LUMBOPELVIC PAIN

- SENSORY AND MOTOR ASPECTS –

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PREFACE

This PhD is in part based on 3 peer-reviewed papers, referred to in the text as studies I-III. The studies have been conducted in the period 2010 – 2013 at the Center for Sensory Motor Interaction, Aalborg University, Denmark and at the School of Physiotherapy, Curtin University, Perth, Australia.

Study I.

Palsson, T.S and Graven-Nielsen, T (2012). Experimental pelvic pain facilitates pain provocation tests and causes regional hyperalgesia. *Pain.* 153(11):2233-40.

Study II.

Palsson, T.S., Hirata, R.P. and Graven-Nielsen, T. (2014). Experimental pelvic pain impairs the performance during the Active Straight Leg Raise test and causes excessive muscle stabilization. (*submitted*).

Study III.

Palsson, T.S., Beales, D., Slater, H, O'Sullivan, P.B. and Graven-Nielsen, T. (2014). Lumbopelvic pain in pregnancy is characterised by widespread deep-tissue sensitivity, a facilitated response to manual orthopedic tests and poorer self-reported health. (*Submitted*)

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The studies for this PhD were carried out at the Center for Sensory Motor Interaction, Aalborg University, Denmark and at the School of Physiotherapy, Curtin University, Perth, Australia between 2010 and 2013.

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1 INTRODUCTION

Despite accumulated knowledge on the topic, we still face a great task when managing musculoskeletal pain, both in general as well as related to specific areas such as the low back and pelvic girdle. This is well reflected in the increase of reported incidences (Harkness et al., 2005) going hand-in-hand with the fact that musculoskeletal pain is amongst the largest contributors to decreased quality of life (Collaborators, 2013, Vos et al., 2012). This, more than anything indicates that our understanding of the mechanisms underlying the pain condition is either lacking or the ability to convey the knowledge gained from clinical or experimental pain studies to clinical practice needs improvement.

When assessing a person suffering from low back- and pelvic girdle pain (lumbopelvic pain, LPP) there is a consensus on which factors is important to identify and investigate in clinical practice (Konstantinou et al., 2012). These include the temporal characteristics, location and quality of pain, the person's functional limitations and an identification of to what extent psychosocial factors affect the pain condition. There is however, mixed evidence regarding the possible underlying cause of LPP (in pregnant and non-pregnant populations) where several biological and psychological factors have been suggested as the underlying driver of the condition.

1.1 Pregnancy related lumbopelvic pain – a naturally occurring phenomenon?

It is well known that LPP is a difficult condition to manage and treat which may be related with the large gaps there are in our understanding of the neurobiological mechanisms underlying the pain condition. In pregnancy, this is evident in a recent review (Pennick and Liddle 2013) which demonstrated that the effect sizes from various treatment options are small and that no single intervention is superior to the other. This may relate to the multifactorial nature of pain in general which clinicians and researchers are encouraged to acknowledge in the current guidelines for pelvic girdle (Vleeming et al., 2008) and chronic low back pain (Airaksinen et al., 2006). Accepting the fact that LPP normally follows pregnancy, given the high number of reported incidences (Bastiaanssen et al., 2005, Mogren and Pohjanen, 2005), is one thing but simultaneously raises the fundamental question of what maintains the pain condition into the months and years post-partum when the pregnancy-related changes have returned to normal.

One of the key factors in understanding pain is the mechanism underlying it, its evolvement in the transition from acute into chronic pain and the contribution of peripheral and facilitated central mechanisms in the maintenance of the given pain condition. Such an understanding can to some extent be gained by investigating how healthy subjects react to a short duration of experimental

pain. In an experimental setting, pain is often induced using exogenous (chemical, mechanical and electrical) methods which have proven useful in investigating the sensory (Sinclair et al., 1948, Tsao et al., 2010, Arendt-Nielsen et al., 1996, Kellgren, 1939, Slater et al., 2011, Baad-Hansen et al., 2009, Schmidt-Hansen et al., 2007, Gibson et al., 2006b) and motor aspects (Arendt-Nielsen et al., 1996, Svensson et al., 2003b, Slater et al., 2005, Hirata et al., 2011, Tsao et al., 2010) of musculoskeletal pain but this enables the investigator to bypass the many comorbidities that are known to accompany complicated pain conditions (Giamberardino and Jensen, 2012). This knowledge has then successfully been used in translational studies looking into common musculoskeletal conditions such as low back pain (O'Neill et al., 2007, Giesecke et al., 2004b, Giesbrecht and Battié, 2005, Farasyn and Meeusen, 2005), whiplash-related disorders (Scott et al., 2005, Banic et al., 2004), tennis elbow (Slater et al., 2005) and osteoarthritis (Arendt-Nielsen et al., 2010, Skou et al., 2013) which have indicated the possible role of facilitated central pain mechanisms in patients. In pregnancy, widespread pain sensitivity has been demonstrated, becoming less prominent towards the end of third trimester which is considered to be related with an increased activity of descending pain inhibiting mechanisms (Draisci et al., 2012, Bajaj et al., 2002b). However, it still is unclear what mechanisms underlie pregnancy-related pain and increased pain sensitivity, why it seems to naturally accompany pregnancy and how/if changes in sensitivity of the peripheral and central nervous system are a part of this process.

In pregnancy-related LPP, the sacroiliac joint complex is frequently implicated as a source of symptoms. Therefore, a pain model for this structure was developed in the current studies to elucidate, in healthy subjects, the sensory manifestations and motor effects of sacroiliac joint complex pain and was furthermore used as a proxy to describe such changes in pregnancy-related LPP (Figure 1.1). In this model, quantitative sensory testing was used to assess the pain intensity, pain referral patterns and pain sensitivity in local and referred pain areas. Furthermore, these findings were compared with the outcome of manual clinical tests to see if pain per se could change their outcome.

The knowledge gained from the current studies has provided a more in-depth understanding of the pain mechanisms involved in LPP in general and also how they can affect the outcome of manual clinical tests. Although it is outside the scope of the current findings to comment on clinical intervention, it is clearly demonstrated that the pain and pain sensitivity are important factors to consider in clinical decision making. More importantly, it is essential to appreciate the various factors that can increase pain sensitivity in LPP as this may prime the pain system, rendering it

more susceptible to nociceptive input. An improved understanding of this complex interaction may result in improved mechanisms-based treatment and management strategies with hopefully improved outcomes for this clinical population.

1.2 Aims of the project

I) To investigate whether pain per se might facilitate the positive outcome of manual orthopedic tests, commonly used in assessment of lumbopelvic pain.

II) To explore the somatosensory profile related with lumbopelvic pain with special focus on the sensitivity of pain mechanisms and their relationship with the outcome of manual orthopedic tests.

III) To assess the somatosensory profile in clinical lumbopelvic pain and comparing the sensitivity of pain mechanisms with the perceived pain and disability.

IV) To investigate a possible association between the outcome of manual clinical tests and the psychophysical and psychometric profile.

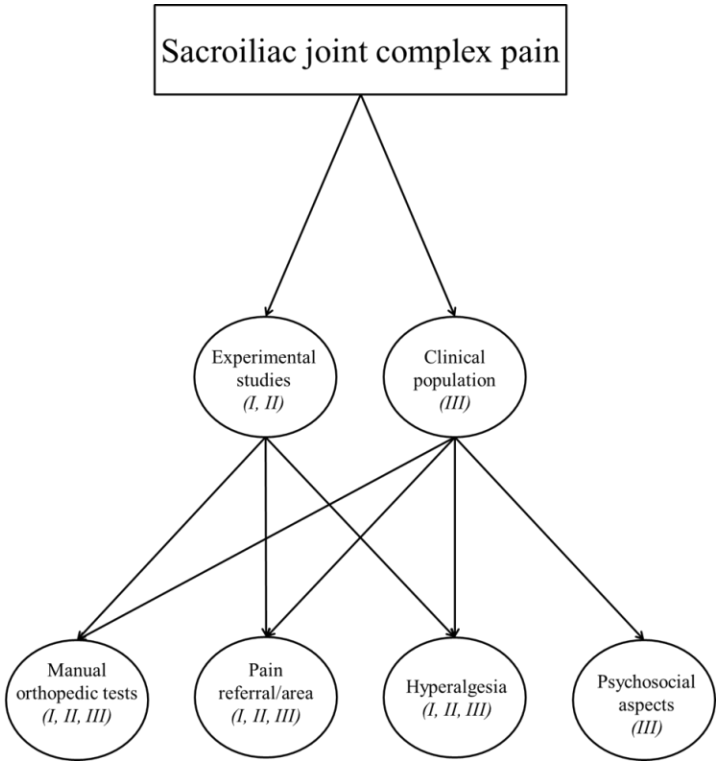

Figure 1.1 *This thesis is derived from three studies reported in three papers including the development of the experimental model of sacroiliac joint pain (I), the effect of pain on manual clinical tests in an experimental (I, II) and clinical (III) setting.*

2 CURRENT PERSPECTIVES ON CLINICAL LUMBOPELVIC PAIN

2.1 Taxonomy

There is little consensus on the taxonomy of pain in the lumbopelvic area. This can be related with many factors such as the complexity of diagnosing the problem, a large overlap in gross-anatomy and neuro-anatomy and close proximity of structures capable of producing pain in the area. In pregnancy, descriptions of lumbopelvic pain exist from the year 400 B.C. (see Abramson et al. 1934) but it was in the beginning of the 20th century people started paying closer attention to this phenomenon (Goldthwait and Osgood, 1905) and questioning whether e.g. the relaxation of pelvic ligaments was related with pain (Abramson et al., 1934). With increasing knowledge it is becoming clear that pain only follows anatomical boundaries to a certain degree which is well reflected in the current findings from study I and II (Fig. 4.4) but to differentiate between pain of musculoskeletal origin and visceral pain, the guidelines propose that the term pelvic girdle pain is used instead of pelvic pain (Vleeming et al., 2008). The distinction between low back pain and pain from the posterior aspect of the pelvic girdle is not clear with different terminology being used when investigating the painful condition in pregnant and non-pregnant populations. This is perhaps best reflected in the two separate guidelines that exist for pelvic girdle pain (Vleeming et al., 2008) and low back pain (Airaksinen et al., 2006) but clinically, there is often an overlap in symptoms from these two areas.

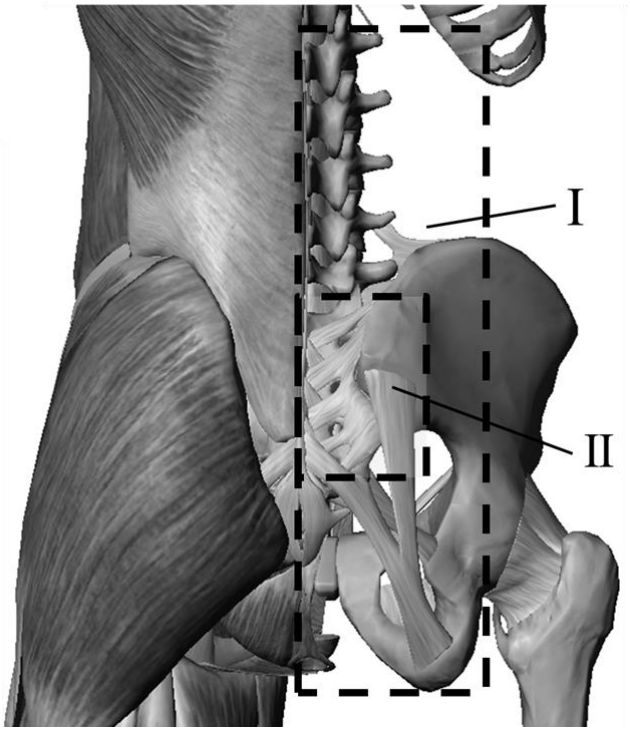

Figure 2.1. *Boundaries of the lumbopelvic region (I) and the sacroiliac joint complex (II).*

In the current thesis, the term *lumbopelvic pain* is chosen as it is not the intention to make a clear distinction between pain originating in the pelvic girdle or low back (Wu et al., 2004) (Fig. 2.1). This is done to include the whole area which is traditionally involved in pain conditions affecting the region but in study III, pregnancy is used as a clinical model to investigate the underlying pain mechanisms. Furthermore, sacroiliac joint (SIJ) pain indicates that the origin of pain is within the joint cavity of the SIJ. This is however, unclear (see section 2.4.1) and therefore

the term *sacroiliac joint complex* has been adopted to encapsulate all the structures belonging to SIJ (intra- and extra-articular).

2.2 Epidemiology

Pain in the lumbopelvic area is particularly common in pregnancy where it is estimated that up to 84% of women develop pain in the region at some stage antepartum (Bastiaanssen et al., 2005, Mogren and Pohjanen, 2005, To and Wong, 2003), with the point prevalence estimated to be between 16-20% (Albert et al., 2002, Larsen et al., 1999, Ostgaard et al., 1991). This is in line with the current findings from study III where 95% of subjects reported of some LPP but these high numbers indicate that pain is a naturally occurring phenomenon in pregnancy which, in most cases, is self-limiting, resolving in the months following delivery (Albert et al., 2002, Röst et al., 2006). However, 7-10% of women suffer from varying degrees of pain and disability beyond the time when all pregnancy related changes are expected have returned to normal (Wu et al., 2004, Röst et al., 2006). It is possible that prolonged pain and suffering after delivery is related with increased sensitivity of pain mechanisms which may be affected by several factors (see section 2.6) but this however, speculative. The frequency of reported incidences has been shown to be similar across continents (Björklund and Bergström, 2000) indicating that the prevalence of pregnancy-related LPP is not affected by cross-cultural differences but rather increased sensitivity of pain mechanisms which may be triggered by the changes the female body undergoes during this period.

The impact pregnancy-related LPP has on the sufferer has been demonstrated where widespread musculoskeletal pain, sleeplessness, sexual problems, and difficulties performing activities of daily life have been reported (Skaggs et al., 2007, Vermani et al., 2010, Mogren, 2006) and its effect on work performance indicates that a vast majority of pregnant women are absent from work due to pain (Dørheim et al., 2013) with the inevitable economic burden it lays on the sufferer and the society.

