients for the pilot study was inadequate, and therefore no statistical analysis was performed. Eventually, the evaluation of primary outcomes, maternal and fetal outcomes, and satisfaction of TENS were discarded in Study III.

4.4. SUMMARY OF METHODS

A coherent research design was considered for the three studies. First, a systematic review and meta-analysis were conducted to evaluate the efficacy of TENS for labor pain control. For this purpose, a literature search was conducted on PubMed, Embase, Cochrane Library, and Web of Science with specific criteria. After a screening, deselection, some of the outcomes from the selected papers were analyzed in a meta-analysis. In studies II and III, the materials and methods were similar with slightly different inclusion criteria. The recruitment of the parturients was conducted at the labor ward at Gødstrup Hospital. The eligible women based on the screening questionnaire were recruited. Primary outcomes measures included VAS and PPT, measured three times: baseline, 10 min, and 30 min. Primary and secondary outcomes were statistically analyzed and interpreted for Study II, but not for Study III, as included subjects were limited.

CHAPTER 5. RESULTS

5.1. KEY FINDINGS OF STUDY I

The systematic review included 26 RCTs with 3348 parturients, of which 1282 were exposed to TENS, whereas 2066 received control interventions, i.e., sham-TENS, routine care, no treatment, oxytocin administration, and other non-pharmacological treatments.

Mainly, it was aimed (aim 1) to investigate TENS' efficacy and safety based on treatment effects, including pain relief, duration of labor, supplemental analgesia, Apgar scores, and the satisfaction of TENS. Further, the quality of the studies was also of interest, based on randomization, allocation concealment, blinding, and GRADE.

First, the change in pain intensity of parturients experiencing moderate (>30%) or strong reduction in pain intensity (>50%) was investigated in a responder analysis of pooled data from 11 RCTs with 700 parturients receiving TENS and 626 parturients receiving a control treatment. The forest plot showed a small but statistically significant reduction in pain intensity with pooled RR of 1.52 (95% CI [1.35, 1.70]) in favor of TENS (see Figure 2 of Paper 1). However, the heterogeneity was significant with I^2 of 89% ($p < 0.00001$), suggesting inconsistency of included studies. However, the overall effect was significant with $Z = 7.13$ ($p < 0.00001$) (103).

Second, 22 studies reported change in the duration of labor, while most of the studies tend to show a non-significant reduction, only 7 studies showed a significant decrease in duration of labor (17,73,75,93,116–118).

Third, the use of additional analgesia was investigated in the forest plot with 10 studies of 501 women receiving TENS and 401 receiving control intervention. No significant efficacy was shown, though a tendency toward fever interventions in TENS groups was found (pooled RR of 0.96, 95% CI [0.91, 1.03]) (see Figure 3, Paper 1) (103).

Fourth, no significant differences were found between TENS and control groups for Apgar scores in the studies.

Fifth, 5 studies investigating the satisfaction of TENS were evaluated in a forest plot, with 404 women receiving TENS and 414 women receiving a control treatment. It showed a non-significant tendency of higher satisfaction using TENS (pooled RR of 1.03, 95% CI [0.90, 1.18] (see Figure 4, Paper 1) (103).

Sixth, the quality of studies was rated using GRADE. No studies reached the highest GRADE level, indicating a general poor methodological quality of studies. Most of

the studies had inadequate descriptions of the methodologies, including randomization and allocation concealment. The frequently used type of sham-TENS was inactive units (in 11 out of 13 studies), though this method is prone to bias as it is not clear if the parturient or the investigator were blinded to the treatment. Since the Cochrane review, several RCTs have been published in which 5 out of 7 studies were graded +++ on GRADE (28,64,75,117,119).

5.2. KEY FINDINGS OF STUDY II

Based on the initial screening process, 158 laboring women admitted to the labor ward during the study period were assessed for eligibility, of which only 23 women were enrolled. Subsequently, 11 women were excluded due to withdrawal of consent or missing data, and eventually, 12 women were included in Study II (see Figure 4, Paper 2) (104).

It was aimed (aim 2) to explore the effective alternating frequencies of TENS in labor pain for Study II, including low-to-high (4/100 Hz) (TENS1) and high (80/100 Hz) (TENS2) varying frequencies were compared to sham-TENS. For this purpose, the pain scores (i.e., VAS), mean PPTs, and satisfaction of TENS were evaluated.

