Persistent pain after Cesarean Delivery - A Danish multicenter cohort study

Document date: Uploaded on Clinical Trials 30.01.2024.

NCT number: Awaiting. ID 101

Steering group:

Patricia Duch[1], Christoffer Calov Jørgensen[1,] Helene Korvenius Nedergaard[2,3], Kim Wildgaard[4,5]

1. Department of Anesthesia, University Hospital of Copenhagen, Northern Zealand, Hillerød, Denmark
2. Department of Anesthesia and Intensive care, University Hospital of Southern Denmark, Kolding
3. Department of Regional Health Research, University of Southern Denmark
4. Department of Anesthesia, Surgery, and Intensive Care, University Hospital of Copenhagen, Herlev, Denmark
5. Anaesthesia, Critical and Emergency Care Science Unit, Copenhagen University Hospital, Herlev, Denmark

The study is part of CEPRA: Collaboration for Evidence-based Practice and Research in Anaesthesia: A consortium initiative for perioperative research (Nørskov et al. 2023).

Background

In Denmark, around 12,700 patients undergo cesarean delivery (CD) annually, constituting approximately 20% of all childbirths in the country (Danish Birth Registry 2023). Worldwide, the number is increasing yearly with more than 20 million CDs performed annually (Betran et al. 2021).

Postoperative pain after CD is typically moderate to severe in intensity and still constitutes a significant challenge, balancing effective pain relief and potential side effects (Duch, Jørgensen and Nedergaard 2023; Lindelof et al. 2022; Roofthooft et al. 2021). Correlations between moderate to severe acute pain and the development of persistent pain after CD is still unclear (Eisenach et al. 2008; Nikolajsen et al. 2004; Sun and Pan 2019; Yimer and Woldie 2019).

Persistent pain is observed after various surgical procedures, posing a challenge for many patients (Kehlet, Jensen, and Woolf 2006). The reported incidence of persistent pain after CD varies considerably among studies; in a review of persistent pain after CD (Sun and Pan 2019) 11-27% of patients reported pain after six months. Four Danish studies have addressed acute pain following CD in the Danish population (Duch,

Jørgensen, and Nedergaard 2023; Hansen et al. 2019; Lindelof et al. 2022; Nikolajsen et al. 2004). One of these studies has also examined the occurrence of persistent pain (Nikolajsen et al. 2004); in a single-center study including 220 patients with a mean follow-up time of 10.2 months (range 6-17.6). Nikolajsen et al. concluded that 5.9% of the patients experienced pain from the cesarean scar area, daily or almost daily. To our knowledge, no studies have prospectively explored the potential effects of postoperative pain on functional outcomes and the ability to care for the infant beyond the early postoperative period.

Both pre-, intra-, and postoperative factors have been associated with an increased risk of persistent pain after surgery (Kehlet, Jensen, and Woolf 2006; Sun and Pan 2019). Current approaches to persistent pain prevention aim to use surgical techniques that avoid nerve damage, reduce tissue injury, optimize multimodal analgesia, and reduce acute postoperative pain (Kehlet, Jensen, and Woolf 2006; Sun and Pan 2019, Tan et al. 2022). The current predominance of evidence emphasizes an association between the severity of acute pain after surgery and the development of persistent pain (Yimer and Woldie 2019).

Postsurgical persistent pain is a significant, often unrecognized clinical problem that causes distress and diminishes the quality of life for patients (Kehlet, Jensen, and Woolf 2006). Despite advances in understanding the factors contributing to persistent post-surgical pain and an increased focus on identifying patients at risk, the management and prevention of post-surgical persistent pain are still inadequate (Kehlet, Jensen, and Woolf 2006).

It is important to gain further insights into this population, and we have a unique opportunity to do so by following the national cohort from the ongoing Danish multicenter cohort study on pain after cesarean section (Duch et al. 2023) over an extended follow-up period. This involves continued prospective registration of patient-reported outcomes in the months and years after the CD, thereby investigating the occurrence of both acute and persistent pain after CD.

Objective

This study aims to describe the occurrence of persistent postoperative pain in a cohort of Danish patients who have undergone elective CD. The outcomes are focused on pain levels, the impact of pain on physical function, and neuropathic pain characteristics in the months and years following the CD. The study also aims to explore the relationship between persistent and acute pain.

