

Pain following hysterectomy: Epidemiological and clinical aspects

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THE 4 ORIGINAL PAPERS ARE

- Brandsborg B, Nikolajsen L, Hansen CT, Kehlet H, Jensen TS. Risk factors for chronic pain after hysterectomy – a nationwide questionnaire and database study. *Anesthesiology* 2007;106:1003-12.
- Brandsborg B, Dueholm M, Nikolajsen L, Kehlet H, Jensen TS. A prospective study of risk factors for pain 4 months after hysterectomy. *Clin J Pain* 2009;25:263-8.
- Brandsborg B, Dueholm M, Kehlet H, Jensen TS, Nikolajsen L. Mechanosensitivity before and after hysterectomy: a prospective study on the prediction of acute and chronic post-operative pain. *Br J Anaesth* 2011;107:940-7.
- Brandsborg B, Nikolajsen L, Kehlet H, Jensen TS. Chronic pain after hysterectomy. *Acta Anaesthesiol Scand* 2008;52:327-31. Review.

INTRODUCTION

Chronic pain is a major health and socioeconomic problem in the Western World. Epidemiological studies in Denmark and Europe have shown a prevalence rate of chronic non-cancer pain of about 20%, and the number is rising with an annual incidence rate of 1.8% per year [2-4]. A proportion of patients with chronic pain have developed their pain after surgical procedures.

Until recently, chronic postsurgical pain was not recognized as a major clinical problem, but subsequent studies have emerged showing that pain is indeed an adverse outcome after various types of surgery. Persistent pain has been described after such diverse procedures as limb surgery, hernia operation, cesarean section, sternotomy, breast surgery, and thoracotomy [5-11].

The formation of national registries of surgical procedures, e.g. herniotomy, hip arthroplasty, and breast cancer surgery, has made it possible to study large cohorts in order to examine the magnitude of these problems [12-14]. One condition, hysterectomy, has surprisingly not been studied much despite the high frequency of this procedure. Therefore, the establishment of the Danish Hysterectomy Database in 2003 offered an opportunity to examine pain following hysterectomy.

This thesis describes chronic pain following hysterectomy. The main focus is the epidemiology, risk factors, and predictors of chronic pain after hysterectomy due to non-malignant causes.

CHRONIC POSTSURGICAL PAIN

History

Chronic postsurgical pain has been known for centuries following amputations [15]. Some early case reports of pain after other surgical procedures were reported in the mid 20th century [16-18], but research has expanded mainly within the last 20 years starting with studies of pain after amputation, mastectomy, thoracotomy, and herniotomy [6,19-21]. Some of the first to address the prevalence of chronic postsurgical pain were Crombie et al., who found that among 5130 patients attending 10 pain clinics in North Britain, surgery contributed to pain in 22.5% of the patients [22]. This study stated that it was a large problem, and several studies of the epidemiology and risk factors together with comprehensive reviews were published in the following years [5,23-25]. Interestingly, Crombie et al. also reported that the two most frequent sites of chronic postsurgical pain were the abdomen (47.1%) and the anal, perineal, and genital regions (38.0%).

Definition

Chronic postsurgical pain, or persistent postsurgical pain as it is also termed, has been defined differently. A commonly used definition is pain persisting for more than 3 months after surgery [5,22-24]. Crombie et al. emphasized that the pain had to be a new problem that did not exist before the surgery [22], and Macrae required four criteria: a) pain development after a surgical procedure, b) pain persisting for more than 2 months, c) other causes for the pain should be excluded, and d) pain from a pre-existing problem should be explored and exclusion attempted [23].

Epidemiology

Chronic postsurgical pain is more frequent after some surgical procedures than others, and a list of estimated frequencies after major and minor surgical procedures is seen in Table 1.

Table 1

	Frequency of chronic pain	References
Amputation	33-75%	[26-29]
Breast surgery for cancer	17-33%	[14,19,30,31]
Cholecystectomy	5-42%	[32-34]
Total hip arthroplasty	28%	[13]
Breast augmentation	13-25%	[35,36]
Vasectomy	6-15%	[37-39]
Otoplasty	6%	[40]
Inguinal hernia repair	6-10%	[41,42]
Lung transplantation	5-18%	[43]
Coronary artery bypass surgery	30-56%	[44,45]
Thoracotomy	44-57%	[20,46,47]
Sternotomy	27-28%	[9,48]
Cesarean section	6-18%	[8,49-51]

Table 1. Estimated frequencies of chronic postoperative pain after major and minor surgical procedures.

As can be seen from the table, frequencies not only vary between different procedures, but also within the same type of procedure. Most studies are based on 50-300 patients, and only few studies have collected data with more than 500 subjects [9,42,45,51]. Also, the assessment of pain and the follow-up time are not identical, and these inconsistencies may explain the varying frequencies. To address the question of chronic pain frequency after different surgical procedures, the existing literature calls for future studies to include larger groups of patients. National databases for different surgical procedures provide an excellent platform for conducting studies where potential confounding factors can be controlled for.

Postsurgical pain and possible mechanisms

Normal physiological pain is pain caused by activation of high threshold nociceptors in skin, muscle, connective, and other types of tissue [52]. It is produced by tissue damage from intense noxious mechanical, chemical, or thermal stimuli. This nociceptive pain represents an alarm system warning the organism of threatening tissue damage. Nociceptive neurons express a series of transducer receptors and ion channels that respond to a broad range of different noxious stimuli [53]. Acute nociceptive pain occurs only in the presence of noxious stimuli, and it dies down shortly after the damaging stimulus is removed. In rare cases of lost nociception, such as congenital insensitivity to pain, these individuals sustain major injuries and life-threatening internal infections [54]. So the nociceptive system is a powerful alerting system that is necessary for survival.

Tissue injury due to surgery has two essential elements: an inflammatory and a neuropathic component. In both cases, the pain is characterized by a heightened sensitivity and response to non-noxious or noxious stimuli resulting in an experience of pain [5]. A schematic presentation of the sensory pathways is seen in Fig. 1.

Figure 1

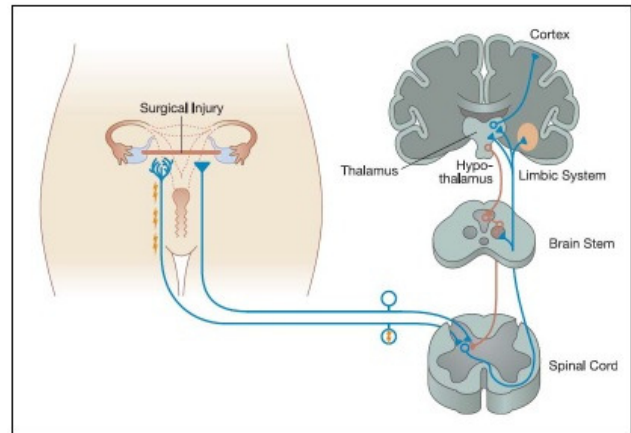


Figure 1. Transmission of nociceptive stimuli during normal and sensitized conditions.