First, no statistically significant differences were found in VAS scores or mean PPT measurements neither in treatment ($F_{(2,20)} = 2.68$, $p = 0.093$; $F_{(2,20)} = 1.33$, $p = 2.288$) nor in timepoints ($F_{(1,20)} = 0.085$, $p = 0.774$; $F_{(1,20)} = 0.149$, $p = 0.703$), respectively. Women who were exposed to TENS1, showed a reduction in VAS compared to sham-TENS with 1.9 ± 3.4 cm at 10 min and 1.0 ± 2.5 cm at 30 min. When comparing timepoints, mean difference from baseline to 10 min was shown as 1.3 ± 1.2 cm. PPT showed also a small change in sensitivity for TENS1 with a mean difference of 18.2 ± 58.7 kPa from baseline to 10 min (see Table 4 in Paper 2) (104).

Second, no substantial differences were found in Apgar scores, arterial pH, birthweight, mode of delivery, and supplemental analgesia (see Table 3, Paper 2) (104). The mode of delivery was not mentioned in Paper 2 as no major differences were found (TENS1: three spontaneous deliveries and one vacuum delivery; TENS 2: three spontaneous deliveries and cesarean delivery (pre-planned); and sham-TENS: 4 spontaneous deliveries).

Third, there were no statistically significant differences across treatment groups for satisfaction with TENS. However, satisfaction with TENS was slightly higher in the TENS1 group compared to the groups receiving TENS2 and sham-TENS, respectively (6.0 ± 1.6; 3.0 ± 2.9; 5.4 ± 4.1) ($F_{(2,20)} = 1.065$, $p = 0.384$) (see Table 5, paper 2) (104).

Half of the women (6 out of 12 women) experienced pain relief, in which 3 of these 6 women received TENS1. In addition, a significant group of the women (8 out of 12 women (67%)) were interested in using TENS for their next labor and would also recommend TENS to others (see Table 5, Paper 2) (104).

No safety issues were reported.

5.3. KEY FINDINGS OF STUDY III

Based on the initial screening process, a total of 86 laboring women admitted to the labor ward during the study period were assessed for eligibility, of which only 10 women were enrolled. Subsequently, three women were excluded due to withdrawal of consent, while four additional women were excluded due to improper TOCO registration of uterine contractions or technical problem associated with either DS5/Matlab or attachment of electrodes, leaving three women for final analysis in Study III (see Figure 2, Paper 3) (105).

It was mainly aimed (aim 3) to develop a technique combining TENS with TOCO for automated TENS stimulation for labor pain control shown with optimal pain relief using this combination by comparing TENS with sham-TENS.

The graphs of TOCO registration of three women (Figure 3, 4, 5A, and 5B in Paper 3) showed a feasible model for labor pain control by combining TOCO with TENS to achieve an automated technology controlling the duration and intensity of the stimulation during and between uterine contractions. No safety issues were reported (105).

Even though the primary outcomes, including VAS and PPTs were collected, it was not possible to conduct statistical analysis on these data due to the very low sample size. As a consequence, secondary outcomes were also discarded.

5.1. SUMMARY OF KEY FINDINGS

The summary of key findings of each aim (with responses to hypotheses in bullet points) corresponding to each study is presented in Figure 5-1.

