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ACUPUNCTURE FOR LABOUR PAIN

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Acupuncture for Labour Pain

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ABSTRACT

Background: Acupuncture involves puncturing the skin with thin sterile needles at defined acupuncture points. Previous studies are inconclusive regarding the effect of acupuncture on labour pain, but some studies have found a reduction in the use of pharmacological pain relief when acupuncture is administered. The appropriate dose of acupuncture treatment required to elicit a potential effect on labour pain has not been fully explored. The dose is determined by many different factors, including the number of needles used and the intensity of the stimulation. In Sweden, manual stimulation of the needles is common practice when acupuncture is used for labour pain, but electrical stimulation of the needles, which gives a higher dose, could possibly be more effective. The overall aim of this thesis was to evaluate the effectiveness of acupuncture with manual stimulation (MA) of the needles as well as acupuncture with a combination of manual and electrical stimulation (EA) in reducing labour pain, compared with standard care without any form of acupuncture (SC).

Methods: The study was designed as a three-armed randomised controlled trial in which 303 nulliparous women with normal pregnancies were randomised to MA, EA, or SC. The primary outcome was labour pain, assessed using the Visual Analogue Scale (VAS). Secondary outcomes were relaxation during labour, use of obstetric pain relief, and associations between maternal characteristics and labour pain and use of epidural analgesia respectively. Also, labour and infant outcomes, recollection of labour pain, and maternal experiences, such as birth experience and experience of the midwife, were investigated two months after the birth. The sample size calculation was based on the potential to discover a difference of 15 mm on the VAS. Data were collected during labour before the interventions, the day after birth, and two months later. Besides using the VAS, information was collected by means of study specific protocol, questionnaires and medical records.

Results: The mean VAS scores were 66.4 in the MA group, 68.5 in the EA group, and 69.0 in the SC group (mean differences: MA vs. SC 2.6 95% CI -1.7 to 6.9, and EA vs. SC 0.6 95% CI -3.6 to 4.8). Other methods of pain relief were used less frequently in the EA group, including epidural analgesia, MA 61.4%, EA 46%, and SC 69.9%. (EA vs. SC OR 0.4 95% CI 0.2 to 0.7). No statistically significant differences were found in the recollection of labour pain between the three groups two months after birth (mean VAS score: MA 69.3, EA 68.7 and SC 70.1). A few maternal characteristics were associated with labour pain (age, dysmenorrhea, and cervix dilatation), but none of the investigated characteristics predicted the outcome of the acupuncture treatment in MA or EA. Women in the EA group experienced acupuncture as being effective for labour pain to a higher extent than women who received MA, MA 44.4%, EA 67.1% (EA vs. MA OR 2.4 95% CI 1.2 to 4.8). Women in the EA group also spent less time in labour (mean 500 min) than those who received MA (mean 619 min) and SC (mean 615 min) (EA vs. MA HR 1.4 95% CI 1.0 to1.9, EA vs. SC HR 1.4, 95% CI 1.1 to 2.0), and had less blood loss than women receiving SC, (EA vs. SC OR 0.1 95% CI 0.3 to 0.7).

The women's assessment of the midwife as being supportive during labour (MA 77.2%, EA 83.5%, SC 80%), overall satisfaction with midwife care (MA 100%, EA 97.5%, SC 98.7%), and having an overall positive childbirth experience (MA 64.6%, EA 61.0%, SC 54.3%) did not differ statistically. No serious side effects of the acupuncture treatment were reported.

Conclusion: Acupuncture, regardless of type of stimulation, did not differ from standard care without acupuncture in terms of reducing women's experience of pain during labour, or their memory of pain and childbirth overall two months after the birth. However, other forms of obstetric pain relief were less frequent in women receiving a combination of manual and electrical stimulation, suggesting that this method could facilitate coping with labour pain.

LIST OF SCIENTIFIC PAPERS

I.   Linda Vixner, Lena B. Mårtensson, Elisabet Stener-Victorin, and Erica Schytt, "Manual and Electroacupuncture for Labour Pain: Study Design of a Longitudinal Randomized Controlled Trial," *Evidence-Based Complementary and Alternative Medicine*, vol. 2012, Article ID 943198, 9 pages, 2012. doi:10.1155/2012/943198

II. Linda Vixner, Erica Schytt, Elisabet Stener-Victorin, Ulla Waldenström, Hans Pettersson and Lena B. Mårtensson "Acupuncture with manual and electrical stimulation for labour pain: a longitudinal randomised controlled trial*". BMC Complementary and Alternative Medicine* 2014, 14 :187 http://www.biomedcentral.com/1472-6882/14/187

III. Linda Vixner, Lena B. Mårtensson and Erica Schytt "Acupuncture with manual and electrical stimulation for labour pain: a two month follow up of recollection of pain and birth experience*" Re-submitted*

IV. Linda Vixner, Erica Schytt, Elisabet Stener-Victorin, Ulla Waldenström and Lena B. Mårtensson "Associations between maternal characteristics and labour pain in women receiving acupuncture with manual stimulation, acupuncture with a combination of manual and electrical stimulation, or standard care" *Manuscript*

CONTENTS

LIST OF ABBREVIATIONS

95% CI	95% Confidence Interval
AR(1)	First order Autoregressive Model
BMI	Body mass index (Kg/m^2)
CNS	Central nervous system
CONSORT	Consolidated Standards of Reporting Trials
Cox	Cox regression model
EA	Acupuncture with a combination of both manual and electrical stimulation
EDA	Epidural analgesia
EPDS	Edinburgh Postnatal Depression Scale
GABA	Gamma-aminobutyric acid
GLM	Generalised linear model
HR	Hazard Ratio
KM	Kaplan Meier
LMM	Linear Mixed Model
LR	Logistic Regression
MA	Acupuncture with manual stimulation
MD	Mean Difference
MR	Medical Record
OR	Odds Ratio
PAG	Periaqueductal grey
Q	Questionnaire
RCT	Randomised Controlled trial
SC	Standard Care
SD	Standard Deviation
SE	Standard Error
SP	Study Protocol
STRICTA	Standards for Reporting Interventions in Clinical Trials of Acupuncture
TENS	Transcutaneous Electrical Nerve Stimulation
VAS	Visual Analogue Scale

1 INTRODUCTION

Women's experience of pain during labour may vary from extremely severe and unbearable to moderate and tolerable [1]. Labour pain is highly correlated with women's overall assessment of childbirth [2], and a painful labour may have long-term consequences for women's health and wellbeing [3].

In Sweden, pain relief during labour is available to all women, and a woman's request should be respected as long as medical safety for her or the infant is not jeopardized [4]. The different pain relieving treatments available are both pharmacological and non-pharmacological [5]. The most common pharmacological methods used in Sweden in 2013 were nitrous oxide (nulliparae 88%, multiparae 78%) and epidural analgesia (nulliparae 51%, multiparae 20%). The most common non-pharmacological methods were immersion in water (nulliparae 13%, multiparae 5%) and acupuncture (nulliparae 8%, multiparae 3%) [6]. The evidence regarding the effects of non-pharmacological methods on labour pain is limited, however, they have fewer adverse effects than pharmacological methods, and seem to be safe for both the mother and infant [5].

In 1984, acupuncture for chronic pain was approved by the Swedish National Board of Health and Welfare for use by licensed health care personnel within the health and welfare sector [7]. Since 1993, acupuncture has been approved for use for all conditions if evidence of its effect is provided [8]. In the 1990s the use of acupuncture for labour pain increased in Swedish labour wards, and was used by nearly 25% of nulliparous and 15% of multiparous women in 1996 [6]. Since then, the use of acupuncture has declined, and in 2013 the total rate of use was 5% of all deliveries [6]. The reasons for this decline are not fully known but midwives' lack of acupuncture skills and fewer requests from the women have been discussed [9]. Another explanation for the decline could be the recommendation issued by the Swedish National Board of Health and Welfare in 2001 to use acupuncture only in connection with research due to the lack of evidence of its effect [10].

Even though a woman's requests and choice of pain relieving method during labour have to be respected, all methods provided by the health care system need to be evidence based. This does not only apply to the use of pharmacological pain relief but also to non-pharmacological methods. The overall aim of this thesis was to evaluate the effectiveness of acupuncture with manual stimulation (MA) of the needles as well as acupuncture with a combination of manual and electrical stimulation (EA) in reducing labour pain, compared with standard care without any form of acupuncture (SC).

2 BACKGROUND

2.1 LABOUR PAIN

Pain is a multidimensional experience [11] that is always subjective and a psychological state. It is a combination of both sensations in the body and an emotional experience [12]. The pain experience during labour is highly variable and influenced by both physical and psychosocial characteristics of the woman, the birth environment, and the care provided [13]. There is no general definition of labour pain, however Lowe [13] captures the nature of labour pain in her description: *The experience of labour pain is a complex, subjective, multidimensional response to sensory stimuli generated during parturition….Unlike other acute and chronic pain experiences, labour pain is not associated with pathology but with the most basic and fundamental of life experiences −the bringing forth of new life.*

Fear of pain and anxiety is correlated with intense labour pain, and a woman's confidence in her ability to cope with labour pain is strongly associated with less pain [13]. The affective component of pain is greater in the early stage of labour in nulliparous women than in multiparous women, and it tends to decrease in both groups in the second stage of labour [13]. Most women who have been in labour describe the pain as the most intense they have ever experienced [14]. Women's experiences of a painful labour and birth are not only important during the process of labour but may also have long-term consequences for their health and wellbeing [3], a recollection of severe labour pain at two months after birth is an important risk factor for a negative childbirth experience [15], and a negative childbirth experience is an important predictor of depressive symptoms during the first year of motherhood [16]. Labour pain is associated with previous pain experiences. Dysmenorrhea is associated with higher pain intensity during labour [13, 17, 18], and non-gynaecological pain experiences are associated with less pain during labour [13]. Antenatal fear of pain and anxiety also increases the pain intensity experienced during the subsequent labour [13]. Other maternal characteristics associated with both increased and decreased labour pain are level of education, maternal age, and cultural background [13].

Labour pain is a visceral pain. Visceral pain is not always linked to an injury, it is often referred to other locations and is often accompanied with motor and autonomic reflexes such as nausea and vomiting [19]. The pain system is very complex and entails a series of mechanisms which occur at different levels in the nervous system: in the periphery, in the spinal cord, and in supra spinal centres and cortico-limbic structures [20]. Nociception is the term for the process where potentially harmful stimuli affect specialised free nerve endings in the tissue, so-called nociceptors.

When the nociceptors are activated, nerve signals are transmitted to the spinal cord and eventually projected to cortical and limbic regions of the brain [21]. The processing of such signals in the brain gives rise to the sensory, discriminative dimension of pain and involves components such as intensity, location and duration [20]. The affective-cognitive dimension of pain is the relationship between nociception and mind. It includes attention to the pain and the ability to cope with and tolerate pain [20].
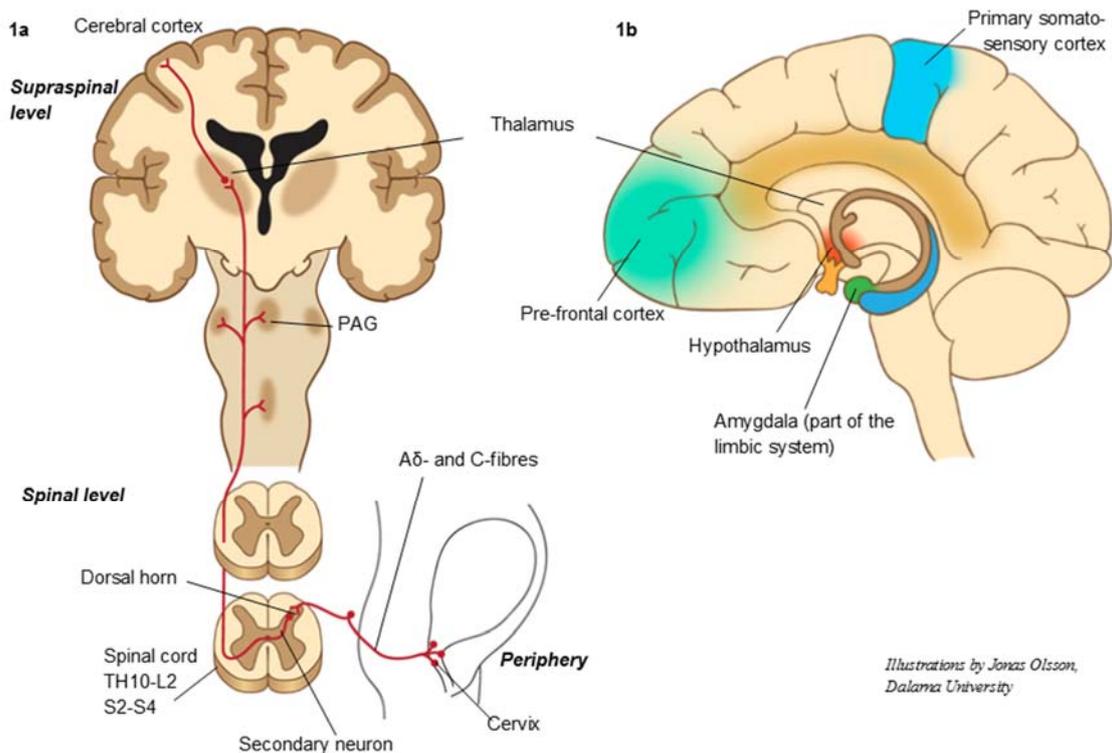
Figure 1. Neural pathways for nociceptive information during labour (1a), and brain areas essential for processing of the pain experience (1b) PAG= nucleus periaqueductal grey

The nociceptive origin of labour pain is primarily associated with an inflammatory process, the cervical ripening, that takes place to enable the passage of the infant. During labour, there is an increase in the local concentrations of cytokines, which activate the nociceptors reacting to chemical stimuli [22] (Figure 1). The inflammation causes a peripheral sensitisation (a lowering of nociceptor activation threshold) of the most common neurons, Aδ- and C-fibres [21, 23]. Another origin of nociceptive signals during labour is mechanical activation of nociceptors. During labour, uterine contractions and cervical dilatation occurs. This activates nociceptors reacting to mechanical stimuli [24]. However, a preceding sensitisation of these nociceptors seems to be necessary to make them sensitive to the uterine contractions [25], and the sensitisation increases the signalling to the dorsal horn in the spinal cord [21, 23].

