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Risk factors for persistent pain and its influence on maternal wellbeing after cesarean section

Running title: Persistent pain and cesarean section

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Conflicts of Interest
The authors have no conflict of interest.
Abstract

Objectives. To investigate the overall incidence and risk factors for persistent pain and its interference with daily life after cesarean section (CS).

Design. Prospective long-term follow up study. Setting. Karolinska University Hospital, Stockholm, Sweden. Population. 260 healthy women who underwent elective CS. Methods: Information on demographics, medical history, postoperative pain and analgesic requirements was collected. A questionnaire consisting of the Brief Pain Inventory was posted at 3, 6 and 12 months after surgery. Women rated pain intensity as well as interference with factors related to general function and quality of life. Main outcome measures. To investigate the overall incidence and risk factors for persistent postoperative pain at the three time points. To characterize the persistent pain was considered a secondary outcome. Results: At 3, 6 and 12 months 40%, 27% and 22% of patients, respectively, reported pain in one or more locations, in the surgical site as well as in other areas. A psychological indication, as well as a first CS, increased the risk for pain at 3 months. Severe postoperative pain in the immediate postoperative period or undergoing a first CS were significant independent risk factors for the development of persistent pain up to 6 months after CS. Parameters related to quality of life were significantly impaired in women with persistent pain.

Conclusion: Several factors, including severe postoperative pain, were shown to influence the risk for persistent pain after CS. Long-term pain markedly affected women’s wellbeing.
Keywords

Cesarean section, postoperative pain, persistent pain, risk factors, quality of life

Abbreviations

CS, cesarean section; BMI, body mass index; BPI, Brief Pain Inventory; NRS, numerical rating scale; OR, odds ratio; CI, confidence interval; n.s. not significant

Key message box

Severe postoperative pain, a first time CS and if the operation was performed for psychological reasons were risk factors for developing persistent pain. Parameters related to quality of life were significantly impaired in women with long-term pain.
**Introduction**

Persistent pain is a well-known risk not only after major surgery, such as limb amputation, breast and thoracic surgery, but also following common surgery, like groin hernia repair (1). This also applies to women undergoing gynecological and obstetric surgery, i.e. cesarean section (CS) (2, 3). Definition of chronic pain or persistent pain by the International Association for the Study of Pain (IASP) is pain that has lasted for three months or more: “persisted beyond the normal tissue healing time” (4).

Several reports demonstrate that insufficient post-operative pain management is common in patients subjected to different types of surgery (5-7), including CS (2, 3, 8, 9). Not only tissue damage but also other factors contribute to pain (9). Peripheral and central sensitizations are risk factors for chronic postsurgical pain and are a current topic for discussion. It may be that individuals whose pain persists longer than what is considered normal have dysregulation of the pain inhibitory systems that leads to central sensitization (10). However, to our knowledge no studies have previously been conducted to prospectively and in detail investigate the correlation between pain in the immediate postoperative period and persistent pain in this group of women. We have earlier reported the effects of perioperative local anesthesia during CS and the present study is based on the same patient group (11).

The primary aim of this follow-up study was to prospectively investigate the overall incidence and risk factors for persistent postoperative pain at 3, 6 and 12 months after the CS. The secondary aim was to characterize the pain, as to intensity, body location and impact on daily life.
Material and methods

The present study is a long-term follow-up of previously reported clinical trial (11). In that placebo controlled double-blind randomized trial the effect of a subcutaneous injection of bupivacaine close to the fascia on postoperative pain and analgesics requirements was investigated. Morphine consumption and pain assessment using a Likert numerical rating scale (NRS) were documented throughout the hospital stay, with the women rating their pain from 0 to 10 where 0 was “no pain at all” and 10 the “worst pain”. Mean and maximum (max) pain at rest and provoked pain (uterine palpation) was recorded, as well as the number of occasions with breakthrough pain. The pain was assessed by regularly asking the patient and breakthrough pain was diagnosed when the patient asked for rescue medication. In accordance with departmental routines patients were mobilized over a 24 hour cycle, irrespective of the time of day at surgery. No differences were observed between the intervention and control groups, i.e. injection of bupivacaine-adrenaline or saline solution, regarding pain parameters recorded in the immediate postoperative period and pain at three, six and 12 months. Therefore data from both groups were pooled for all further calculations. The demographic data collected included age, weight and body mass index (BMI) at the time of surgery, indication for CS, parity and number of previous CS.