Inflammatory pain is pain occurring in response to tissue injury and is accompanied by a neurogenic inflammation. In the acute phase it is characterized by the classical signs of inflammation: 1) redness with vasodilatation, 2) edema, and 3) pain. It results from the release of mediators and signaling substances including substance P and calcitonin gene-related peptides from primary afferent neurons and the local release from tissue of inflammatory mediators such as PGE2, bradykinin, endothelin, cytokines, leukotrienes, nerve growth factor, etc. and will either sensitize or directly activate peripheral nociceptors and contribute to a peripheral sensitization. The result is a reduced threshold of nociceptors innervating the inflamed tissue and an increased response to activation. These mediators in turn give rise to a cascade of intracellular signaling events which contribute to a more persistent sensitization with a subsequent spread to the CNS and development of a central sensitization [55]. The changes following inflammation are generally all reversible, and the sensitivity of the system will be restored when the inflammation disappears. In inflammatory pain, the nociceptive signaling pathways are intact, but in a sensitized state to secure optimal healing conditions. The swelling, the reddening, and the pain in the damaged area are protective, and with healing the inflammation gradually disappears together with the pain.

Neuropathic pain is the other element in tissue injury caused by surgical procedures. This part is induced by damage to the nerves traversing the surgical field. As a consequence of such lesion to the peripheral nervous system, there may be motor, sensory, or autonomic changes. In practice it is the damage to afferent sensory nerves that is responsible for the neuropathic pain part. When lesions occur, they may cause sensory loss in the innervation territory corresponding to the damaged nerves or the peripheral projections of central nervous system structures. So, an important distinguishing feature in several neuropathic types of pain is the paradoxical combination of sensory loss and pain with or without sensory hypersensitivity phenomena in the painful area [56]. Following injury to nerves, there is spontaneous activity at the peripheral nerve ending, with changes in ion channels and release of pro-inflammatory cytokines, chemokines, and neurotrophic factors.

These factors interact with damaged or intact nerve fibers and generate an increased barrage of input to the central nervous system giving rise to a central sensitization.

In some cases, the pain can become independent of peripheral input in certain chronic pain conditions. Central sensitization is also thought to explain how low-threshold A β mechanoreceptors gain access to pain-transmitting systems causing normally non-painful stimuli to be perceived as painful [57,58]. The molecular mechanism in the central sensitization cascade is beyond the scope of this thesis. Suffice to say that while central sensitization usually dies down when the peripheral inflammation subsides, the central sensitization following nerve damage will often persist because of long-lasting or even permanent changes in the cellular circuitry involved in pain processing.

Conclusion: In postsurgical pain there is probably a combination of both an inflammatory and a neuropathic component. It is possible that the neuropathic component may be the one that plays a major role for the maintenance of pain and sensitization in patients having chronic pain following surgery.

Risk factors

Since only a fraction of patients undergoing surgery develop chronic pain (Table 1, page 9) despite a similar surgical injury, it seems that certain individuals are at risk for development of such pain. This raises the question whether pain can be predicted before surgery. Several studies have looked at the risk factors for chronic postsurgical pain and have shown that preoperative, intraoperative, and postoperative factors are involved, but the relative contribution of each factor varies with the type of surgery.

Overall, women are more disposed to develop chronic pain [32,59], as are subjects of younger age [9,60,61] and subjects with psychosocial problems [62]. Preoperative pain in the location of surgery [27] as well as pain problems elsewhere are risk factors [49]. Type of surgery and nerve damage contribute to chronic pain frequency in some types of surgery [9,46], but not others [63,64]. Postoperatively, acute postoperative pain intensity has proved a major risk factor for chronic pain after several types of surgery [33,47,65], but it is unclear whether acute pain increases the risk due to a susceptibility to develop both acute and chronic pain or because inadequate postoperative pain management increases the risk. Finally, genetic factors have been suggested to influence the development of chronic pain [66]. It is possible that perioperative events may trigger the development (or not) of pain in individuals who are already genetically predisposed to develop chronic pain.

Prediction

The relationship between preoperative experimental pain testing and acute postoperative pain has been tested in some studies, while only few have studied the relation to chronic pain. Since acute postoperative pain is an important risk factor for the development of chronic postsurgical pain, it is of interest to predict the intensity of acute postoperative pain [67]. Most studies have found a positive relation between some of the preoperative tests and acute postoperative pain [68-76].

A few studies have examined preoperative tests in relation to chronic pain. Bisgaard et al. found chronic pain after cholecystectomy to be associated with acute postoperative pain, but not with the response to a preoperative cold pressor test [33].

A recent study assessed DNIC efficiency in patients undergoing thoracotomy (diffuse noxious inhibitory control: pain reduction during exposure to another noxious stimulus at a remote body area). It was found that preoperative DNIC efficiency and acute postoperative pain intensity predicted chronic postthoracotomy pain, while preoperative heat pain thresholds did not predict chronic pain [77].

In conclusion, the current literature on the prediction of chronic postsurgical pain is sparse, and it emphasizes the importance of studying different methods of prediction and the transition from acute to chronic postoperative pain.

HYSTERECTOMY

Indications and frequency

Hysterectomy may be performed on either malignant or benign indication. Hysterectomy for a benign indication includes removal of the corpus of uterus and usually also the cervix and represents around 80% of hysterectomies in Denmark [78]. Radical hysterectomy performed in women with cancer (20%) is a much more extensive procedure and includes removal of the uterus, cervix, top part of the vagina, ovaries, fallopian tubes, lymph nodes, lymph channels, and tissue in the pelvic cavity that surrounds the cervix. In this thesis, only hysterectomy on benign indication is studied, and all the following text refers to hysterectomy for a benign indication.

Hysterectomy is one of the most common gynecological operations with annual rates of 1.8/1000 (Denmark), 2.1/1000 (Sweden), and 5.0/1000 (USA) [78-80].

The Danish Hysterectomy Database

In Denmark, the Danish Hysterectomy Database (DHD) was established in 2003 with the purpose of studying and improving the outcome of hysterectomy. The DHD includes data on preoperative diagnosis, types of surgery and anesthesia, complications, and other factors registered by the treating physicians. More than 95% of the approx. 5000 annual hysterectomies are registered in the database (for details, see www.kliniskedatabaser.dk, in Danish). The recent frequencies of main indications for benign hysterectomy in Denmark are bleeding disorders (34%), uterine fibromata (24%), uterine prolapse (15%), pain (8%), premalignant disease (3%), benign ovarian tumor (2%), endometriosis (2%), and other (12%) [81].

Surgical methods

The type of hysterectomy depends on the surgical route (abdominal, vaginal, or laparoscopic) and whether it is a total or a subtotal removal of the uterus (leaving cervix in situ). The most suitable approach depends on the patient's specific condition and the surgeon's experience, but usually a vaginal hysterectomy is performed whenever possible [82]. In Denmark, the types of hysterectomy are total abdominal hysterectomy (49%), subtotal abdominal hysterectomy (8%), vaginal hysterectomy (37%), total laparoscopically assisted vaginal hysterectomy (5%), and subtotal laparoscopically assisted vaginal hysterectomy (1%) [81].

Pain after hysterectomy

A review of chronic pain following hysterectomy (Paper IV) was published in 2008. As shown in Table 2, 11 studies with information on long-term pain were identified [83-93]. The reported prevalence rates of pain varied from 5-32%. The methodology varied in each of the studies so direct comparison was not possible.

