BJA

British Journal of Anaesthesia, 121 (2): 417–426 (2018)

doi: 10.1016/j.bja.2018.04.033

Obstetric Anaesthesia

OBSTETRIC ANAESTHESIA

Prediction of outliers in pain, analgesia requirement, and recovery of function after childbirth: a prospective observational cohort study

R. Komatsu[1,2,*], B. Carvalho[1] and P. Flood[1]

[1]Department of Anaesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA, USA and [2]Department of Anaesthesiology and Pain Medicine, University of Washington, Seattle, WA, USA

*Corresponding author. E-mail: ryukomatsu80@gmail.com

This article is accompanied by an editorial: Undertreated or Overtreated? Opioids for Postdelivery Analgesia by Wong & Girard, *Br J Anesth* 2018:121:339–342, doi: 10.1016/j.bja.2018.05.061.

Abstract

Background: Prediction models to identify parturients who experience protracted pain, prolonged opioid use, and delayed self-assessed functional recovery are currently inadequate.

Methods: For this study, 213 nulliparous women who planned vaginal delivery were enrolled and assessed daily until they completed three outcomes: (1) pain resolution; (2) opioid cessation; and (3) self-assessed functional recovery to predelivery level. The primary composite endpoint, 'pain and opioid-free functional recovery' was the time required to reach all three endpoints. The subjects were divided into two categories (the worst (longest time) 20% and remaining 80%) for reaching the primary composite endpoint, and each individual component. Prediction models for prolonged recovery were constructed using multivariate logistic regression with demographic, obstetric, psychological, and health-related quality of life characteristics as candidate predictors.

Results: Labour induction (*vs* spontaneous labour onset) predicted the worst 20% for the primary composite endpoint in the final multivariate model. Labour induction and higher postpartum day 1 numerical rating score for pain were predictors for being in the worst 20% for both functional recovery and pain burden. Labour type, delivery type, Patient-Reported Outcomes Measurement Information System (PROMIS) anxiety score, RAND 36 Item Health Survey 1.0 (SF-36) physical health composite score, and postpartum breastfeeding success were predictive of delayed opioid cessation.

Conclusions: Labour induction and elevated numerical rating score for pain are predictive of poor recovery after childbirth. Further research is necessary to determine whether modification would benefit mothers at risk for poor recovery.

Keywords: analgesia; pain; postpartum period

Editorial decision: 2 May 2018; **Accepted:** 2 May 2018

Editor's key points

- A minority of women remain on prolonged opioids after childbirth, with potential long-term harms.
- Identifying those at risk at the time of delivery would allow targeted management and support.
- This study explored factors associated with worse pain, continued opioid use, and poorer functional recovery.
- Induction of labour and high pain scores on day 1 were predictors of poorer outcomes.

Most women report opioid-free functional recovery approximately 3 weeks after vaginal delivery and 4 weeks after Caesarean delivery.[1] However, outliers report severe pain for months and may never stop taking the opioids they were introduced to at childbirth.[2] In the USA, the majority of women are discharged home with a prescription for opioids, and therefore childbirth is a common source of opioid exposure in a large population. Limited information is available to predict which women will have poor recovery or require opioids for protracted period.[2] Patient-centred management incorporating these expectations is important. A 'one size fits all' model is a significant hazard as larger opioid prescriptions enhance risk for conversion to chronic opioid use.[3]

Severe acute postpartum pain,[4,5] previous pain diagnosis,[4] and history of chronic disease have been reported as risk factors for persistent pain after childbirth, while degree of tissue trauma and previous pain diagnosis have been associated with acute pain. However, risk factors for protracted postpartum recovery in healthy parturients may remain unidentified, and an information gap exists because pain assessment beyond hospital stay has only been conducted at remote time points months after delivery.[6]

The objective of this study was to identify factors that identify parturients who are likely to have a difficult postpartum recovery with respect to pain, opioid use, and recovery of function. The aim of this analysis was to identify demographic, obstetrical, and psychological risk factors for being in the worst 20 percentile for a composite endpoint of pain and opioid-free functional recovery to allow for future individualised intervention.

Methods

We conducted a prospective, daily, longitudinal, observational cohort study of three study endpoints (pain resolution, opioid cessation, and self-reported functional recovery to predelivery level) in nulliparous parturients. For functional recovery outcome, we defined predelivery as the last week of pregnancy before the delivery while the patients were not in pain. A participant's completion of the study was predefined as the completion of the composite outcome ('pain and opioid-free functional recovery'; i.e. when all three of the above-mentioned study endpoints were attained). We considered that attainment of all three individual recovery endpoints (i.e. pain resolution, opioid cessation, and functional recovery) are equally important with regard to length of medical leave after childbirth, and related employment and social policy. Therefore, we opted to use the composite outcome as the primary endpoint, which is the time to all three endpoints are met. We obtained institutional review board approval from Stanford University (Protocol #30758, approved on July 11, 2014) for this study. Written informed consent was obtained from all participants. This manuscript adheres to the applicable Equator guidelines.

We attempted daily contact with women to determine pain scores, analgesic use, and functional status after both vaginal and Caesarean delivery. A detailed description of the outcome inter-individual variability has been published previously.[1] In this work, we identified that some patients have prolonged recovery associated with severe pain and continued need for opioids. The construction of a prediction model was planned *a priori*, was part of the original institutional review board protocol and the neuropsychological testing was conducted before delivery. The descriptive data was reported previously; this predictive modelling was a planned subsequent analysis. The current manuscript investigates prediction of these severe outliers using demographic, obstetric and neuropsychological testing administered prepartum.