Method

Study design

Prospective Danish multicenter cohort study based on Patient-Reported Outcome Measures (PROM) collected by SMS-based questionnaires and clinical data from electronic health records.

Inclusion criteria

Patients, aged > 18 years, who undergo planned CD under spinal anesthesia.
Patients who speak and read Danish and can provide informed consent to participate.
Patients who have a smartphone that can receive an SMS with a link to a questionnaire that can be accessed on an online website on the phone. Patients who, after participating in the Danish multicenter cohort study on pain after CD (Duch et al. 2023), consent to continue receiving questionnaires about persistent pain.

Number of participants

We aim to include at least 300 patients from all 5 regions in Denmark. The final number of participants will depend on the cohort size from the ongoing study (Duch et al. 2023).

Outcomes

All outcomes related to **pain**, refer to pain in or around the surgical area. Assessments are conducted at 5 weeks, 2, 3, 6, and 12 months, and after that every 6 months until 3 years after surgery.

Primary outcome

The percentage of patients reporting pain equivalent to an NRS score > 3 after 6 months

Secondary outcomes

1. Severe pain during the last 24 hours. NRS 0-10
2. Pain at rest during the last 24 hours. NRS 0-10
3. Use of analgesic medication in the past week due to pain (Paracetamol, Non-Steroidal Anti-Inflammatory Drug, opioid). Yes/No. What kind.
4. Pain's affect on daily activities. 1-5: Not at all, a little, to some extent, to a great extent, cannot do due to pain.
5. Pain's affect on engaging in strenuous physical activity. 1-6: Not at all, a little, to some extent, to a great extent, cannot do due to pain, I don't know - I haven't tried.
6. Pain's affect on meeting the infant's needs. 1-5: Not at all, a little, to some extent, to a great extent, cannot do due to pain.
7. Pain's affect on sleep. 1-4: Not at all, a little, to some extent, to a great extent.
8. Pain's affect on mood. 1-4: Not at all, a little, to some extent, to a great extent.
9. Pain/discomfort when sitting down or standing up from a chair. 1-5: Not at all, a little, to some extent, to a great extent, cannot do due to pain.
10. Pain/discomfort when walking on stairs. 1-5: Not at all, a little, to some extent, to a great extent, cannot do due to pain.

11. Pain/discomfort when getting in or out of bed. 1-5: Not at all, a little, to some extent, to a great extent, cannot do due to pain.
12. Pain/discomfort when carrying the infant. 1-5: Not at all, a little, to some extent, to a great extent, cannot do due to pain.
13. Pain/discomfort when sitting up for less than 30 minutes. 1-5: Not at all, a little, to some extent, to a great extent, cannot do due to pain.
14. Pain/discomfort if sitting up for more than 30 minutes. 1-6: Not at all, a little, to some extent, to a great extent, cannot do due to pain, I don't know - I haven't tried.
15. Pain/discomfort when moving around at home. 1-5: Not at all, a little, to some extent, to a great extent, cannot do due to pain.
16. Pain/discomfort if walking for more than 30 minutes. 1-6: Not at all, a little, to some extent, to a great extent, cannot do due to pain, I don't know - I haven't tried.
17. Pain/discomfort when bending down. 1-5: Not at all, a little, to some extent, to a great extent, cannot do due to pain.
18. Pain/discomfort during or after sexual intercourse. 1-7: Not at all, a little, to some extent, to a great extent, cannot do due to pain, I don't know - I haven't tried, I prefer not to answer.

Neuropatic pain (Andersen et al. 2019):

19. Pins and needles, tingling or stabbing sensations in or around the area of the surgery? Yes/No
20. Electric shock like sensation or jabbing feelings in the skin area in or around the area of the surgery? Yes/No
21. Heat or burning sensations in or around the area of the surgery? Yes/No
22. Pain caused by the lightest of touches in or around the area of the surgery? Yes/No
23. Pain caused by cold temperatures in or around the area of surgery? Yes/No?

Exploratory outcomes

1. Recall of acute pain at 12 and 24 hours after CD. Asked 12 months after CD.
2. Percentage of patients experiencing pain with an NRS > 3 at 1, 2, 3, and 12 months, as well as 2, 3, 4, and 5 years after CD.
3. Association between severe acute pain (NRS > 6) during the first 24 hours and the occurrence of persistent pain at 6 and 12 months after CD.
4. Prevalence of chronic pain before pregnancy.
5. Prevalence of chronic pain before pregnancy and its association with the development of persistent pain at 6 and 12 months, and 2, 3, 4, 5 years after CD.
6. Association between uterine exteriorization versus in situ repair in CD and the occurrence of persistent pain at 6 and 12 months, as well as 2, 3, 4, and 5 years after CD.