Table 2

Authors	n	Study design	Pain preoperatively	Pain at follow-up	Acquired/-increased pain at follow-up ^b
Stovall et al., 1990 [83]	99	Review of medical records 12-64 months postop.	100%	22.2%	5%
Carlson et al., 1994 [84]	418	Interview/questionnaire before, 3, 6, and 12 months postop.	85%	13%	3%
Hillis et al., 1995 [85]	308	Interview before and 12 months postop.	100%	26.2%	2.9%
Tay et al., 1998 [86]	98	Interview/questionnaire 12 months postop.	100%	16.3%	0%
Meltomaa et al., 1999 [87]	687	Questionnaire 4-6 weeks and 12 months postop.	NA	14.8%	NA
Thakar et al., 2002 [88]	279	Questionnaire 6 and 12 months postop.	NA	4.7%	NA
Gimbel et al., 2003 [89]	319	Questionnaire before, 2, 6, and 12 months postop.	76.8%	22.8%	NA
Hartmann et al., 2004 ^a [90] Kjerulff et al., 2000 ^a [91]	1299	Interview before, 6, 12, 18, and 24 months postop	59.6%	6.7%	1.0%
Sprung et al., 2006 [92]	89	Interview before, 2, 4, 8, and 12 weeks postop. Randomized spinal/general anesthesia	NA	NRS 0.0±0.2/ 0.1±0.3 ^c	NA
Brandsborg et al., 2007 [93]	1135	Questionnaire 12 months postop. Preoperative data from national database.	61.9%	31.9%	14.9%

Table 2. Studies on chronic pain after hysterectomy. NA: not applicable; NRS: numerical rating scale 0-10. ^aSame population in both studies [90,91]. ^b“Acquired pain” is pain as a new symptom at follow-up. “Increased pain” is pain in women with preoperative pain. ^cAverage NRS in 24-hr for groups of spinal/general anesthesia.

The main findings of this survey were:

- 1-15% of women had acquired or increased pain at long-term follow-up [83-85,91,93].
- Preoperative pain was a risk factor for pain at long-term follow-up [90,93].
- The type of hysterectomy did not affect the prevalence of chronic pain [83,84,88,89,91,93].
- The type of histopathological diagnosis was not related to chronic pain [83,91].
- Preoperative depression was associated with chronic pain [90].
- Spinal anesthesia was associated with a lower pain frequency in one study [93] , but not in another [92].

The current literature emphasizes the need for more detailed descriptions of the pain, and also risk factors should be explored.

Prediction of pain after hysterectomy

Five studies have tested pain thresholds prior to gynecological surgery ([68-72], Table 3) , and as can be seen from the table, all studies found a positive relation between some of the preoperative tests and acute postoperative pain. None of the studies have expanded the observation time to chronic pain, and it is therefore unknown whether the preoperative experimental tests are also related to chronic pain after gynecological procedures.

Table 3

Author, year	n	Procedure	Pain testing	Pain assessment	Prediction (+/-)
Granot et al, 2003 [68]	58	Cesarean section	Heat pain threshold on volar forearm	VAS at rest and during activity	Pain threshold (-) Suprathreshold (+)
Hsu et al, 2005 [69]	40	Hysterectomy or myomectomy	Pressure pain on pulp of third finger	VAS at rest	Pain threshold (-) Tolerance threshold (+)
Pan et al, 2006 [70]	34	Cesarean section	Heat pain threshold on volar forearm and lower back	VAS at rest and during activity	Pain threshold (-/+)
Strulov et al, 2007 [71]	47	Cesarean section	Heat pain threshold on volar forearm	VAS	Tonic pain threshold (+)
Nielsen et al, 2007 [72]	39	Cesarean section	Electrical pain threshold	VAS at rest and during activity	Pain threshold (+)

Table 3. Prediction of acute postoperative pain after gynecological surgery

AIM

The aim of this thesis was to study the epidemiology of chronic pain after benign hysterectomy, describe the clinical characteristics of pain, and to identify risk factors and potential predictors for the development of chronic pain after hysterectomy.

The thesis had the following specific questions:

1. What is the frequency and characteristics of chronic pain after hysterectomy?
2. Do preoperative factors such as preoperative pain, pain problems elsewhere, and psychosocial factors contribute to the development and/or persistence of chronic pain?
3. Is chronic pain after hysterectomy related to the surgical procedure itself (nerve damage) with the characteristics of neuropathic pain?
4. Is preoperative sensitization of the nervous system, as expressed by hyperexcitability to experimental pain testing, a predictor of acute and chronic pain following hysterectomy?

Overall, four papers are published/submitted:

PAPER I:

A postal survey of pain one year after hysterectomy combined with data from the Danish Hysterectomy Database.

PAPER II AND PAPER III:

A prospective study of women undergoing hysterectomy with pain questionnaires (Paper II) and experimental pain testing (Paper III) before and after hysterectomy.

PAPER IV:

A review of chronic pain after hysterectomy.

METHODS: PAPER I

This study was a postal questionnaire study of pain one year after hysterectomy combined with data from the Danish Hysterectomy Database.

PATIENTS

Women were recruited from the Danish Hysterectomy Database. All women consecutively registered in the database between October 1, 2003 and April 1, 2004 (6 months) received a postal questionnaire (n = 1299). The questionnaire was mailed to the women one year after hysterectomy. All subjects gave signed informed consent, and study procedures were in accordance with the Declaration of Helsinki (World Medical Association, 2004).

THE DANISH HYSTERECTOMY DATABASE

The following data were retrieved from the Danish Hysterectomy Database (DHD): duration of surgery, age, type of hysterectomy, main indication, type of incision, other procedures performed, type of anesthesia, epidural analgesia during surgery, pain as an indication for surgery, endometriosis, complications, postoperative NSAIDs, and postoperative epidural analgesia.

PAIN ASSESSMENT

Pain was defined as being present in women answering yes to having pelvic pain within the last three months.

Women were told to report the intensity of pain on a numerical rating scale (NRS) with the numbers 0-10 (0 representing no pain and 10 representing worst pain imaginable). No distinction was made between pain at rest and pain during movement.

Pain questionnaire

No pre-existing validated questionnaire to assess pain before and after hysterectomy was found among previous studies. We therefore decided to sample items from well-known pain questionnaires with new questions related to the uterine disorder and the surgical procedure.

The main purpose of the questionnaire was to assess: chronic postoperative pain yes/no, pain intensity – average and worst pain, affect of pain on daily living, frequency of pain, pain location, pain characteristics (type of pain), consumption of analgesics, preoperative pain, scar pain, and other pain problems.

We used the McGill Short Form pain descriptors together with our own questions [94]. Briefly, the construction of the questionnaire was as follows:

After a literature study of well-known pain questionnaires and brain storming with the academic supervisors, the author Birgitte Brandsborg constructed a pain questionnaire. This was read and commented by supervisors and co-workers at the Danish Pain Research Center. A revised version was sent to 20 women with previous hysterectomy (identified from the DHD), and after evaluation of the responses, the final version of the pain questionnaire (Paper I) was created (enclosure I).

STATISTICS

The statistical software was Intercooled Stata version 9, StataCorp LP, Texas, USA. All p-values less than 0.05 were considered to be statistically significant.

Descriptive statistics using median (range) and mean (standard deviations) were used to describe basic data. Chi-squared test (X²) was used to compare categorical variables.