The study was conducted between September 2006 and April 2008 at the obstetric unit, Karolinska University Hospital, Huddinge, Sweden. Two hundred and sixty patients were enrolled and randomized into the study, when visiting the clinic for preoperative assessment the day before CS. Healthy women, 18-49 years old, with a medically normal pregnancy, scheduled for elective CS under spinal anesthesia from 38 full weeks of gestation and understanding the Swedish language were considered eligible for inclusion.
Persistent pain and Cesarean section

Ongoing treatment for chronic pain or psychiatric disorder history of illicit drug abuse and any intolerance against opioids, local anesthetics or other analgesic drugs given in the study constituted exclusion criteria.

The present investigation was a non-interventional long-term follow-up study with questionnaires posted to all women at three, six and 12 months after the planned CS. To minimize loss to follow-up a new questionnaire, with a reminder letter, was sent within three weeks after the first questionnaire was sent. If necessary a telephone call was made five weeks after mailing the first questionnaire. The second and third questionnaires (6 and 12 months) were sent out even if no answer had been obtained to the previous questionnaire(s) and the same procedure to secure answers was used as at three months. Previously recorded baseline data on demographics and medical history, as well as study data from the postoperative period of the original randomized controlled study, were included in the analyses.

The questionnaire was sent to all patients from the intervention- and control groups in the previous study (11). A pain assessment instrument, the Brief Pain Inventory (BPI), was used (Table 1). Women were asked if they experienced any pain at present and during the last week and also received instructions to mark their pain on the body map. They were asked to rate their worst, least, average and current pain intensity using a NRS. Pain intensity was categorized as follows: NRS 1-3 was classified as mild pain, NRS 4-6 as moderate, NRS 7-8 corresponded to severe and NRS 9-10 to very severe pain. The questionnaire also included questions about to which extent pain interfered with the women’s daily life, with NRS 0 to 10 (0 “does not interfere”, 10 “interferes completely”), regarding interference with seven functional domains (general activity, mood, walking ability, normal working capacity, relations with other people, sleep and enjoyment of life) (12, 13). The questionnaire was extended to include information about intake of analgesics, general wellbeing and with an open ended question where women could add more information (Table 1). The free text responses were divided into nine
categories; pain, mobility, scar sensations, problems with carrying the child/children or other heavy things, sleeping difficulties, breast feeding related problems, interruption of mood, problems with sex life or bowel function.

Approval was obtained from the Regional Ethics Committee in Stockholm, Sweden (2006/628-31/1), and the Swedish Medical Products Agency, (151:2006/30029). Verbal and written informed consent was obtained by all participants.

**Statistical analysis**

The statistics software, IBM PASW Statistics, version 20.0, was used to conduct the analyses. Pearson’s chi-squared test and two-tailed Student’s t-test were used to compare the demographic data. The sample size calculation was based on the sample size for the previous randomized controlled trial (11). Statistical analyses of factors possibly related to long-term pain at three, six and 12 months were performed by stepwise multiple logistic regression analysis, with backward elimination of possible predictors. In order to avoid confounders related to the pharmacological intervention in the randomized controlled study with local bupivacaine vs. placebo (11), pain at 12-24 hours was used as baseline variable. The following co-variates were used and analyzed separately: max NRS, mean NRS, number of breakthrough pain episodes, parity (0/≥1), previous CS (no/yes) and psychological indication (yes/no) for the CS.

Significance was calculated by Pearson’s chi squared test. The proportion of women with pain at three, six and 12 months was compared in pairs using the Fischer’s exact test. To evaluate how persistent pain influenced parameters related to quality of life, as assessed by BPI, the Spearman’s rank test was used. Correction for multiplicity was performed according to Bonferroni. In all calculations a level of $p \leq 0.05$ was considered significant.
Results

Demographic data and obstetric characteristics included age (median/range; 35/21-49), parity (1/0-4) and body mass index (29.1/20.3-45.3). One hundred and twenty-five women out of 231 had a previous CS (missing information for 22 women). Fifty-one women were primiparous and 202 were multiparous. The response rate for the questionnaires was 91% (231/253) at three months, 90% (228/253) at six months and 85% (215/253) at 12 months. The percentage of responders who reported pain at any body location at three months was 40%, at six months 27% and one year after the CS, 21%. The same proportion of non-responders was seen in women reporting pain as in those without pain.