The nociceptive signals associated with the ripening and dilatation of the cervix in the initial stage of labour are transmitted to the posterior root ganglia of the lower thoracic to the upper lumbar spinal cord (Th10 to L1-L2), and as labour proceeds, the nociceptive stimuli additionally originate from the spinal segments S2-S4 [13, 24]. Repeated afferent impulses cause an increased sensitivity of the secondary neurons in the dorsal horn, a central sensitisation that results in an increased signalling in the ascending pathways to the brain [26, 27]. This sensitisation can be triggered very rapidly (over minutes) [20].

The noxious stimuli are perceived by the labouring woman as pain, and the intensity of labour pain increases as labour proceeds [1, 13, 24, 28]. This is partially explained by peripheral and central sensitisation [13]. Women often localise the pain to the back, abdomen, and groin, which is a result of referred pain [19]. The phenomenon of referred pain during labour was described as early as in 1936 [29]. Thalamus, located in the diencephalon, functions as a relay station where all the nociceptive pathways from the spinal cord form synapses on their way to the cerebrum. Thalamus relays information to the somatosensory cortex where the sensory-discriminative aspects of pain, such as location, intensity and duration, is processed. Furthermore, thalamus interlinks with the limbic system which participates in the affective-emotional aspects of pain, and the pre-frontal cortex, considered to be the most important area for the cognitive-evaluating dimensions of pain. Both prefrontal and limbic regions are considered to be involved in the regulation of mood and symptoms of anxiety, and activation of these areas may intensify the perception of pain [20]. Another important structure for pain modulation is the brain stem nucleus periaqueductal grey (PAG). Much of the opioid-induced antinociception originates from this structure [30, 31], and it is a major site for the descending, inhibitory pathways to the dorsal horn [20, 31]. PAG receives nociceptive input from the dorsal horn, and is also reciprocally connected to the hypothalamus, the frontal cortex, and amygdala, regions important for the control of emotions, in particular anxiety and fear, which can explain how emotions may modulate the perception of pain [30].

2.2 ACUPUNCTURE

Acupuncture involves puncturing the skin with thin sterile needles at defined acupuncture points and has been a part of Traditional Chinese Medicine for more than two millennia [32, 33]. Within Chinese acupuncture, meridians are considered to be a network of acupuncture points where so-called Qi (energy) is flowing, and the cause of pain is regarded as a blockade of these meridians. Acupuncture clears the blockade resulting in a smooth streaming of Qi [32]. Western medical acupuncture is an adaption of Chinese acupuncture, using knowledge of anatomy and physiology to explain its effect rather than the concept of Yin/Yang and circulation of Qi [33, 34]. The rationale of acupuncture in this thesis is based on Western medical theories, described in section 2.2.1 Physiology of acupuncture.

Western medical acupuncture was approved by the Swedish National Board of Health and Welfare in 1984 to be used by licensed health personnel – initially for pain only [7], but since 1993 for any condition that has evidence of its effectiveness [8].

2.2.1 Physiology of acupuncture

There are a few theories within western medical acupuncture describing different physiological mechanisms that are proposed to explain the pain relieving effects of acupuncture. Within Western medical acupuncture, two forms of stimulation of the acupuncture needles are most commonly used in the clinic; manual stimulation or electrical stimulation. With manual stimulation, the needles are twisted back and forth until a feeling of DeQi is reached. DeQi is described as a sensation of numbness, soreness, or heaviness reflecting activation of the afferent nerve fibres. With electrical stimulation, the needles are connected to an electrical stimulator delivering currents with different frequencies to the inserted needles [32]. In addition to the stimulation technique, the number of needles and their placement and depth are components that may affect the outcome of acupuncture treatment [35].

2.2.1.1 Peripheral mechanisms

When twisting an acupuncture needle back and forth, the connective tissue wraps around the needle and creates a "whorl" around the needle, which results in a stretching of the connective tissue. In response to this stretching, the fibroblasts are affected and could be responsible for the release of adenosine [36]. Adenosine has anti-nociceptive properties and recent studies show that manual stimulation of the acupuncture needles directly activates analgesic mechanisms in the tissue via the release of adenosine [37, 38]. In addition, acupuncture needles stimulate afferent nerve fibers, $A\alpha/\beta/\delta$ and C-fibers, and locally, via antidromic axon reflexes, neuropeptides are released, causing vasodilatation and increased blood flow [39-41]. Whether electrical stimulation causes a stretch of the fibroblast and release of adenosine is not known.

2.2.1.2 Spinal mechanisms

Activation of afferent nerve fibres is transmitted to the spinal cord and inhibits pain transmission from the primary to the secondary sensory neuron. This inhibition is the basis of the gate control theory, first described by Melzack and Wall [42]. Activation of sensory afferents activates inhibitory interneurons releasing gamma-aminobutyric acid (GABA) and glycin, inhibiting the pain transmission between the primary and secondary neuron. Analgesia due to this phenomenon is relatively short-lasting and requires that the acupuncture points selected lay within the same innervation area as the origin of pain [43]. The effect is dependent on the number of needles stimulated and how often they are stimulated. If needles are stimulated electrically, a high-frequency is used with as high intensity as possible without causing discomfort [44].

2.2.1.3 Supraspinal mechanisms

After transmission to the spinal cord, ascending and descending pathways involved in the central pain transmission are activated [32]. In the central nervous system acupuncture triggers the release of opioids including β-endorphin, enkephalin, dynorphin, and endomorphin which modulates the descending pain inhibitory system [45].

One of the most crucial structures within the pain modulating system is the PAG, a control centre for descending inhibition of nociceptive signals [30, 31]. PAG has an important role in acupuncture analgesia since it is activated by pain and acupuncture stimulation and releases opioids [45, 46]. It further activates the raphe nuclei, which in turn release serotonin and noradrenalin projecting to the spinal cord where it activates inhibitory neurons releasing opioids causing central pain inhibition. Acupuncture also deactivates limbic areas in the brain that contribute to the emotional aspects of pain such as fear and anxiety [32, 46-48], which supports the hypothesis that the limbic system is central to the effects of acupuncture. In addition, acupuncture modulates the stress response including the activity in the hypothalamus-pituitary-adrenal axis, which may affect the pain inhibitory response [49].

2.2.1.4 Manual and electrical stimulation

Pain relief through manual stimulation of the needles and electrical stimulation have many similarities but there are also differences. Both manual acupuncture and electro-acupuncture stimulate all types of afferent nerve fibers (Aα/β/δ and C-fibers) [41], affecting both the spinal and the central pain inhibitory mechanisms described earlier.

Manual stimulation is intermittent and occurs only when the needles are twisted back and forth until the feeling of DeQi is achieved [50]. Manual stimulation affects both the skin and underlying tissues such as the connective tissue [36].

Electrical stimulation, on the other hand, is continuous during the whole treatment period. Electro-acupuncture depolarizes the resting membrane potential resulting in action potentials and signalling cascades [50]. As with manual stimulation, electrical stimulation causes a release of neuropeptides locally and modulates pain transmission at both spinal level and in the central nervous system (CNS). Low-frequency electrical stimulation mainly facilitates the release of encephalin, endomorphin, and β-endorphin in the CNS whereas high-frequency stimulation facilitates the release of dynorphin at spinal level and CNS [51]. It is possible that high-frequency stimulation produces stronger pain inhibition to visceral pain than low-frequency stimulation [52] and electrical stimulation seems to have a larger positive impact than manual stimulation on some of the structures in the limbic system that contribute to the emotional aspects of pain [48].

One could therefore expect that a combination of manual and electrical stimulation would reduce pain more effectively than manual stimulation alone [32].

2.2.1.5 Dose

The dose of acupuncture is determined by many different factors; in both manual and electrical stimulation, the depth of needle insertion, number of needles, stimulation frequency, and the intensity of the stimulation are important factors affecting the outcome [35]. The duration of treatment as well as how often the treatment is repeated are also factors needing to be considered. The dose will also vary depending on the treated health condition [35]. The appropriate dose of acupuncture treatment required to elicit a potential effect on labour pain has not been fully explored.

2.2.2 Acupuncture research

Methodology problems in acupuncture research are extensive [35, 53]. Clinical trials of acupuncture should follow two guidelines, Consolidated Standards of Reporting Trials (CONSORT) [54] and Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [55]. CONSORT constitutes the evidence based minimum set of recommendations for reporting clinical trials and STRICTA is an extension of CONSORT that includes instructions for reporting acupuncture studies specifically. However, the majority of acupuncture trials have methodological flaws, for example, they lack sample size calculations or descriptions of the randomisation procedure, or lack information specific to acupuncture trials, such as detailed descriptions of the acupuncture treatment (number of needles, number of treatment sessions, duration of treatment), or the different types of controls used in the trial [53]. It has been acknowledged that studies without these limitations are needed, to provide findings that would allow comparisons between studies in systematic reviews or meta-analyses [53, 56].

Another problem with comparisons and interpretations of results from acupuncture studies is that clinical trials can have different focuses, either on effectiveness or efficacy of the treatment [57]. Effectiveness is *a measure of the extent to which a specific intervention, procedure, regimen, or service, when deployed in the field in the usual circumstances, does what it is intended to do for a specified population* [58]. Efficacy refers *to the extent to which a specific intervention, procedure, regimen, or service produces a beneficial result under ideal conditions* [58]. Within acupuncture research, effectiveness trials study the effect of acupuncture when used in routine care with a population that is more heterogeneous than those in efficacy studies [57]. These studies are often pragmatic designs where the acupuncture is mostly added to standard care and is compared to standard care without acupuncture [59]. Efficacy studies evaluate the effects of acupuncture where the acupuncture intervention often is compared to sham treatments [57].

Sham is a term used for different types of procedures that are regarded as placebo controls [56]. The definition of the term placebo is: *a medication or procedure that is inert* [58], and the ideal placebo control within acupuncture research should have two properties: physiologically inert and psychologically believable [56, 58]. There is a great variety of different types of sham treatments [60-62], the four most common types being: shallow

needling, non-penetrating needles, using non-acupuncture points, and "wrong" acupuncture points [56]. In *shallow needling*, the needles are inserted superficially into the skin, not reaching the prescribed depth of the acupuncture point. There are different types of *non-penetrating needles* but the main feature is that they create an illusion of the needle penetrating the skin with different methods. One is that the shaft of the needle moves back into the handle when the needle is applied to the skin. When the needles are inserted at locations away from traditional acupuncture points the term *non-acupuncture points* is often used. Finally, some sham controls use actual acupuncture points that are considered *"wrong"* in that perspective that they are not traditionally used for that particular condition [56]. The terminology for how to report these controls has not been standardised [61], meaning that the term sham can be used for all different types of controls described above. In the last decade, however, there have been more recommendations regarding what terminology should be used, for example "penetrating sham" or "non-penetrating sham" treatments [61], and in STRICTA, item 6, a whole section argues for the necessity of using a detailed description of the sham interventions [55].

It is problematic that the term sham has been confused with the term placebo [56]. From a biomedical point of view, shallow needling, non-acupuncture points, and "wrong" acupuncture points are all active treatments that produce a physiological response. Even the non-penetrating needles can produce a physiological response when the needle applies pressure to the skin or on occasional pierces the skin [56]. Sham acupuncture in this sense could rather be seen as a low-intensity form of therapeutic needling and not as an inert procedure [56, 63]. The theories regarding the mechanisms underlying the effects of acupuncture in Traditional Chinese Medicine and Western medical acupuncture differ. Hence, one sham control that is regarded as truly inert (placebo) in one tradition, can be physiologically active within the other tradition [55, 56, 60, 61, 64]. This is problematic when comparisons of studies are made.