2.3 Aetiology

According to the European guidelines for the diagnosis and treatment of pelvic girdle pain (Vleeming et al., 2008), pain in the pelvic girdle typically arises in relation to pregnancy, a direct trauma to the pelvis and arthritis and/or osteoarthritis. The sacroiliac joint has often been implicated as the origin of pain in this area in both pregnant and non-pregnant populations (Maigne and Planchon, 2005, Katz et al., 2003, Liliang et al., 2011, Schwarzer et al., 1995) and therefore the current studies (I, II, III) focused on the sacroiliac joint complex as a generator of LPP

acknowledging the potential contribution from other adjacent tissues (somatic and visceral). It is not possible to neglect the contribution of cognitive and emotional factors in any clinical pain condition and therefore these factors are accounted for as well in study III although an in-depth discussion of their potential role is outside the scope of the project.

2.4 Clinical presentation and response to diagnostic tests

The prevalence of low back pain originating within the SIJ complex has been estimated to lie between 16-35% (Maigne and Planchon, 2005, Katz et al., 2003, Liliang et al., 2011, Schwarzer et al., 1995) and the structure is frequently implicated as the source of symptoms in pregnancy-related LPP. The pain is usually felt locally over the SIJ but is also frequently felt in a large area, between the lower leg (van der Wurff et al., 2006a, Fortin et al., 1994a, Fortin et al., 1994b, Fukui and Nosaka, 2002) and the low back (Slipman et al., 2000) (see appendix 1 for overview of experimental design and findings) which is in line with the current findings from studies I and II (see section 4.1.1). In pregnancy, the clinical history usually involves an insidious onset of symptoms where levels of pain and disability do not seem to be related with gestation week (Gutke et al., 2006). Pregnant women often complain of symptoms in the low back and pelvic girdle (Bastiaanssen et al., 2005, Albert et al., 2002, Ostgaard et al., 1991, Berg et al., 1988) encompassing the whole area between the thoracolumbal junction above to the gluteal lines below but symptoms can be aggravated by activities requiring unilateral weight bearing and transferring load across the pelvic girdle (walking, walking stairs, rising up from a chair and rolling over in bed) (Larsen et al., 1999). Additionally, women often report of multiple pain areas during pregnancy (Brown and Johnston, 2013, Borg-Stein et al., 2005), which is in line with the current findings (see section 4.1.2) but this has been associated with higher levels of disability in non-pregnant populations (Kamaleri et al., 2008). Thorough medical history is an important part of any clinical assessment but has been shown unsuccessful in differentiating SIJ pain from other sources of pain (Dreyfuss et al., 1996) potentially due to the diversity in the clinical picture with regards to temporal and spatial characteristics, aggravating factors and previous history.

2.4.1 Sacroiliac joint pain provocation tests

A set of non-invasive manual clinical tests are commonly used to identify the source of symptoms and to differentiate between the many structures possibly contributing to the pain in the lumbopelvic area. The pain provocation tests of the sacroiliac joint are considered positive in a clinical setting if they provoke the subject's habitual pain and have been employed in several studies including both pregnant (Albert et al., 2000, Ostgaard et al., 1994, Kristiansson and

Svärdsudd, 1996, Hansen et al., 1999) and non-pregnant (Maigne et al., 1996, Carmichael, 1987, Potter and Rothstein, 1985, Laslett and Williams, 1994) populations where the overall outcome is that they are considered highly specific to detect pain of sacroiliac joint origin (Vleeming et al., 2008, Laslett, 2008, Laslett et al., 2005) (see appendix 2 for an overview of study designs and implications for clinical practice). The sensitivity of the tests however, is lower and the outcome of a single test is for that reason of little value. Therefore, it is recommended to employ a multiple-test regimen, where the outcome of 5 or more tests are combined, for detecting and diagnosing pain originating in the SIJ complex (Laslett et al., 2005, van der Wurff et al., 2000, Kokmeyer et al., 2002, Szadek et al., 2009, Laslett, 2008, Vleeming et al., 2008). The battery of tests in the current study consisted of six tests all together (Fig. 2.2); (1) the Sacral thrust: here the subject lay in prone and an anteriorly directed force was applied over the spinous process of S2 (I). A modified version of the test was also used in study III as the pregnant subjects were not able to lie prone. Instead, they lay on the side and a force was applied in a posterior-anterior direction on the center of the sacrum, causing an anterior shearing force of the sacrum against both ilia. (2) The Patrick–Faber test (III) was performed with the subject lying supine on the bed, with the examiner standing next to the subject on the side being tested. The examiner brought the subjects´ ipsilateral hip and knee into flexion and positioned the heel slightly above the knee on the opposite limb and then fixated the contralateral anterior iliac spine to ensure that no rotation occurred the lower back. The ipsilateral knee was then lowered towards the bed and light overpressure applied at the end of range to the subject's knee. This test is to stress both the anterior sacroiliac ligament and the hip joint. During the (3) Compression test (I, III) the subject lay on the side with hips and knees in a comfortable flexed position. The examiner applied a force vertically downward on the anterior tip of the iliac crest causing a bilateral compression on the SIJ. (4) The thigh thrust test (I, III) was performed with the subject in supine lying with the hip and knee flexed at 90˚ and slightly adducted. With one hand on the sacrum, the examiner used the other hand to apply pressure on the knee,

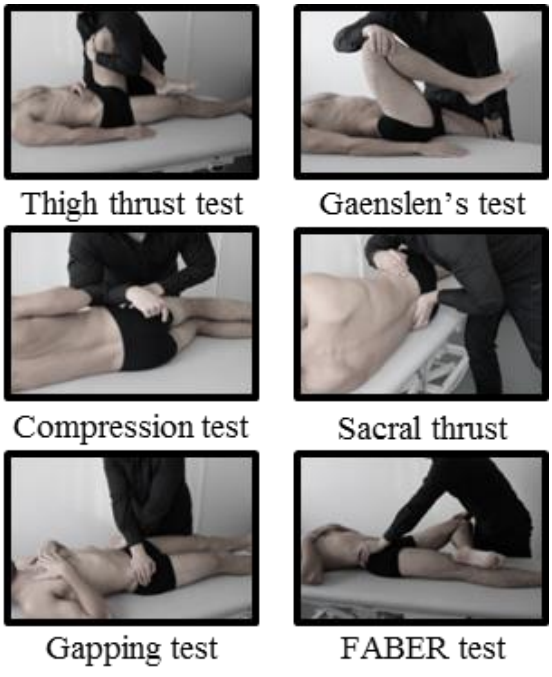

Figure 2.2 *Pain provocation tests employed (I & III); the thigh thrust test, the Gaenslen's test, compression test, a modified version of the sacral thrust test (III), the gapping test and the FABER test (III).*

along the line of the femur, resulting in a unilateral posterior shearing force to the SIJ. During the (5) Distraction test (I, III) the subject lay in supine position. The examiner applied a posteriorly directed force to both anterior superior iliac spines causing bilateral distraction of the anterior aspects of the SIJ. The (6) Gaenslen's test (I, III) was performed with the subject in supine with one leg hanging over the edge of the bed and the other flexed towards the chest. Firm pressure was applied to the flexed knee with counter pressure applied to the hanging leg, towards the floor. This was repeated on both sides causing a posterior rotation force to the SIJ on the side of the flexed knee whilst causing an anterior rotation force on the extension side. The subject was asked if any pain was experienced in the lumbopelvic region and/or if any of the tests reproduced familiar symptoms.

It is important to acknowledge that 4 of the tests employed in the current studies (I,III) (Gaenslen's test, the sacral thrust, compression and gapping tests,) are bilateral in nature meaning that both sacroiliac joints are stimulated simultaneously.

The 'Gold-standard' for the diagnostic ability of these tests are intra-articular blocking protocols which only account for pain originating with the sacroiliac joint cavity but not the superficial structures and therefore questioning the validity of these tests (Vleeming et al., 2008, Szadek et al., 2009).

2.4.2 Lumbar spine pain provocation tests

To accurately identify the painful segment in the low back, a force applied in a posterior-anterior direction is commonly applied either to the spinous process (central) or over the facet joints (unilateral). This method was included in the protocol of study III to differentiate between SIJ complex pain and pain from the lumbar spine but such methods have been shown to be highly accurate when detecting the painful segment in low back pain patients (Phillips and Twomey, 1996) and are commonly used both as part of the assessment (Powers et al., 2003, Fritz et al., 2005, Abbott et al., 2005) as well as treatment (Powers et al., 2008, Chiradejnant et al., 2002, Goodsell et al., 2000). This test regimen is considered highly specific although lacking in sensitivity (Fritz et al., 2005, Abbott et al., 2005) as the outcome of the test only indicates which segments are affected without identifying the underlying cause. Furthermore, although the stimulation can be precise from an anatomical standpoint it is not possible to selectively stimulate only one segment at a time as movement also occurs at the adjacent levels (Powers et al., 2003).

2.4.3 The Active Straight Leg Raise (ASLR) test

Clinically, the ASLR test has widely been used to assess the disease severity of pregnancy related LPP (Mens et al., 2002, Stuge et al., 2004, Vøllestad et al., 2012, Robinson et al., 2010b) and is recommended in guidelines for the diagnosis and treatment of pelvic girdle pain (Vleeming et al., 2008). The test is considered a useful tool to assess the ability to transfer load across the pelvic girdle (Mens et al., 1999, Beales et al., 2010, de Groot et al., 2008, Hu et al., 2012) but it involves lifting one leg at a time 20 cm off the bed and holding it steady for 5 seconds (Mens et al., 2002) (Fig. 2.3). The difficulty of performing the task is then determined with the help of a 6-point Likert scale (*0 = not difficult at all, 1 = minimally difficult, 2 = somewhat difficult, 3 = fairly difficult, 4 = very difficult, 5 = unable to perform*) (Mens et al., 2002) where the sum of scores from both sides is used as the outcome. Healthy subjects traditionally demonstrate an asymmetrical activation of trunk and thigh muscles during the test (Beales et al., 2009b, Hu et al., 2012) where trunk muscles ipsilateral to the leg being lifted are primarily active while the activity of the biceps femoris muscle on the contralateral side increases to resist the anterior rotation forces created by the hip flexors on the ipsilateral side (Hu et al., 2012)**.** In LPP patients however, a more bilateral activation pattern (bracing) is demonstrated (Beales et al., 2009a, de Groot et al., 2008) regardless of which leg is lifted (ipsilateral or contralateral to the painful side). The outcome of the test has previously been shown to be related with both the overall pain (Mens et al., 2012) as well as the pain sensitivity in the long posterior sacroiliac ligament in clinical populations (Vleeming et al., 2002). Such a relationship has however, not been investigated using standardized methods.

Figure 2.3 *The active straight leg raise (ASLR) test.*

2.5 Tissue structures and mechanisms

The sacroiliac joint is a large joint consisting of the two iliac bones with the sacrum wedged between them. Although the morphology of the joint varies between individuals (Prassopoulos et al., 1999) it normally appears as an auricular shaped joint with rough bony ridges and covered in fibrocartilage (Puhakka et al., 2004, Bakland and Hansen 1984, Bowen and Cassidy, 1981) causing restrictions to translation within the joint (Vleeming et al., 1990a, Vleeming et al., 1992). In

addition to the structural integrity provided by the joint surfaces, an intricate network of ligaments adds stability to the joint both in the front, by the anterior sacroiliac ligament, and within the joint cavity by the interosseous ligaments. On the posterior side, the formation of ligaments is more complex with the ligamentous tissue intertwined with aponeurosis of the low back and lower limbs (Vleeming et al., 1995). Within this tissue, three distinct ligamentous structures are considered to contribute most to the stability of the sacroiliac joint; the sacrotuberal- and sacrospinal ligaments and the long posterior sacroiliac ligament (Vleeming et al., 1996). The long posterior sacroiliac ligament or the long dorsal ligament (LDL) is of special interest, both because of its functional role, acting as a link for force transduction between the trunk and lower extremities (Snijders et al., 1993a, Snijders et al., 1993b, Eichenseer et al., 2011, Vleeming et al., 1990b), and also because of its potential role in lumbopelvic pain (Vøllestad and Stuge, 2009, Ronchetti et al., 2008, Vleeming et al., 1996). The ligament is the most superficial to the three ligaments and is easily palpable.

Through an extensive network of muscles (trunk, hip and thigh), fascia and the sacroiliac joint ligaments, three sets of slings have been described (Vleeming et al., 1990a, Vleeming et al., 1990b, Pool-Goudzwaard et al., 1998) which together in a joint effort are considered capable of increasing the dynamic stability of the sacroiliac joint by adding compression to it and thereby creating a self-locking mechanism. A change in any of the elements the slings consist of e.g. reduced muscle activity or unfavourable posture may therefore potentially lead to insufficiency of the system and an excessive load on surrounding tissues (de Groot et al., 2008, Hu et al., 2010, Pool-Goudzwaard et al., 1998).

The sacroiliac joint is an important link between the trunk and the lower limbs, acting interchangeably as a stable and flexible structure (Vleeming and Stoeckart, 2007). Therefore, considerable focus has been on the joint in research and clinical practice as a potential source of symptoms in clinical cases. However, studies have shown that very little movement is available in the SIJ where up to a mean of 2° rotation occur in the sagittal plane (Egund et al., 1978, Tullberg et al., 1998, Sturesson et al., 1989, Sturesson et al., 2000b) and that movement of the joint (hyper-/hypomobility) does not seem to be related with pain in clinical conditions (Sturesson et al., 2000a, Sturesson et al., 1989, Sturesson et al., 2000b, Tullberg et al., 1998, Kibsgård et al., 2014). This is in line with the outcome of clinical studies which have been unsuccessful in establishing a direct link between joint movement and pain related disability in LPP (see appendix 3 for an overview of study designs and main outcomes). Therefore, other factors, in addition to structural and biomechanical dysfunction, may be important to investigate in clinical conditions. The role of pain

in this respect is highlighted in studies I and II where experimental SIJ pain brought on similar changes as described in clinical groups (see section 5).