A multivariate logistic regression model was used to assess the main risk factors for pain one year after hysterectomy. The dependent variable was "chronic pain". The eight independent variables were 1) preoperative pelvic pain, 2) previous cesarean section, 3) pain problems elsewhere, 4) indication for hysterectomy, 5) type of hysterectomy, 6) spinal anesthesia, 7) epidural anesthesia during surgery, and 8) postoperative epidural analgesia. Variables number 4 and 5 were categorically based on the categories registered in the DHD. The other variables were all dichotomous.

METHODS: PAPER II

This was a prospective study of women undergoing hysterectomy for a benign indication. Women completed questionnaires about pain, quality of life, coping strategies, and gynecological symptoms before and 3 weeks and 4 months after hysterectomy (Paper II).

Table 4 summarizes the schedule and the methods of examination carried out in this prospective study.

Table 4**Timetable for Paper II and Paper III.**

Method	Paper	Before	Day 1	3 weeks	4 months
Pain questionnaire	II	x		x	x
Pain diary	II		x (day 1-14)		
SF-36	II	x			
Coping Strategies Questionnaire	II	x			
Uterine Fibroid Symptom Score	II	x			x
Abdominal wind-up-like pain	III	x	x		x
Abdominal brush/pinprick	III	x	x		x
Abdominal pressure pain	III	x	x		x
Vaginal Pressure pain	III	x	x		x

PATIENTS

All women referred for a hysterectomy on benign indication at Aarhus University Hospital, Skejby between August 1, 2006 and April 30, 2007 (9 months) were identified. Women who met the inclusion criteria received an invitation letter preoperatively to participate in the study (n = 149).

Inclusion criteria: Women scheduled for a hysterectomy because of bleeding disorder and/or uterine fibroids.

Exclusion criteria: Women with uterine prolapse, endometriosis, malignant disease, pelvic pain (main indication), or inability to provide informed consent.

All subjects gave signed informed consent, and study procedures were in accordance with the Declaration of Helsinki (World Medical Association, 2004). The study was approved by the Danish National Committee on Biomedical Research Ethics (ID: 20060101).

PAIN ASSESSMENT

Pain was measured by questionnaires before and 3 weeks and 4 months after hysterectomy, and the women were told to score the intensity of their pain on a numerical rating scale (NRS) with the numbers 0-10 (0 representing no pain and 10 representing worst pain imaginable). No distinction was made between pain at rest and pain during movement.

Pain was defined as women reporting pelvic pain within the last week and at the same time rating the effect of pain on daily living as "some", "a lot", or "very much". Women who reported pain that affected daily living "not at all" were not considered to have clinically relevant pain. For the acute postoperative pain intensity, patients scored their average pain intensity daily in a pain diary, and an average of 14 days was used.

QUESTIONNAIRES***Pain questionnaire and pain diary***

A draft questionnaire similar to the pain questionnaire in Paper I was given to 10 women referred for a hysterectomy at Aarhus

University Hospital, Skejby. The women gave written and oral comments after which the final version was created.

The pain questionnaire (Paper II) was addressed to women both before and after hysterectomy with similar questions before and after, but the text was slightly different according to the time of questioning (enclosures IIa and IIb).

Women completed a pain diary for the first 14 days after surgery. It included one daily rating of the perceived average pain intensity.

Short Form-36 General Health Questionnaire

The Short Form-36 General Health Questionnaire (SF-36) is a widely used and validated survey of patient health and quality of life. The SF-36 consists of 36 questions assembled in eight subscales. The eight scales are: Physical Function, Role-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role-Emotional, and Mental Health, the first four representing "physical health" and the last four "mental health" [95]. For recent updates see the homepage www.sf-36.org.

Coping Strategies Questionnaire

The Coping Strategies Questionnaire (CSQ) is a validated questionnaire to assess the coping strategies of pain patients [96]. It consists of 50 questions and a total score is calculated for each of the eight subcategories: Diverting Attention, Reinterpreting Pain Sensations, Coping Self-Statements, Ignoring Pain Sensations, Praying or Hoping, Catastrophizing, Increasing Activity Level, and Increasing Pain Behavior. Also, Perceived Control Over Pain and Ability to Decrease Pain are evaluated.

Uterine Fibroid Symptom Score – Quality of life

The Uterine Fibroid Symptom Score – Quality of life (UFS-QoL) is a questionnaire constructed to assess the severity of symptoms and quality of life in women with uterine fibroids [97]. Only the first part (Uterine Fibroid Symptom score) was used to quantify the severity of symptoms before and after hysterectomy. Questions are about bleeding pattern, micturition, fatigue, and abdominal heaviness feeling.

STATISTICS

The statistical software was Intercooled Stata version 9, StataCorp LP, Texas, USA. All p-values less than 0.05 were considered to be statistically significant.

Descriptive statistics using median (range) and mean (standard deviations) were used to describe basic data. Wilcoxon's signed rank test (paired data) and Mann-Whitney's test (unpaired data) were used for continuous variables and chi-squared test (X²) for dichotomous variables.

For the acute postoperative pain intensity, a summary measurement of the numerical pain rating of the first 14 days (area under curve) was used [98].

METHODS: PAPER III

This paper is based on the same prospective study as Paper II.

Women were examined with quantitative sensory testing before hysterectomy, on day 1, and after 4 months. The results of quantitative sensory testing and their predictive role in chronic pain are reported in paper III. A timetable of the methods is shown in Table 4 (page 20).

PATIENTS

Patients were included as described for Paper II.

PAIN ASSESSMENT

Pain was measured after quantitative sensory testing, and women were told to score the intensity of their pain on a numerical rating scale (NRS) with the numbers 0-10 (0 representing no pain and 10 representing worst pain imaginable). No distinction was made between pain at rest and pain during movement.

For the acute postoperative pain intensity, an average of 7 days was used (because many women reported absent or very low intensity of pain in the second postoperative week).

QUANTITATIVE SENSORY TESTING

A quantitative sensory testing protocol was performed before hysterectomy, on day 1, and 4 months after hysterectomy, and 3 sites were examined each time:

Abdominal test site: the midline abdominal wall approx. 2 cm proximal to the theoretical line of a Pfannenstiel incision.

Vaginal test site: the ischial spines by vaginal exploration.

Brush/pinprick

Brush-evoked allodynia was assessed by lightly stroking the abdominal wall using a brush which was moved from outside the affected area towards the theoretical line of a Pfannenstiel incision. Pinprick hyperalgesia was determined in the same manner using a von Frey hair no. 5.88. For brush-evoked pain, individuals were asked if and when the sensation of touch changed to a sensation of pain. For pinprick hyperalgesia, individuals were asked if and when then the sensation of pinprick became more painful.

Wind-up-like pain

Wind-up-like pain was tested on the abdomen with a von Frey hair (no. 5.88), which was repeatedly applied to the abdomen for 30 seconds with a frequency of 2 Hz. The women rated their pain on an NRS immediately after stimulation.