Development and validation of questions

PROMs are collected through SMS-based questionnaires. The questionnaires were developed with inspiration from studies on chronic pain (Kehlet 2006) and studies specific for the CD population (Eisenach et al. 2008; Nikolajsen et al. 2004; Sun and Pan 2019; Yimer and Woldie 2019). The Numeric Rating Scale (NRS) 0-10 was employed for pain assessment (Eisenach et al. 2008) and a 1-5/6 scale was utilized for PROMs related to function.

As part of the process of developing the questionnaires, we sought input from patients, anesthetists, and obstetricians to identify key areas relevant to representing recovery and pain in the months and years after CD, and we conducted five structured interviews with CD patients 3–6 months post-surgery. Subsequently, questions were developed and tested using standardized survey design methods (Duffett et al. 2011; Eysenbach 2004). The questionnaires underwent initial testing on professionals and the same five CD patients who had participated in the interviews. Adjustments were made based on this feedback. The questionnaires were then re-tested on both professionals and the five CD patients, with no further adjustments needed. Following this, the questionnaires were programmed into the web-based REDCap database (Research Electronic Data Capture) (Harris et al. 2009) and optimized for presentation on smartphone screens. Finally, the questionnaires were set-up to be sent out as an SMS via an external server (Sure-SMS, Denmark) with links to the questionnaires in REDCap. The questionnaires sent at various time points consist of 23 short questions, that can be answered on the phone in less than 5 minutes.

Data collection

The questionnaires are sent at fixed time intervals: at 5 weeks, 2 months, 3 months, 6 months, and 12 months, and thereafter every 6 months until 5 years after CD. Reminders are sent the day after the initial questionnaire in case of no response. All questionnaire data are entered directly into the closed and secure system REDCap. Data from journal entries are also entered into REDCap. At all hospitals, a data manager can retrieve data for the patients included in the project. The primary investigator holds the overall responsibility for the data.

Ethics and approvals

This study complies with the Helsinki declaration. Participation was voluntary and consent could be withdrawn at all times. The protocol will be made available on the website clinicaltrials.gov.

Data Protection Authority

Approval for data collection, handling and storage has been granted by the data protection authority for the Capital Region (Region Hovedstaden) with case number P-2023-90. This includes approved data agreements between the Danish Regions, with a designated data manager from each participating hospital.

Research Ethics Committee

The Research Ethics Committee (VEK) and the regional research ethics committee for the Capital Region of Denmark (Region Hovedstaden) have been presented with the project description and protocol and have waivered the need approval due to Danish legislation. Case number F-23004686.

Informed consent

Verbal informed consent is obtained during the inclusion process for the cohort study on acute pain after cesarean section (Duch et al. 2023) and a written description of the consent is electronically sent to the patients. The study concludes with a questionnaire after 30 days. In this questionnaire, patients are asked if they wish to continue participating in the survey with questionnaires at 5 weeks, 2, 3, 6, and 12 months after their CD. They provide consent by checking the questionnaire, and then receive a written consent statement with information that participation is voluntary, that their data will be securely stored and a description of how to withdraw consent. In the questionnaires after 12 months, 2, 3, and 4 years, the patients are once again asked about their willingness to continue participating in the survey. If they consent, a new consent statement is sent to them annually. This is approved by the data protection authority for the Capital Region of Denmark (Region Hovedstaden) with case number P-2023-90.

Data Processing and statistics

All data will be handled in the REDCap database. Descriptive statistics will be used to analyze data. Continuous data will be summarized as median (interquartile range) or mean (standard deviation) if the data is normally distributed, and categorical data as frequency (percentage). Subgroup analyses are planned for: Severe acute pain and the association of persistent pain; the association between uterine exteriorization versus in situ repair and the occurrence of persistent pain; as well as the prevalence of chronic pain before pregnancy and its association with the development of persistent pain.
We will try to minimize missing data as much as possible by sending questionnaires directly to the participants mobile phones and sending reminders. The amount of missing data will be accounted for when describing data. The sample size is determined by convenience, with an expected participation rate of approximately half of the 700 patients from the initial cohort study agreeing to continue with the questionnaires on persistent pain. We analyze the data when the last of the included patients have completed the 12-month questionnaire and again after every year.