2.6 Pain mechanisms

The sacroiliac joint and the ligamentous structures surrounding it are densely supplied by a mixture of neural fibers mainly derived from the dorsal rami of spinal nerves L5 – S4 (McGrath and Zhang, 2005, Willard et al., 1998) with contribution from higher spinal levels in some cases (Murata et al., 2000, Umimura et al., 2012). For this reason, any afferent input from the area (painful and non-painful) may potentially reach the spinal cord at multiple levels. Intra-articular blocking protocols are considered the ´gold standard´ in accurately diagnosing sacroiliac joint pain (van der Wurff et al., 2006b, Maigne et al., 1996, Broadhurst and Bond, 1998, Laslett et al., 2003) but the importance of the superficial ligamentous structures has been emphasized in clinical studies where they have been shown to contribute substantially to SIJ pain (Murakami et al., 2007, Luukkainen, 2007, Luukkainen et al., 1999, Luukkainen et al., 2002, Dreyfuss et al., 2009, Dreyfuss et al., 2008, Borowsky and Fagen, 2008). Studies using immunohistochemical staining have established the presence of calcitonin gene-related peptide and substance P immunoreactive nerve fibres in the cartilage and ligamentous structures within the SIJ (Szadek et al., 2008, Murata et al., 2007, Szadek et al., 2010) and substance P immunoreactive nerve fibres are found in the ligamentous structures superficial to the joint (Fortin et al., 2003). Furthermore, the morphology, mechanical thresholds and conduction velocities of nerve fibers in ligamentous tissue lying superficial to the SIJ indicates that the majority of units have the characteristics of group III fibres (Sakamoto et al., 2001). Additionally, many of them have high-threshold characteristics implicating their role as nociceptors (Schaible, 2006). With this in mind, it is clear that structures both within and outside the joint cavity of the SIJ can act as the source of SIJ pain highlighting the difficulty of interpreting the outcome of manual clinical tests accurately but this is one of the conclusions in the current study I (see section 5.1.2).

Based on the above, it is clear that any direct damage to an intra- or extra-articular structure can cause pain (Chou et al., 2004) but biomechanical factors e.g. changes in posture may also lead to a painful overload of the ligamentous and joint structures in the area (see section 2.5), due to swelling or stretching of superficial ligamentous structures (Willard et al., 1998, Vleeming et al., 2002, O'Sullivan et al., 2002, Mens et al., 1999).

Psychological conditions are often linked with chronic pain states (Linton, 2000, Linton, 2005, Main and Watson, 1999) where suffering from a comorbid chronic psychological condition is

known to increase the risk of developing spinal pain (Dominick et al., 2012). In pregnancy, high anxiety scores and depression seem to be strongly related with LPP (Kovacs et al., 2012) which may by amplified by somatic hypervigilance and dysfunctional cognitive coping strategies (Gerwin, 2005, McBeth et al., 2001). Moreover, the role of sleep quality has been shown to be considerable where the underlying mechanisms can be related with an up-regulation of pro-inflammatory biomarkers (Steptoe et al., 2007, Haack et al., 2009, Chennaoui et al., 2011) and an impairment of the endogenous inhibitory pain control system, influencing the pain sensitivity through descending control (Smith et al., 2007, de Souza et al., 2009). A relationship between pain intensity and sleep quality has been demonstrated in low back pain (Bahouq et al., 2013) but the intensity of back pain does only seem to have a weak association with sleep disturbance (Alsaadi et al., 2011), suggesting that sleep deprivation alone is not sufficient to cause and maintain the condition but rather that it coincides with other contributing factors such as depression and anxiety (Smith et al., 2001, Palermo et al., 2011, Dørheim et al., 2012). In specific clinical conditions such as pregnancy, the female body undergoes many changes e.g. in posture, hormonal balance and in the reproductive organs but gonadal hormones, which are rapidly up-regulated in pregnancy (Abbassi-Ghanavati et al., 2009, Hinson et al., 2010), can have an indirect effect on pain sensitivity by modulating emotional factors, mainly by affecting the dopamine, norepinephrine and serotonin systems (Gasbarri et al., 2012). Pregnancy-related depression has also been linked with increased sensitivity to estrogen signalling (Mehta et al., 2014). These hormones may have a direct influence on pain sensitivity, potentially via modulation of responses in primary neural afferents, the activity of dorsal horn neurons and at supraspinal sites (Traub and Ji, 2013) through estradiols and their effect on enhanced glutamatergic nociceptor activity and the synthesis/degradation of serotonin (Craft, 2007). Morover, it has been shown that descending pain modulation varies during the normal menstrual cycle (Rezaii et al., 2012, Tousignant-Laflamme and Marchand, 2009) which can be affected by the intake of oral contraceptives (Rezaii and Ernberg, 2010) further underlining the role of gonadal hormones on the pain system. The influence of the hormone relaxin on LPP in pregnancy is also commonly suggested, but studies investigating this relationship have consistently negated such an association (Albert et al., 1997, Vøllestad et al., 2012, Aldabe et al., 2012).

In summary, both physical, emotional and cognitive factors may increase the sensitivity of central and peripheral pain mechanisms.

3 EXPERIMENTAL DEEP TISSUE PAIN MODELS

Human experimental pain models are commonly used to deepen our understanding of the neurobiological mechanisms underlying musculoskeletal pain, both acute and chronic. In the current study, a novel approach to investigate the pain mechanisms underlying lumbopelvic pain was presented.

3.1 An experimental model of sacroiliac joint pain

To explore the pain mechanisms underlying sacroiliac joint pain, a human experimental pain model was developed. In general, the criteria for using experimental pain models in humans is that it elicits pain resembling the clinical condition in a safe manner (Svensson and Arendt-Nielsen, 1995) but to pass as an appropriate model for SIJ complex pain in this study the method had to 1) cause a pain referral pattern similar to what is shown in clinical populations and 2) facilitate the positive outcome of clinical orthopedic tests. To demonstrate internal and external validity the method 3) had to be applied in a sample suffering from clinical lumbopelvic pain with similar responses to the measured variables.

3.1.1. Model selection

Initially, a standardised pain model was developed which could mimic SIJ complex pain without penetrating the joint itself. This was done to protect the participants from sustaining potential damage to articular structures as intra-articular injections require fluoroscopy guidance because of an otherwise poor success rate (50% at best) (Rosenberg et al., 2000, Hansen, 2003). Such a method would also expose the participants to unnecessary radiation and would limit the abilities of perfoming the testing due to the short duration of experimental pain (see fig. 4.2). The anatomical construct of the joint is such that intra-articular and extra-articular components of the joint complex share innervation (see section 2.6) indicating that pain from the superficial structures surrounding the joint and intra-articular structures would have the same implications in terms of response to clinical tests and pain referral pattern. Pain was therefore induced by injecting hypertonic saline (0.5 ml, 5.8%) into the LDL. This method has frequently been used to induce a transient pain experience in different somatic structures such as Hoffa's fat pad in the knee (Henriksen et al., 2010), spinal muscles and ligaments (Arendt-Nielsen et al., 1996, Tsao et al., 2010, Kellgren, 1939, Sinclair et al., 1948), tendons (Gibson et al., 2006b, Slater et al., 2011) and musculotendinous junctions (Gibson et al., 2006a), and is considered safe and effective (Graven-Nielsen, 2006). Isotonic saline

(0.5 ml, 0.9%) was used as a control substance to account for the possibility of a volume effect (Tsao et al., 2010).

3.1.2. Methodological considerations

Injection site

The long posterior sacroiliac ligament was chosen as it lies relatively superficial to the skin, making it easily accessible, and because of its functional importance acting as a link in transferring load between the trunk and lower extremities (Vleeming et al., 1996, Vleeming et al., 1990a, Vleeming et al., 1990b, Vleeming et al., 2002, Eichenseer et al., 2011). Hypertonic saline causes tonic pain (Graven-Nielsen et al., 1997c) but people suffering from clinical SIJ pain usually have their pain brought on by physical activity which is relieved by rest. To account for this, the subjects were asked while the test was performed (pain provocation tests of the SIJ) whether they experienced an increase in the pain they already had from the hypertonic saline (I). To ensure that the injection hit the target tissue (LDL) (I & II) the following procedure was conducted; The ligament was identified with manual palpation with the subject in prone position and its orientation was marked on the skin. Ultrasound imaging was then used to identify the anatomic landmarks surrounding the LDL and the depth of the ligament relative to the skin (Fig. 3.1). The ligament is not directly visible on ultrasound but the anatomic landmarks (based on ultrasound) and skin markings (based on palpatory findings) were used to establish its orientation. First, the subject was asked to extend the back by lifting the upper body off the bed resulting in a contraction of the sacral part of the multifidus muscle lying immediately medial to the ligament. The subject was then asked to lower the trunk back to the bed and asked to extend the hip causing a contraction of the gluteal muscles lying lateral to the ligament. The area in between these two structures where no movement occurred was assumed to be the target structure but this was confirmed by comparing the ultrasound findings with the markings on the skin.

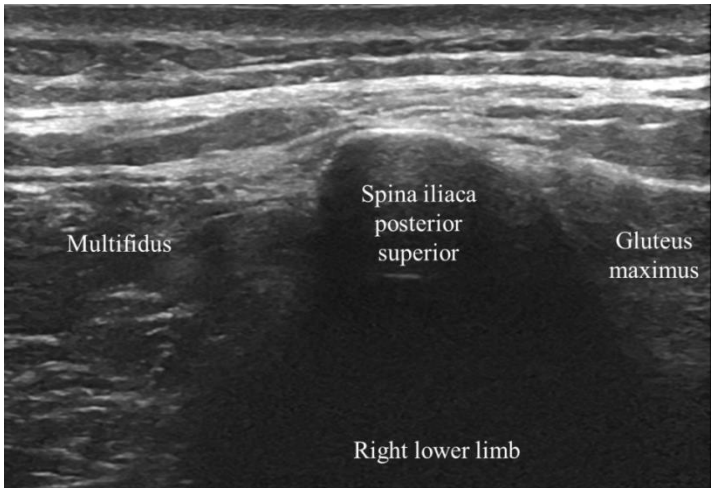

Figure 3.1 *Ultrasound image of right lower limb is shown in resting position. Medial to the posterior superior iliac spine is the sacral part of multifidus and lateral lies gluteus maximus. These anatomical landmarks allow access to the LDL by locating the posterior superior iliac spine and then following the ligaments orientation in a medial-caudal direction. The ultrasound imaging was performed with a 5 – 15 MHz linear probe using an LOGIQ S7 Expert (General electric, Wauwatosa, USA)*

Assessment of pain intensity and pain areas

The pain intensity was assessed using an electronic VAS scale (I & II) and a numeric rating scale (III). Pain areas were indicated on a body chart. For the electronic VAS (I, II) zero on the 10 cm line was anchored with 'no pain' and the high-end was anchored with 'worst pain imaginable' but the scale has proven useful in clinical (Jensen et al., 1986, Ogon et al., 1996) as well as experimental pain conditions (Graven-Nielsen et al., 1997b). Pain reported using a numeric rating scale, as done in study III, or a visual analogue scale has been shown to give fairly consistent findings (Hjermstad et al., 2011) allowing for a comparison of the results from experimental (I, II) and clinical (III) pain studies.

Quantitative sensory testing

Quantitative sensory testing (QST) involves non-invasive, psychophysical methods to measure subjective sensory thresholds to various stimulation modalities. Testing was performed at sites that were standardised based on anatomical landmarks; at the gastrocnemius (mid-way between the popliteal line and calcaneus) (I, II,III), LDL (I,II,II), lateral to the spinous process of S2 (I,II,II), 3-5 cm lateral to the spinous process of L5 (I, III) and at the deltoideus, mid-way between acromion and the deltoid tuberosity (III). The measurements from the L5, LDL and S2 sites were considered to represent pain sensitivity in the lumbopelvic region while the gastrocnemius and deltoideus sites were included as distant control sites. Pressure algometry (*Algometer®, Somedic, Sweden*) was used in all studies and light brush *(SENSELab^{TM} – Brush – 05, Somedic, Sweden)* and pin-prick (*Optihari2-Set, Marstock Nervtest, Germany*) was added to the protocol in study III. A digital pressure algometer such as used in the current studies I, II and III is considered to give the most accurate reading (Rolke et al., 2005) but in all of the studies the pressure was increased slowly with a ramp of 30 kPa/s. The purpose of including light brush and pin-prick to the protocol was to account for potential sensory disturbances (hyper/hyposensitivity) of superficial structures (Treede et al., 1992) as opposed to pressure algometry which is considered to give an estimate of deep tissue sensitivity (Kosek et al., 1995, Graven-Nielsen et al., 2004). It must however be acknowledged that most of the force from the algometer is absorbed in the upper most layers of subcutaneous tissue (Finocchietti et al., 2013). Pressure algometry has frequently been used in both clinical (Bajaj et al., 2001, Bajaj et al., 2002a, Granot et al., 2001, Bajaj et al., 2002b, Schliessbach et al., 2010, Farasyn and Meeusen, 2005, Giesbrecht and Battié, 2005, O'Neill et al., 2007, Clauw et al., 1999, Giesecke et al., 2004b) and experimental pain studies (Slater et al., 2003, Gibson et al., 2006a, Graven-Nielsen et al., 1997, Svensson et al., 2003a) and it is considered reliable (Kosek et al., 1993,

Chesterton et al., 2007) and shown to correlate with clinically meaningful variables in different pain conditions (Hooten et al., 2013, O'Neill et al., 2013). Factors such as gender (Chesterton et al., 2003), the female menstruation cycle (Isselée et al., 2001), and tissue type (Rolke et al., 2005) have been shown to affect the measurements in healthy subjects. The results of quantitative sensory testing may also be affected by a range of cognitive, emotional and sleep-related problems (see section 2.6) but this was accounted for in study III.

Manual clinical tests

The sacroiliac joint pain provocation tests are traditionally performed in prone, side-lying or supine depending on which test is being performed (Laslett et al., 2005) but to standardize and maintain consistency in the force applied during each test, the mattress the subject lay on was fitted with a scale (I). The sacral thrust test is traditionally performed in prone but as it was not possible for all the pregnant subjects to lie in this position, an adapted version was used where the subjects lay on the side (III).