Pressure pain

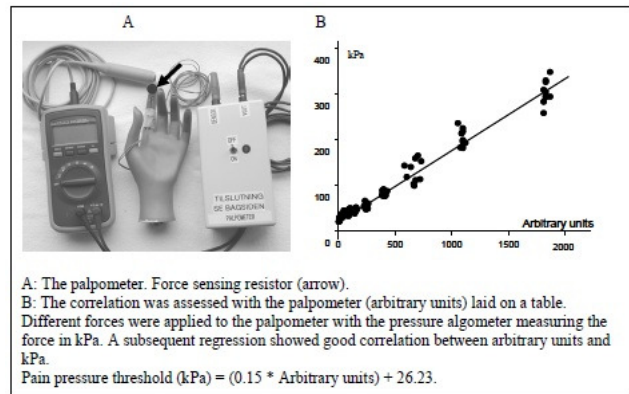
Abdominal pressure pain detection thresholds (PPDTs) were measured using a handheld electronic pressure algometer (Somedic AB, Sweden) with a 1 cm² probe area and an application rate of 20 kPa/s. Patients were instructed to activate a pushbutton when PPDT was perceived. The average of three measurements was used to define PPDT.

Vaginal pressure pain detection thresholds (PPDTs) at the ischial spine were measured with a modified pressure algometer applicable for vaginal examination. The tissue around the ischial spine was chosen because of the large variability when measuring at other vaginal sites during exploration. The palpometer was attached to the index finger of the examiner with adhesive tape (Micropore) and covered with an examination glove during testing. Patients were instructed to activate a pushbutton when PPDT was perceived, and the average of six measurements (three on each side) was used to define PPDT. The palpometer consisted of a force-sensing resistor (FSR151, Interlink Electronics, Inc.) connected to a meter. The FSR was a polymer thick film (diameter: 10 mm, thickness: 0.33 mm), which exhibited a decreasing electrical resistance with increasing force applied to the device. The proportional change in current was converted into arbitrary units (0-2000). Before study start, the palpometer was calibrated towards the pressure algometer, and a linear regression showed a correla-

tion between arbitrary units and kPa ($r = 0.97$). Consequently, all results are presented in kPa, see Figs. 2A and 2B.

Figure 2

Fig. 2A and 2B. Paper III. The palpometer.



STATISTICS

The statistical software was Intercooled Stata version 9, StataCorp LP, Texas, USA. All p-values less than 0.05 were considered to be statistically significant.

Descriptive statistics using median (range) and mean (standard deviations) was used to describe basic data. Wilcoxon's signed rank test (paired data) and Mann-Whitney's test (unpaired data) were used for continuous variables and chi-squared test (χ^2) for dichotomous variables.

Spearman's rho was used for correlations between pre- and postoperative variables.

RESULTS: PAPER I

Missing data and excluded patients

The response rate to the postal questionnaire was 90.3% and 38 subjects were excluded, leaving 87.4% ($n = 1135$) for the final analysis. Overall, the included questionnaires had very few missing data, with a median response rate to each question of 98.6%. The Danish Hysterectomy Database receives data from more than 95% of hysterectomies in Denmark, and data from DHD are more than 95% complete.

Pain frequency and pain characteristics

One year after hysterectomy, 362 women (31.9%) reported pain in the pelvic area, and 703 (61.9%) recalled having preoperative pain [93]. Among the 362 women with chronic pain, 92 subjects (8.1% of total) had pain constantly or every day, and pain affected daily living "a lot" or "very much" in 66 (5.8% of total). "Pain intensity on average" was 4 (range 0-10) and "pain at its worst" was 6 (range 1-10). Pain medication (primarily paracetamol and NSAIDs) were used by almost half of the women ($n = 161$). The most frequent location of pain was in the middle of pelvis (45.0% of pain patients), but 70 women (19.3% of pain patients) reported pain in the abdominal scar.

Most women were relieved of their pain or pain was decreased in duration and intensity, but 54 women with pain (4.8% of total) did not recall having pain before the operation. The surgical procedures in these women were abdominal hysterectomy (66.7%), vaginal hysterectomy (31.5%), and laparoscopically assisted vaginal hysterectomy (1.9%). Pain affected daily living "a

lot" or "very much" in 16.7% (n = 9). The most frequent locations of pain in these women were in the middle of the pelvic region (n=15) and in the abdominal scar (n=15).

Risk factors for chronic pain

Eight potential risk factors for pain after hysterectomy were tested in a multiple logistic regression model (Table 6). Preoperative pelvic pain, previous cesarean section, pain problems elsewhere, and pain as an indication for surgery all increased the odds ratio for having pain one year after hysterectomy, while spinal anesthesia was associated with a decreased odds ratio for chronic pain.

Table 5

Paper I: Multiple logistic regression of risk factors for chronic pain.

N = 1135	Odds ratio (CI) for pain at follow-up	p-value
1. Preoperative pelvic pain	3.25 (2.40-4.41)	<0.01*
2. Previous cesarean section	1.54 (1.06-2.26)	0.03*
3. Pain problems elsewhere	3.19 (2.29-4.44)	<0.01*
4. Primary indication for surgery		<0.05*
Leiomyoma	1.00 (ref. variable)	
Menorrhagia	1.30 (0.86-1.98)	0.21
Metrorrhagia	1.45 (0.95-2.20)	0.08
Prolapse	1.53 (0.82-2.87)	0.19
Dysmenorrhea	1.32 (0.74-2.36)	0.35
Pain	2.98 (1.54-5.77)	<0.01*
Cervical dysplasia	1.91 (0.87-4.20)	0.11
Endometriosis	2.60 (0.86-7.86)	0.09
Other	1.18 (0.67-2.06)	0.56
5. Type of hysterectomy		0.26
Total abdominal	1.00 (ref. variable)	
Subtotal abdominal	1.20 (0.77-1.86)	0.43
Vaginal	0.70 (0.46-1.06)	0.09
Laparoscopically assisted vaginal	1.27 (0.62-2.60)	0.51
Laparoscopic	0.70 (0.19-2.57)	0.59
6. Spinal anesthesia	0.42 (0.21-0.85)	0.02*
7. Epidural during surgery	0.76 (0.50-1.17)	0.22
8. Postoperative epidural	1.02 (0.66-1.59)	0.93

RESULTS: PAPER II

Missing data and excluded patients

Women who met the inclusion criteria received an invitation letter preoperatively to participate in the study (n = 149). Ninety-eight women agreed to be included and 90 completed the study and were left for the final analysis.

Pain frequency and pain characteristics

Before surgery, 46 women (51.1%) had pelvic pain, while 15 (16.7%) reported pain after 4 months.

Pain characteristics before hysterectomy and after 3 weeks and 4 months are reported in Table 5. Four months after hysterectomy, 15 women (16.7%) reported to have pelvic pain that affected daily living "some" (n = 10) or "a lot" (n = 5). Based on comparisons of pain location and McGill pain descriptors reported preoperatively and after 4 months, together with the women's own judgments, the pain was classified as either "pain likely to be continuing from before surgery" or "newly acquired pain". Among the 15 women, 11 women had "pain likely to be continuing from

before surgery" and their pain intensity (NRS) was either unchanged (n = 6) or decreased (n = 5) compared with the preoperative pain. The types of hysterectomy were abdominal (n = 9) and vaginal (n = 6). Four women reported "newly acquired pain" in the form of scar pain (n = 3) and pain after a postsurgical hematoma (n = 1).