Collaboration Agreement

A collaboration agreement has been established between project leaders and site coordinators, outlining mutual obligations and rules for data usage concerning the patients included in the study: 'Pain after Cesarean section – A Danish multicenter cohort study' (Duch et al. 2023). The same patients are included in this study and the mutual obligations specified in the collaboration agreement also apply to this study.

Inclusion Period

01.11.2023-30.07.2024, 2-7 months depending on the rate of inclusion at the different sites.

Participating Departments

In total 19 out of all 22 Danish hospitals, where elective CD are performed has agreed to participate in enrolling patients. The following Danish hospitals participate:
Hillerød, Herlev, Hvidovre, Rigshospitalet, Roskilde, Slagelse, Holbæk, Nykøbing F, Kolding, Odense, Åbenrå, Esbjerg, Aarhus, Horsens, Viborg, Gødstrup, Randers, Ålborg, Hjørring

Data collected from the patient's medical record

Patient characteristics

- Pre-pregnancy BMI
- Parity
- Indication for CD: Maternal request/Previous CD as the only indication/Breech presentation/Maternal indication/Obstetric indication/Fetal indication/Other indication.
- Previous number of CD: 0, 1, 2, 3, or ≥4
- Previous abdominal surgeries: Yes/No. If yes: Laparoscopic or laparotomy
- Chronic pain patient, and/or receiving regular opioid and/or other pain treatment besides NSAIDs and PCM prior to pregnancy: Yes/No
- Inflammatory bowel disease (Crohn's disease or ulcerative colitis): Yes/No
- Pregnancy-related illness? No/Gestational hypertensive disorder (Preeclampsia including HELLP, Gestational hypertension)/Gestational diabetes, Other).

Anesthesia information

- Spinal anesthesia: Bupivacaine, sufentanil, fentanyl, morphine. Mg and ml.
- Was the patient given an epidural-spinal? Yes/No
- Was general anesthesia administered as the initial preference for the patient? Yes/No
- Was the spinal anesthesia converted to epidural? Yes/No
- Was the spinal anesthesia converted to general anesthesia? Yes/No
- Was the spinal repeated following a failed spinal? Yes/No
- Was it necessary to supplement the spinal anesthesia with opioids, nitrous oxide, or similar due to breakthrough pain during the operation? Yes/No
- Did the patient have an epidural when going to the maternity ward after the recovery period? Yes/No. If yes: When was the epidural discontinued? Date and Time.

Operation information

- Operation time (minutes)
- Intraoperative bleeding. ml.

- Has the uterus been exteriorized during the operation? Yes/No/The information was not found in the medical record.
- Postoperative bleeding within the first 48 hours requiring blood transfusion. Yes/No
- Reoperation within the first 30 days: Yes/No. If yes: Abdominal bleeding/Vaginal bleeding/Suspected retained tissue or endometritis/Infection at the incision site/other reason

Pain management

- Nerve blockade within the first 24 hours after the CD: Yes/No; Time; Block type, dose, medication, reason.
- Placement of an epidural within the first 24 hours after the CD: Yes/No; Time, reason
- Opioid consumption within 0-24 hours, mg oral morphine equivalents
- Opioid consumption within 25-48 hours, mg oral morphine equivalents
- Administration of dexamethasone within the first 24 hours after CD: Yes/No. Dose.
- Administration of antihistamine as itch relief within the first 24 hours: Yes/No
- Administration of naloxone as itch relief within the first 24 hours: Yes/No

Maternal hospitalization

- Duration of total hospital lengths of stay after CD (number of days)
- Ogilvie's syndrome/ileus, that requires surgery or neostigmine within the first 7 days after CD: Yes/No

Appendix 1-8

1. Project approval from the research lawyer at The Capital Region (Region Hovedstaden) Center for Data Notifications. Approval number P-2023-90.

2. Ethical approval assessment, journal number F-23004686.

3-6. Data agreements for research projects between the regions.