2.2.3   Previous research on acupuncture for labour pain

In the last five years, two extensive systematic reviews of acupuncture for labour pain have been published; the Cochrane review from 2011 by Smith et al. [65] (nine acupuncture trials), and a systematic review from 2010 by Cho et al. [66] (ten acupuncture trials). The included trials differ regarding research questions, design of the studies, and outcome measures, which made comparisons between these trials problematic [59]. The conclusions of the review by Cho et al. [66], who primarily focused on pain intensity (efficacy), contrast with the conclusion by Smith et al. [65] who focused on pain management (effectiveness). Cho et al. [66] concluded that the evidence does not support the use of acupuncture for pain relief in labour whereas Smith et al. [65] concluded that acupuncture may have a role in reducing pain, the use of pain relief, caesarean section rates, and increasing satisfaction with pain management.

Of the included studies in the Cochrane review [65] three investigated pain management [67-69] and six investigated pain intensity [70-75]. The authors found a reduction of pain intensity when acupuncture was compared to no treatment at all [74, 76-78], and no differences when acupuncture was compared to sham or standard care. They also found a reduced use of pharmacological analgesia when acupuncture was administered compared to standard care [65]. The review by Cho et al. [66] included the same three trials about pain management [67-69] but the trials of pain intensity were not entirely the same [70-72, 74, 75, 77, 78]. The authors found a reduction in pain intensity when acupuncture was compared to no treatment at all and when EA was compared to sham EA. They also found a reduced use of pharmacological analgesia when acupuncture was compared to standard care [66]. Despite the similar results found in the two studies, their conclusions differed, which could be explained by both the different focus on efficacy/effectiveness in the reviews and by the differences in research questions, design, and the outcome measures of the included trials.

The trials included in the two reviews included different types of controls. These were conventional analgesia [67-69], sham needling at non-acupuncture points [70, 74, 75], transcutaneous electrical nerve stimulation (TENS) [67, 71], sterile water injections [72], local massage epidural analgesia, and breathing [71]. In other studies, no pain relief was used as the control[74, 76-78], and in two of these studies, placebo electro-acupuncture with non-penetrating needles at Sp6 was used in a second control group [77, 78].

Qu and Zhou [76] were the authors of the only study using electro-acupuncture published in English that was included in any of the reviews [65]. Two additional studies, Ma et al.[79] and MacKenzie et al. [80] were published later. Qu and Zhou [76] found that women receiving electro-acupuncture at modulating frequency (2-100 Hz) had lower labour pain intensity than women receiving no pain relief at all. Ma et al. [79] found that women receiving electro-acupuncture at modulating frequency (4-20 Hz) had lower pain scores than women receiving standard care. MacKenzie et al. [80] was the only study using low frequency alone (2Hz), and in addition they only included women with induced labour. They found no differences between acupuncture, sham, or standard care in the use of epidural analgesia.

2.2.4 Acupuncture for labour pain, clinical considerations

The majority of previous trials used manual stimulation of needles that were placed at local points located in muscle tissue in the pain area with the same somatic innervations as the cervix and uterus, and in addition distal points in the head, hands, and feet. The number of available acupuncture points varied from a few to approximately 40, however, the actual number of needles used was seldom reported. The time from inserting the needles to removal also varied, ranging from a few minutes [69, 75] to several hours [68-70, 74, 75]

The studies using EA used either modulating frequency or low frequency stimulation. They all used distal points with 2-8 needles. Qu and Zhou [76] used a frequency of 2-100 Hz at two distal points bilaterally, Ma et al. [79] used a frequency of 4-20 Hz at one distal point

bilaterally, and finally MacKenzie et al. [80] used 2 Hz stimulation at four distal points bilaterally. None of these trials used local points within the same somatic innervations as the cervix and uterus, the basis of the gate control theory [42]. However some of their distal points were located within this innervation area.

2.3 OBSTETRIC CARE IN SWEDEN

According to Swedish clinical practice, women receive care from midwives throughout labour and birth and from obstetricians in collaboration with the midwife in cases of deviation from normal progress. The World Health Organization defined a normal birth in 1996 as: *"Spontaneous in onset, low-risk at the start of labour and remaining so throughout labour and delivery. The infant is born spontaneously in the vertex position between 37 and 42 completed weeks of pregnancy. After birth mother and infant are in good condition* [81]. This definition was adopted by The Swedish National Board of Health and Welfare [10]

Approximately 110 000 women give birth in Sweden annually and the mean age of nulliparous women giving birth in Sweden in 2013 was 28.5 years [6]. The most common pharmacological pain relief used during labour in Sweden in 2013 was nitrous oxide, which was used in 82% of all deliveries (88% nullipara and 78% multipara). On average 51% of all nulliparous women used epidural analgesia (EDA) during labour, however this varied between hospitals (21%-71%) [6]. There is evidence that suggests that both nitrous oxide and epidural analgesia have an effect on labour pain, however they also have adverse effects. Women receiving nitrous oxide are more likely to experience vomiting, nausea, and dizziness [5]. Women receiving EDA have a higher rate of instrumental births, caesarean sections for fetal distress, and a longer second stage of labour. In addition, they are more likely to experience hypotension, fever, and urinary retention [5, 82].

Among the non-pharmacological pain relief methods used during labour in Sweden in 2013, immersion in water was the most common and was used in 8% of all deliveries (nullipara 13%, multipara 5%). Both acupuncture and TENS were used in 5% of all deliveries (acupuncture: nullipara 8%, multipara 3%), (TENS: nullipara 7%, multipara 3%). Sterile water injections were used in 4% of all deliveries (nullipara 6%, multipara 2%) [6]. There is some evidence that immersion in water [5] and acupuncture may improve the management of labour pain and satisfaction with the pain relief [5, 65, 66, 83, 84]. There is insufficient evidence for both TENS and sterile water injections [5]. However, all non-pharmacological methods have very few adverse effects and seem safe for both women and infants [5].

Acupuncture is available at all Swedish delivery wards and midwives in Sweden use acupuncture for a number of conditions, both antenatally for hyperemesis and pelvic girdle pain, during labour for retained placenta as well as for pain and relaxation, and after delivery for post-labour pains, milk stasis, and urinary retention [9].

3 RATIONALE

Acupuncture seems to help women manage labour pain and avoid pharmacological pain relief [59, 65, 66, 83, 84]. The pharmacological pain relief methods used today have adverse effects, the most serious of which are associated with the use of EDA [5, 82]. Whether acupuncture can reduce pain intensity is still unclear. When compared to no treatment at all, acupuncture seems to reduce pain intensity [65, 66], however, when compared to sham treatments, acupuncture does not seem to reduce pain effectively [65, 66]. If sham acupuncture actually is a low-intensity form of therapeutic needling [56, 63], pain relief could be dose dependent. It has previously been reported that sterile water injections, which can be consider as a high dose sensory stimulation, reduced the intensity of labour pain more effectively than acupuncture with manual stimulation only [72]. One way to increase the dose of the treatment is to increase the number of needles and to use electro-acupuncture. High-frequency stimulation may produce stronger pain inhibition to visceral pain than low-frequency stimulation [52], but this has not yet been evaluated in the context of labour pain.

There is a lack of knowledge regarding whether a higher dose of acupuncture treatment has a better effect on labour pain, if it can help women manage labour pain better and avoid pharmacological pain relief to a larger extent, or if there are any long-term effects of acupuncture on both labour pain and the birthing experience in general. Moreover, there is very little known about whether specific maternal characteristics are associated with a positive effect of acupuncture treatment during labour.

4 AIMS AND OUTCOME MEASUREMENTS

The overall aim of this thesis was to evaluate the effectiveness of acupuncture with manual stimulation of the needles (MA) and acupuncture with a combination of manual and electrical stimulation (EA) in reducing labour pain, compared with standard care without any form of acupuncture (SC).

4.1 SPECIFIC AIMS

- To describe the study design following the CONSORT and STRICTA recommendations (Paper I).
- To evaluate the effectiveness of acupuncture with manual stimulation of the needles as well as the combination of manual and electrical stimulation in reducing labour pain, compared with standard care without any form of acupuncture (Paper II).
- A long-term follow up on the recollection of labour pain and the birth experience comparing acupuncture with manual stimulation, acupuncture with combined electrical and manual stimulation, and standard care without any form of acupuncture. (Paper III).
- To investigate the associations between maternal background characteristics and 1) assessments of labour pain, and 2) the use of epidural analgesia in women who receive acupuncture using manual stimulation or a combination of manual and electrical stimulation of the needles, and women who receive standard care without any form of acupuncture (Paper IV).

4.2 OUTCOME MEASUREMENTS

4.2.1 Primary outcome

- Women's assessments of labour pain on the visual analouge scale (VAS) (Paper II).

4.2.2 Secondary outcomes

- *Methods of pain relief*: use of epidural analgesia and other forms of pain relief, and women's experience of having received adequate pain relief (Papers II and III).
- *Relaxation*: experience of relaxation during labour and recollection of relaxation two months after birth (Papers II and III).
- *Labour outcomes*: mode of delivery, augmentation of labour, duration of labour, and perineal trauma (Paper II).
- *Infant outcomes*: Apgar score, umbilical cord pH, and neonatal transfer (Paper II).
- *Treatment*: experience of the effect of acupuncture on reducing pain and increasing relaxation, and experience of any adverse effects of the acupuncture treatment (Papers II and III).
- *Recollection of labour pain*: recollection of labour pain, experienced labour pain in relation to expectations and the difference between peak pain during delivery and the labour pain assessed two months later (Papers II and III).

- *Psychological outcomes*: depressive symptoms, emotions during labour and overall birth experience (Paper III).
- *Associations between maternal characteristics and assessments of labour pain* (Paper IV).
- *Associations between maternal characteristics and use of epidural analgesia* (Paper IV).

5 METHODS

A full description of the study design is provided in Paper I. The study protocol followed CONSORT recommendations [54] for reporting randomised controlled trials (RCT) as well as STRICTA recommendations [55], which is a complement for reporting acupuncture studies specifically.

5.1 SETTING

The recruitment of participants took place between November 2008 and October 2011 at two hospital delivery wards in Sweden, Norra Älvsborgs Länssjukhus (NÄL) and Falu lasarett. NÄL had approximately 3200 births per year during the study period and Falu lasarett 2800.

A total of 38 midwives at both delivery wards were part of the study. Their training and experience of administering acupuncture during labour varied and details of this are provided in Table 1, Paper I. To assure that the intervention procedures were performed correctly, we conducted a one-day study-specific course, which included theoretical sessions with a Western medical approach to acupuncture physiology, practical sessions in MA and EA, and lectures on research methodology with a focus on RCT. The course was repeated each semester during the time of data collection. In addition, all midwives had access to a website (www.akupunkturstudien.se) which included instructional videos and written information about the study. Intermittent check-ups at the delivery wards were made to assure that the interventions followed study protocol. Midwives at the antenatal clinics also received in-depth information about the study and the mechanisms of acupuncture before commencement of the study. They gave all nulliparous women who were in gestational week 34-36 and attended regular check-ups at the antenatal clinics written and oral information about the study, and an address to the study website which also included information about pain relief during labour in general, acupuncture, and study-specific information.

The study was designed as a three-armed RCT with an effectiveness approach. The randomisation was computerised (www.randomization.com) by the author and conducted in blocks of 9, 12 and 15, which were varied randomly. Sequentially numbered, opaque, sealed envelopes were prepared by the author and included a study protocol and four questionnaires where each number was linked to one of the three groups. Women were asked to give consent to participate in the study when admitted to the labour ward. When a woman had given her written consent to participate, the assisting midwife picked the envelope with the lowest number on which she wrote the participant's name and social security number, opened it and could see which group the woman was randomised to.

The trial included 303 nulliparous women who were randomised into MA, EA, or SC. Inclusion criteria were: spontaneous onset of labour, admission to the labour ward in latent or active phase of labour, nulliparity, singleton pregnancy, cephalic presentation, gestation 37+0 to 41+6 (weeks + days), expressed need for labour pain relief and, finally, knowledge of the Swedish language good enough to understand written and oral instructions.

The exclusion criteria were: intake of pharmacological pain relief medication within 24 hours prior to inclusion into the study with the exception of paracetamol, preeclampsia, treatment with oxytocin at the time point of allocation, or treatment with anticoagulant or pacemaker.

5.2 INTERVENTIONS

Women in all three groups received care from midwives throughout labour and birth according to Swedish clinical practice, in cases of a deviation from normal progress, obstetricians were responsible for the care in collaboration with the midwife. The participants in all three groups had access to all pharmacological and non-pharmacological analgesia available in Swedish maternity care. However, women in the SC group did not have access to any form of acupuncture.

5.2.1 Acupuncture (MA and EA)

Women in the two acupuncture groups manual acupuncture (MA), or the combination of manual and electrical stimulation (EA), were treated with 13-21 needles, at 3 bilateral distal points and 4-8 bilateral local points, all within the same somatic area as the cervix and uterus. Hegu Xeno needles for single use were used, sized 0.30x30 mm and 0.35x50 mm. A complete list of the points allowed to be used in the study is provided in Table 2, Paper I. The choice of local and distal points was left to the midwife with the instructions to use points with regard to the pain location.