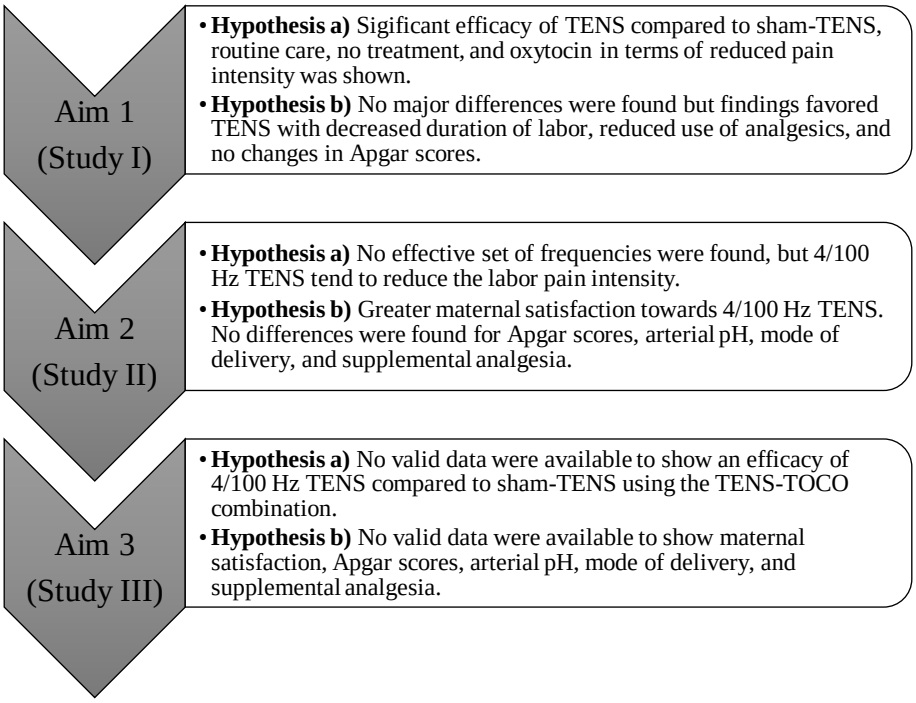

Figure 5-1. Overview of summary of main findings specified for each aim with hypotheses corresponding to each study.

CHAPTER 6. DISCUSSION AND FUTURE PERSPECTIVES

This thesis is based on three studies and their corresponding original papers. In the following sections, the main findings of the studies will be presented, then the outcomes of the systematic review and meta-analysis (Study I), the pilot study testing of varying frequencies of TENS (Study II), and the feasibility study of the open-loop system of TENS and TOCO (Study III) will be discussed. In the end, the limitations and future perspectives of the studies will be emphasized.

6.1. MAIN FINDINGS

The overall objective of this PhD project was to explore new aspects of the use of TENS for labor pain management in terms of methodological and technical aspects. For this purpose, a comprehensive systematic review and meta-analysis were conducted to evaluate TENS for labor pain management. Eventually, a significant difference in reduction of labor pain intensity using TENS was found based on a responder-analysis. The present systematic review and meta-analysis are the first study to prove TENS' significant efficacy on labor pain reduction (120). Further, the duration of labor, additional analgesia, and Apgar scores all tend to favor TENS except for the satisfaction of TENS. Based on this review, it was possible to design the methodology of Study II and Study III. The selected randomization, blinding, sham-TENS, etc., were all based on findings from Study I. Even though it was not possible to find a significant difference in the clinical efficacy of TENS in Study II, a tendency showed that low-to-high frequencies were optimal compared to high frequencies and sham-TENS. Additionally, a high level of maternal satisfaction with TENS was observed, with half of the women experiencing labor pain reduction, while 67% of the women were interested in using TENS for their next labor and recommending it to others. Based on these outcomes, a low-to-high set of frequencies were used in Study III for TENS stimulation for the automated combination of TOCO and TENS. This model showed to be feasible, but due to the small sample size, no efficacy of TENS could be shown. No safety issues were reported in Study II and Study III.

6.2. TENS

TENS has been controversial in evaluating its efficacy in several pain conditions (121). For example, Cochrane reviews evaluating TENS showed evidence that TENS reduced pain intensity compared to control treatment in acute pain (122), primary dysmenorrhea (123), while other reviews were inconclusive in terms of chronic pain (124), phantom and stump pain (125), chronic neck pain (126), neuropathic pain (127), and labor pain (6). Essentially the reason is suggested to be methodological issues in the included RCTs of the reviews, including randomization, allocation concealment, blinding, and the control treatment (6).