7. Collaboration agreement.

8. Overview of the questions that are set up as questionnaires in REDCap and sent to the patient via a link in SMS.

References

Andersen, Kenneth G, Mathias Kvist Mejdahl, Karl Bang Christensen, and Kenneth Geving Andersen. 2019. 'Literature Review Development and Validation of a Screening Tool for Surgery-Specific Neuropathic Pain: Neuropathic Pain Scale for Postsurgical Patients'. *Pain Physician* 22(2): E81–90. www.painphysicianjournal.com.

Betran, Ana Pilar et al. 2021. 'Trends and Projections of Caesarean Section Rates: Global and Regional Estimates'. *BMJ Global Health* 6(6).

Danish Birth Registry. 2023. 'Danish Birth Registry'. *Danish Birth Registry*. https://www.esundhed.dk/Emner/Graviditet-foedsler-og-boern/Nyfoedte-og-foedsler-1997- (December 8, 2023).

Duch, Patricia et al. 2023. 'Pain after Cesarean Section - A Danish Multicenter Cohort Study.' *clinicaltrials.gov, NCT06012747*. https://classic.clinicaltrials.gov/ct2/show/NCT06012747?cond=NCT06012747&draw=2&rank=1 (December 27, 2023).

Duch, Patricia, Jørgensen, Christoffer C. and Nedergaard, Helene K. 2023. 'SMS-Based Questionnaires for Patient-Reported Outcome Measures after Cesarean Section - A Feasibility Study'. *Submitted for publication. Please contact the corresponding author for further information*.

Duffett, Mark et al. 2011. 'Consent in Critical Care Trials: A Survey of Canadian Research Ethics Boards and Critical Care Researchers'. *Journal of Critical Care* 26(5): 533.e11-533.e22.

Eisenach, James C. et al. 2008. 'Severity of Acute Pain after Childbirth, but Not Type of Delivery, Predicts Persistent Pain and Postpartum Depression'. *Pain* 140(1): 87–94.

Eysenbach, Gunther. 2004. 'Improving the Quality of Web Surveys: The Checklist for Reporting Results of Internet E-Surveys (CHERRIES)'. *Journal of Medical Internet Research* 6(3).

Hansen, Christian K. et al. 2019. 'Ultrasound-Guided Transmuscular Quadratus Lumborum Block for Elective Cesarean Section Significantly Reduces Postoperative Opioid Consumption and Prolongs Time to First Opioid Request: A Double-Blind Randomized Trial'. *Regional Anesthesia and Pain Medicine* 44(9): 896–900.

Harris, Paul A. et al. 2009. 'Research Electronic Data Capture (REDCap)-A Metadata-Driven Methodology and Workflow Process for Providing Translational Research Informatics Support'. *Journal of Biomedical Informatics* 42(2): 377–81.

Kehlet, Henrik, Troels S. Jensen, and Clifford J Woolf. 2006. *Lancet* 367: 1618–25.

Lindelof, Kim. et al. 2022. 'Satisfaction after Cesarean Section: Danish Prospective Multicenter Study'. *Abstract, Danish Anesthesiologist's yearly meeting. Unpublished. Please contact the corresponding author for further information*.

Nikolajsen, L., H. C. Sørensen, T. S. Jensen, and H. Kehlet. 2004. 'Chronic Pain Following Caesarean Section'. *Acta Anaesthesiologica Scandinavica* 48(1): 111–16.

Nørskov, Anders K, Jakobsen, Janus C, Afshari, Arash, et al. 2023. Collaboration for Evidence-based Practice and Research in Anaesthesia (CEPRA): A consortium initiative for perioperative research. Acta Anaesthesiol Scand. Jul;67(6):804-810.

Roofthooft, E. et al. 2021. 'PROSPECT Guideline for Elective Caesarean Section: Updated Systematic Review and Procedure-Specific Postoperative Pain Management Recommendations'. *Anaesthesia* 76(5): 665–80.

Sun, K. W., and P. H. Pan. 2019. 'Persistent Pain after Cesarean Delivery'. *International Journal of Obstetric Anesthesia* 40: 78–90.

Tan, Hon Sen; Taylor, R Cameron; Sharawi Nadir et al. 2022. Uterine exteriorization versus in situ repair in Cesarean delivery: A systematic review and meta-analysis. Can J Anaesth. Feb;69(2):216-233.

Yimer, Hailu, and Haile Woldie. 2019. 'Incidence and Associated Factors of Chronic Pain After Caesarean Section: A Systematic Review'. *Journal of Obstetrics and Gynaecology Canada* 41(6): 840–54.