In the MA group, needles were inserted and stimulated manually until DeQi was achieved and thereafter stimulated at ten-minute intervals. In the EA group, needles were inserted and first stimulated manually until DeQi was achieved. Then, eight of the local needles were connected to an electrical stimulator that was set at high frequency (80 Hz) stimulation (Cefar Acus 4, CEFAR, Lund, Sweden). The remaining needles were stimulated manually until DeQi at ten-minute intervals. The decision regarding which local needles were to be connected to the stimulator was made by the midwife based on the location of pain. The woman adjusted the intensity of the electrical stimulation herself to a level just under the pain threshold. The needles were removed after 40 minutes in both groups [33]. The treatment was repeated after two hours, and thereafter it was available on request.

After the first treatment with acupuncture, women had access to all the other pharmacological and non-pharmacological methods of pain relief available on the delivery wards.

5.2.2 Standard care (SC)

Women in the standard care group (SC) had access to all pharmacological and non-pharmacological analgesia available with the exception of acupuncture. The choice of which pain relief to use was made by the woman in consultation with the midwife.

5.3 DATA COLLECTION

Data were collected during labour before the interventions, after the birth, before leaving the delivery ward, the day after birth, and two months later by means of study protocols and questionnaires. The first fifteen women were considered test cases in order to evaluate the study protocol and the questionnaires. The women and the midwives were asked to leave comments on questions that were difficult to understand or were at risk of being misunderstood. No comments were submitted and consequently no changes were made to the protocols and questionnaires after the inclusion of the first women. Data on their pregnancies, labours, and infants were collected from computerised medical records.

5.3.1 During labour

The study protocol was used to collect data on labour pain, relaxation, and details on the interventions and the labour. A complete description of the content of the study protocol is provided in Table 3, Paper I.

Before the interventions started, women were asked to complete the baseline questionnaire (Q1), which included questions on social-demographic background, previous experience of acupuncture, experience of menstrual pain, and worries of the labour pain. A complete description of the content of Q1 is provided in Table 4, Paper I.

During labour women assessed their labour pain and relaxation at two different scales before the first treatment, immediately after the first treatment, and then every 30 minutes for five hours, and thereafter every hour until birth or until epidural analgesia was administered. A different person from the one who administered the intervention (assistant nurse, midwife, or partner) assisted the women in the procedure of measuring pain and relaxation, however, blinding of that person was not possible. They used the VAS, which is a 100 mm horizontal ungraded scale with two endpoints: 'no pain'/'relaxed', to the left corresponded to 0, and 'worst imaginable pain'/'very tense', to the right corresponded to 100. The VAS is a common instrument for assessing pain and has been used in many studies on acupuncture for labour pain [67, 69, 70, 72, 74, 75].

5.3.2 After the birth, before leaving the delivery ward

The midwives completed the study protocol with information of additional pain relief, adverse events in the MA and EA groups, and labour and infant outcomes. Women in the MA and EA groups completed the second questionnaire (Q2), which included questions regarding experience of the acupuncture treatment, effects of the treatment, and adverse effects, if any. A complete description of the content of Q2 is provided in Table 4, Paper I. About two hours after the birth, the women were transferred to a postpartum ward and were cared for by midwives other than those on the labour ward.

5.3.3 Day after birth

Once on the postpartum ward, women in all three groups were asked to complete the third questionnaire (Q3), which included questions regarding labour pain, relaxation, labour pain in relation to what was expected, sufficiency of pain relief, overall experience of the midwife, and satisfaction of the group allocation. Women in the MA and EA groups also answered questions regarding the effectiveness of acupuncture for labour pain and relaxation, if they would select the same treatment again, the midwives' skills when administering acupuncture, and adverse effects, if any. A complete description of the content of Q3 is provided in Table 4, Paper I.

5.3.4 Two months after birth

The fourth questionnaire (Q4) was sent home to the women in all three groups and included questions regarding labour pain, relaxation, labour pain in relation to what was expected, sufficiency of pain relief, emotions during labour, and overall birth experience. Depressive symptoms were assessed by the Edinburgh Postnatal Depression Scale (EPDS) which is a 10-item self-report scale [85] that has been validated in Sweden [86]. Each item is scored on a scale of 0-3, giving a total minimum of 0 and maximum of 30 points, and scores ≥13 indicate depressive symptoms. One of the items concerned whether the woman had thoughts of injuring herself. If she had a score of 3 on that item, the midwives at the two delivery wards responsible for collecting all questionnaires were instructed to contact the woman or her antenatal midwife. Women in the MA and EA groups were also asked whether they had found acupuncture to reduce labour pain and relaxation effectively. A complete description of the content of Q4 is provided in Table 4, Paper I.

5.4 STATISTICS

A complete description of the different outcome measurements is presented in the Appendix.

The sample size calculation was based on the primary outcome: women's assessments of labour pain. A difference of 15 mm on the VAS [72, 87] was regarded as clinically relevant, and the detection of such a difference would require 41 women per group. A previous study [72] reported that only 47% of the women had registered data on pain or relaxation two hours after the first treatment (personal communication with Dr Mårtensson, January 2008), and compensation for a similar dropout rate would require 88 women per group. Finally, we compensated for an additional dropout rate of 15% due to women discontinuing their participation in the study or midwives being unable to participate because of heavy workloads. In total, we aimed to include 303 women, i.e. 101 women per group. The Bonferroni adjusted significant level was 0.017, power 0.80, and a standard deviation of 20.4 mm was based on previous research [68].

5.4.1 Primary outcome

To investigate associations between treatment (MA, EA, SC) and women's assessment of pain on the VAS over time (Paper II), a linear mixed model for repeated measures was performed. Firstly, a fixed effect model was estimated with all main effects (treatment, time) and adjusted for the background factors that differed between groups despite the randomisation i.e. age and education. Secondly, an interaction was added between time and treatment to study if the three groups differed at different time points. For both models it was assumed that covariance structure for time was a first order Autoregressive Model AR(1). Since the estimated VAS scores in these two models was very similar, the model was primarily used without interaction, as it estimated fewer parameters (n=23) than the model with interaction (n=53).

5.4.2 Secondary outcomes

We used the same linear mixed model for repeated measures as the primary outcome to investigate associations between treatment (MA, EA, SC) and women's assessment of relaxation on the VAS over time, Paper II.

To investigate associations between treatment (MA, EA, SC) and continuous variables, we used a two-way ANOVA in Paper II. In Paper III, we used a generalised linear model, which enabled adjustments for maternal age and education.

To estimate the time from baseline to delivery, as well as the time from baseline to epidural analgesia in the three groups (MA, EA, SC), we used a Kaplan-Meier survival curve and a Cox regression model to make adjustments for maternal age and education, Paper II.

To investigate associations between treatment (MA, EA, SC) and discrete variables, logistic regression analyses were used in Papers II and III. Adjustments were made for maternal age and education.

To investigate the associations between maternal characteristics and women's assessments of labour pain on the VAS over time in Paper IV, we performed two different linear mixed models for repeated measures that included two different time periods 1) baseline to 60 minutes (three time intervals, in close proximity to the treatment), and 2) baseline to 240 minutes (eight time intervals). We assumed that the covariance structure for time was a first order Autoregressive Model AR (1). First, we included all baseline characteristics, and from this model we removed characteristics one by one that had a p-value greater than 0.25. To investigate if there were any associations with the treatment administered (SC, MA, or EA) we added treatment to this model, which resulted in our final model. To this final model we added an interaction term between treatment and each characteristic that had a p-value below 0.05 one by one.

To investigate the associations between maternal characteristics and the use of epidural analgesia in Paper IV, we used logistic regression using the same strategy for the analyses as described above.

Baseline characteristics are reported as means for continuous variables and percentages for discrete variables. Characteristics of the women randomised and those included in the final analyses are presented in Table 1.

6 ETHICS

The Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects is a statement of ethical principles for medical research involving human subjects to ensure respect for all human subjects and protect their health and rights [88]. We have carefully considered all principles that apply to our study. The design and performance of a study involving human subjects should be clearly described, so to assure this we designed our study according to CONSORT [54] and STRICTA [55] and we also decided to publish our study protocol, see Paper I.

Even though there are a few previous studies that evaluate acupuncture during labour [59, 65, 66, 83, 84] there is still a need for more knowledge regarding the dose of the acupuncture treatment. In addition, there is a lack of knowledge of the long-term effects of acupuncture on both labour pain and the birthing experience in general and if there are any specific maternal characteristics that are associated with a positive effect of the acupuncture treatment. Interventions during labour should be avoided if possible since it is a unique situation for women and their partners, experienced only once or a few times in a lifetime. When forming the study protocol we aimed to avoid unnecessary examinations and interventions as it was important for us to disturb the labour process as little as possible.

Since medical research involving humans must be conducted by individuals with the proper training and qualifications, all women received care from midwives throughout labour and birth according to Swedish clinical practice, and in cases of a deviation from normal progress, obstetricians were responsible for their care in collaboration with the midwife. In addition, participating midwives received a one-day study-specific course, which included theoretical sessions with a Western medical approach to acupuncture physiology and practical sessions in MA and EA. To assure that the study was performed at a high quality we also included lectures on research methodology, particularly RCT. We did not want to risk that the women's participation would be of no purpose if the midwives did not fully understood the importance of following the study protocol precisely.

Women who were in gestational week 34-36 and attended regular check-ups at the antenatal clinics, received written and oral information about the study which included information of potential risks, that their participation in the study was voluntary and that their decision whether or not to participate would not affect their current or future treatment. If they decided to participate they were free to withdraw at any time and all data would be unidentified.

The same written and oral information was given when they arrived at the labour ward, and thereafter they were asked to give consent to participate in the study. The women who agreed to participate in the study signed a written consent form.

We have assured that all data are protected and that all data published are unidentified. The electronic data files include information connected to the randomisation number only, and the identification key is stored in a separate location to the original questionnaires and study protocols. The author, her supervisors, and the statistician had access to the unidentified electronical data and only the author had access to the data files with the identification key.

Measures have been taken to minimise the risks of the acupuncture treatment. Acupuncture may cause minor discomfort, most commonly tiredness or minor bruising, however no serious adverse events have been reported in previous trials on acupuncture during labour.

The study was approved by the Regional Ethical Review Board in Gothenburg, 2008-05-15, Dnr: 136-08 and it was registered at Clinical Trials.gov: NCT01197950. Due to a misunderstanding in the process, the study was not registered in Clinical Trials before commencing the data collection. The trial was registered one year prior to completion of the study (August 26, 2010), and no changes were made from inclusion of the first woman until completion of the study.

7   RESULTS

7.1   SAMPLE, RESPONSE RATE, AND DATA ON THE INTERVENTIONS

Recruitment and participation are presented in the flow chart below (Figure 2). Of the approximately 4300 eligible women, 679 were approached and asked to participate in the study. A total of 303 accepted and they were randomised as follows; MA 99, EA 103, and SC 101. The interventions were given to 253 women; MA 83, EA 87, and SC 83. The intention to treat analysis included all women randomised whereas the per protocol analysis excluded women who were randomised despite them not fulfilling inclusion criteria (MA 3, EA 5, SC 8), or who did not receive the interventions as planned (MA 16, EA 30). There were no differences in primary outcome measurements when analyses were performed according to the principles of intention to treat and per protocol respectively. All results presented in Papers II-IV are analysed according to intention to treat.
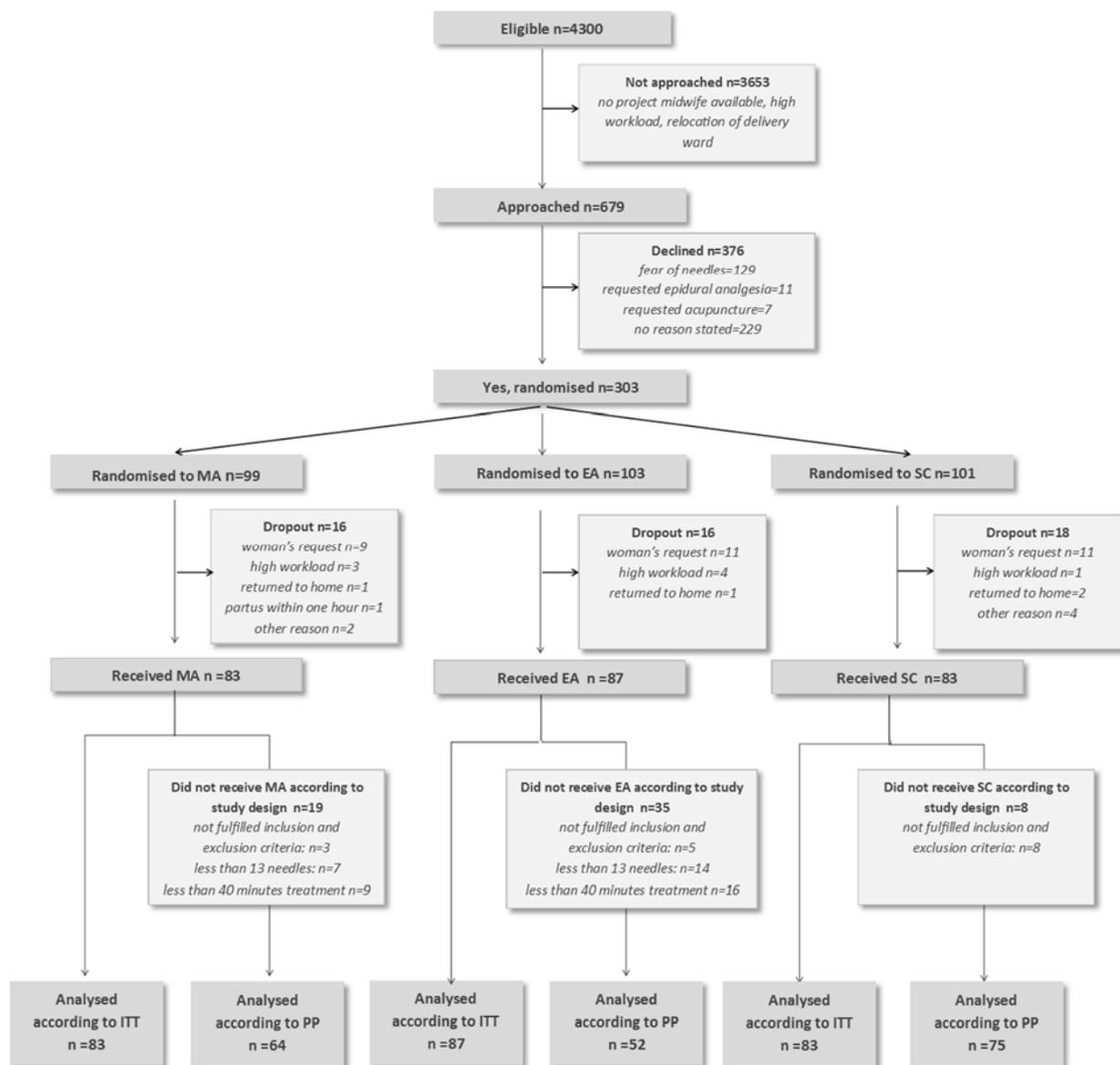