Pain provocation tests for the lumbar spine are traditionally performed in prone position but in study III this was not possible due to the pregnancy. Therefore, a modified version of the test was performed in side lying in the following manner: The hips and knees were placed in a comfortably flexed position, maintaining the curvature (lordosis) of the lumbar spine as close as possible to what was seen in standing position. The examiner placed the thumb over the facet joints of the upper most L5/S1 segment and applied an anteriorly directed force. The test was considered positive as per usual clinical best practice based on whether it provoked a painful response (muscle guarding, apprehension). Whilst applying the pressure the subject was asked whether any pain was detected at the stimulation site and/or at sites adjacent or distant to the stimulation site. This was repeated for the L4/L5 segment and then for the consecutive segments above, running the length of the lumbar spine up to the thoracolumbal junction and then repeated on the other side after the subject had switched sides. The first instance the stimulation caused pain, the pressure was relieved and the test registered as being positive but this was done to avoid unnecessary discomfort for the participants during and/or after the test. Pain provocation tests for the low back have been shown to have excellent sensitivity and specificity when a verbal response is given (Phillips and Twomey, 1996). For data analysis the values from both sides were added.

The ASLR test is traditionally performed in supine position where the subject lifts one leg at a time ~20 cm off the bed, with the ankle in neutral and the knee straight and holding the leg steady for 5 seconds (Mens et al., 2001). In study II, the test was standardised further in a manner where

the subject had to lift the lower limb up to 20 degrees of hip flexion. This was done to ensure that the movement created by the prime movers (hip flexors) and the work load of the stabilizing muscles (trunk muscles and the posterior thigh muscles on the contralateral side) was comparable between subjects. A 20 cm distance was kept between the feet at the starting point. The hip angle was determined with a goniometer and a bar was positioned so that the anterior part of the talocrural joint would touch it at 20 degrees of hip flexion. During the test, the subjects were instructed to lift the leg up to the bar, at a self-selected speed and hold it steady for approximately 5 seconds. This was done three times consecutively with approximately 1 second stop between lifts and then repeated for the opposite side. When the subjects performed the ASLR test, the motor performance was measured objectively by using superficial EMG from trunk and lower limb muscles (II) but the perceived difficulty of performing the task was assessed by using a 6-point Likert scale (*0 = not difficult at all, 1 = minimally difficult, 2 = somewhat difficult, 3 = fairly difficult, 4 = very difficult, 5 = unable to perform*) (II & III). In clinical samples the added value of both sides represents the outcome of the test (Mens et al., 2002) but this procedure was followed in the clinical study III. In the experimental study (II) however, a separate analysis was run for each side (injected and non-injected side) as the subjects only had pain on one side.

Emotional, cognitive and qualitative descriptors of pain

To account for the possibility of cognitive and emotional factors as well as sleep disturbance affecting the measured variables, a set of validated questionnaires were filled out by all participants (III). Also, the quality of pain was assessed in all three studies to investigate if there where common descriptors of experimental pain and clinical LPP. The *SF-36 health survey* was used to measure health related quality of life (Ware, 2000) and *DASS-21* was used to measure emotional functioning (Henry and Crawford, 2005, Osman et al., 2012). To measure sleep quality, *the Pittsburgh Sleep Quality Index* (PSQI) was used (Backhaus et al., 2002, Buysse et al., 1989) and the fear of movement and injury was quantified by using the TAMPA scale of kinesiophobia but the scale has been validated for low back pain (French et al., 2007, Woby et al., 2005, Roelofs et al., 2004, Vlaeyen et al., 1995). The extent of catastrophic cognitions in relation to past painful experiences was quantified by using the *Pain Catastrophizing Scale* (PCS) (Osman et al., 1997, Sullivan et al., 1995) and the *Pelvic Girdle Questionnaire* (PGQ) was included as a validated tool to assess the disability of subjects in pregnant and post-pregnancy populations (Stuge et al., 2011). Finally, the quality of pain was assessed using the English (Melzack and Torgerson, 1971) or Danish (Drewes et al., 1993) versions of the McGill Pain Questionnaire (MBQ) (I, II, III). This is a reliable tool (Byrne

et al., 1982) which is widely used in clinical and experimental pain studies to describe the different aspects of pain (sensory, affective, evaluative and miscellaneous).

Standardization procedures used in the current studies are summarised in table 3.1

Experimental parameters	Method	Standardization procedure
Injection site	Protocol for injection site based on anatomical location	Imaging: Ultrasound imaging done prior to injection to confirm injection site
Injection paradigm	Manual injection	Volume: 0.5 ml (I;II) Concentration: • Hypertonic saline (5.8%) • Isotonic saline (0.9%) Infusion rate approximately 10 sec
Saline-induced pain intensity, onset and duration	Electronic VAS (sampling rate 20Hz)	Computer controlled data collection (I,II)
Clinical pain	Numeric rating scale	Questionnaire data (III)
Saline-induced pain referral (I,II) Pain areas (III)	Body chart	• Overlap of pre-defined pain areas counted and reported (I,II) • Digitized and calculated in arbitrary units (III)
Pain descriptors (saline-induced, I;II and clinical, III)	McGill Pain Questionnaire (Danish/English)	Words chosen by ≥ 30% used in data analysis (I;II;III)
Tissue sensitivity	Pressure algometer (I;II;III) Light brush and von Frey filaments for pin-prick (III) Tissue sensitivity measured at 5 (I;III) or 3 (II) sites bilaterally	Light brush: (III) • Rate of application: 2 cm/3-5 sec Pin-prick: (III) • Stimulation intensity: von Frey filament; bending force of 512 mN Algometer: (I;II;III) • stimulation area: 1 cm^2 • rate of application: 30 kPa/s to detection of pain threshold peak value: Average of 3 readings per site
Pain provocation	Sacroiliac joint pain provocation tests (I;III) Lumbar spine pain provocation tests (III)	• Scale fitted in mattress under the subject to measure the force applied (I) • Verbal response to indicate a positive test • Verbal numeric rating scale to indicate pain and pain intensity • Force applied registered
Weight transferring ability across the pelvis	The active straight leg raise test	• Lower limb lifted to 20° of hip flexion • Activity of trunk, hip and thigh muscles recorded • Tremor of leg recorded (II) • Lower limb lifted 20 cm of the bed (III) • Lower limb held steady for 5 seconds • 6-point Likert scale to estimate difficulty (II;III)
Disability	The Pelvic Girdle Questionnaire (PGQ)	Questionnaire data (III)
Cognitive profile and sleep quality	Validated and standardized questionnaires	SF-36, TAMPA scale of Kinesiophobia, Pain Catastrophizing Scale, Pittsburgh Sleep Quality Index, DASS-21.

Table 3.1 *Standardization of test procedures and experimental methods in the current clinical and experimental pain studies of lumbopelvic pain.*

4 SOMATOSENSORY EFFECTS IN CLINICAL AND EXPERIMENTAL LUMBOPELVIC PAIN

This chapter examines the qualitative and quantitative manifestations of experimental and clinical lumbopelvic pain.

4.1 Local and referred pain in clinical and experimental sacroiliac joint complex pain

4.1.1 Experimental findings

Hypertonic saline injections into spinal ligaments (Tsao et al., 2010) and muscles (Graven-Nielsen, 2006) have been shown to cause pain of average intensities which is in line with the current findings from studies I and II (Fig. 4.1). Furthermore, such injections into deep tissue have consistently been shown to cause pain around the injection site both in spinal ligaments (Sinclair et al., 1948, Tsao et al., 2010), back muscles (Arendt-Nielsen et al., 1996, Kellgren, 1939), tendons (Slater et al., 2011, Gibson et al., 2006b) and orofacial structures (Baad-Hansen et al., 2009, Schmidt-Hansen et al., 2007) with pain referral to varying degrees. This is also consistent with the findings from studies I and II where a majority of subjects reported pain outside the injection site with symptoms being felt into the thigh and lower leg. Interestingly, the percentage of subjects reporting pain at areas distal to the injection site was almost identical to what has been shown in clinical SIJ pain (Slipman et al., 2000, Fortin et al., 1994a, van der Wurff et al., 2006a) illustrating the close proximity of the experimental pain model (I & II) and clinical SIJ pain. The size of the painful area depends on the intensity of the pain (O'Neill et al., 2009, Graven-Nielsen, 2006) concurring with the present findings (I, II). One of the most significant findings from studies I and II was that over 70% of subjects experienced proximal pain referral to the low back. This is not a universal finding in clinical conditions although it has been reported of (Slipman et al., 2000).

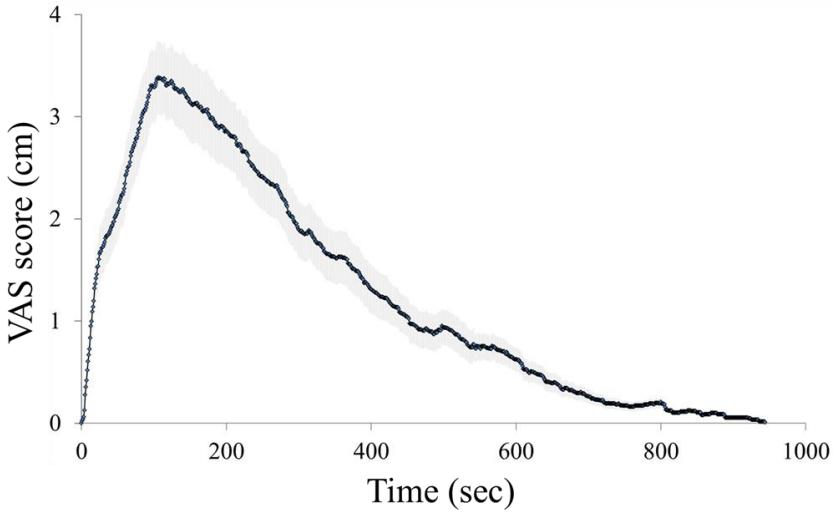

Figure 4.1 *Mean visual analog scale (VAS) profiles from studies I & II (±SE, n = 64 subjects) over time after infusion of hypertonic into the long posterior sacroiliac ligament.*

4.1.2 Clinical findings

It is difficult to diagnose pain from the sacroiliac joint based on medical history and physical examination alone (Dreyfuss et al., 1996) which may become ever more problematic in pregnancy with multiple painful sites as seen in study III. Over 1/3 of back pain in non-pregnant populations originates in the SIJ complex (Maigne and Planchon, 2005, Katz et al., 2003, Liliang et al., 2011, Schwarzer et al., 1995, Bogduk, 1995) where the pain is usually located in the area overlying the joint (Merskey and Bogduk, 1994, van der Wurff et al., 2006a); an area referred to as the Fortin area (Fortin et al., 1994b) but is also felt in areas far beyond its anatomical boundaries (Slipman et al., 2000, van der Wurff et al., 2006a, Fortin et al., 1994a, Fortin et al., 1994b, Fukui and Nosaka, 2002). This is in line with the current findings (III) where the pregnant subjects indicated a large area with pain, located both in the low back and pelvic girdle in 56% of cases (Fig. 4.3) (III). Furthermore, the frequency of referred pain into the low back or lower limb was similar to what is seen in clinical SIJ pain (van der Wurff et al., 2006a, Slipman et al., 2000, Fortin et al., 1994a) and experimental SIJ pain (I & II) (Fortin et al., 1994b) (Fig. 4.2).

The mechanisms underlying pain referral in general are not fully understood but are considered to relate to a convergence of nociceptive input from various anatomically unrelated structures (somatic and visceral) onto the same spinal segment (Mense, 1994). In chronic low back pain, an extensive pain area is well described (Ohnmeiss et al., 1999, Mooney and Robertson, 1976, Schwarzer et al., 1994) which is in accordance with what is seen in study III. The reason for this may be an ongoing bombardment of incoming signals from nociceptive fibres on to the second-order neurones of the dorsal horn (Hoheisel et al., 1993, Schadrack and Zieglgänsberger, 2000) which lowers their threshold, making them more sensitive to converging input from other anatomically unrelated structures. This,

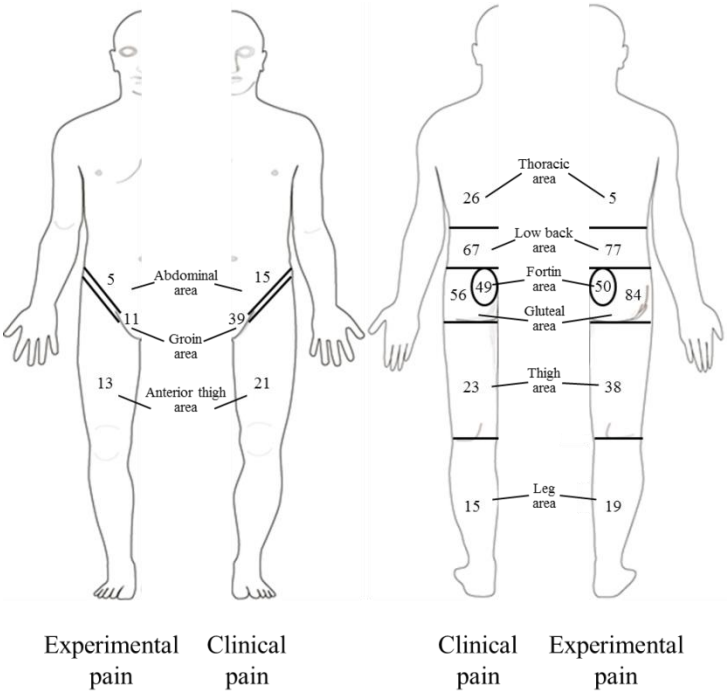

Figure 4.2 *Frequency of affected areas in the trunk and lower limbs in clinical (n = 39) and experimental (n = 64) lumbopelvic pain. The numbers indicate in how many subjects (%) a given area was affected. Data extracted from studies I, II & III.*

along with descending facilitation of incoming signals (Vanegas and Schaible, 2004, Sandkühler, 2009) may increase the excitability of central mechanisms as has been well described (Latremoliere and Woolf, 2009, Woolf and Salter, 2000). Such a modulation in responsiveness of the central nervous system has been suggested in clinical musculoskeletal pain conditions (Kosek and Januszewska, 2008, O'Neill et al., 2007, Sörensen et al., 1998) where a larger painful area is reported after a nociceptive stimulus in distant areas to the original pain, supporting the notion that the nervous system as a whole is affected in long lasting pain conditions.