At three months 56% of all responders with pain reported pain in and around the surgical site and 32% of those experiencing pain marked more than one location. At six months 25% of the responders with pain marked more than one location on the body map. At that time point 60% of the responders with pain marked it around the surgical site and the corresponding proportion at 12 months was 26%. The total number of women with pain localized to the abdomen decreased over time from 52 (3 months), to 37 (6 months) and finally 12 (12 months) (Fig. 1). However, only 14 women reported abdominal pain at both three and six months and another six women had pain at this location at all three time points.

In a stepwise multiple logistic regression analysis we found that women undergoing a first CS had a significantly higher risk for persistent pain at three and six months. The three most common indications for elective CS were psychological/maternal request (36.5%), previous CS (18.1%), breech presentation (17.7%) and previous sphincter/perineal rupture (13.1%). If the indication for CS was psychological (maternal request) a significantly higher risk for persistent pain at three months was observed, but not at later time points. High postoperative maximum and mean NRS, but not the number of episodes with breakthrough pain, significantly increased
the risk for pain at six months. Expecting a first child had a tendency to influence pain at six months ($p=0.051$) (Table 2). No explanatory function was seen at three months for any of the pain related parameters or parity and no explanatory variable at all could be identified at 12 months.

In the BPI the intensity of the overall pain was rated by the NRS. The number of women with pain at the different time points is presented in Table 3. A significantly higher proportion of women reported pain at three months than at six and 12 months. Responders with pain marked how much their pain interfered with activities of daily life, using the 0-10 NRS scale. The extent to which pain had a negative impact on daily life at three months was mainly moderate to severe, and pain was mostly indicated in other body locations than the abdomen. The dependency between the variables pain intensity and interference with all seven functional domains related to function and quality of life showed significant correlation ($p \leq 0.01$) for all time points and domains with correlation coefficients ranging between 0.61 and 0.87.

At three months 26% (n=24) of the women with pain had sleeping difficulties (NRS 4-10). The corresponding number at six months was 22% (n=14) and at 12 months 33% (n=15). Twenty two percent (n=20) of all patients with pain at three months reported a moderate to very severe (NRS 4-10) impact of pain on enjoyment of life. This rate was essentially unchanged after six and 12 months (Fig. 2).
Discussion

The present study shows a relation between pain in the immediate postoperative period and persistent pain for up to six months. Other risk factors for persistent pain were a first time CS and if the CS was performed for psychological reasons. Pain after CS has been studied but, to our knowledge, this is the first prospective long-term-follow up study on the development of persistent pain and the impact of pain on daily activities at three time points after elective CS. A strength of the study was that the response rate was high, with 85% of the patients recruited on the day before the CS remaining in the study by answering and returning the questionnaire at 12 months. Another strength was that the collection of the first set of data was performed in close connection to the CS. In other studies investigating persistent pain after CS the patients had to recall the memory of pain (8, 9). A limitation of the study was that any history of chronic pain before the CS was not recorded which might have interfered with the evaluation of persistent pain after CS.

This set of prospective data confirms previous retrospective studies, indicating that high pain scores during the first post-operative day are a risk factor for chronic pain (2, 8, 9). General anesthesia, preoperative anxiety as well as a history of previous persistent pain have also been suggested as predictors for development of chronic postoperative pain after CS (8, 14). Interestingly, Johansen and coworkers found co-morbid pain to be strongly associated with persistent pain in the surgical site (15).