Figure 2. Flow-chart of the study participants. MA= Manual acupuncture, EA=Acupuncture with a combination of manual- and electrical stimulation, SC= Standard Care, ITT=Intention to treat, PP= Per protocol

Before the beginning of the interventions all women were given Q1. A Total of 80 women (96%) in the MA group responded, 87 (100%) in the EA group, and 82 (99%) in the SC group, with no differences between the groups. After the birth and before leaving the delivery ward, women in the MA and EA groups were given Q2, where 72 women (87%) in the MA group and 79 women (91%) in the EA group responded, with no differences between the groups. At the postpartum ward, the day after birth, women in all three groups were asked to complete Q3. It was completed by 77 women in the MA group (93%), 79 in the EA group (91%), and 77 in the SC group (93%). The mean amount of days after birth for responding to the questionnaire was; MA 3.5, EA 2.2, and SC 2.6, with no differences between the groups. Q4 was sent home to the women two months postpartum, and it was completed by 67 women in the MA group (81%), 78 in the EA group (90%), and 72 in the SC group (87%). The mean amount of days after birth for responding to the questionnaire was; MA 65.7, EA 68.3, and SC 69.2, with no differences between the groups.

The mean time (minutes) from inclusion in the study to the start of the first treatment did not differ between the groups; MA 19.8, EA 15.6, and SC 30.2. According to protocol, the duration of the acupuncture treatment was 40 minutes and the number of needles used was 13-21 and this was reached in both groups. There was no difference in the mean duration of the first acupuncture treatment; 50 minutes in the MA group and 48 minutes in the in the EA group. In addition, the mean number of needles was over 13 in both groups; MA 14.9 and EA 14.9. The proportion of women who did not receive the first acupuncture treatment as intended (less than 13 needles or less than 40 minutes) did not differ between the groups. Despite the intention to repeat the acupuncture treatment after two hours, and then on the woman's request, very few women received a second treatment, MA 9 (10.8%) and EA 7 (8%), and only one woman in the EA group, received a third treatment.

Characteristics of the women included in the final analyses are presented in Table 1. Women in the SC group were older and more educated than women who received MA, but no other differences were found. To test the representativity of the sample, we obtained data on maternal age, relationship status, smoking status, and body mass index for all women who were eligible for the study. We made an additional application to the Regional Ethical Review Board in Gothenburg, 2011-09-16, Dnr: 136-08, to get approval for collecting these data. Our study sample did not differ from this larger group except regarding smoking, which was less common in the study sample.

7.2 LABOUR PAIN AND PAIN RELIEF

The main findings regarding labour pain and the use of pain relief reported in Papers II, III, and IV are presented in this section.

Table 1. Characteristics of the women included in the final analyses for Papers II-IV

	MA		EA		SC	
	n		n		n	
Background characteristics						
Age (years), mean (SD)	83	26.5 (4.8)	87	27.6 (4.6)	83	28.3 (5.0)
≤25 (%)		45.8		33.3		30.2
26 – 34 (%)		48.2		38.4		54.2
≥35 (%)		6.0		5.7		10.8
Born in Sweden (%)	80	91.3	87	89.7	82	90.2
Higher education (%)	80	35.0	87	44.8	82	54.9
Single status (%)	83	14.5	87	18.4	83	15.7
Smoking three months prior to pregnancy (%)	74	23.0	77	22.1	71	19.7
Body mass index in early pregnancy, mean (SD)	72	24.4 (5.0)	75	24.2 (3.8)	68	24.9 (4.1)
BMI ≥25 (%)		34.7		36.0		41.2
Dysmenorrhea	83	73.5	87	72.4	82	59.8
Acupuncture treatment prior to present pregnancy	82	9.6	87	10.8	80	6.8
Worried about labour pain	80	68.8	86	61.6	80	67.5
Worried about pain in daily life	83	12.0	87	8.0	81	7.4
Status at admission to labour ward						
Gestational week, mean	83	40+0	87	39+6	83	40+0
Undiagnosed breach presentation (%)	83	0	87	0	83	1.2
Cervix dilatation at admission (cm), mean (SD)	81	3.6 (1.5)	80	4 (1.6)	79	3.6 (1.8)
>3 cm (%)		53.1		61.3		48.1
Membranes ruptured before admission (%)	82	30.5	87	28.7	81	33.3
Pharmacological pain relief prior to recruitment, except for paracetamol (%)	83	2.4	87	3.4	83	8.4
Treatment with oxytocin at the time point of allocation (%)	53	1.9	47	4.3	48	2.1
Infant						
Head circumference (cm), mean (SD)	83	34.9 (1.4)	87	34.9 (1.3)	83	35 (1.3)
Birth weight (grams), mean (SD)	83	3508 (410)	87	3590 (456)	81	3654 (493)

MA= Manual acupuncture, EA= Acupuncture with a combination of manual- and electrical stimulation, SC= Standard care, SD= Standard deviation, BMI=Body mass index (Kg/m^2)

7.2.1 Labour pain measured prospectively (primary outcome)

There were no statistically significant differences between the groups on the primary outcome women's assessment of labour pain on the VAS. The mean estimated pain scores on the VAS from baseline to 480 minutes were: MA 66.4 Standard Error (SE) 2.0, EA 68.5 (SE 2.0), and SC 69.0 (SE 1.8). (Figure 3 and Table 2).
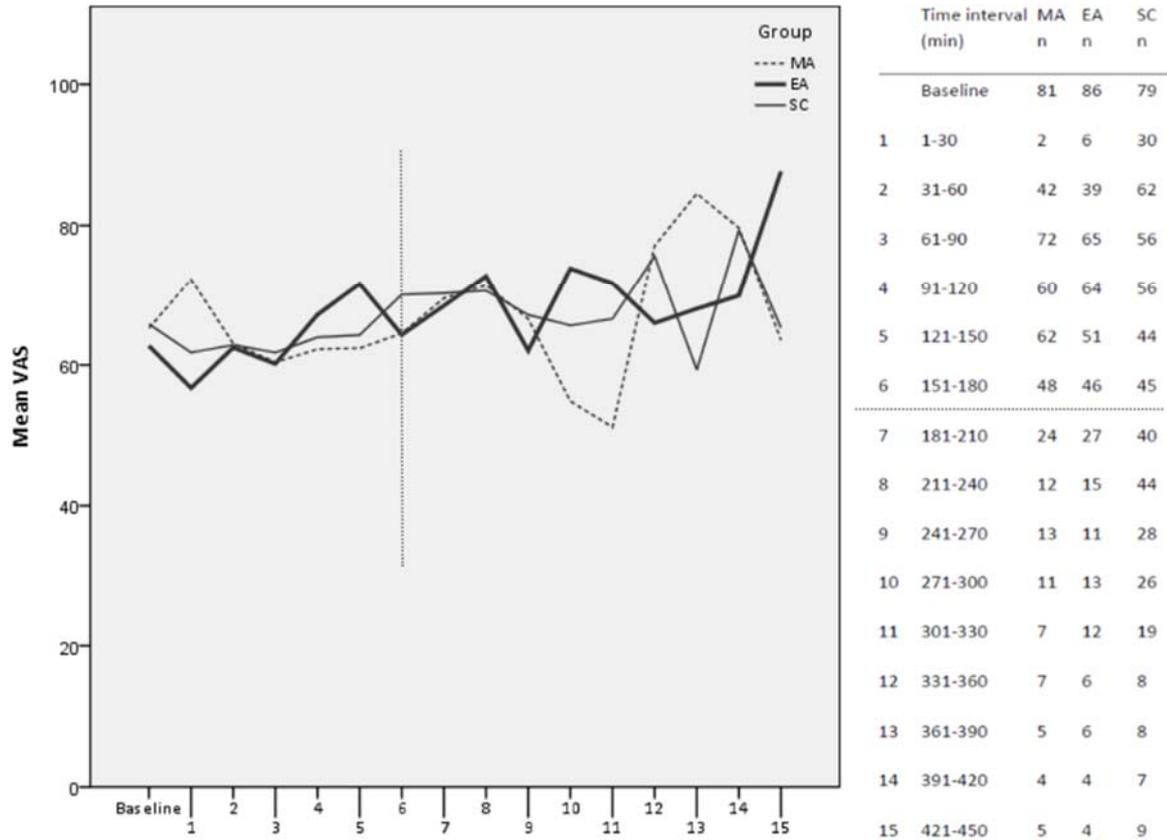

	Time interval (min)	MA n	EA n	SC n
	Baseline	81	86	79
1	1-30	2	6	30
2	31-60	42	39	62
3	61-90	72	65	56
4	91-120	60	64	56
5	121-150	62	51	44
6	151-180	48	46	45
7	181-210	24	27	40
8	211-240	12	15	44
9	241-270	13	11	28
10	271-300	11	13	26
11	301-330	7	12	19
12	331-360	7	6	8
13	361-390	5	6	8
14	391-420	4	4	7
15	421-450	5	4	9

Figure 3. Mean pain scores on a visual analogue scale (VAS) from time point 1 (baseline) to 15 (450 minutes). MA = manual acupuncture, EA = acupuncture with a combination of manual- and electrical stimulation, SC = standard care, n = number of valid observations at each time interval, the sample size calculation gave 41 in each group and after time interval 6, n < 41 in MA and EA, after time interval 8, n < 41 in SC. The model with interaction was used to identify time intervals when the three groups differed in pain scores on the VAS, Paper II[89].

7.2.2 Associations between labour pain and maternal background characteristics (secondary outcomes)

Two maternal characteristics were associated with the women's assessments of labour pain from baseline to 60 minutes. Low pain scores were associated with higher maternal age and a cervical dilatation of more than 3 cm on admission. For the longer time period (from baseline to 240 minutes), low pain scores were associated with higher maternal age, and high pain scores were associated with dysmenorrhea. Since our interest was to investigate if any characteristic could predict a better response to the acupuncture treatment, we analysed the interactions between treatment and the maternal characteristics that were associated with women's assessments of labour pain. We found no interactions between treatment and any of the maternal characteristics (Table 3).