In pregnancy, it is difficult to determine the exact origin of pain but from studies using intra-articular blocking protocols in non-pregnant populations (see above) it is evident that the origin of pain lies in the deeper structures of the low back and pelvic girdle e.g. ligaments and muscle. Interestingly, the pain areas reported in the present studies (I, II) are similar to what is shown with stimulation of tender spots in the region (Travell and Simons, 1998) such as the gluteal muscles or muscles of the low back indicating that several structures from the same region can elicit the same response in terms of pain referral when exposed to a specific painful stimulation. Furthermore, when comparing the pain areas from the clinical study (III) and the experimental pain studies (I & II) it is clear that the pattern is similar, indicating that nociceptive input from the SIJ complex is one of the pain generators in pregnancy-related LPP. The small discrepancy in pain areas when comparing the clinical group with experimental pain (Fig. 4.2) may to some extent be related with the difference in pain intensity which was on average lower in the clinical group (2.9 ± 0.3) than in experimental pain (4.1 ± 0.4).

In summary, the pain model developed and presented here is capable of inducing pain referral patterns similar to what is seen in clinical conditions and the results implicate the SIJ complex as one of the potential sources of pregnancy-related LPP.

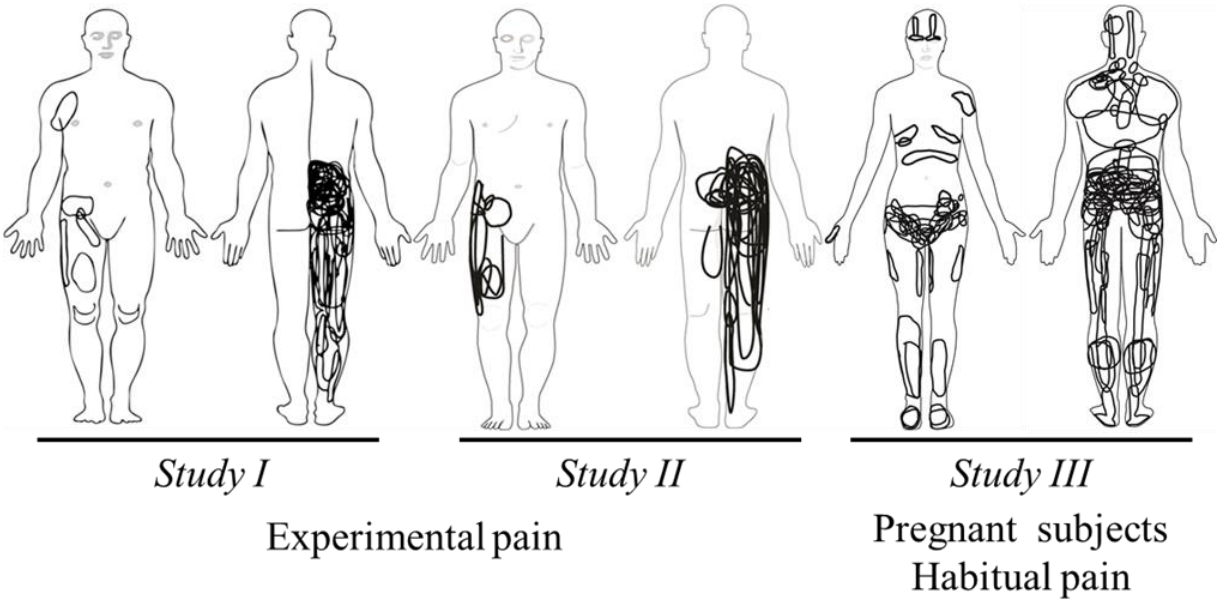

Figure 4.3 *Superimposed body chart pain drawings from healthy subjects after hypertonic saline injection into the long posterior sacroiliac ligament in healthy subjects (n = 32, I and n = 34, II) and the habitual pain of pregnant subjects (n = 39, III). Pregnant subjects reported both areas of pregnancy related pain and other pre-existing pain areas.*

4.2 Deep tissue hyperalgesia in clinical and experimental lumbopelvic pain

4.2.1 Experimental findings

Primary hyperalgesia is defined as increased pain from a stimulation that usually is painful (Loeser et al., 2011) without indicating the underlying mechanism but may be both the cause and consequence of clinical signs and symptoms (Sandkühler, 2009). In studies I and II, hyperalgesia was found in the region surrounding the injection site (Fig. 4.4) which is consistent with other experimental pain studies (Schliessbach et al., 2010, Slater et al., 2011, Gibson et al., 2006b). No increase was found in deep tissue sensitivity distal to the stimulation area despite the large area of pain referral which is in accordance with what has been demonstrated previously (Graven-Nielsen et al., 1998a, Ge et al., 2003). Interestingly, a decrease in pain sensitivity (hypoalgesia) was found on the side contralateral to the injection site (I) which has been seen before after hypertonic saline injections (Ge et al., 2003, Graven-Nielsen et al., 1998b, Slater et al., 2011, Gibson et al., 2006b) and reflects a possible role of conditioned pain modulation, where specific brainstem-mediated inhibitory mechanisms modulate the nociceptive and non-nociceptive sensory inputs (Yarnitsky, 2010).

4.2.2 Clinical findings

Widespread hyperalgesia has been demonstrated in various clinical conditions such as chronic non-specific low back pain (Clauw et al., 1999, Giesbrecht and Battié, 2005, Giesecke et al., 2004b, O'Neill et al., 2007), neck pain (Scott et al., 2005, Chien and Sterling, 2010), elbow pain (Fernández-Carnero et al., 2009, Slater et al., 2005), and knee pain (Arendt-Nielsen et al., 2010) which is accordance with what was seen in study III where the pregnant group demonstrated widespread hyperalgesia reflected by the increased pain sensitivity to pressure at the deltoid and gastrocnemius muscles. The onset of widespread hyperalgesia has been shown to occur soon after the initiating painful episode in a clinical sample (Sterling et al., 2003) but the mechanisms underlying these changes are poorly understood with regards to temporal characteristics and the intensity of the stimulus needed to develop the sensitisation (Graven-Nielsen and Arendt-Nielsen, 2010). Experimental pain studies have shown that in healthy subjects, low-intensity nociceptive activity can cause spreading of pain and hyperalgesia (Andersen et al., 2008, Hayashi et al., 2013) although this is not seen in strong acute pain (I & II). A spreading in sensitivity as a result of an initiating localized painful stimulus may potentially indicate a system where central processing is facilitated (Graven-Nielsen et al., 2000, Latremoliere and Woolf, 2009, Woolf and Salter, 2000) causing hyper-excitability of second-order dorsal horn neurones (Hoheisel et al., 1993, Schadrack and Zieglgänsberger, 2000), an opening of latent neuronal synapses at the dorsal horn (Graven-Nielsen and Mense, 2010), and a changed balance in the supra-spinally mediated descending control (Vanegas and Schaible, 2004). In the third study, the pregnant subjects where included solely due to their pregnancy and therefore they had varying degrees of pain and disability. Pain during pregnancy is a condition which usually evolves over time without a clear onset and it is therefore only possible to speculate on the pathways through which the sensitisation occurs. One factor may be the postural changes which naturally occur as pregnancy progresses (Okanishi et al., 2012) potentially causing a painful overload of the ligamentous and joint structures in the lumbopelvic region (Snijders et al., 2004, Vleeming et al., 1996, Smith et al., 2008). This process can then lead to a sensitisation of central mechanisms similar to what has been demonstrated in other pain syndromes affecting somatic structures in the region (Giesbrecht and Battié, 2005, Giesecke et al., 2004b). To rule out the possibility of hyperalgesia in the superficial structures (LaMotte et al., 1991, Magerl et al., 2001), light brush and pin-prick were included in the protocol (III) where no significant difference was found between the groups. The current findings (III) were therefore considered to be related with hypersensitivity of deeper somatic structures.

The pelvic organs are also exposed to changes during pregnancy and must be acknowledged given the relationship between hypersensitivity of visceral structures in the pelvis and somatic structures which has been demonstrated (Jarrell, 2011, Jarrell, 2010, Bajaj et al., 2003, Giesecke et al., 2004a). In pregnancy-related pain, such a relationship has also been indicated where regaining menstruation post-partum caused an increase in a pre-existing musculoskeletal pain condition (Nielsen, 2010). This is potentially caused by the regular afferent barrage of nociceptive input accompanying menstruation, converging on similar spinal segments as somatic structures (L1/L2 and S2/S4) (Agur and Dalley, 2013) which may result in increased sensitivity to stimuli in this region.

Pregnancy-related hormonal changes are frequently implicated as a potential cause of pain but an up-regulation of gonadal hormones occurs during pregnancy (Abbassi-Ghanavati et al., 2009), which increases significantly towards the end of the third trimester (Hinson et al., 2010). These hormones can modulate the sensitivity of the central nervous system (Aloisi and Bonifazi, 2006) where estrogen and progesterone have been shown able to both increase and decrease pain sensitivity (de Leeuw et al., 2006, Lee and McEwen, 2001, McRoberts et al., 2007, Stening et al., 2007) resulting in systemic changes of pain sensitivity potentially contributing to the perceived pain as previously concluded (Marnach et al., 2003). Although the direct influence of hormones on pain sensitivity was outside the scope of this project it is possible that these factors add to the sensitivity of the central nervous system and are important to account for with regards to the interpretation of the current findings. However, the changes the female body undergoes in relation to a normal pregnancy (hormonal and postural) are fairly consistent and are therefore unlikely to fully account for the pain and disability reported of in study III. Furthermore, these changes are highly unlikely the cause of the persistence of pain after the pregnancy-related changes have returned to normal as seen in a significant proportion of women (Wu et al., 2004, Röst et al., 2006, Albert et al., 2001).

In the third study presented here, the stage of pregnancy of the participants lay in both the 2nd and 3rd trimester indicating that their bodies had not all undergone the same biomechanical and hormonal changes but interestingly the stage of pregnancy did not correlate with disability, pain and hyperalgesia which is in line with previous findings (Gutke et al., 2006). Factors other than hyperalgesia therefore, seem to affect the pain condition concurring with previous findings where widespread hyperalgesia has been shown not to predispose for developing chronic back pain (O'Neill et al., 2011). Furthermore, in line with the current findings (III), pain sensitivity can only be weakly related to the day-to-day pain experience in a clinical condition (Kamper et al., 2011) and

it has been questioned whether pain sensitivity is as related with the reported pain and disability as often assumed (Hübscher et al., 2013).

In summary, the pain model developed and used in studies I and II reduces the pressure-pain thresholds in the lumbopelvic region in healthy control subjects towards what is seen in pregnant subjects (III) (Fig. 4.4). The underlying cause for widedspread hyperalgesia amongst the pregnant subjects cannot be determined from the current data but is unlikely to be caused and maintained by physical, pregnancy-related changes alone although these factors may contribute to the overall pain sensitivity.

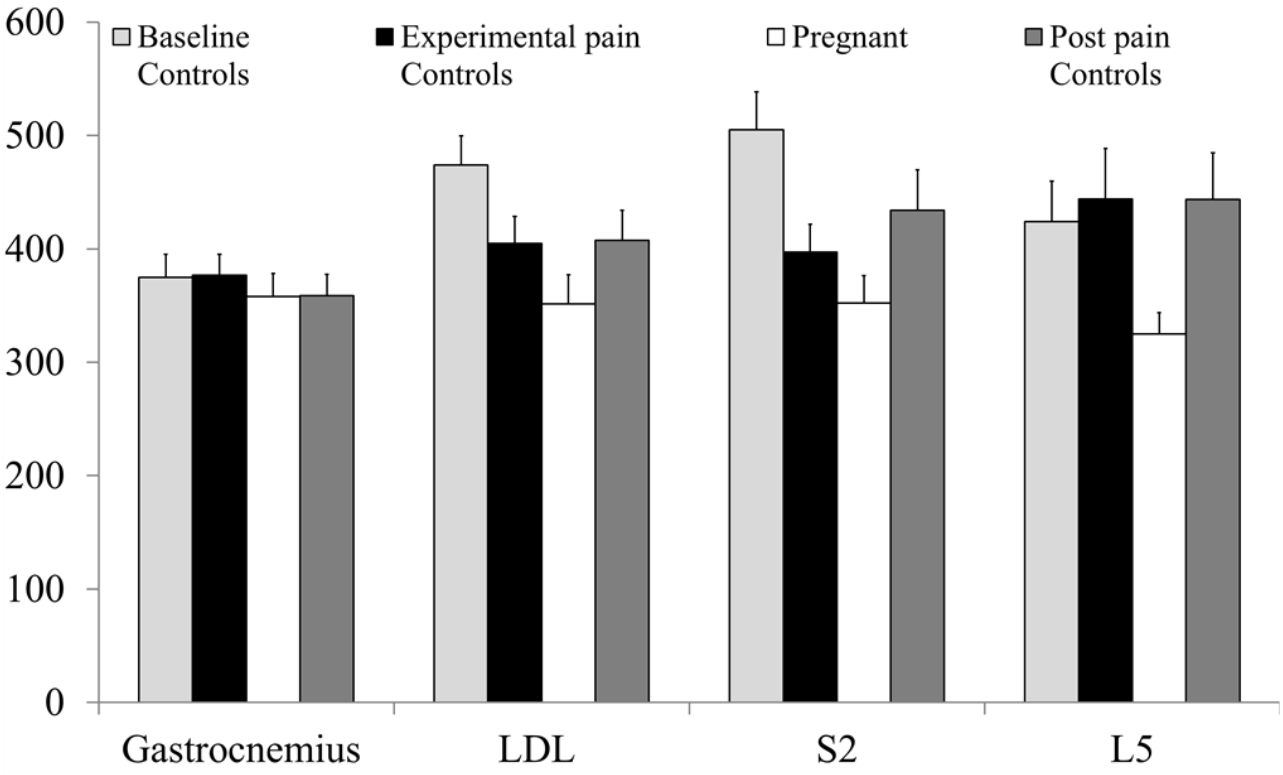

Figure 4.4 *Pressure pain thresholds comparing healthy female controls (n=32 for gastrocnemius, LDL and S2. n=15 for deltoid) at baseline (light grey bars), immediately after hypertonic saline injection (black bars) and post-pain (dark grey bars) with pregnant subjects (n=39)(open bars). Values for experimental pain are shown for the injection side but for pregnant subjects as an average of left and right side. No significant difference is found in pain sensitivity at any of the sites (NK: P > 0.05). Data extracted from studies I, II & III.*

4.3 Qualitative aspects of clinical and experimental lumbopelvic pain

4.3.1 Quality of pain - Experimental and clinical findings

For data analysis, words chosen by more than 30% of subjects were extracted in accordance with procedures in other experimental pain studies (Graven-Nielsen et al., 1997, Slater et al., 2011, Gibson et al., 2006b). In the studies I and II, the words chosen most often were ‘pressing´ and ´spreading’ which relate to the sensory components of the questionnaire which concurs with what has previously been described in experimental muscle pain (Slater et al., 2011, Slater et al., 2005) and tendon pain (Slater et al., 2011). The words most frequently used in clinical LPP (III) were ´sharp´, ´hurting´, ´tender´ and ´annoying´ but these words belong to the same components of the McGill Pain questionnaire as the words chosen in studies I and II. The difference in quality comparing the two pain conditions may reflect the difference in pain generators (where most likely multiple tissues are affected in clinical pain; see section 2.6), pain intensity and duration of pain. This is clearly demonstrated when looking at the pain sensitivity (regional and widespread) in the clinical group (III) and comparing it with the experimental pain groups (I, II) as well as the duration of pain which is only 10-15 minutes at the most in experimental pain (I, II) (Fig. 4.1).