Study I revealed a small but significant efficacy of TENS on labor pain reduction, differentiating from the available Cochrane review evaluating TENS in labor pain (6,103). This efficacy was based on the responder analysis based on 11 studies (17,64,74,75,84,86,91,116,118,128). Mainly, it should be noted that the placement of electrodes, use of TENS parameters, duration of TENS stimulation were different in the studies. Thus, the studies were not comparable in methodological approaches, but eventually, studies explored different approaches to reduce labor pain. The use of additional analgesia is a parameter used to investigate if TENS influenced or delayed pharmacological pain management, but this was not the case in Study I, as no differences were found. Through Apgar scores, duration of labor, and mode of delivery, the safety of TENS is usually investigated. However, in Study I, Apgar scores and duration of labor were only included to restrict the paper's focus. As expected, Apgar scores and duration of labor were not affected by TENS. Moreover, all outcomes tend to be in favor of TENS treatment except for the satisfaction of TENS. The number of studies included in the meta-analysis to verify the satisfaction was limited, which might be one of the reasons (103). In Study II, the fetal and maternal outcomes, including Apgar scores, arterial pH, mode of delivery, additional analgesia, and satisfaction of TENS, were investigated. No major differences were found across the groups, suggesting that either the results tend to favor TENS or the limited sample size inhibited the findings. Satisfaction with TENS favored TENS with 4/100 Hz compared to TENS with 80/100 Hz and sham-TENS. Three of the six responders (50%) rated TENS with 4/100 Hz better pain relief. Further, 8 of the 12 women (67%) were interested in using TENS again for their next labor and were willing to recommend TENS to others (104).

As mentioned above about Cochrane reviews, the major drawbacks in the included RCTs in Study I are the methodological quality, including lack of appropriate description of the method or an inadequate selected method of randomization and blinding. The GRADE approach evaluated the quality of methods applied in the RCTs included in Study I. Even though several other grading systems exist, including the Pedro scale, GRADE provided transparent criteria to rate the certainty of the evidence and the strength of the recommendations (90). Based on the grading of the studies using GRADE, no studies reached the highest level of evidence. Most of the studies

were rated at low to moderate levels, which future studies are recommended to improve. Only 35% (9/26) of the included studies reported an adequate randomization method, while 12% (3/26) of the studies had a sufficient description of allocation concealment with sealed or shuffled envelopes (103). The extensively problematic issue in TENS studies is using an appropriate authentic placebo to blind the investigator and parturient (82,129). Most of the studies reported the use of inactive sham-TENS units (11/13 studies) (17,64,83,84,86–89,91,117,128,130), while only two studies used an active TENS (73,74). The purpose of allocation concealment is to prevent selection bias, while blinding prevents observer bias (90). Other risks of biases that need to be considered include an equal distribution of nulliparous and multiparous women and equal sample size across groups, which seemed problematic in 7/26 studies (17,65,86–88,91,93). Further, four studies did not report sufficient information on the distribution of nulliparous and multiparous in each treatment arm (64,76,116,118).

In Study II and Study III, it was aimed to design an adequate similar study design based on the findings and drawbacks from Study I. Therefore, double-blinded randomized controlled trials were designed for Study II and Study III. For the double-blinding process, sham-TENS was aimed to blind the investigator and the parturient. Initially, the selection of sham-TENS was based on the method of transient sham-TENS developed by Rakel et al. (2010), in which the sham unit applies TENS in a constant mode with a pulse rate of 100 Hz and pulse duration of 100 μs at the highest tolerable intensity for 30 seconds, and eventually the current ramps off over the next 15 sec to 0 mA (82). Even though this model increases the chances of blinding, the susceptibility to observer bias will still be uncertain (82). Further, it was evaluated that the transient sham-TENS and inactive sham-TENS units were similarly effective at blinding, with approximately 50-60% of the subjects identifying them correctly (131). Additionally, the investigator applying TENS could not differentiate between transient and inactive TENS units but correctly identified all 100% of the inactive sham-TENS units, suggesting the blinding of sham-TENS units needs to be improved (131). Based on that, in Study II, inspired by Chao et al.'s study (2007), the sham-TENS was selected with an intensity kept below 5 mA throughout the stimulation period (74). In opposite, this small intensity could be suggested to affect the labor pain reduction. However, it was not the case in Study II, as sham-TENS seemed not to affect the labor pain reduction, characterized by no difference in VAS and PPT between TENS groups and sham-TENS. The randomization was conducted using a computer-generated list, while allocation concealment was not possible to add due to difficulties in recruitment of the subjects (later emphasized in subchapter 6.5). However, we recruited half of the nulliparous women in Study II, but in Study III, the TENS-receivers were all nulliparous while the sham-TENS receiver was multiparous. Even the sample size was unequal in Study III. All these methodological issues are summarized in Table 6-1.