To our knowledge our findings regarding first time CS and psychological indication for the operation as risk factors for persistent pain have not previously been reported. It is tempting to speculate that both these factors could be related to psychological elements, in analogy with the previously mentioned preoperative anxiety shown to increase the risk for chronic pain.
In the present study 22% of the responders still experienced pain at 12 months. The most common location was back- or low-back pain, reported by 46% (n=21) of these women. These findings are in accordance with other studies regarding pain after childbirth (16-18). Several studies report that women have health problems, such as fatigue, tiredness, headaches, backaches, abdominal or pelvic pain after childbirth (16, 17, 19-22). There are inconsistent data regarding pain after CS compared to vaginal deliveries (23-25). When comparing mode of delivery both Deqlercq et al. and Kainu and coworkers found that persistent pain was more common after CS than after vaginal birth (3, 26).

In a survey about chronic pain in Europe Breivik et al. found that 19% of adult Europeans suffer from long lasting pain of moderate to severe intensity seriously affecting their daily activities and social life. In the Swedish part of the Breivik study, the overall prevalence of pain was 18%. In this group 54% were women and 40% of these were between 18-40 years of age (27). Pain at 12 months in the present study is not necessarily related to the CS. Few women had abdominal pain at this time point and the pain reported could just as well be consistent with health status in women previously giving birth, regardless of mode of delivery, or it could reflect the health condition observed in women of childbearing age in general. The data regarding persistent pain observed here are in a similar range as in other studies (3, 8). In Kainu’s report pain was mostly related to negative sensations at the site of the scar (3). Our data show that abdominal pain was present in 5.6% of women responding to the questionnaire at 12 months. Similar findings were reported by Liu and coworkers who found an incidence of 4.2% at the same time point (28).

The majority of women reporting pain at the three time points experienced mild to moderate pain (≤NRS 6). However, it is worth noting that 9% of the women with pain at three months described the pain to be severe to very severe. It is even more striking that as many as 28% of the women who still experienced pain after one year graded their pain to be severe or very
severe and that nearly 20% reported that their pain interfered with enjoyment of life, as could be expected. There was a significant difference, for all three time periods, between patients with pain, compared to patients with no pain, as to the impact on different kinds of physical activity, mood, relations to others and enjoyment of life. Schytt et al. found that one in four women had sleeping problems one year after childbirth irrespective of mode of delivery (17). Tiredness related to, among other things, sleeping problems, is often reported after childbirth (17, 18, 21). In the present study, 7% out of all responders reported sleep disturbances one year after the CS. This was less than reported by Schytt and coworkers (17). However, the number of women reporting sleeping problems might have been more frequent if the question about sleep had not been put forward only in relation to pain.

The indications for CS vary in different settings. It is rather common that women request CS for non-medical reasons and it is important to be able to inform them about the long-term risks associated with abdominal surgery in young healthy women. Even if the proportion of women reporting pain at 12 months would have pain only corresponding to that in the general population it is unambiguous that a significantly higher proportion of women report pain three months after the CS. Scar sensations not connected to pain were reported by many of the responders. It is relevant to inform the women that numbness and lack of sensory perception in the skin after the CS is not uncommon and that these symptoms usually decline over time.

Protocols for post-operative pain management vary in different parts of the world, not only with respect to analgesic drugs used or available, but also regarding mode of administration and duration of treatment. However, we believe that pain treatment has some level of generalizability, irrespective of the specific protocol used. Our data support that optimal pain-control after CS is essential for the women’s wellbeing for an extended period of time after surgery.
Acknowledgments

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References

**Figure legends**

**Figure 1**

Pain locations indicated in body charts by the women at three, six and 12 months after cesarean section. Percentage of women reporting pain at each location is indicated in the bar charts. The women could indicate pain at several locations. Total numbers of women reporting pain were 93 at three months, 63 at six months and 46 at 12 months.

**Figure 2**

Impairment of function and quality of life items from the Brief Pain Inventory due to pain at three, six and 12 months in women reporting pain with NRS >3/10. Numbers in boxes indicate number of responders.
Tables

Table 1 Three, six and 12 month’s questionnaire about severity and impact of pain after cesarean section. Pain assessment was performed using the Brief Pain Inventory.

We want you to answer how the pain was when it was at its worse, least and average on a scale this last week. Most people experience occasional pain from time to time, such as headache, toothache or sprains. Have you the past week experienced a different kind of pain than those mentioned above? Please mark on the body map where you have or have had pain the past week.