In summary, although experimental and clinical lumbopelvic pain was described using words from the sensory component of the McGill pain questionnaire there was little unanimity on the exact qualitative description of experimental and clinical pain which may to some extent be explained by the pain intensity and the temporal and spatial characteristics of the pain.

4.3.2 Physical and emotional health – clinical findings

The majority of the pregnant subjects in study III reported disability to some degree which did however, not seem to be associated with levels of pain or hyperalgesia (see section 4.2.2). Emotional factors such as depression and anxiety have been shown to account for a significant proportion of disability during everyday activities in pregnancy (Bindt et al., 2012, Kovacs et al., 2012) and have been linked with an increased risk of developing LPP in late pregnancy (Robinson et al., 2010b, Bakker et al., 2013).

In study III, the pregnant women scored significantly higher on variables regarding emotional factors, sleep and pain-related cognition (except pain catastrophizing) (Table 4.1) which is highly interesting given the association between pain sensitivity and elevated anxiety and stress levels in healthy subjects (Schuh-Hofer et al., 2013, Crettaz et al., 2013). This is also in line with findings from clinical conditions (de Souza et al., 2009, Klauenberg et al., 2008) and may be related with a lack of supraspinally mediated descending inhibition (Jans et al., 2006) resulting in increased pain

sensitivity and facilitated temporal summation as has been described in clinical depression and stress (Klauenberg et al., 2008, Crettaz et al., 2013).

Sleep is known to be an independent predictor of depression and pain in non-pregnant (Ohayon and Roth, 2003) and pregnant populations (Okun et al., 2013, Dørheim et al., 2012) which is relevant with regards to the present findings where the pregnant subjects reported of both poorer sleep quality and emotional well-being compared with controls. Furthermore, it has been shown that lumbopelvic pain is associated with insomnia, but not with depressive symptoms (Dørheim et al., 2012) indicating a self-perpetuating vicious cycle where a cascade of factors affecting the pregnant subjects can all contribute to the overall pain sensitivity. Insomnia can increase pain sensitivity directly (Schuh-Hofer et al., 2013, Ağargün et al., 1999) but the mechanisms through which this occurs are considered to be related with both impairment of endogenous inhibitory pain control (Smith et al., 2007, Haack et al., 2012) as well as an up-regulation of pro-inflammatory biomarkers such as prostaglandin (Haack et al., 2009), interleukin-6 (Haack et al., 2007) and TNF-α (Chennaoui et al., 2011). In study III, sleep disturbance was the factor that contributed most to overall score on the Pittsburgh Sleep Quality Index (table 4.1). This

	Control group (n=22)	**Pregnant group (n=39)**
Characteristics		
PGQ Disability (IQR)	0 [0 - 0]	27 [13 - 49]*
Average pain (NRS) (IQR)	0 [0 - 0]	3.0 [1 - 4]*
DASS - 21 (IQR)		
Depression	0 [0 - 2]	2 [0 - 4]*
Anxiety	0 [0 - 2]	2 [2 - 6]*
Stress	4 [0 - 8]	8 [4 - 12]
Sleep quality (PSQI) (IQR)		
Duration	0 [0 - 0]	0 [0 - 1]
Disturbance	1 [1 - 1]	2 [1 - 2]*
Onset latency	1 [0 - 1]	1 [0 - 2]
Day dysfunction	1 [0 - 1]	1 [1 - 2]
Efficiency	0 [0 - 0]	1 [0 - 2]
Quality	1 [0 - 1]	1 [1 - 2]
Sleep medication	0 [0 - 0]	0 [0 - 0]
Total sleep quality	3 [2 - 5]	7 [4 - 9]*
SF - 36 (SEM)		
Physical health	94.6 ± 1.5	60.8 ± 2.6*
Emotional health	85.1 ± 2.9	72.8 ± 2.5*

Table 4.1 *Results from questionnaires (III) showing disability (Pelvic girdle questionnaire, PGQ), average pain intensity (numeric rating scale, NRS), depression, anxiety and stress (DASS-21, Sleep quality (Pittsburgh Sleep Quality Index, PSQI) and overall physical and emotional health (SF-36). Results are shown for non-pregnant and pregnant subjects and pregnant subjects reporting low- and high disability. Significant difference from controls (*, $P < 0.05$, Bonferroni corrected).*

is common during pregnancy (NSF, 1998) but sleep disturbance has been shown to mostly affect endogenous pain inhibition and hence spontaneous pain but not pain thresholds (Smith et al., 2007) which may explain the lack of correlation between pain sensitivity and sleep quality in the clinical group (III). These findings may indicate that poor sleep quality can affect the pain system and to some extent account for multiple pain areas and idiopathic, spontaneous pain which is often reported of in pregnancy (Brown and Johnston, 2013, Borg-Stein et al., 2005).

Emotional, cognitive as well as physical factors may all affect the nociceptive system in a similar fashion (Sandkühler, 2009) and may explain the findings in study III where all the pregnant subjects had poorer outcomes than the controls regarding sleep and emotional health which may, via similar pathways, sensitize central pain mechanism. The lack of associations between emotional factors, sleep and other outcome variables may be related with the relatively low levels of emotional distress measured in study III but also the lack of power. However, aalthough speculative, it is possible that the absence of significant associations between the factors mentioned above and pain and hyperalgesia may be caused by different underlying drivers (on an individual level) of the sensitization, resulting in the widespread hyperalgesia.

It was beyond the scope of this study to investigate the impact of cognitive and emotional functioning on the sensitivity of pain mechanisms. Nevertheless, the imminent relationship between psychophysical and psychometric variables measured here (III) forms neurobiological grounds for assessing patients within a bio-psycho-social framework as it indicates that different individuals may present with similar clinical symptoms which are driven by different, parallel mechanisms all capable of priming the nociceptive system and thereby rendering it more susceptible to input (nociceptive and non-nociceptive).

In summary, emotional health, cognitive functioning and sleep are important factors to evaluate in pregnancy-related LPP especially because of their shared ability to increase sensitivity of the pain system. These findings support the need of assessing patients with lumbopelvic pain within a bio-psycho-social framework.

5 OUTCOME OF PAIN PROVOCATION TESTS AND MOTOR FUNCTION

Accurately identifying the source of symptoms is a challenge clinicians are faced with when examining their clients. Useful additions to the examination process are manual tests which have been developed, validated and their diagnostic abilities thoroughly described but the mechanisms underlying the outcomes of the tests are poorly understood. In the current studies the standardized pain induction protocol described above (section 3.1.2) was used to investigate how and if pain

would affect the outcome of pain provocation tests of the sacroiliac joint (I), the active straight leg raise test (II) as well as the relationship between the outcome of the tests with pain sensitivity. Similar relationships were then investigated in a group of pregnant women where LPP frequently occurs (III).

5.1 Pain provocation tests

5.1.2 Experimental findings

Manual pain provocation tests of the sacroiliac joint add load to many structures of the SIJ complex (intra and extra-articular) simultaneously, making it a challenge to identify the painful structure with accuracy (Laslett, 1998, Szadek et al., 2009). Previous studies have used a multiple provocation-test regimen (Kokmeyer et al., 2002, Robinson et al., 2007, van der Wurff et al., 2006b, Laslett et al., 2003) consisting of tests with good inter-examiner reliability (Laslett and Williams, 1994), in detecting pain originating in the sacroiliac joint complex. The tests are considered valid and reliable to pin-point the location of pain in intra-articular pain conditions (van der Wurff et al., 2006b, Maigne et al., 1996, Broadhurst and Bond, 1998, Laslett et al., 2003) but fail to account for a potential extra-articular contribution to the pain (Vleeming et al., 2008, Szadek et al., 2009). By using the experimental pain model which was developed (I) it was possible to change the outcome of the pain provocation tests from negative to positive to a significant degree although it did not reach the diagnostic criteria of 3 or more positive tests (see figure 5.1) which is considered important for accurate diagnosis (Laslett et al., 2005, van der Wurff et al., 2000, Kokmeyer et al., 2002, Szadek et al., 2009, Laslett, 2008, Vleeming et al., 2008). The current findings indicate that not only extra-articular pathologies are detectable with the clinical tests.

5.1.1 Clinical findings

In study III, a set of pain provocation tests for two regions were performed; the SIJ and for the lumbar spine. The pregnant group demonstrated an increased number of positive tests in both regions compared with controls but interestingly, no significant relationship was found between the outcomes of pain provocation tests in the two regions. Furthermore, the outcome of the SIJ tests correlated positively with disability (PGQ) whereas no such relationship was seen for the tests of the lumbar spine indicating that the SIJ complex was a larger contributor to perceived disability in this pregnant cohort.

In summary, pain from a structure lying superficial to the sacroiliac joint results in a similar response to pain provocation tests of the joint as is seen in pregnancy (Fig. 5.1). The outcome of the test correlates significantly with pregnancy-related disability, making the tests useful for clinical purposes. The lumbar spine becomes more sensitive to pain provocation during pregnancy without being associated with the overall pain or disability.

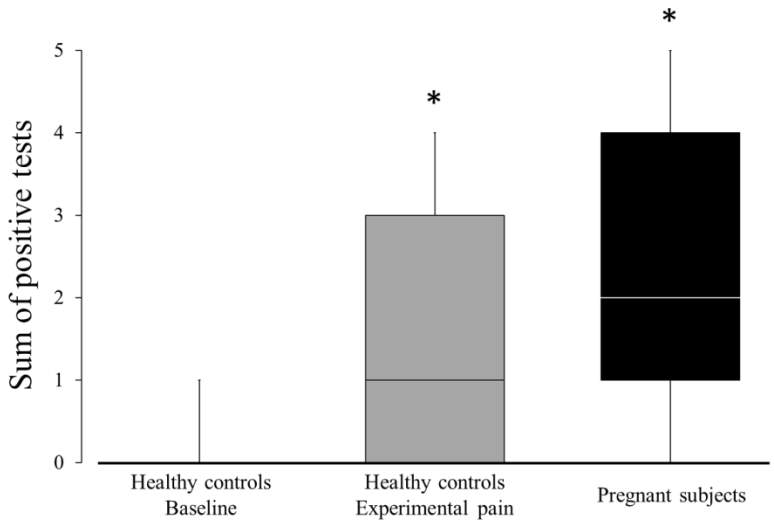

Figure 5.1 *Median [IQR] Sum of positive SIJ pain provocation tests. Summary of findings from experimental (I) and clinical (III) study on lumbopelvic pain. Healthy subjects (n =30) following hypertonic saline-induced pain (grey box) and pregnant subjects (n = 39)(black box) had significantly more positive pain provocation tests of the SIJ than baseline values for healthy controls (P < 0.05). No significant difference was found in sum of positive tests after experimental pain in healthy controls and pregnant subjects. Data extracted from studies I & III.*

5.2 Active straight leg raise (ASLR)

5.2.1 Experimental findings

By inducing experimental pain into the LDL, a significant increase in both the objective (RMS EMG) and subjective (Likert-scale) effort during the task was seen (II). In this study the subjects demonstrated a unilateral muscle activation pattern of trunk and thigh muscles in the pain-free state, consistent with what has previously been shown in asymptomatic individuals (Hu et al., 2012, Beales et al., 2009b). Of particular interest however, were the changes in muscle activity in the pain state where subjects adapted a more bilateral activation of trunk muscles similar to what is seen in clinical populations (Beales et al., 2009a, de Groot et al., 2008). The participants experienced an increase in difficulty when lifting the leg on the painful side as seen on the Likert-scale scores (II) which correlated significantly with both the levels of pain and pain sensitivity in the area surrounding the injection site. Such a relationship has been indicated indirectly in previous clinical studies (Vleeming et al., 2002, Mens et al., 2012) which is confirmed here and has implications with regards to interpreting the outcome of the test. Furthermore, an increase in movement variability (tremor) was found when lifting the leg on the non-injected side which is in line with previous findings where experimental pain has been shown to disturb motor performance (Salomoni

et al., 2013, Salomoni and Graven-Nielsen, 2012) causing difficulty in accurately controlling the given movement.

It is unclear why the subjects adapted an excessive activation of trunk muscles similar to what is seen in clinical pain (see section 2.4.3). A plausible explanation is that intense lumbopelvic pain changes the excitability of corticomotor areas representing the trunk muscles (Tsao et al., 2011b) which has been shown to cause an increased activation of functionally unrelated areas in acute (Apkarian et al., 2013) and recurring low back pain (Tsao et al., 2011a). This is interesting as it demonstrates the ability of the motor system to modulate its activity almost instantly in the presence of pain as it searches for the most optimal way of performing the task in a less painful manner using trial and error (Moseley and Hodges, 2006). From a clinical standpoint, this is also important to note as such a reorganization serves an important role in musculoskeletal conditions (Graven-Nielsen and Arendt-Nielsen, 2008) as the sufferer adapts a protective movement pattern where the stress on the injured body part is reduced. Although such a functional adaptation may be beneficial in the acute phase, it has been suggested that it may be unfavorable in the long term given the sustained increase in spinal loading and muscle fatigue (Hodges and Tucker, 2011) which may be highly relevant when investigating the transition from acute to chronic lumbopelvic pain.