Table 6-1. Summary table of methodological issues in each study

	STUDY I	STUDY II	STUDY III
RANDOMIZATION	Problematic (9/26 studies)	Adequate	Adequate
ALLOCATION CONCEALMENT	Problematic (3/26 studies)	Problematic	Problematic
BLINDING	Problematic (11/13 studies)	Adequate	Adequate
OTHER BIASES (UNEQUAL DISTRIBUTION OF SAMPLE SIZE AND PARITY)	Problematic (7/26 (11/26) studies)	Adequate	Problematic

In Study II, the selected alternating frequencies were inspired by other studies, including Tong et al.'s study (2007), in which they investigated alternating frequencies including 2/100 Hz for mechanical and thermal pain thresholds, while Baez-Suarez et al. (2018) investigated 80/100 Hz for labor pain control. Authors found superior results of these types of frequencies. Even Baez-Suarez et al. found a significant efficacy toward 80/100 Hz compared to fixed continuous stimulation of 100 Hz (64). Though some studies did not find superior results using alternating frequencies (132,133). In Study II, low-to-high varying frequencies (4/100 Hz) showed to be more prominent compared to 80/100 Hz. This might be due to the activation of several opioid receptors at the spinal level and in the rostral ventral medulla, releasing opioids to cause hypoalgesia to various types of frequencies (51). Based on the theory, low frequencies below 10 Hz active μ-opioid receptors, while high frequencies above 50 Hz activate δ-opioid receptors (51). Another theoretical suggestion behind the mechanism of analgesia could be related to the gate-control theory as high frequency stimulates Aβ fibers, which are involved in closing the 'pain gate', resulting in reduced noxious information reaching the brain (134).

6.3. PAIN ASSESSMENT

Assessment of pain is essential and one of the core outcome domains in clinical pain research (135,136). Several tools have been developed to assess pain intensity. Mainly, a self-report single-item measure such as VAS is widely used in various clinical and research settings (135). VAS commonly consists of a 10-cm horizontal

line, with 0 cm expressing 'no pain', while 10 cm is considered 'worst imaginable pain' (137,138). One of the disadvantages of this tool is the difficulty of the subject/patient to respond to such an overall question, considering all aspects of the pain into one single rating (137). Mentionable, VAS is remarked as a reliable and valid tool for evaluating pain intensity in rehabilitation (137,139). Several studies reported the use of VAS to assess labor pain reduction (28,64,65,73–75,117,128). Though this method is prone to subjectivity, there is a need for other assessment tools to evaluate labor pain reduction. Quantitative sensory testing was considered for Study II and Study III as a supplementary method to differentiate from the subjective evaluation of pain (i.e., VAS) (112). For that purpose, PPT was selected to be one of the primary outcomes after VAS. PPT is considered 'semi-objective' and has proven its reliability (81,131,140,141). PPT as an assessment tool for labor pain reduction is unique and has not been reported in previous studies. Though, several studies used PPT when evaluating TENS stimulation in experimental pain (51,81,82,100,131,142). Further, in future studies, it is recommended to use either PPT or other quantitative sensory testing tools to assess the pain in different dimensions rather than only using VAS or other pain rating scales (143).

6.4. TENS-TOCO SYSTEM

In Study III, a novel technique combining TENS with TOCO in an open-loop system was introduced. No previous studies have reported this unique combination. This automated technology, which increases in intensity during uterine contraction and lowers back to basic stimulation between uterine contractions, showed to be a feasible technique. Though, this model could be improved further. The TOCO threshold can be adjusted optimally based on the TOCO registration of uterine contractions. If the pressure wave of uterine contraction reaches 100%, it is recommended to use a TOCO threshold around 60-70% to avoid response to noise. Maternal movements often lead to noise on the TOCO registration (97).

The clinical available conventional TENS devices operate similarly to the TOCO-TENS with a basic stimulation given between uterine contraction, and during uterine contraction, the woman can press on a 'boost' button that changes the frequency pattern, while the intensity is possible to adjust individually. One essential difference between these two devices is that conventional TENS is operated by the parturient herself while TENS-TOCO is automated and out of the woman's control. Nevertheless, some parturients might consider this as a positive solution, as some cannot handle the 'boost' button due to increased pain during uterine contraction, while others may prefer having control of the unit. However, it remains unclear if the high satisfaction of TENS among parturients is due to the effect of TENS or self-use of TENS leading to a reduction in anxiety, providing a distraction, and increasing the sense of control of the parturients (6,46). This TOCO-TENS model can clear this

problem by providing information of TENS' efficacy is due to the administration of electrical impulses or providing a distraction from labor pain.