- How strong has your pain been the past week when it was at its worst?
- How strong has your pain been the past week when it was at its lowest?
- How strong has your average pain been over the past week?
- How strong is your pain right now?

If you still have pain or pain that requires medication, please answer the following questions (regarding the past week). How much has pain medication eased your pain during the last week? Please circle the percentages that best describe your experience.

The BPI also assesses the degree to which pain interferes with the patient’s function, to assess the impact of pain on some key domains of daily living. For the following questions, please mark the number that best matches your experience during the last week.

- Try to remember how the pain has interfered with your daily activities?
- To what extent has your mood been affected by pain?
- To what extent has your walking capacity been affected by pain?
- To what extent has your normal work been affected by pain?
- To what extent have your relations to others been affected by pain?
- To what extent has your sleep been disturbed by pain?
- To what extent has your enjoyment of life been affected by pain?

Open ended question:
Have you got additional comments?
Table 2  Logistic regression analysis of risk factors for persistent pain after planned cesarean section. Numerical rating scale represents pain parameters 12-24 hour postoperatively.

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95 % CI</th>
<th>p ≤ 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max NRS</td>
<td>1.04</td>
<td>0.95-1.15</td>
<td>n.s.</td>
</tr>
<tr>
<td>Mean NRS</td>
<td>1.06</td>
<td>0.95-1.18</td>
<td>n.s.</td>
</tr>
<tr>
<td>Breakthrough NRS</td>
<td>1.01</td>
<td>0.81-1.25</td>
<td>n.s.</td>
</tr>
<tr>
<td>Psychological indication (yes/no)</td>
<td>2.04</td>
<td>1.15-3.70</td>
<td>0.02</td>
</tr>
<tr>
<td>Parity (0/≥1)</td>
<td>1.47</td>
<td>0.76-2.82</td>
<td>n.s.</td>
</tr>
<tr>
<td>Previous CS (no/yes)</td>
<td>1.96</td>
<td>1.11-3.44</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>6 months</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max NRS</td>
<td>1.13</td>
<td>1.01-1.27</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean NRS</td>
<td>1.14</td>
<td>1.01-1.31</td>
<td>0.04</td>
</tr>
<tr>
<td>Breakthrough NRS</td>
<td>1.25</td>
<td>0.99-1.60</td>
<td>n.s.</td>
</tr>
<tr>
<td>Psychological indication (yes/no)</td>
<td>1.42</td>
<td>0.73-2.78</td>
<td>n.s.</td>
</tr>
<tr>
<td>Parity (0/≥1)</td>
<td>1.98</td>
<td>0.99-3.92</td>
<td>n.s.</td>
</tr>
<tr>
<td>Previous CS (no/yes)</td>
<td>2.31</td>
<td>1.23-4.44</td>
<td>0.01</td>
</tr>
</tbody>
</table>

No explanatory variable was identified at 12 months.
Table 3 Incidence and intensity of pain at three, six and 12 months postoperatively. Assessment on the numerical rating scale – NRS (% of women with pain at the specific time point).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>3 months n=231 n (%)</th>
<th>6 months n=228 n (%)</th>
<th>12 months n=215 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of women reporting no pain</td>
<td>138 (60)</td>
<td>165 (72)</td>
<td>169 (79)</td>
</tr>
<tr>
<td>Number of women reporting pain</td>
<td>93 (40)</td>
<td>63¹ (28)</td>
<td>46¹ (21)</td>
</tr>
<tr>
<td>Mild pain (NRS 1-3)</td>
<td>31 (33)</td>
<td>25 (40)</td>
<td>15 (33)</td>
</tr>
<tr>
<td>Moderate pain (NRS 4-6)</td>
<td>54 (58)</td>
<td>25 (40)</td>
<td>18 (39)</td>
</tr>
<tr>
<td>Severe pain (NRS 7-8)</td>
<td>7 (8)</td>
<td>13 (20)</td>
<td>11 (24)</td>
</tr>
<tr>
<td>Very severe pain (NRS 9-10)</td>
<td>1 (1)</td>
<td>0</td>
<td>2 (4)</td>
</tr>
</tbody>
</table>

¹ Significantly different from the proportion of women with pain at 3 months (Chi-Squared test \(p \leq 0.05\).