Table 2. Labour pain and obstetric pain relief

	MA	EA	SC	MA vs. SC	EA vs. SC	MA vs. EA
Labour pain				MD (95%CI)[1]	MD (95%CI)[1]	MD (95%CI)[2]
Women's assessments of labour pain, during labour, mean (SE)	66.4 (2.0)	68.5 (2.0)	69.0 (1.8)	2.6 (-1.7-6.9)	0.6 (-3.6-4.8)	-2.1 (-6.3-2.2)
Recollection of labour pain, two months after birth, mean (SE)	69.3(3.0)	68.7(2.8)	70.1(2.8)	0.8 (-6.3-7.9)	1.3 (-5.5-8.1)	0.5 (-6.4-7.4)
Pain difference two months after birth, Mean (SE)	11.7 (3.0)	14.1(2.8)	13.7 (2.8)	2.0 (-5.1-9.2)	-0.4 (-7.2-6.4)	-2.4 (-9.3-4.5)
				OR (95% CI)[1]	OR (95%CI)[1]	OR (95%CI)[2]
Pain worse than expected, day after partus (%)	51.9	54.4	65.8	0.5 (0.3-1.1)	0.6 (0.3-1.2)	1.2 (0.6-2.3)
Pain worse than expected, two months after birth (%)	42.4	42.7	47.1	0.8 (0.4-1.6)	0.8 (0.4-1.6)	1.0 (0.5-2.0)
Pain relief (%)						
Nitrous Oxide	95.1	95.4	93.8	1.9 (0.4-8.4)	1.5 (0.4-6.0)	0.8 (0.2-3.8)
Sterile water injections	12.2	4.7	10.0	1.2 (0.4-3.1)	0.4 (0.1-1.4)	0.4 (0.1-1.2)
TENS	14.5	12.6	48.1	*0.2 (0.8-0.4)*	*0.2 (0.7-0.3)*	0.9 (0.4-2.3)
Morphine	9.6	1.1	4.8	2.3 (0.6-8.0)	0.2 (0.3-2.1)	*0.1 (0.0-0.9)*
Epidural analgesia	61.4	46.0	69.9	0.6 (0.3-1.2)	*0.4 (0.2-0.7)*	0.6 (0.3-1.1)
Sufficient pain relief, day after partus	76.6	81.0	73.7	1.3 (0.6-2.8)	1.7 (0.8-3.7)	1.3 (0.6-2.8)
Sufficient pain relief, two months after birth	75.4	84.4	75.0	1.2 (0.5-2.9)	2.1 (0.9-4.9)	1.7 (0.7-4.0)
Acupuncture effective for reducing pain, immediately after birth	44.4	67.1				*2.4 (1.2-4.8)*
Acupuncture effective for reducing pain, 2 months after birth	34.3	50.7				1.8 (0.9-3.6)

Adjusted for age and education. SC=Standard Care, MA= manual acupuncture, EA=Acupuncture with a combination of manual- and electrical stimulation, MD= Mean difference, OR= Odds Ratio, 95% CI= 95% Confidence interval, SE= Standard Error, TENS= Transcutaneous Electrical Nerve Stimulation, [1] SC is reference, [2]MA is reference

Table 3. Associations between maternal characteristics and women's assessments of labour pain on the VAS from baseline to 60 and 240 minutes and the use of epidural analgesia

	n	Adj. Mean Estimates (SE) (0-60 min)	Mean Difference (95% CI)	Inter-actions p	n	Adj. Mean Estimates (SE) (0-240 min)	Mean Difference (95% CI)	Inter-actions p	EDA%	OR(95% CI)	Inter-actions p
Age, years											
<25	162	58.9 (3.7)	Ref		457	67.0 (1.6)	Ref				
26 – 34	238	56.5 (3.6)	-2.3 (-7.2-2.5)		658	63.0 (1.3)	*-3.9 (-7.8- -0.5)*		57.2		
>35	27	45.8 (5.9)	*-13.2 (-23.4- -2.9)*		72	55.2 (3.7)	*-11.8 (-19.6- -3.9)*		57.9		
Dysmenorrhea*	289	55.8 (3.9)	4.1 (-1.0-9.2)		809	64.5 (1.6)	*5.5 (1.6-9.5)*		57.2	0.6 (0.3-1.0)	
Acupuncture treatment prior to present pregnancy*									69.1	*2.8 (1.3-6.1)*	
Cervix dilatation >3 cm at admission*	219	51.2 (4.0)	*-5.0 (-9.6- -0.5)*		562	60.7 (1.7)	-2.1 (-5.8-1.6)		46.2	*0.2 (0.1-0.5)*	
Treatment											
SC	171	55.5 (4.1)	Ref		412	63.6 (1.9)	Ref		69.9	Ref	
MA	125	52.9 (4.1)	-2.6 (-8.1-3.0)		391	59.8 (2.0)	-3.8 (-8.3-0.7)		61.4	0.6 (0.2-1.2)	
EA	131	52.9 (4.1)	-2.6 (-8.2-3.0)		384	61.7 (2.0)	-1.9 (-6.5-2.7)		46.0	*0.3 (0.1-0.6)*	
Interactions											
Treatment*Age				0.44				0.44			
Treatment* Cervix dilatation >3 cm at admission				0.35							
Treatment* Dysmenorrhea								0.22			
Treatment*Time interval				0.71				0.21			
Treatment*Acupuncture treatment prior to present pregnancy											0.61
Treatment* Cervix dilatation >3 cm at admission											0.18

Interactions (Tested one by one in the final model) * Reference is women not exposed to the variable studied. SC=Standard care, MA=Manual Acupuncture, EA= Acupuncture with a combination of manual- and electrical stimulation, BMI=Body mass index (Kg/m2), Adj= Adjusted, SE= Standard Error, the estimate represents scale steps on the Visual Analogue Scale (VAS), from 1-100., 95% CI= 95% Confidence Interval. A positive mean difference means that the reference group had lower pain scores on the VAS than the comparisons, a negative number means lower pain scores. 15 was regarded as a clinically significant difference. OR= Odds ratio

7.2.3 Recollection of labour pain (secondary outcomes)

Women's assessments of the overall labour pain at two months after the birth did not differ between the groups; MA 69.3(SE 3.0), EA 68.7(SE 2.8), and SC 70.1 (SE 2.8) and were very similar to the assessments during labour (Table 2). The pain difference, i.e. the change from the estimated peak pain during labour to the estimated pain two months after birth, did not differ between the groups. The estimated mean pain was lower two months after birth in all three groups. Correspondingly, the day after birth approximately 50% of the women reported that they had experienced worse pain than expected during labour regardless of treatment, and two months later this rate was reduced to approximately 40%.

7.2.4 Relaxation (secondary outcome)

Women's assessments of relaxation during labour did not differ between the groups, the adjusted mean estimates were: MA 61.0, EA 62.9, and SC 64.6. The mean differences were as follows: SC vs. MA mean difference (MD) 3.6 CI 95% -1.4 to 8.7, SC vs. EA MD 1.7 CI 95% CI -3.2 to 6.7, and MA vs. EA MD -1.9 CI 95% -6.9 to 3.1. Similarly, there were no differences in the mean scores for recalled relaxation in each group two months after birth, MA 52.8, EA 53.1, and SC 55.8. The mean differences were as follows: SC vs. MA MD 3.0 CI 95% -5.3 to 11.2, SC vs. EA MD 2.7 CI 95% CI -5.3 to 11.2, and MA vs. EA MD -0.3 CI 95% -8.3 to 7.8.

7.2.5 Use of pain relief (secondary outcomes)

The use of epidural analgesia was lower in the EA group than in the other groups: MA 61.4%, EA 46.0%, and SC 69.9% (Table 2). Women in the EA group also used less TENS than women who received SC (12.6% vs. 48.1%) and less morphine than women who received MA (1.1% vs. 9.6%). The majority of women in all three groups were satisfied with their overall pain relief the day after partus and two months later (Table 2).

7.2.6 Associations between the use of epidural analgesia and maternal background characteristics (secondary outcomes)

Three characteristics were associated with the use of epidural analgesia: prior experience of acupuncture increased the odds of having an epidural, whereas cervix dilatation of greater than 3 cm on admission and being allocated to the EA group reduced the odds. There were no interactions between treatment and previous acupuncture experience or between treatment and cervix dilatation on admission (Table 3).

7.2.7 Experience of the acupuncture treatment (secondary outcomes)

The majority of women who received EA (67.1%) stated immediately after partus that acupuncture was effective for reducing pain, which was a higher rate than among women who received MA (44.4%).Two months later, there were no differences between the groups; EA (50.7%) and MA (34.3%) (Table 2). No differences between the groups were found in reported negative side effects, EA 7% and MA 10%. These were mostly related to pain

associated with the insertion of the needles, numbness, and tiredness. The majority of women reported that they felt confident regarding the midwives' skills when providing acupuncture treatment; EA 88.8% and MA 92.4%, with no differences between the groups.

7.3   LABOUR AND INFANT OUTCOMES (SECONDARY OUTCOMES)

Women in the EA group spent less time in labour (mean 500 min) than those who had received MA (mean 619 min) and SC (mean 615 min), with MA vs. EA Hazard Ratio (HR) 1.4 95% CI (1.0 to 1.9), and SC vs. EA HR 1.4 95% CI (1.1 to 2.0) (Figure 4). Other obstetric and neonatal outcomes, such as mode of delivery, perineal trauma and Apgar score at 5 minutes were very similar in the three groups with the exception of estimated blood loss, which was lower in the EA group than in the SC group. A total of 2.3% of the women receiving EA had an estimated blood loss larger than 1000 ml and 12.2% in the SC group EA vs. SC OR 0.1 95% CI (0.3 to 0.7).
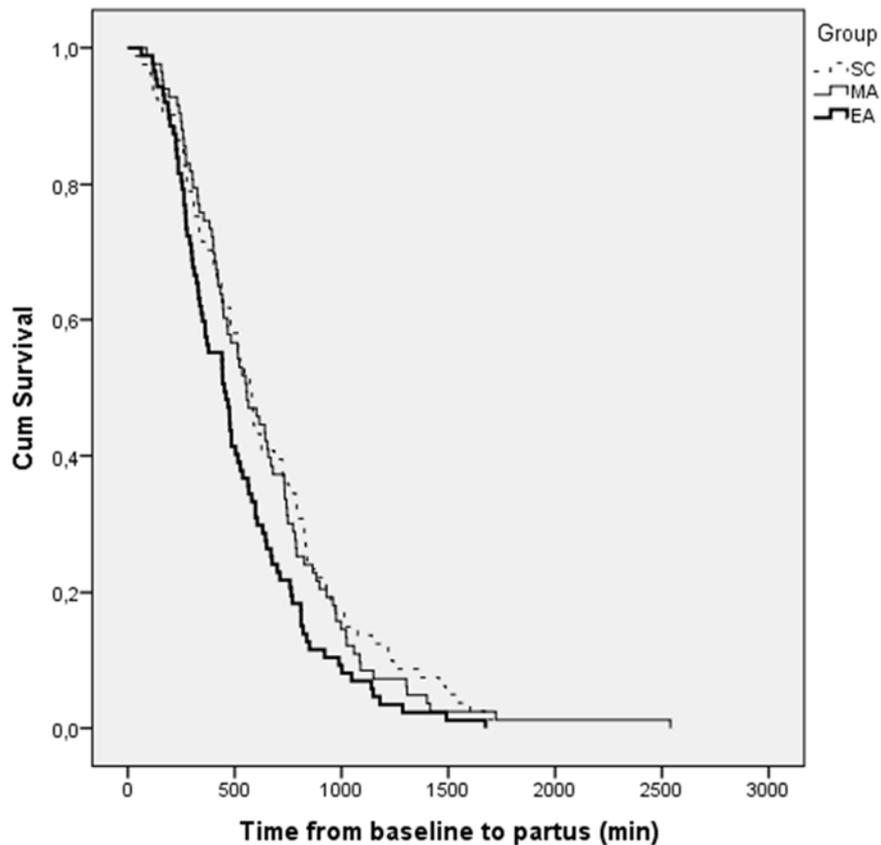
Figure 4. Time from baseline to partus in women who received manual acupuncture, acupuncture with a combination of manual- and electrical stimulation, or standard care described by Kaplan-Meier survival curve. Unadjusted values. SC=Standard Care, MA= manual acupuncture, EA=Acupuncture with a combination of manual- and electrical stimulation

7.4 EMOTIONS AND SUPPORT (SECONDARY OUTCOMES)

Regardless of treatment, the number of positive and negative emotions during labour did not differ between the groups, and in addition the majority of all women had overall positive emotions during labour; MA 87.9%, EA 84.6%, SC 81.9%. Regardless of treatment, most women had a positive overall birth experience, MA 64.6%, EA 61.0%, SC 54.3% assessed the day after birth and few women had depressive symptoms assessed with the Edinburgh Postnatal Depression Scale two months later, MA 4.5%, EA 5.1%, SC 8.3%. Regardless of treatment, the vast majority of women had a positive overall experience of their midwife, both when assessed the day after birth and two months later. They were also satisfied with the support she had offered during labour and birth. However, the number of women who were satisfied was lower in all three groups at two months after birth than the day after birth (Figure 5).
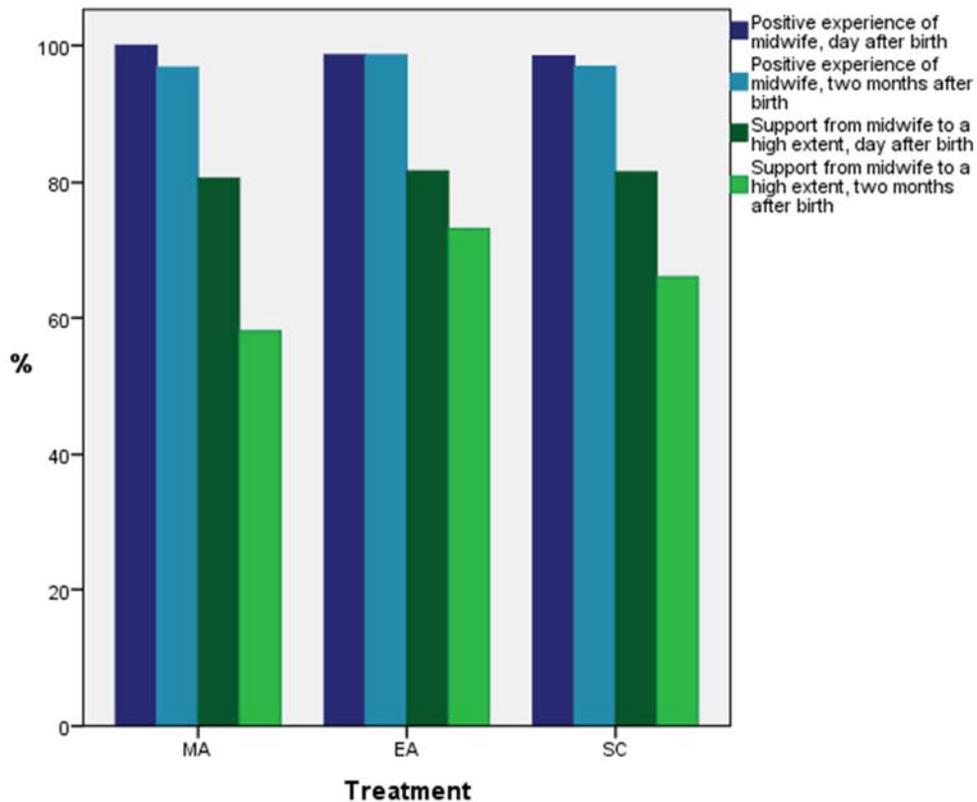
Figure 5. Women's experience of their midwife and her support
MA= manual acupuncture, EA=Acupuncture with a combination of manual- and electrical stimulation, SC=Standard Care