6.5. LIMITATIONS

The systematic review and meta-analysis are considered one of the gold-standard in evaluating the benefits of treatments. However, this is limited to the availability of the numbers of RCTs with adequate methodological considerations and low heterogeneity among the included studies (90). Study I included a substantial number of studies that suffered from methodological issues, making the findings less interpretable. Even though pain intensity was reduced significantly, the quality of the methodology among the included studies made it difficult to make a firm conclusion (103).

RCTs are considered another gold standard in evaluating treatment effects next to systematic review and meta-analysis. Study II and Study III were designed as RCTs with proper methodology, including inclusion and exclusion criteria and sample size calculation, but later it was considered that parturients are a vulnerable population, and eventually, the recruitment process will be inhibited. During recruitment of the parturients, it was realized that the inclusion and exclusion criteria further inhibited the significant number of parturients available. In Study II, recruitment of healthy parturients with no prior exposure to pain management was one of the main reasons for excluding the subjects. In Study III, recruitment of parturients allocated to conventional CTG was one of the main inclusion criteria. For ethical reasons, healthy parturients usually are not allowed to use conventional CTG as the latter is associated with an increased chance of cesarean sections or instrumental vaginal births (97,98). As a result of this, a significant number of subjects were excluded due to this reason. Exactly 135 women from Study II (see Figure 3 of Paper 2) and 76 women from Study III were excluded due to inclusion and exclusion criteria (see Figure 4 of Paper 3) (104,105). This led to a limited study population and thereby difficulties in generalizing the outcome of the findings from Study II and Study III. Especially in Study III, the outcome measures were removed from the final analysis in Study III due to the limited number of parturients included.

Based on the main objective, hypotheses were proposed in each study. For Study I, it was possible to accept the two hypotheses, as it was possible to find a significant effect of TENS for labor pain reduction compared to sham-TENS. Second, a trend of a decreased duration of labor, reduced use of analgesics, and no changes in Apgar scores were shown. Though it was not possible to show a high maternal satisfaction, that was limited by the available data from the included studies. In Study II, it was not possible to show a significant difference between TENS and sham-TENS, neither of the low-to-high set of frequencies nor the high varying frequencies. Though, it was possible to establish a trend of reduction of VAS scores for 10 min and 30 min, while PPT was

increased from baseline to 10 min for 4/100 Hz. Half of the parturients receiving TENS reported high satisfaction. However, all these findings were limited to the small number of subjects recruited. As already mentioned, the inclusion and exclusion criteria restricted the number of available parturients for recruitment. This problem was also challenging in Study III and led to shelving data analysis of pain assessment. Therefore it was not possible to explore the hypotheses in Study III. In Study II, the inclusion criterion of healthy parturients was one of the repeated reasons for limited recruitment of parturients as several women had a diagnosis, e.g., pre-eclampsia, gestational diabetes, etc. In contrast, in Study III, the availability of parturients using CTG was another frequent limitation. Moreover, the principal investigator could only recruit parturients while available at the labor ward, limiting the number of parturients available during work hours. Another central fact was the limited number of admitted parturients at the labor ward. Gødstrup Hospital has an estimated 2600 childbirth each year, leading to an average of 7 childbirths every day. The midwives were not involved in data collection due to difficulties managing the device. Therefore, in future studies, the challenges associated with recruitment need to be highly considered. Even training of the midwives for using the device for data collection could also be considered.

In Study II and Study III, several improvements could be made with respect to optimizing the placements of electrodes and parameters of TENS, including pulse duration and frequency. Therefore, it was decided to go for long pulse durations and individually adjusted intensity, which has proven effective in other studies (28,64,85,103,119). However, electrode placement in studies II and III was only achieved with one set of electrodes at the S2-S4 spinal level. Typically, the placements of electrodes also include T10-L1 (28,64,85,103,119). Though it was decided to stimulate close to the site of pain at the S2-S4 level in studies II and III, even though S2-S4 is considered more involved in the second stage of labor. Usually, clinical available dual-channel TENS devices for labor pain management consist of two separate channels to control the current flow through each set pair of electrodes (144). However, the DS5 is only available with one channel, and therefore it was not possible to achieve TENS stimulation of two sites at once. Foremost, the use of dual-channel devices was inhibited in studies II and III, based on Ohm's law that current will flow towards less resistance. Therefore, when two sets of electrodes are placed, the current would not equally stimulate each site but will flow towards the area of less resistance (e.g., skin impedance) (145). Only one set of electrodes was used, and DS5 was chosen for stimulation to avoid this unequal current flow distribution. Although in Study II, a slight tendency of reduced pain intensity was seen, it is not clear if the electrodes placed at T10-L1 might have shown an optimal pain relief compared to S2-S4.