Risk factors for chronic pain

Twelve possible risk factors for chronic pain at 4 months were evaluated. Women with preoperative "pain problems elsewhere" and women with a "higher acute postoperative pain intensity" were more likely to have pelvic pain 4 months after hysterectomy (p < 0.01 and p = 0.03). Likewise, there was a tendency towards "preoperative pelvic pain" being associated with pain at 4 months (p = 0.06). "Age", "previous pelvic surgery", "Uterine Fibroid Symptom Score", "indication for hysterectomy", "type of hysterectomy and anesthesia", "weight of uterus", and "pain at 3-week follow-up" were not associated with having pain at 4 months.

Psychosocial characteristics

Women with pain after 4 months rated their preoperative quality of life significantly lower in 4 subscales of the SF-36 (Physical Functioning, Role-Physical, Vitality and Social Functioning, p < 0.05). The remaining 4 subscales (Bodily Pain, General Health, Role-Emotional and Mental Health) were not different between the groups.

The Coping Strategies Questionnaire showed that the women with chronic postoperative pain more often used the coping strategies Reinterpreting Pain Sensations and Coping Self-Statements (p = 0.02 and p = 0.02 preoperatively), and they also reported less control of the pain (p = 0.02).

Table 6

Paper II. Pain characteristics (n = 90). Data are n (%) or median (range).

Symptoms within the last week	Before surgery	3 weeks after	4 months after
Pain in the pelvic area ¹	46 (51.1)	48 (53.3)	15 (16.7)
Affect of pain on daily living			
Some	26 (56.5)	34 (70.8)	10 (66.7)
A lot	14 (30.4)	12 (25.0)	5 (33.3)
Very much	6 (13.0)	2 (4.2)	0 (0.0)
Location of pain			
Middle of pelvis	33 (71.7)	24 (50.0)	11 (73.3)
Vagina	4 (8.7)	2 (4.2)	1 (6.7)
Groin	5 (10.9)	8 (16.7)	2 (13.3)
Right/left side	34 (73.9)	36 (75.0)	11 (73.3)
Scar	-	11 (22.9)	3 (20.0)
Other	6 (13.0)	11 (22.9)	1 (6.7)
Pain ≥ 5 days a week	24 (52.2)	36 (75.0)	6 (40.0)
Average pain ≥ 3 (NRS 0-10)	37 (80.4)	30 (62.5)	10 (66.7)
Worst pain ≥ (NRS 0-10)	44 (95.7)	46 (95.8)	12 (80.0)
Pain disturbed sleep	21 (45.7)	20 (41.7)	5 (33.3)
Medication for pelvic pain	29 (63.0)	33 (68.8)	5 (33.3)
Paracetamol	19 (65.5)	30 (62.5)	5 (33.3)
NSAIDs	15 (51.7)	23 (47.9)	3 (20.0)
Opioids and other	3 (10.3)	1 (2.1)	0 (0.0)
Days on medication	3 (1-7)	7 (1-7)	7 (2-7)

RESULTS: PAPER III

Missing data and excluded patients

Women who met the inclusion criteria received an invitation letter before surgery to participate in the study (n = 149). Ninety-eight women agreed to be included and 90 completed the study and were left for the final analysis.

Quantitative sensory testing

Preoperatively, women with pain more often had accompanying brush allodynia and pinprick hyperalgesia compared with women without pain (p = 0.04 and p = 0.02, respectively). Brush-evoked allodynia and pinprick-evoked hyperalgesia was found in fewer patients after 4 months than preoperatively (p < 0.01 and p < 0.01, respectively).

Wind-up-like pain on the abdomen was median 2 (range 0-9) on an NRS before hysterectomy, unchanged median 2 (range 0-9) on day 1 (Mann-Whitney, p = 0.89), and decreased to 1.5 (range 0-7) after 4 months (p < 0.01). Women with pain before hysterectomy and women with pain after 4 months did not have increased wind-up-like pain at any time points (all p-values > 0.05).

Pressure pain detection threshold (PPDT) in women with and without preoperative pain before and at different time points after operation are shown in Fig.3. For both groups together, abdominal and vaginal PPDTs decreased significantly immediately after surgery (p < 0.01 and p < 0.01), but at 4 months there was no difference from the preoperative baseline values (p = 0.66 and p = 0.70, respectively).

Before hysterectomy, women with pelvic pain had decreased abdominal PPDT, but postoperatively there were no differences between women with and without preoperative pain (p = 0.04 (before), p = 0.39 (day 1) and p = 0.20 (4 months)). On the contrary, women with preoperative pain had decreased vaginal PPDT at all time points (p < 0.01 (before), p = 0.02 (day 1), and p = 0.03 (4 months)).

Subsequent analyses of pain and quantitative sensory testing in relation to spinal or general anesthesia and abdominal or vaginal hysterectomy found no differences (all p-values > 0.05), for details see Paper IV.

Figure 3

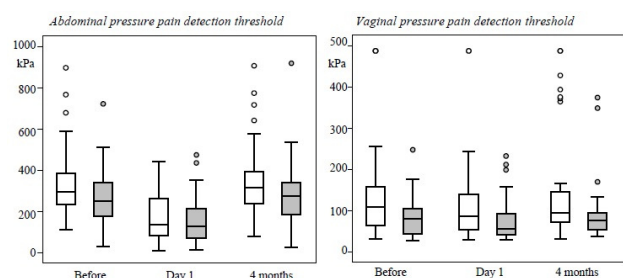


Figure 3. Pressure pain threshold in women with (grey, n = 46) and without (white, n = 44) pain before hysterectomy.

Prediction of chronic pain

Preoperative brush-evoked allodynia was significantly associated with a higher intensity of acute postoperative pain (p = 0.04) and a higher pain intensity at 4 months (p < 0.01). Preoperative pinprick-evoked pain was also significantly associated with a higher intensity of acute (p < 0.01), but not chronic postoperative pain at 4 months (p = 0.16).

Preoperative wind-up-like pain was not correlated to acute or chronic pain intensity (Spearman's rho = 0.21 and 0.15, respectively (p = 0.06 and p = 0.15)).

Fig. 4 shows the correlation between preoperative abdominal and vaginal pressure pain sensitivities and the intensity of acute postoperative pain in the first week and the intensity of chronic pain after 4 months. As can be seen, preoperative abdominal PPDT was not correlated to the intensity of acute or chronic postoperative pain (Spearman's rho: -0.17 and -0.08, respectively (p = 0.12 and 0.48)). Preoperative vaginal PPDT was correlated to acute, but not chronic postoperative pain (Spearman's rho: -0.30 and -0.09, respectively (p < 0.01 and p = 0.43)).

Figure 4

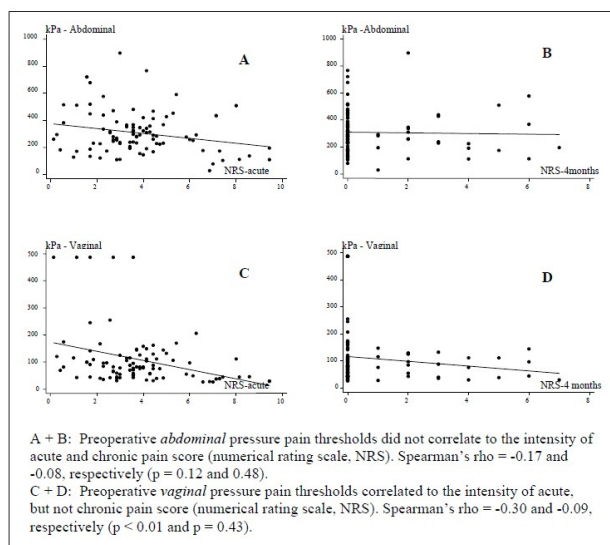


Figure 4. Preoperative PPT in relation to acute and chronic pain scores.