8 DISCUSSION

The effect of acupuncture with manual stimulation of the needles or acupuncture combining manual and electrical stimulation did not differ from standard care without acupuncture in terms of reducing women's experience of pain during labour. Also, women's recollection of pain and assessment of childbirth in general at two months after the birth, and the assessments of relaxation; during labour and two months later were similar in all three groups. In addition, women's assessments of their midwives as being supportive during labour, their overall satisfaction with midwifery care, and having experienced childbirth overall as a positive experience were similar in all three groups. However, women who received acupuncture combining manual and electrical stimulation used other forms of pain relief to a lesser extent, including epidural analgesia, than women who received acupuncture with manual stimulation or standard care. Furthermore, they stated immediately after partus that acupuncture was effective for reducing pain to a higher extent than women who had received acupuncture with manual stimulation. They spent less time in labour than women who received acupuncture with manual stimulation or standard care, and had less blood loss than women receiving standard care. Maternal characteristics such as maternal age, dysmenorrhea, and cervix dilatation were associated with labour pain, but none of all the investigated characteristics could predict the outcome of the acupuncture treatment with manual stimulation or a combination of manual and electrical stimulation for labour pain.

8.1 THE EFFECTIVENESS OF ACUPUNCTURE ON LABOUR PAIN

Acupuncture did not reduce labour pain when compared to standard care, despite the effort to optimize the intensity of the treatment. During labour, the pain system is highly sensitised and the intensity of labour pain increases as labour proceeds [1, 13, 24, 28], which places high demands on the given pain relief. Postoperative pain is in some ways similar to labour pain with a large acute inflammatory component, and studies evaluating the effect of acupuncture on this type of pain are contradictory [90, 91]. It seems that acupuncture can reduce the need for postoperative analgesia, however the effects on the experienced pain are contradictory [91]. This is in contrast to chronic pain conditions, where acupuncture has been found effective [92]. It is likely that acupuncture is not effective enough to reduce high-intensity pain such as labour pain, though it does have an effect on chronic pain, which is not as intense.

Our hypothesis was that a high intensity of acupuncture treatment could possibly reduce women's labour pain compared with standard care. The majority of previous trials used manual stimulation, the time from inserting the needles to removal varied from a few minutes to several hours and the number of needles used were mostly unreported. When acupuncture was compared to no treatment, acupuncture seemed to reduce pain intensity [65, 66], however, when acupuncture was compared to sham treatment or standard care, acupuncture does not seemed to reduce pain effectively [65, 66], indicating that the pain relief could be dose dependent. We designed an intervention with a high dose sensory stimulation by means of a high number of needles (13-21) and by combining manual and electrical stimulation.

Most women received the treatment as intended, except for that only a few had a second treatment as the protocol stated, because the midwives were short of time. Our intention was to compare a lower dose of sensory stimulation (acupuncture with manual stimulation) and a higher dose sensory stimulation (acupuncture with a combination of manual and electrical stimulation) with *no* acupuncture, i.e. *no* sensory stimulation. However, a large proportion of the women who received standard care used sensory stimulation other than acupuncture; 10% used high dose sensory stimulation sterile water injections as compared to 6% of nulliparous women in general in Sweden, and 48% used another sensory stimulation technique, TENS, which is a much higher rate than in nulliparous women in general in Sweden (7% in 2013). Sterile water injections are shown to reduce the intensity of labour pain more effectively than acupuncture with manual stimulation [72], and TENS and manual acupuncture have shown similar effects [67]. This means that many women in the SC group were treated with methods that possibly have similar mechanisms of action as acupuncture. Consequently, our findings indicate that a combination of manual and electrical acupuncture *is not superior* to other sensory stimulation or combinations of sensory stimulation on labour pain.

Women who receive continuous one-to-one support during labour are less likely to use any forms of intrapartum analgesia [93]. Acupuncture is a relatively time consuming intervention that requires a high level of attendance from the midwife in the labour room and a lower pain intensity in both acupuncture groups than in the SC group could have been expected. We were not able to measure time spent with the women by the midwives however, as proxies we used the level of satisfaction with the midwife and her support, which was not higher in either of the acupuncture groups than in the standard care group, and the overall assessment of emotions during labour (positive/negative) was similar between the groups.

The lack of difference between the groups regarding experience of pain during labour may be explained by the fact that women in the EA group continued to contribute with pain assessments in a later and more painful stage of labour than the other two groups since the VAS assessments were aborted when EDA was administered. Consequently, the effect of acupuncture with electrical stimulation may have been underestimated.

8.2   THE EFFECTIVENESS OF ACUPUNCTURE ON SECONDARY OUTCOMES

The finding that the effect of acupuncture with manual stimulation or with combined manual and electrical stimulation on labour pain did not differ from standard care is further supported by the fact that there were no differences between the groups in women's assessments of relaxation during labour, which were assessed at the same time. Relaxation is suggested to facilitate coping with pain [94], and in clinic many midwives use acupuncture for relaxation. However, a more direct way to assess women's ability to cope with labour pain would have been to ask whether the pain was manageable or not.

We found a reduced use of pharmacological analgesia, particularly epidural analgesia, in women who received acupuncture with combined manual and electrical stimulation.

This result is supported by the two most recent reviews on acupuncture for labour pain [65, 66] but needs to be interpreted with caution. We chose not to use epidural as a primary outcome, since the decision to use epidural analgesia is not made independently by the labouring woman but rather in consultation with the midwife and in accordance with the local culture of the labour ward [95]. There was a risk that the midwives could be biased in favouring the acupuncture treatment in this un-blinded trial, and may not have offered or encouraged the use of an epidural. The midwives could have been in favour of manual acupuncture since the majority had several years of experience of such treatment. On the other hand, they could have been in favour of acupuncture with the combination of manual and electrical stimulation since it was introduced as a higher dose. However, differences in the use of epidural analgesia were only seen when comparing EA with SC but not between MA and SC. Consequently, an actual difference between the women's need for an epidural cannot be dismissed. One concern was that the women in the EA group had been denied the pain relief they actually needed, and thereby were at risk of having a more negative birth experience [2]. However, we could not detect any differences for women in the EA group compared to the other two groups, neither in their overall birth experience, in their satisfaction with the overall pain management, nor in their assessments regarding whether the experienced pain was worse than expected, both the day after birth and two months later.

The reduced rate of epidural may also be explained by the fact that acupuncture with the combination of manual and electrical stimulation was partly self-managed, which may have increased the women's experience of control. The women adjusted the intensity of the electrical stimulation themselves to a level just under the pain threshold during the contractions of varying intensity, thus gaining control over the stimulation and intensity of treatment. Having an influence on decisions regarding one's care and having a feeling of control are important factors in managing labour pain [96-98]. Except for the self-management aspect, acupuncture deactivates limbic areas in the brain that contribute to reducing emotional aspects of pain, such as fear and anxiety [32, 46-48], and acupuncture with electrical stimulation seems to have a larger impact on some of these structures than manual acupuncture [48]. Women were also more satisfied with the effectiveness of acupuncture using a combination of manual and electrical stimulation than of acupuncture solely using manual stimulation.

We were not able to identify any maternal characteristics that could predict the outcome of the acupuncture treatment with manual stimulation or a combination of manual and electrical stimulation for labour pain, however there are some limitations. There is a possibility that we did not find any associations due to the sample size being too small, or that the maternal characteristics were not selected primarily to making these predictions.

8.3   METHODOLOGICAL CONSIDERATIONS

8.3.1   Strengths

This is one of the largest trials evaluating the effectiveness of acupuncture on labour pain, and we followed the CONSORT [54] and STRICTA [55] recommendations; in the design of the study, in reporting requested details in a study protocol publication, and in reporting the results. Since there was a lack of knowledge regarding whether a higher dose of acupuncture treatment may have a better effect on labour pain, we optimised the treatment by using a large number of needles within the same innervation area as the cervix and uterus. We also used high intensity stimulation in the combination of manual and electrical stimulation.

Another strength of the study is the statistical approach. To make comparisons of labour pain over time needs some considerations. The nature of labour pain is different from other pain conditions since it is closely correlated to the labour progression and will increase as the labour proceeds [1, 13, 24, 28]. There were no differences between the groups in the mean cervix dilatation at admission, or the time from admission to baseline, which implies that all women were approximately in the same stage of labour at baseline when the first pain assessment was made. The following assessments of pain and relaxation were made every 30 minutes for the first five hours with regard to the effect of the progression of labour on the pain experience. We used a linear mixed model for repeated measures in our analysis, which have not been done in any of the previous trials evaluating the effect of acupuncture on labour pain. Generally, longitudinal data, i.e. repeated observations for the same individual, are often correlated. This correlation violates the assumption of independence necessary for more-traditional, repeated-measures analysis, and leads to bias in regression parameters. A linear mixed model for repeated measures enables handling the integration of time-varying factors as well as missing data [99, 100].

To assure that the study was performed at a high standard, the participating midwives were given training in both theoretical and practical sessions in acupuncture with manual stimulation and acupuncture with combined manual and electrical stimulation. Lectures on research methodology were also included, particularly regarding the rigor of conducting an RCT. In addition to this, all midwives had access to a website with instructional videos and information on the study. Intermittent check-ups at the delivery wards were made each semester to assure that the interventions followed study protocol. The study protocol was evaluated, as were the questionnaires for the first fifteen women. The women and the midwives were asked to leave comments on questions that were difficult to understand or were at risk of being misinterpreted. No comments were submitted and consequently no changes were made to the protocols and questionnaires.

The midwives' experience of acupuncture with manual stimulation and acupuncture with combined manual and electrical stimulation within this randomised controlled trial was investigated by means of a web-based survey after the completion of the study. This was published as two master degree projects in Sexual, Reproductive, and Perinatal Health at Karolinska Institutet [101, 102]. The midwives found the trial important yet complicated and time consuming in a busy labour ward. The majority of midwives thought that acupuncture with manual stimulation and acupuncture with combined manual and electrical stimulation were effective for labour pain; 77% and 91% respectively.

8.3.2 Limitations

We discontinued the pain assessments when epidural analgesia was administered, however, it would have been valuable to have continued assessments of labour pain since epidural analgesia does not always lead to a reduction in pain.

Another problem was that women in the SC group had the option of having forms of pain relief with similar relieving mechanisms as acupuncture, namely TENS and sterile water injections, and therefore did not constitute a control group without sensory stimulation as intended. From an ethical perspective it would have been problematic to deny the women sterile water injections and TENS, especially in the SC group where acupuncture was not an option.

Some of the methodological issues in this trial could have been avoided if we had done one or more small pilot studies evaluating the most important details in the interventions and in the design [103]. We could have discovered that a prolonged first treatment would have been more feasible than repeated treatments, and that only women in the acupuncture groups were asked about adverse effects, which is a limitation. A prolonged first treatment would have inhibited pain at the spinal level over a longer time period. A process evaluation within the trial, with the aim to study contextual factors that could affect the outcome would have been valuable. Also, assessments of the midwives' views of the different treatments during the trial and not only afterwards as we did in the web-based survey, could have given additional information [104].

8.3.3 Validity

Validity is defined as an instrument's ability to measure what it is intended to measure [105]. We used a single primary outcome according to the CONSORT recommendations: Women's assessments of labour pain on the VAS, which is the most commonly used instrument for assessment of pain, and that has been validated to detect changes in pain intensity [106, 107]. It has also been used in nearly all acupuncture studies for labour pain [67, 69, 70, 72, 74, 75]. We asked how painful the last contraction was with 'no pain' (left) and 'worst pain imaginable' (right) as endpoints. There is, however, a problem with response shift. As the labour proceeds, the pain intensity increases and there is a possibility that the meaning of a value on the VAS is changed (recalibrated) due to the higher pain intensity [108]. However, this would apply for all three groups to the same extent.