5.2.2 Clinical findings

In study III, the pregnant subjects reported increased difficulty performing the ASLR compared with controls. The outcome of the test did however, not correlate with disability, pain intensity or hyperalgesia in contrast with experimental (II) and clinical findings (Vøllestad and Stuge, 2009, Robinson et al., 2010a). No significant relationship was demonstrated between the stage of pregnancy and outcome of the test, indicating that factors other than an unfavourable length-tension relationship of the trunk muscles and hormonal-driven instability of the SIJ are the underlying cause.

The activity of trunk muscles was not assessed in the clinical group. Nevertheless, the subjective outcome scores (Likert scale) in study III where similar to what has been demonstrated previously (de Groot et al., 2008) and may potentially be a manifestation of a mixture of neurological, emotional and cognitive factors which can induce an altered motor output via shared neurophysiological mechanisms (Hodges and Smeets, 2014).

In summary, the perceived difficulty of performing the ASLR increases during a short duration of experimental SIJ pain to an extent where no significant difference is found between experimental and clinical lumbopelvic pain (Fig. 5.2). In pregnancy, the outcome of the test is not associated with the stage of pregnancy, disability, pain or hyperalgesia. The findings from studies II and III challenge previous theories stating that the outcome of the test is related with biomechanical instability of the pelvic girdle.

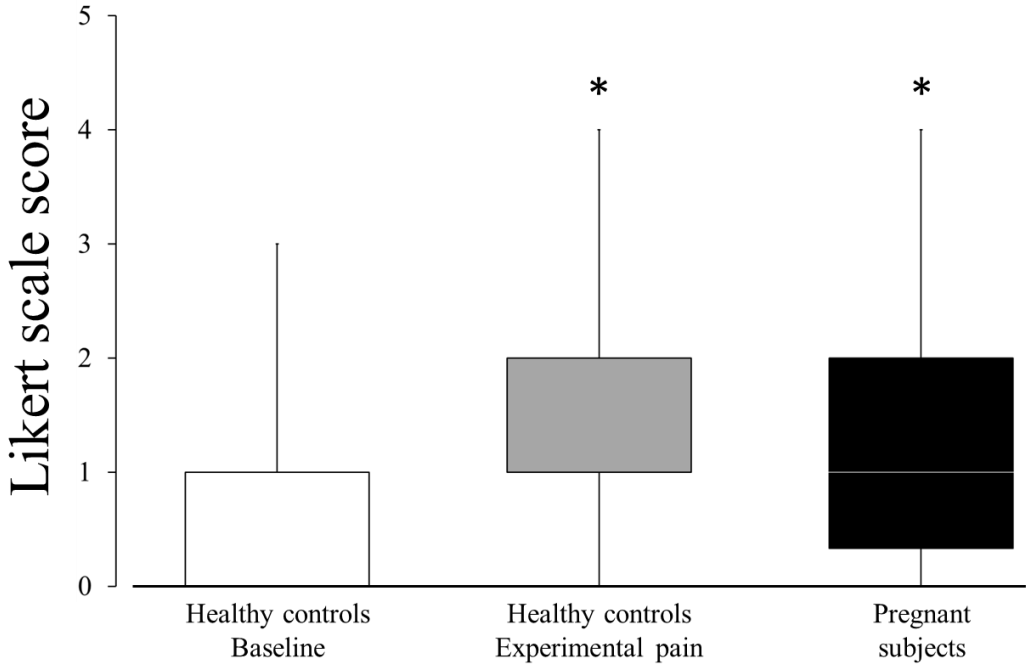

Figure 5.2 *Median [IQR] Following hypertonic saline-induced pain, healthy subjects (n =30) and pregnant subjects (n = 39) reported significantly more difficulty performing the test compared with baseline values for healthy controls (P < 0.05). No significant difference was found in sum of positive tests after experimental pain in healthy controls and pregnant (P > 0.05). Data extracted from studies II & III.*

6 SUMMARY AND CLINICAL IMPLICATIONS

In the current thesis, a novel and reliable human in vivo experimental pain model mimicking the somatosensory and motor characteristics of clinical lumbopelvic pain (LPP) was developed (I,II). The model consisted of pain originating in the long posterior sacroiliac ligament which has frequently been implicated as an important structural and functional part of normal lumbopelvic function. The relevance of this pain model for clinical populations was investigated by comparing experimental findings with pregnant women where LPP is frequently a problem.

The experimental pain model caused transient sensory-motor changes in healthy subjects comparable to what is seen in the pregnant group: 1) deep tissue hyperalgesia, 2) referred pain to the low back and into the lower limb, and 3) a positive response to manual clinical tests.

The sensory changes seen in healthy subjects following a short duration of experimental pain (I, II) demonstrate similarities between pain originating in the ligamentous structures lying superficial to the sacroiliac joint, within the sacroiliac joint and the lumbar spine with regards to pain referral. These findings may be related with an overlap of innervation of somatic structures in the two areas which converge on the same spinal segments. Amongst the pregnant participants (III), the multiple pain areas and widespread hyperalgesia may reflect a central modulation of afferent nociceptive and non-nociceptive signals. This may be initiated and modulated by physical, hormonal, cognitive and emotional factors that increase pain sensitivity via shared pain pathways including an upregulation of pro-inflammatory biomarkers, changed balance of descending pain modulation, and increased sensitivity of dorsal horn neurones.

The active straight leg raise tests and pain provocation tests of the sacroiliac joints and the low back are commonly used in clinical practice and are considered useful in differentiating between the many potential sources of pain in the area and the ability to transfer load across the lumbopelvic region. In two experimental studies (I, II) it was shown that pain from the ligamentous structures superficial to the SIJ facilitates the positive outcome of these tests resembling findings reported of in the literature as well as what was seen in a clinical population (III). The results indicate that pain per se can affect the outcome of such tests directly via increased sensitivity of pain mechanism (central and peripheral) and potentially through supraspinally facilitated sensory-motor activity. Therefore, the current findings challenge the common assumptions that pain in the area is a result of a biomechanical dysfunction such as instability of the pelvic girdle joints.

Changing the way pain conditions are managed relies on identifying the mechanisms driving the condition but in pregnancy this may be challenging as many of the physical changes which occur (and are considered natural) have frequently been related with LPP. Although most of these changes revert to normal post-partum, a significant group of women develops a chronic pain condition after delivery. This may indicate interplay between physical and psychological factors resulting in a mal-adaptive pain behaviour. Excessive muscle activity, sub-optimal loading, poor emotional health and sleep quality as well as unfavourable coping strategies are factors which are frequently found in clinical conditions as well as in the current studies which may all perpetuate the

condition, add to the pain and pain sensitivity and sustain the disability beyond pregnancy (Fig. 6.1).

Based on the series of studies a model has been developed which may explain how pain and pain sensitivity alone may affect the outcome of clinical orthopedic tests which are commonly used for diagnostic purposes. Future studies assessing clinical lumbopelvic pain will benefit from a deeper understanding of the mechanisms underlying the pain condition and how they can affect the findings during clinical examination. A battery consisting of physical and psychometric assessment as well as quantitative sensory testing may be beneficial clinically to monitor the progression of a clinical pain condition such as pregnancy-related LPP. More importantly though, developing screening tools for early identification of those at risk of developing severe pain and disability would improve the management of this condition. Currently it is not known which factors would have the best predictive value for such purposes but there is evidence suggesting that QST measurements can be beneficial (Yarnitsky et al., 2008, Weissman-Fogel et al., 2009). More studies on the topic are therefore clearly warranted where the focus should be on how and if the pain mechanisms change through the course of clinical LPP and if such changes would be related with changes in psychometric variables.

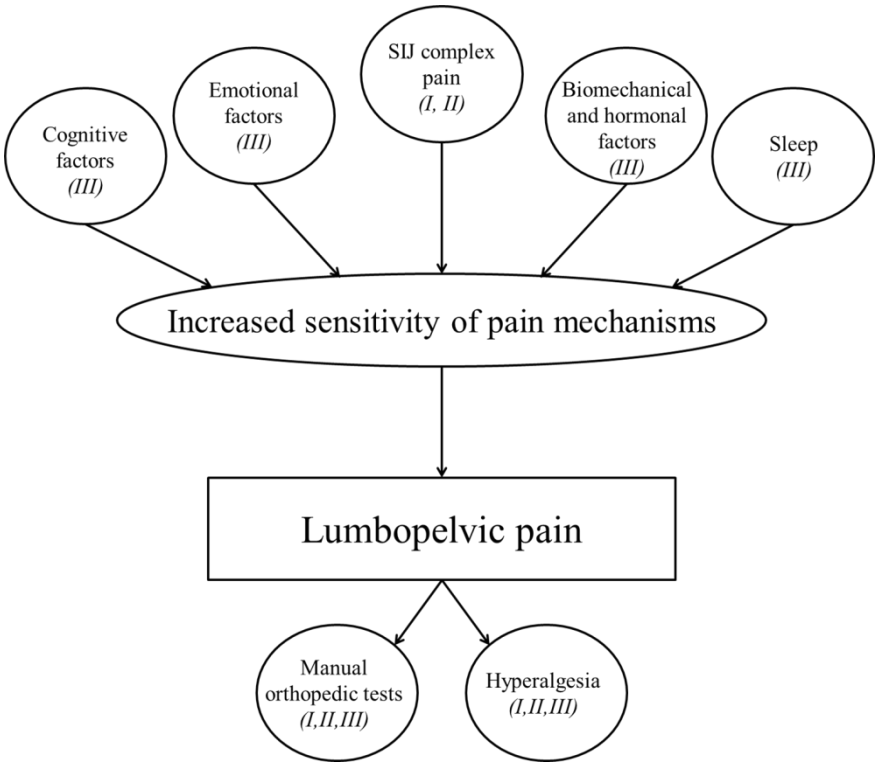

Figure 6.1 *This contemporary model of lumbopelvic pain is based on the current findings and supplemented with results from other relevant studies. The model indicates that several, parallel factors can increase the sensitivity of central and peripheral pain mechanisms resulting in lumbopelvic pain. The pain condition can be evaluated by manual orthopedic tests and an assessment of deep tissue sensitivity.*

7. DANSK SAMMENFATNING

I denne afhandling introduceres en ny og pålidelig human eksperimentel smertemodel som blev udviklet for at efterligne de sensoriske og motoriske faktorer som ses ved klinisk lumbopelvine smerte (I, II). Modellen inkludere smerte fra det lange dorsale sacroiliac ledbånd, der ofte er impliceret som en vigtig strukturel og funktionel del af den normale lumbopelvine funktion. Relevansen af denne smertemodel for kliniske populationer blev undersøgt ved sammenligning af eksperimentelle resultater med en gruppe af gravide kvinder, hvor lumbopelvine smerte ofte er et problem.

Den eksperimentelle smertemodel forårsager kortvarige sanse-motoriske ændringer hos raske forsøgspersoner der er sammenlignelig med tilsvarende set i den gravide gruppe: 1) hyperalgesi i dybere strukturer, 2) udstrålende smerter til lænden og ned i benet, og 3) en positiv respons til manuelle kliniske tests.

De sensoriske ændringer, der ses hos raske forsøgspersoner efter en eksperimentel smerte (I, II) demonstrerer ligheder mellem smerte med oprindelse i de ledbåndsstrukturer liggende overfladisk til SI-leddet, i selve SI-leddet og lænderyggen med hensyn til udstrålende smerte. Disse resultater kan være forbundet med et overlap af innervation fra de somatiske strukturer i de to områder, der konvergerer på de samme spinale segmenter. Blandt de gravide deltagere (III), kan de mange smerteområder og udbredt hyperalgesi afspejle en central modulering af afferente nociceptive og ikke-nociceptive signaler. Dette kan være udløst og moduleret af fysiske, hormonelle, kognitive og emotionelle faktorer, der øger smerteføls omhed via fælles smertebaner, herunder en opregulering af pro-inflammatoriske biomarkører, ændret balance af descenderende smertemodulation og overfølsomhed af dorsal hornets neuroner.

Aktiv strakt benløfts test og smerte provokationsteste af både SI-leddene og lænden er almindeligt anvendt i klinisk praksis og betragtes som nyttige til at skelne mellem de mange potentielle kilder til smerter i området, og evnen til at overføre kræfter i lumbopelvine regionen. To eksperimentelle studier (I, II) viste, at smerter fra de ledbåndsstrukturer overfladisk til SI-leddet øger forekomsten af positive tests hvor resultaterne er sammenlignelige med litteraturen samt fundene fra det kliniske studie (III). Resultaterne indikerer, at smerte i sig selv kan påvirke udfaldet af disse tests direkte via øget overfølsomhed af smertemekanismer (centrale og perifere) og potentielt gennem øget sanse-motorisk aktivitet på supraspinal niveau. Disse fund stiller derfor et spørgsmålstegn ved de antagelser, at smerte i området er et resultat af en biomekanisk dysfunktion af strukturer i regionen såsom ustabilitet i SI-leddet.

For at kunne ændre på hvordan forskellige smertetilstande behandles og håndteres er det nødvendigt at identificere de mekanismer, der driver smertetilstanden. Dog kan det være udfordrende i forbindelse med graviditet, da mange af de fysiske ændringer, der sker (og betragtes som naturlige) ofte er blevet forbundet med lumbopelvine smerter. Selv om de fleste af disse graviditets-relaterede ændringer normaliseres efter overstået graviditet er der en betydelig andel kvinder som udvikler en kronisk smertetilstand efter fødsel. Sammenholdt med fundene i denne afhandling, kan dette indikere et samspil mellem fysiske og psykologiske faktorer, som resulterer i en uhensigtsmæssig smerteadfærd. Øget muskelaktivitet, sub-optimal belastning, dårlig emotionel sundhed, nedsat søvnkvalitet samt dårlige copingstrategier er faktorer, som ofte findes i kliniske tilstande samt i de studier præsenteret her, der direkte kan øge smerte og smerteføIsomhed samt fastholde et nedsat funktionsniveau (Fig. 6.1).