DISCUSSION

This thesis describes the epidemiology, risk factors, and predictors of chronic pain after hysterectomy for a benign indication.

Pain frequency and severity

Previous studies have reported frequencies of chronic pain after hysterectomy varying from 5-32% [99]. The diversity is also reflected in this thesis where a retrospective epidemiological questionnaire study found a prevalence rate of 32%, while a prospective study found a 4-month prevalence rate of 17%. Several factors may explain this difference:

Pain assessment. In Paper I, pain was defined as pain in the pelvic region within the last 3 months, and the pain frequency was 32% [93]. For Paper II, pain was defined as pelvic pain within the last week that affected daily living some, a lot, or very much, and 17% had chronic pain [100].

Follow-up time. Chronic pain was assessed after 1 year and 4 months, respectively, so it was assumed that women had fully recovered after 4 months, and that no major changes happened from 4 months to one year. However, some studies of other surgical procedures have found decreasing frequencies after several years of follow-up [41,60,61].

Inclusion criteria. In Paper I, women were consecutively recruited from the DHD, and indications for surgery were very different with some of the women having endometriosis and chronic pelvic pain and others having pain-free bleeding disorders. In contrast, women with preoperative pain as an indication for surgery were excluded from Paper II, and only women with leiomyoma or bleeding disorders were included. Therefore, a lower pain frequency was expected and seen in Paper II.

It can be argued whether chronic postsurgical pain merely represents the average frequency of pelvic pain in a population. Epidemiological studies of pelvic pain in women aged 18-50 years have found 3-months pain prevalence rates of 15-24% in the United States of America and the United Kingdom [101,102], but this does not exclude the existence of chronic posthysterectomy pain, since this may also contribute to the frequencies found in epidemiological studies. To answer the question more accurately, a control group of age-matched, non-hysterectomized women should have been included. This was done in a study of postmastectomy pain, in which the location of postmastectomy pain differed from breast-related pain in a normal population [30]. Also, in several studies, including the two conducted in this thesis, a small group of women reported acquired or increased pain after hysterectomy [83-85,90,93,100], indicating that pain is a potential outcome of hysterectomy.

In both Paper I and Paper II, pain affected daily living "a lot" or "very much" in 66/1135 (5.8%) and 5/90 (6%) of patients, respectively. This is accordance with other studies of chronic postsurgical pain, in which 5-10% of patients suffer severe pain [8,9,30,103].

Chronic pain after hysterectomy

In the introductory paragraphs, pain was divided into categories that are often used in the literature, i.e. nociceptive, inflammatory, and neuropathic [52,53,55,56]. There is another type of pain, visceral pain, which is pain elicited from internal organs. Visceral pain may have both nociceptive, inflammatory, and possibly also neuropathic components, although it is not as well described or delimited as pains elicited from somatic structures. It is characterized by a diffuse localization, referral to other tissues such as muscle and skin, and there are often associated autonomic reflexes. Visceral pain may be elicited by a noxious stimulus or, in the case of visceral sensitization, without an obvious noxious input [104-106]. In the present studies, the most common location of pain was in the middle of the pelvic region both before and after hysterectomy. Preoperatively, women with pain had pronounced signs of hyperalgesia to different modalities (brush, pinprick, vaginal and abdominal pressure pain thresholds). This is in accordance with studies of other visceral pain syndromes in which pain was associated with hyperalgesia in the referred pain area [107-111]. After surgery, however, the hyperalgesia resolved in favor of hypoalgesia and hence the signs of visceral pain are less obvious. This suggests that chronic pain after hysterectomy is in most cases not related to peripheral or central sensitization, or the pain may not be severe enough to induce hyperalgesia measurable by the applied tests.

In conclusion, chronic pain after hysterectomy may be neuropathic in a minor group of patients, but none of the identified pain patients had clear signs of neuropathic pain with sensory loss and hyperalgesia/allodynia as seen after, e.g., amputation, thoracotomy, and mastectomy. This lack of obvious "neuropathic signs" may reflect that no major nerves traverse the surgical field in hysterectomy, and it may possibly also explain why abdominal hysterectomy is not associated with a high risk of chronic pain.

Risk factors for chronic pain

Paper I and Paper II identified the following risk factors for chronic pain after hysterectomy: preoperative pelvic pain, preoperative pain problems elsewhere, previous cesarean section, pain as the main indication for surgery, preoperatively lower self-reported quality of life, preoperatively less perceived control of pain, and acute postoperative pain intensity.

Some of the most important factors not associated with chronic pain were uterine fibroid symptom score, age, indication for hysterectomy (except pain indication), type of hysterectomy, weight of uterus, pain at the 3-week follow-up. As can be seen, most risk factors are related to individual pain perception, especially pain before surgery and acute postoperative pain. Other factors related to the surgical procedure were insignificant, suggesting an inherent susceptibility to the development of chronic pain.

The above findings are in accordance with other studies of chronic postsurgical pain, except that some studies have found the type of surgery and nerve damage to be important [9,46]. This may be explained by less nerve damage in some surgical procedures than others.

Prediction of acute and chronic pain

Previous studies have found that preoperative reduced thresholds to experimental pain stimuli are associated with acute postoperative pain [68-76], while the link to chronic pain is unclear [77,103,112].

In Paper III, women with preoperative cutaneous and vaginal hyperalgesia had a higher average intensity of acute postoperative pain. This is in accordance with other studies in which preoperative tests predicted a higher acute postoperative pain frequency and intensity [68-76]. Preoperative hyperalgesia to experimental stimuli may represent a sensitization of the nervous system induced by, e.g. preoperative pain, or it may reflect a fundamental difference in pain modulation.

In Paper III, only preoperative brush allodynia was associated with chronic pain, while preoperative pinprick hyperalgesia, wind-up, or abdominal and vaginal pain pressure thresholds were not correlated to chronic pain. It may be, however, that more advanced experimental stimuli, e.g. DNIC or heat pain thresholds, are better measures of the endogenous pain modulation. The tests applied in Paper III were chosen because pressure pain thresholds have previously predicted acute pain after hysterectomy [69], and also they were easy to implement in a clinical setting where women were tested both the day before and the day after hysterectomy.

Prevention of chronic pain

Conflicting results are reported about central blockade (spinal and epidural anesthesia) to prevent the development of chronic postsurgical pain. In theory, a central block of afferent noxious input during surgery may prevent central sensitization and hence the development of chronic postsurgical pain (preemptive analgesia). Some studies suggest that epidural analgesia may have a protective role against central sensitization during surgery (amputation and thoracotomy) [113-116], while others find no difference (amputation, thoracotomy and gynecological surgery) [117-119]. Likewise, spinal anesthesia was associated with a reduced risk for developing chronic pain in two non-randomized studies (including Paper I) [8], while the frequency of long-term pain was not reduced in another randomized study [92].