A pain experience includes more aspects of pain than merely the intensity [11], which can be difficult to capture with this assessment only [109]. We could have used additional assessments for other aspects of pain such as fear and anxiety, or if the pain was manageable or not, to be able to make more nuanced interpretations.

Some of the other secondary outcomes have been validated and used in previous studies such as birth experience [110, 111], emotions during labour [112], EPDS [86], and perception of the midwife[113], however not all of them are validated (e.g. sufficient pain relief, if pain was worse than expected, and support from midwife). Despite them not being previously validated, the results on these outcomes correspond well with results from the other validated ones.

8.3.3.1 Internal validity

One threat to the internal validity in a trial is bias. In clinical research, bias is a systematic deviation of the estimated intervention effect, away from the truth, caused by either deficiencies in the trial design, management of the trial, or analysis and publication of the results [114].

Selection bias occurs if there are systematic differences in the way participants are included in a trial, however, a proper randomisation reduces this risk [54]. In our trial we used a computerised randomisation (www.randomization.com) which was made in blocks that varied randomly in order to keep the respective number of participants in the three groups as equal as possible, as well as to reduce the possibility of guessing which treatment alternative is in the next envelope. In addition, we used sealed, opaque envelopes to assure allocation concealment. When a woman spontaneously reported a reason why she declined to participate, this was registered by the midwife and the most common reason was fear of needles. This could imply a selection bias in our sample towards women who can accept acupuncture as a treatment for labour pain, however this is acceptable since acupuncture for women with a fear of needles is not appropriate and they are thereby not within our target population.

If the interventions are not handled equally with regard to all of the study procedures, there is a bias in study management [114]. To avoid this, the participating midwives were trained and given access to the website with instructional videos and information on the study and the interventions. The course was repeated each semester and intermittent check-ups at the delivery wards were made to assure that the interventions followed study protocol.

Observer bias occurs when midwives and the women are aware of the treatment assignment and the best way of avoiding this is blinding. Blinding in acupuncture trials is problematic as discussed earlier in section *2.2.2. Acupuncture research*, and we decided not to use sham treatments as controls. However, the lack of blinding could have affected the use of EDA and other pain relief, as discussed earlier.

Bias introduced by exclusions after randomisation may occur if some of the participants drop out before the completion of the trial or if some of the measurements were not made correctly or not done at all [114]. One way to handle this is to make an intention to treat analysis where all women are analysed regardless of whether they completed the trial according to protocol or not. We made an intention to treat analysis and in addition to this, we also made an analysis according to per protocol on the primary outcome. There were no differences in primary outcome measurements when analyses were performed according to the principles of intention to treat and per protocol respectively, and all results presented in this thesis are analysed according to intention to treat. Furthermore, the statistical method used for analysing the primary outcome (linear mixed model for repeated measures) enables handling missing data [99, 100]. The proportion of drop outs in this trial is similar to the drop-outs in most other trials evaluating acupuncture for labour pain [67, 68, 72], and slightly higher than two other trials [70, 76].

To avoid publication bias, we have registered our trial at ClinicalTrials.gov: NCT01197950 and we also published our study protocol (Paper I).

8.3.3.2 *External validity*

The external validity refers to the generalizability of the results of the targeted population [114]. Of approximately 4 300 eligible women, only 679 were approached and asked to participate, which resulted in 303 accepting. There is no information as to why more women were not approached, however the reasons were probably connected to midwives having heavy workloads and that both delivery wards were relocated during the study time due to renovations. We did test the representativity of our sample in relation to all women who were eligible for the study on the following: maternal age, relationship status, smoking, and body mass index. Our study sample did not differ from those eligible except regarding smoking, which was less common in the study sample.

8.3.4 Reliability

Reliability concerns the level of agreement between different assessments of the same outcome, made by the same rater at different time points, or by different raters [105]. The test-retest reliability of the VAS has been established in an acute pain setting[115]. Reliability also concerns the agreement between the data in the protocols and questionnaires, and the data in the computer files used in the statistical analyses. All data in the protocols and questionnaires were manually entered into an Excel file by a research midwife at each delivery ward. Data entered by one midwife were then checked both by herself and then by the other midwife to assure that the entries were made correctly. All data in Excel were then imported to SPSS, and additional data checks were made by searching for implausible values.

8.4 CONCLUSION

Treatment using acupuncture, regardless of type of stimulation, did not differ from standard care without acupuncture in terms of reducing women's experience of pain during labour, or their memory of pain and childbirth overall two months after the birth. However, other forms of obstetric pain relief were less frequently used in women receiving a combination of manual and electrical stimulation, suggesting that this method could facilitate coping with labour pain.

8.5 CLINICAL IMPLICATIONS

Acupuncture with manual stimulation of the needles or acupuncture combining manual and electrical stimulation does not reduce women's experience of pain during labour compared to standard care. Though acupuncture using the combination of manual and electrical stimulation seems to help women cope with labour pain and thereby decrease their need for pain relief, and though it seems safe for both the woman and the infant, there is still a need for more research before it is introduced into clinical use.

8.6 FUTURE RESEARCH

– Additional effectiveness trials for acupuncture during labour which include both quantitative and qualitative outcome measures as well as a health economic evaluation.

– Development of better measurement instruments of labour pain which consider the progression of pain during labour and include other aspects of pain than merely the intensity.

– Evaluate different combinations of sensory stimulation for labour pain.

9 ACKNOWLEDGEMENTS

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APPENDIX

Outcomes, measurements, and reference variables

Outcome	Survey question	Measurement	Reference	Collected	Paper
Primary outcome					
Women's assessments of labour pain on the VAS over time	How painful was your last contraction?	VAS: endpoints 'no pain' and 'worst imaginable pain'. Before the first treatment, immediately after the first treatment, then every 30 min for 5h, thereafter every hour until birth, or until EDA		SP	Paper II, IV
Secondary outcomes					
Labour pain					
Overall assessment of labour pain two months after birth	In summary, how painful was your delivery?	VAS: endpoints 'no pain' and 'worst imaginable pain'		Q4	Paper III
Pain difference	VAS	Mean difference between peak pain during labour and the assessment of pain at 2 months after the birth		SP, Q4	Paper III
Pain worse than expected	Compared to your expectations, what was your experience of pain?	'Yes' Much worse than expected + Worse than expected /'No' As expected + Milder than expected + Much milder than expected	No	Q3, Q4	Paper II, III
Pain relief					
Sufficient pain relief	In summary, what is your assessment of all pain relief you were given during labour?	'Enough'/'Not enough'	No	Q3, Q4	Paper II, III
Other pain relief					
Nitrous oxide		'Yes'/'No'	No	SP,MR	Paper II
Sterile water injections		'Yes'/'No'	No	SP,MR	Paper II
TENS		'Yes'/'No'	No	SP,MR	Paper II
Morphine		'Yes'/'No'	No	SP,MR	Paper II
Epidural analgesia (EDA)		'Yes'/'No'	No	SP,MR	Paper II, IV

Cervix dilatation when EDA was given	cm	mean		MR	Paper II
Time from baseline-EDA	minutes	mean		SP, MR	Paper II
Relaxation					
Women's assessment of relaxation	During your last contraction, how relaxed or tense were you?	VAS: endpoints: relaxed and very tense. Before the first treatment, immediately after the first treatment, then every 30 min for 5h, thereafter every hour until birth, or until EDA		SP	Paper II
Overall assessment of relaxation two months after birth	In summary, how relaxed or tense were you during delivery?	VAS: endpoints: relaxed and very tense		Q4	Paper III
Treatment					
Satisfaction with allocation	Are you satisfied with the group allocation?	'Yes'/'No'	No	Q3	Paper II
Duration of acupuncture treatment	minutes	mean		SP	Paper II
Number of needles	number	mean		SP	Paper II
Number of acupuncture treatments	number	mean		SP	Paper II
Treatment with fewer than13 needles or less than 40 minutes of treatment		'Yes'/'No'	No	SP	Paper II
Overall assessment of acupuncture for reducing pain and increasing relaxation	In summary, what is your assessment of the acupuncture treatment for pain relief/relaxation?	'Effective' Very effective + Rather effective/'Not effective' Not very effective + Not effective at all	Not effective	Q2, Q4	Paper II, III
Midwife's acupuncture skills		'Competent' Very competent + Quite competent/ 'Not competent' Not very competent + Not competent at all	Not competent	Q3	Paper II
Adverse effects	How competent did you think the midwife was when she administered acupuncture	'Yes'/'No'	No	Q2 SP	Paper II

Choose the same treatment again	If you give birth again, would you choose the same treatment again?	'Yes'/'No'	No	Q3	Paper II
Labour outcomes					
Time from baseline to partus	minutes	mean		SP, MR	Paper II
Mode of delivery					
Normal vaginal		'Yes'/'No'	No	MR	Paper II
Instrumental vaginal		'Yes'/'No'	No	MR	Paper II
Caesarean		'Yes'/'No'	No	MR	Paper II
Estimated blood loss	Over 1000 ml	'Yes'/'No'	No	MR	Paper II
Augmentation of labour		'Yes'/'No'	No	MR	Paper II
Perineal trauma	Third and fourth degree	'Yes'/'No'	No	MR	Paper II
Infant outcomes					
Transferred to neonatal clinic		'Yes'/'No'	No	SP MR	Paper II
Apgar score less than 7 at 5 min		'Yes'/'No'	No	MR	Paper II
Cord arterial pH	pH	mean		SP MR	Paper II
Cord venous pH	pH	mean		SP MR	Paper II
Psychological outcomes					
Overall perception of the midwife	In summary, what was your perception of the midwife?	'Positive'/'Negative'	Negative	Q3	Paper II
Overall birth experience	How was your overall birth experience?"	'Positive' Very positive+Positive/ 'Negative' Mixed emotions+ Negative+Very negative	Negative	Q4	Paper III
Depressive symptoms	EPDS score >13	'Yes'/'No'	No	Q4	Paper III

Emotions during labour	Circle all the words that described what you had felt during labour	Strong/ Weak/ Happy/ Sad/ Calm/ Frightened/ Alert/ Tired/ Secure/ Worried /Involved/ Lonely/ Detached/ Independent/ Empowered/ Abandoned/ Determined/ Tense/ Trust in my own capacity/ Challenged/ Focused/ Panic/ Disappointed/ Present		Q4	Paper III
Overall assessment of emotions during labour	In summary, what was your emotional state during delivery?	'Positive'/'Negative'	Negative	Q4	Paper III
Midwife					
Support from midwife during labour to a high extent	Did your midwife give you the support you required during delivery?	'Yes' Yes, to a high extent/ 'No' Yes, to a rather high extent+No, to a rather low extent+No, not at all.	No		
Overall positive experience of the midwife	In summary, what was your impression of your midwife?	'Positive'/'Negative'	Negative		
Associations between background characteristics and assessments of labour pain and epidural analgesia					
Higher education	What is your level of formal education?	'Yes' University or other higher education/ 'No' Elementary school + Secondary school		Q1	Paper IV
Age, years		≤25/ 26-34/ ≥35	≤25	MR	Paper IV
Single status		'Yes'/'No'	No	MR	Paper IV
Smoking three months prior to pregnancy		'Yes'/'No'	No	MR	Paper IV
Overweight or obesity (BMI ≥25) in early pregnancy	Normal/Underweight (BMI <25)/ Overweight/Obese (BMI ≥25)	'Yes'/'No'	No	MR	Paper IV
Dysmenorrhea		'Yes'/'No'		Q1	Paper IV

Worried about labour pain	How do you feel when you think about pain during delivery?	' Worried' Not at all worried + Not very worried/ 'Not worried' Quite worried + Very worried	Not worried	Q1	Paper IV
Worried about pain in daily life	When you think about other types of pain in your daily life, are you worried?	' Worried' Not at all worried + Not very worried/ 'Not worried' Quite worried + Very worried	Not worried	Q1	Paper IV
Acupuncture treatment prior to present pregnancy	Have you ever been treated with acupuncture for pain or other than pain?	'Yes'/'No'		Q1	Paper IV
Membranes ruptured before admission		'Yes'/'No'		SP	Paper IV
Cervix dilatation >3 cm at admission		≤3/ >3	≤3	SP	Paper IV
Treatment		MA/EA/SC	SC	SP	

VAS= Visual analogue scale, BMI=Body mass index (Kg/m^2), LMM= Linear Mixed Model, GLM═Generalised linear model, LR= Logistic regression, KM=Kaplan Meier, Cox= Cox regression, EDA=Epidural analgesia, EPDS= Edinburgh Postnatal Depression Scale, SP= Study protocol, MR= Medical record, Q1-4= Questionnaire 1-4, MA= Manual acupuncture. EA= Acupuncture with a combination of manual- and electrical stimulation, SC= Standard care