Ud fra den række studier præsenteret her er en model blevet udviklet, som kan til dels forklare, hvordan smerte og smerteføIsomhed alene kan påvirke responsen til kliniske ortopædiske tests, som almindeligt anvendes til diagnostiske formål. Fremtidige studier omkring lumbopelvine smerter vil med fordel inkludere undersøgelser af de smertemekanismer, der ligger til grund for smertetilstanden. Et batteri, bestående af fysisk og psykometrisk vurdering samt en sensorisk profilering (QST målinger) kan forbedre den kliniske undersøgelse, hvorefter udviklingen af en klinisk smertetilstand såsom lumbopelvine smerte kan monitoreres. Vigtigere er det dog, at udvikle screeningværktøjer som tidligt kan bidrage til at identificere de personer, der risikerer at udvikle alvorlige smerter og et nedsat funktionsniveau, samt forbedre håndteringen af tilstanden. I dag er det ikke kendt, hvilke faktorer der vil have den bedste prædiktive værdi for sådanne et formål men der er holdepunkter for, at QST målinger kan være et nyttigt redskab at bruge (Yarnitsky et al., 2008, Weissman-Fogel et al., 2009). Flere undersøgelser er derfor berettiget, hvor fokus bør være på, hvordan og hvis smertemekanismer ændres gennem forløbet af kliniske lumbopelvine smerte og om sådanne ændringer kan relateres til ændringer i psykometriske variabler.

8. APPENDICES

Appendix 1. A summary of experimental and clinical studies examining pain referral patterns into the lower limbs originating in the lumbopelvic area

Reference	Subjects	Stimulation paradigms	Target structure	Main findings
(Kellgren, 1938)	n = 3 – 14 Pain free volunteers	Tip of a needle/ 0.1-0.3 mL 6% saline	Gluteal muscle and fascia overlying it Sacrospinal muscle and multifidus at the level of L5 and S1	Fascial stimulation gave localised pain but muscle pain was felt over the whole buttock Pain lying in the buttock and down the lower limb in the injected side following the dermatome pattern Injection at the level of S1 gave pain corresponding to the Fortin area
(Kellgren, 1939)	n = 5 Pain free volunteers	0.1-0.3 mL 6% saline	Interspinous ligaments C5-S2	Widespread pain referral into lower limb from injection at L3-S2
(Lewis and Kellgren, 1939)	n = 6 Pain free volunteers	0.3 mL 6% saline	The periosteum over the upper part of sacrum	Pain in the buttock, and posterior aspect of thigh and calf
(Sinclair et al., 1948)	n = ? Pain free volunteer/s	0.3-0.6 mL 6% saline	Interspinous ligaments at various sites and depths in the lumbar spine	Pain located at and in the immediate area surrounding the injection site
(Hockaday and Whitty, 1967)	n = 28 Pain free volunteers	0.1-0.3 mL 6% saline	All interspinous ligaments C1/C2 - L5/S1	Referred pain followed injection into the interpinous ligament with close relation to the level of injection and adjacent, distal segments Segments innervated by the lumbosacral plexus seldom caused sensory changes into the lower limb
(Fortin et al., 1994b)	n =10 Pain free volunteers	Tip of a needle for pain stimuli 1% lidocaine (volume not given)	Sacroiliac joint	In a non-anaesthetised joint the stimulation gave a vague sensation of pain around the stimulation site, into the buttock and into the posterior thigh
(Fortin et al., 1994a)	n =16 Patients with SIJ pain	1% lidocaine (volume not given)	Sacroiliac joint discography and lumbar facet joint blocks	Pain overlying the Forting area and into the posterior thigh
(Schwarzer et al., 1995)	n = 43 Patients with low back pain	1 mL 2% lignocaine	Sacroiliac joint	Relief of pain in the groin distinguished SIJ pain from lumbar facet joint pain Pain referral patterns from the SIJ and lumbar facet joints were similar
(Slipman et al., 2000)	n = 50 Patients with lumbopelvic pain	2 mL 2% lidocaine hydrochloride	Sacroiliac joint	Pain disappeared from the buttock (94% of subjects) and low back (72%), from the posterior thigh (50%), lower leg (28%), the groin and the foot (14%)
(Fukui and Nosaka, 2002)	n = 28 Patients with	2 mL 1% mepivacaine	Sacroiliac joint	Pain relief overlying the Fortin area (100% of subjects), the buttock

	low back pain	and2 mg dexamethazone		(69%), posterior (31%) and lateral (38%) thigh
(van der Wurff et al., 2006a)	n = 60 Patients with SIJ pain	2 mL 2% lidocaine or 0.25% bupivacaine	Sacroiliac joint	Pain relief in half of the subjects from an SIJ injection where pain disappeared from an area corresponding to the Fortin area as well as the buttock, posterior and anterior thigh, lower leg and lateral side of the foot Pain referral pattern comparing responders and non-responders was similar apart from the spot with most intense pain
(O'Neill et al., 2009)	n = 13 Pain free volunteers	Electrical stimulation 1.5mA (5 Hz, 1 ms bidirectional square wave stimulus) above pain threshold value	Facet joint L3/L4	Pain area from thoracolumbal junction to mid-lower leg Most intense pain around the stimulation site, in the groin and anterior thigh Bilateral pain referral in the lumbopelvic area and down to the ipsilateral posterior thigh

Appendix 2. A summary of clinical intervention studies examining the validity and reliability of sacroiliac joint pain provocation tests					
Reference	**Type trial**	**Type of reference test**	**Purpose**	**Outcome**	**Implications for clinical practice**
(Laslett and Williams, 1994)	Cross-sectional study (n = 51)	None	Assessment of inter-rater reliability of seven pain provocation tests for pain of sacroiliac origin in low back pain patients	5/7 tests had 78%-94% agreement Two tests had marginal reliability	The tests can be used to detect a sacroiliac source of low back pain
(Maigne et al., 1996)	A prospective study (n = 54)	Fluoroscopy-guided Intra-articular injection of Lidocaine (2 mL, 2%) Bupivicaine (dose not given, 0.5%)	To determine the prevalence of sacroiliac pain in a selected population of low back pain patients and to assess the response to pain provocation tests	35% of subjects had a short lasting relief of pain and 19% had a longer lasting relief after intra-articular block	The SIJ is a source of low back pain in a significant proportion of reported cases
(Dreyfuss et al., 1996)	A prospective cross-sectional study (n = 85)	Fluoroscopy-guided intra-articular injection of 1.5 mL of lignocaine (2%) and 0.5 mL of celestone soluspan	To identify a single SIJ test or ensemble of tests that are sufficiently useful in diagnosing SIJ disorders to be clinically valuable	Pain location or response to pain provocation tests does not have any worthwhile clinical value	SIJ pain cannot be identified by subjective and objective examination methods used in this study
(Broadhurst and Bond, 1998)	Double-blind cross sectional study (n = 40)	Fluoroscopy-guided Intra-articular injection of Lidocaine (4 mL, 1%) Saline used as control	To determine the sensitivity and specificity of commonly used SIJ pain provocation tests	The tests had specificity 100% and sensitivity 77-87%	When used in combination, the three tests used in the study have a high predictive value for pain arising from the sacroiliac joint
(Slipman et al., 1998)	A prospective cohort study (n = 50)	Fluoroscopy-guided intra-articular injection with a mixture of 1 mL betamethasone sodium phosphate and acetate suspension (6mg/mL) and lidocaine hydrochloride (2 - 3 mL, 1% - 2%)	To determine the clinical validity of SIJ pain provocation tests to diagnose SIJ pain syndrome	The likelihood (positive predictive value) of SIJ pain provocation tests determining the presence of SIJ pain is 60%	The methods used in the study cannot be used in isolation to diagnose SIJ pain but can be used for differential diagnosis
(van der Wurff et al., 2000)	Systematic review (n = 11)	None	To investigate the reliability of clinical tests for the SIJ	No evidence for the use of mobility tests of	Not mentioned

				the SIJ but reliable results for the use of Gaenslen's test and the P4 test	
(Kokmeyer et al., 2002)	A cross-sectional reliability study (n = 78)	None	To assess the interrater reliability of multitest regimen of 5 sacroiliac pain provocation tests	Weighted kappa statistic showed substantial agreement: 0.70 (95% CI = 0.45-0.95)	Using a multitest regimen of 5 pain provocation tests is a reliable method to assess SU dysfunction but lacks the assessment of validity
(Laslett et al., 2003)	A cross-sectional validation study (n= 48)	Fluoroscopy-guided intra-articular injection of Lidocaine 1.5 mL, concentration not given with Bupivicaine (dose and concentration not given) used as confirmatory block	To assess the diagnostic accuracy of a clinical examination in identifying symptomatic and asymptomatic sacroiliac joints using double diagnostic injections as the reference standard	Clinical examination and reasoning was superior to using SIJ pain provocation tests alone	A specific clinical examination and reasoning process can differentiate between symptomatic and asymptomatic SIJs
(Laslett et al., 2005)	A cross-sectional validation study (n = 48)	Fluoroscopy-guided Intra-articular injection of Lidocaine 1.5 mL(concentration not given) Bupivicaine used as confirmatory block (dose and concentration not given)	To examine the diagnostic power of pain provocation SIJ tests singly and in various combinations	Three or more tests out of six or any two of four selected tests had the best predictive power	When all six provocation tests do not provoke familiar pain, the SIJ can be ruled out as a source of current low back pain
(van der Wurff et al., 2006b)	Prospective, observational study (n = 60)	Fluoroscopy-guided intra-articular injection of Lidocaine 2 mL (2%) or Bupivacaine (0.25%)	To compare the diagnostic accuracy of a multitest regimen of 5 SIJpain provocation tests with fluoroscopically controlled double SIJ blocks	Sensitivity 85%, specificity 79% Positive predictive value 77% and negative predictive value 87%	A test regimen with 3 or more positive tests is indicative of SIJ pain Can be used in early clinical decision making to avoid invasive diagnostic procedures
(Robinson et al., 2007)	A cross-sectional reliability study (n = 56)	None	To assess inter-rater reliability of one palpation and six pain provocation tests for pain of sacroiliac origin	Clusters of pain provocation tests were found to have good percentage agreement, with kappa values	Clinically, conclusions are usually based on results of several tests Clusters of three

				0.51- 0.75 The reliability of the pain provocation tests were moderate to good, and for the palpation test, reliability was poor	and five tests used showed good reliability, although their validity needs to be assessed
(Szadek et al., 2009)	Systematic review (n = 17)	None	To evaluate the diagnostic validity of tests that could be ascribed to the IASP criteria for diagnosing SIJ pain	Using a threshold of 3 or more positive stressing tests, the diagnostic odds ratio of 3 positive provocation test is high in patients with SIJ pain	Due to the lack of a gold standard for SIJ pain, the diagnostic validity of tests related to the IASP criteria for SIJ pain should be regarded with care

Appendix 3. A summary of clinical studies examining the validity and reliability of the Active Straight Leg Raise test and the relationship with joint mobility in the pelvic girdle					
Reference	**Type trial**	**Type of reference test**	**Purpose**	**Outcome**	**Implications for clinical practice**
(Mens et al., 1999)	Cross-sectional study (n = 21)	The effect of compression from a pelvic belt and mobility of the pubic bones measured on x-ray	To develop a clinical test to quantify and qualify disability in women with peri-partum pelvic pain	Pelvic belt improved the performance during the ASLR Greater movement of pubic bones in weight bearing on symptomatic side Strong correlation between mobility of pelvic joints and outcome of ASLR	The test could be a suitable instrument to quantify and qualify disability in diseases related to mobility of the pelvic joints
(Mens et al., 2001)	Cross-sectional study (n = 250)	None	To assess the validity and reliability of the ASLR test	High test-retest reliability (0.87) Intra-class correlation (0.83)	The test can discriminate between patients with pelvic girdle pain and healthy subjects The test is useful to assess the ability to transfer loads between the lumbosacral spine and legs
(Damen et al., 2001)	Cross-sectional study (n = 163)	Doppler imaging to detect movement in the SIJ	To investigate the association between pregnancy-related pelvic pain and SIJ laxity	Asymmetric laxity of the SIJ was related with a positive ASLR test and disability	Increased laxity of the SIJ is not associated with outcome of ASLR whereas asymmetric laxity is
(Mens et al., 2006)	Cross-sectional study (n = 25)	Doppler imaging to detect movement in the sacroiliac joint	To investigate the effect of compression from a pelvic belt on movement of the SIJ	Compression from a pelvic belt reduced the movement of the SIJ which correlated with the outcome of the ASRL	Compression of the pelvic girdle using a pelvic belt significantly decreases mobility of the sacroiliac joints
Hu et al 2010	Cross-sectional study (n = 17)	Pelvic belt for compression	To investigate the effect compression on the pelvic bones had on hip and trunk muscle activity during walking and the ASLR test	Activity in transversus abdominis and oblique muscle reduced when belt was used	Indicates that the belt increases ‘force closure’ in the pelvic girdle
(Vøllestad et al., 2012)	Prospective cohort study	Serum levels of relaxin	To examine the serum relaxin	Significant association	Relaxin contributes to laxity of pelvic

	(n = 212)		levels in pregnancy and a potential relationship with symptoms and clinical tests for pelvic girdle pain	between serum relaxin concentration and outcome on the ASLR test, but no associations to responses to pain provocation tests, pain intensity or disability	joints in pregnancy but does not affect pain or disability
(Hu et al., 2012)	Cross-sectional study (n = 16)	None	To investigate normal muscle activity during the ASLR	The abdominal muscles have multiple tasks Mainly a unilateral activation pattern but considerable activity on the side contralateral to the leg being lifted contributing to the 'force closure'of the SIJ	Increases the understanding of what is a normal muscle activation pattern during the ASLR
Kwong et al 2013	Cross-sectional pilot study (n = 31)	3 independent examiners	To determine the inter-rater reliability of the Active Straight-Leg Raise test	Good inter-examiner reliability; kappa coefficient 0.87, sensitivity 71%, specificity 91% ASLR scores were significantly related with Functional Pelvic Pain Scale (r = 0.77) and disability (r = 0.70)	The ASLR test has good inter-rater reliability but the validity of the test needs to be established

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