In conclusion, it is possible that a blockade of the central impulse traffic by a spinal or epidural anesthetic block has a protective effect on the development of chronic pain in some patients (e.g. those without preoperative pain and sensitization), but additional studies are needed to clarify this issue.

CRITICAL REMARKS

The data from the Danish Hysterectomy Database are almost complete, but the quality of the data relies on the gynecologists involved in the treatment of the women. The database is relatively new, and there has been a great interest and enthusiasm among the responsible gynecologists, so we have every reason to believe that the data are of a very good quality.

The follow-up time of one year (Paper I) may introduce a recall bias. But the important information about pain as an indication for surgery (included in the regression analysis of risk factors) was retrieved from the DHD. The follow-up period of 4 months in Paper II and Paper III was decided because complete healing of the surgical injury was expected at this time. As previously mentioned, no firm follow-up time is demanded in chronic postsurgical pain, but usually a follow-up of 3-6 months is suggested. It is possible, however, that postoperative pain resolves later than 4 months postoperatively in some women.

The applied pain questionnaires have not been used previously, and a comparison with other studies is therefore difficult. But no validated questionnaire existed, and therefore the questionnaires were based on well-known questionnaires for neuropathic pain patients combined with clinical experience regarding this specific surgical procedure.

The studies did not account for differences in pelvic pain related to hormonal status [108]. Women scheduled for a hysterectomy may be either pre- or postmenopausal, and it is not possible to determine the hormonal status by a questionnaire.

No specific examinations, except for the vaginal palpation, were performed at the 4-month visit to exclude other reasons for the pain. At Aarhus University Hospital, there is no scheduled follow-up after hysterectomy, but women are told to see their general practitioner if they suspect complications.

Quantitative sensory testing (QST) represents a subjective measurement of pain, but most importantly, previous studies have found a good reproducibility, and therefore this method is valid for prospective assessment of pain perception in response to experimental stimuli [120]. Several studies have documented the extrapolation from experimental to clinical pain in women [121,122]. The assessment, however, is influenced by the overall circumstances (location, examiner, equipment, information) and the mental state of the patient (e.g. tired, nervous). In this study, all tests were carried out by the same examiner (Birgitte Brandsborg). This is an advantage since tests are performed similarly, but results may also be influenced by the interaction between the patient and the examiner.

A control group without hysterectomy was not included in any of the studies, and this is addressed in the discussion.

FUTURE ASPECTS

Hysterectomy represents an ideal group, since all patients are women, the operation is frequently performed, patients are around the same age and usually in good general health, and surgical data are collected from the Danish Hysterectomy Database. This thesis raised the issue of chronic pain after hysterectomy for a benign indication, and the work has raised the following additional questions:

Acute postoperative pain has proved to be a consistent risk factor for the development of chronic postsurgical pain. It is still unclear whether this is due to an inherent susceptibility to develop chronic pain, or if inadequate postoperative pain management can lead to chronic pain in some patients, but it would be of interest to study if improved acute pain management will lead to a reduction in the development of chronic pain. One possibility is to randomize patients to either conventional treatment or more aggressive treatment of the acute pain. Another possibility is to study the effect of additional analgesics such as ketamine and gabapentin with a potential to reduce central sensitization phenomena. Finally, a wound catheter for continuous local postoperative analgesia is being used with increasing frequency, but the impact of such treatment for the subsequent development of chronic pain is not known.

The question of whether epidural analgesia and/or spinal anesthesia may decrease the development of chronic pain should be addressed in large randomized studies with identical surgical procedures and similar underlying pathology.

To further examine the visceral component of pain, the applied method of pressure on the ischial spine is not an ideal method. Possibly, more advanced experimental pain testing of dynamic responses to nociceptive input may prove to predict the development of chronic pain.

There is an increasing interest in preoperative genetic testing to identify patients at specific risk of developing acute and chronic pain, but large groups of patients are needed for such studies.

DEFINITIONS

Definitions according to the International Association for the Study of Pain (IASP), 1994 [1]

Pain	An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.
Allodynia	Pain due to a stimulus which does not normally provoke pain.
Analgesia	Absence of pain in response to stimulation which would normally be painful.
Hyperalgesia	An increased response to a stimulus which is normally painful.
Hypoalgesia	Diminished pain in response to a normally painful stimulus.
Neuropathic pain	Pain initiated or caused by a primary lesion or dysfunction in the nervous system.
Nociceptor	A receptor preferentially sensitive to a noxious stimulus or to a stimulus which would become noxious if prolonged.
Noxious stimulus	A noxious stimulus is one which is damaging to normal tissues.
Pain threshold	The least experience of pain which a subject can recognize.
Pain tolerance level	The greatest level of pain which a subject is prepared to tolerate.
Peripheral neuropathic pain	Pain initiated or caused by a primary lesion or dysfunction in the peripheral nervous system.

LIST OF ABBREVIATIONS

NRS	Numerical rating scale
VAS	Visual analogue scale
UFS-QoL	Uterine Fibroid Symptom Score – Quality of Life
CSQ	Coping Strategies Questionnaire
SF-36	Short Form -36 General Health Questionnaire
DHD	The Danish Hysterectomy Database
PPDT	Pressure pain detection threshold
PPTT	Pressure pain tolerance threshold
NSAIDs	Non-steroidal anti-inflammatory drugs
DNIC	Diffuse noxious inhibitory control

SUMMARY

It is well known that different surgical procedures like amputation, thoracotomy, inguinal herniotomy, and mastectomy are associated with a risk of developing chronic postsurgical pain. Hysterectomy is the most frequent gynecological procedure with an annual frequency of 5000 hysterectomies for a benign indication in Denmark, but it has not previously been documented in detail to what extent this procedure leads to chronic pain. The aim of this PhD thesis was therefore to describe the epidemiology, type of pain, risk factors, and predictive factors associated with chronic pain after hysterectomy for a benign indication. The thesis includes four papers, of which one is based on a questionnaire study, two are based on a prospective clinical study, and one is a review of chronic pain after hysterectomy.

The questionnaire paper included 1135 women one year after hysterectomy. A postal questionnaire about pain before and after hysterectomy was combined with data from the Danish Hysterectomy Database. Chronic postoperative pain was described by 32%, and the identified risk factors were preoperative pelvic pain, previous cesarean section, other pain problems and pain as an indication for hysterectomy. Spinal anesthesia was associated with a decreased risk of having pain after one year. The type of surgery (i.e. abdominal or vaginal hysterectomy) did not influence chronic pain.

The prospective paper included 90 women referred for a hysterectomy on benign indication. The tests were performed before, on day 1, and 4 months after surgery and included questionnaires about pain, coping, and quality of life together with quantitative sensory testing of pain thresholds. Seventeen percent had pain after 4 months, and the risk factors were preoperative pain problems elsewhere and a high intensity of acute postoperative pain. Type of surgery was not a risk factor. Preoperative brush-evoked allodynia, pinprick hyperalgesia, and vaginal pain threshold were associated with a high intensity of acute postoperative pain, and preoperative brush-evoked allodynia was also associated with pelvic pain after 4 months.

This PhD thesis shows that chronic postoperative pain is present after hysterectomy in 17-32% of women. The identified main risk factors are described above. The findings indicate that it is not the nerve injury itself, but more likely the underlying individual susceptibility to pain that is important for the development of chronic pain after hysterectomy.

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