No side effects or adverse events were recorded among women and newborns in studies II and III comparable to other studies (95,128). Though, it should be mentioned that no systematic monitoring of adverse events of the women was conducted after

the session. However, no reports were received throughout the session. It is essential to monitor unexpected adverse events and side effects due to the treatment (94,104).

6.6. METHODOLOGICAL ADVANCEMENTS

This thesis presented a comprehensive investigation of TENS for labor pain management, focusing on methodological and technical aspects. Future studies might consider improving the study design based on study I-III, including adequate use and description of randomization, allocation concealment, and blinding via an authentic placebo.

In the clinical setting, several TENS parameters could have been interesting to investigate from other perspectives. First, the time duration of exposure to TENS was limited. In studies II and III, the time was limited to 30 min, also based on other studies (28,64,74). Though, a longer duration of TENS stimulation might have shown different results. Further, pain assessment of post-effect of TENS after 30 min could also be an interesting parameter to investigate (146). It could indicate if TENS had an immediate effect or a more prolonged effect after exposure to TENS, which was shown in one recent study (104,147).

The TENS-TOCO system could be improved in terms of a separate system without external CTG to enhance the access of devices for all types of parturients, including high- and low-risk pregnant women (Study III). Further, it was observed that three women discontinued participation in Study III due to no effect of TENS or increased pain caused by the use of TENS. Therefore, future devices may consider an adjustable pattern of frequencies suitable for the individual user (104).

Frequency, intensity, and electrode placement are essential factors of TENS for achieving pain relief during labor (27). As already mentioned, electrodes were placed at S2-S4 spinal level instead of T10-L1. In future studies, the effect of applying electrodes at T10-L1 could be investigated in future studies with first-stage laboring women (104).

For pain assessment, rather than VAS, a verbal rating scale (VRS) could be used (135). It was observed that the parturients had difficulties in rating their pain on VAS. The advantage of VRS is that the pain is rated in mild, moderate, and severe categories that generally are used in communications between patients and health care providers in clinical practice (135).

Finally, the blinding assessment should be considered in studies investigating sham-TENS as a control treatment to check if the investigator and parturient are blinded to the treatment (51,82).

6.7. CLINICAL IMPLICATIONS

Based on the findings in the thesis, it is suggested that the clinical guideline for the use of TENS in intrapartum care could be reconsidered, especially NICE, who recommended not to use TENS for labor pain management in intrapartum care. With the likely efficacy of TENS, no potential safety concerns, and high maternal satisfaction, TENS is suggested to be considered for use in intrapartum care, especially in the latent phase. As already mentioned, TENS could be offered as an alternative treatment to pharmacological management for labor pain control. Further, the use of TENS might likely reduce and delay the use of pharmacological analgesia, which could be beneficial for the woman herself in terms of side effects, while the government and hospitals would experience cost savings in terms of decreased use of pharmacological management and thereby reduced use of health professionals (148).

The introduction of the TENS-TOCO system might increase the use of TENS in labor care, even the increasing effect on the labor pain might be shown in future studies. As Robson et al. (1979) stated in their study that introduction of a new method of pain relief would have no future, except it can be shown to be better and reliable than other methods, safe for the mother and the baby, non-invasive, and require no additional nursing nor medical care (26). Therefore, it is crucial to test this open-loop system in future clinical studies for efficacy, safety, and in comparison with other methods in terms of labor pain reduction with proper sample size.

6.8. RESEARCH IMPLICATIONS

The researchers initially discussed the gate-control theory proposed in 1965 as it did not explain every aspect of how people experience pain, especially chronic pain (149). Even the mechanisms involved in labor pain are yet not fully understood. Hereby, there is a need for mechanistic research of labor pain, including maternal pain biomarkers and investigation of the involvement of sensitization. Kojic et al. (2007) proposed that peripheral sensitization at the uterus level, e.g., a cervical inflammatory reaction caused by cervical ripening and remodeling, activates nociceptors, and eventually central sensitization develops by phosphorylation of N-methyl-D-aspartate (NMDA) receptors of the dorsal root neurons (150). However, Johnson (2007) mentioned briefly that TENS-induced Aδ activity causes depression in central nociceptor cell activity and reduces central sensitization (61). Nevertheless, more studies need to emphasize this topic.

6.9. INDUSTRY IMPLICATIONS

The idea behind this TENS-TOCO combination was initially created as an additional feature to the Centaflow device. Though, this device makes a high impact as a separate device. Several parameters could be developed in the future to personalize the device's functions, including personalized frequency patterns and a separate system without the use of conventional CTG to enhance the use among all types of parturients, including high-risk and low-risk pregnant women.

If this device turns successful, the involvement of artificial intelligence (i.e., machine-learning) of available data could be considered in future devices.

CHAPTER 7. CONCLUSIONS

The present PhD thesis provided an exploration of the current evidence of TENS for labor pain management (Study I), an investigation of two set of alternating frequencies compared to sham-TENS for labor pain control (Study II), and finally, a proposal of a novel combination of TENS with TOCO for automated and personalized labor pain control (Study III).

The thesis' overall objective was to explore new aspects of the use of TENS for labor pain management both in methodological and technical aspects. This objective was addressed with an aim and corresponding hypotheses for each study. Study I revealed to be the first one, among several systematic reviews evaluating TENS for labor pain control, showing a small but significant effect of TENS for labor pain reduction compared to control treatments, i.e., sham-TENS, routine care, no treatment, and oxytocin administration. This was further supported with outcomes, including the duration of labor, additional analgesia, and Apgar scores, all tend to favor TENS, except for the satisfaction of TENS. Even though the latest included studies showed an improvement in methodological quality, many studies suffered from poor quality. The significant efficacy was also affected by the high heterogeneity in the meta-analysis. With this, it is not possible to conclude if the efficacy of TENS was actual or influenced by bias. Study II showed a detailed technical description of the selected varying frequencies. Varying frequencies including 4/100 Hz and 80/100 Hz were investigated compared to sham-TENS. Even though it was not possible to show the efficacy of TENS, a trend of reduced labor pain was shown using 4/100 Hz compared to 80/100 Hz and sham-TENS. In addition, high maternal satisfaction was seen, but the results were inhibited in interpretation due to the limited sample size. Study III showed a feasible model of the TENS-TOCO open-loop system using a frequency pattern of 4/100 Hz, but it was not possible to address the hypotheses due to the limited sample size.

In conclusion, this thesis presented data from three studies showing a trend of possible effects of TENS on labor pain. Especially considering findings from Study I with significantly reduced pain intensity, while in Study II, a non-significant decrease of pain intensity was seen for 4/100 Hz TENS, also a high maternal satisfaction was also observed. These findings suggest TENS could be considered for labor pain management in intrapartum care, especially in the latent phase. The use of TENS in intrapartum care is limited in Denmark due to the uncertain evidence of the effects of TENS. The practice of TENS might be improved by introducing a new technique providing optimal pain relief during uterine contractions (Study III). Further, the TOCO-TENS combination benefits the parturients interested in non-pharmacological management or delaying the procedure of pharmacological interventions. Eventually, the parturients would be able to manage their pain simultaneously they experience

their childbirth without side effects caused by pharmacological management, which might increase maternal satisfaction. However, this new technology needs to be assessed for efficacy and safety in future clinical studies.

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SUMMARY

It is crucial managing labor pain considering the well-being of the parturient, fetus, and the labor progress. Alternative approaches are needed for labor pain management. Transcutaneous electrical nerve stimulation (TENS) has been used for labor pain control for several decades, though it is not routinely used in intrapartum care. The present thesis aimed to investigate TENS for labor pain control through three studies. First, a systematic review and meta-analysis evaluated the efficacy of TENS for labor pain control (Study I). Next, a pilot study investigated the optimal varying frequencies for labor pain control (Study II). Finally, a feasibility study aimed to develop a novel technique of combining TENS with tocodynamometer (TOCO) for automated stimulation during uterine contractions (Study III).

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