Participants

Nulliparous women planning vaginal delivery at Lucile Packard Children's Hospital, Stanford University between August 2014 and June 2016 were approached and enrolled in this prospective cohort study. This was a convenience sample in that women who were admitted to the hospital during nights and weekends were not approached. Women provided written informed consent, and were enrolled before induction, in early labour when they were not in pain, or after labour analgesia had been established. Inclusion criteria were: age $\geq$18 yr, gestational age $\geq$35 weeks, absence of severe maternal or fetal comorbidities, and ability to understand English to provide consent and complete questionnaires. Patients with multiple pregnancy, diabetes mellitus (pre-existing or gestational) requiring pharmacological treatment, hypertension (chronic or gestational) or pre-eclampsia requiring pharmacological treatment, or treatment for depression or anxiety were excluded from participation. Patients with chronic pain or ongoing opioid use were also excluded.

Procedures

Baseline demographic and obstetric data was obtained after enrolment. Starting on postpartum day 1, the subjects were contacted daily by one of two investigators (the first author or a research assistant), either in person during their hospitalisation, and by telephone after discharge. Using a standardised questionnaire (Supplementary Appendix S1), women were asked about their pain (average daily pain using a 0–10 verbal numeric rating scale (NRS) where 0 is no pain and 10 is the worst possible pain), analgesic use and functional recovery. The subjects who underwent Caesarean delivery were specifically instructed to report pain levels in the perineum, pelvis, and surgical site, and those who underwent vaginal delivery were instructed to report pain levels in the perineum and pelvis. All reported medications used on each postpartum day were reviewed by a study physician to ascertain whether opioid, non-opioid analgesic, or both medications were taken. To assess functional recovery, the subjects were asked, "Do you feel you have functionally recovered to the level you were during the last week of pregnancy before delivery?" Daily follow-ups were continued until the participants met all three study endpoints; an additional 5 days after zero average pain and opioid cessation were attained to ascertain there was no

recurrence. If participants had not met all study endpoints after 3 months post-delivery, they were contacted weekly thereafter until they met the study endpoints. Daily assessment via phone took approximately 2–3 min per contact.

Caesarean delivery patients received scheduled oral ibuprofen 600 mg if they tolerated oral intake (otherwise i.v. ketorolac 15 mg) every 6 h for 48 h after surgery during their hospitalisation. In addition, they received scheduled oral paracetamol 650 mg every 6 h for 48 h after surgery. Breakthrough pain was managed with oxycodone 5 mg; for pain ≤4 out of 10, and 10 mg for pain >4 out of 10. Patients were allowed up to 10 mg oral oxycodone every 4 h. If pain control was inadequate with oral medications or a patient was unable to tolerate an oral medication for breakthrough pain, i.v. morphine boluses of 4 mg were offered with a maximum of 20 mg in 6 h. Vaginal delivery pain during the hospital stay was managed with ibuprofen 600 mg and oral opioids (hydrocodone 5 mg with paracetamol 325 mg or oxycodone 5 mg with paracetamol 500 mg) as needed according to patient and obstetrician's preference.

Most of Caesarean delivery patients received discharge prescription of 30 opioid pills, typically hydrocodone 5 mg/paracetamol 325 mg or oxycodone 5 mg/paracetamol 325 mg with instructions to take one or two pills every 4–6 h as needed, and a prescription for ibuprofen 600 mg tablets. There was no standardised regimen used for vaginal delivery patients. The majority of vaginal delivery patients received discharge prescription of ibuprofen and some received opioids at the obstetrical provider's discretion.

The protocol for induction of labour included either misoprostol 50 mg orally then 100 mg orally every 4 h, or dinoprostone vaginal insert 10 mg for cervical ripening, followed by increasing doses of oxytocin (starting at 1 mU min^{-1} and increasing by 2 mU min^{-1} every 30 min to a maximum of 30 mU min^{-1} as necessary).

Demographic, obstetric, and neonatal predictor variables

Baseline demographic variables were collected by both an interview with the woman, and a chart review of medical records before the delivery. Maternal obstetrical and neonatal predictor variables were collected from electronic medical records after delivery.

Psychological and health-related quality of life assessment

Baseline psychological status was assessed in-person before the delivery using several well validated questionnaires (detailed information provided as Supplementary material). Instruments used include the Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety Scale 8a short form (http://www.rehabmeasures.org/Lists/RehabMeasures/Attachments/1112/PROMIS SF v1.0—ED-Anxiety-SF8a.pdf), PROMIS Depression Scale 8a short form (https://ortho.duke.edu/sites/ortho.duke.edu/files/u18/PROMIS SF v1.0—Depression 8a Participant Version.pdf), and Posttraumatic Stress Disorder Checklist—Civilian version (PCL-C; http://www.mirecc.va.gov/docs/visn6/3_PTSD_CheckList_and_Scoring.pdf). The PROMIS Anxiety Scale 8a short form and PROMIS Depression Scale 8a short form each consists of eight questions, each question has five response options ranging from 1 to 5. Total raw score was calculated by summing the values of response to each question. The lowest possible and highest possible total raw scores are 8 and 40, respectively. The total raw score was transformed to standardised T-score distribution as suggested by the scoring manual (http://www.assessmentcenter.net/documents/PROMIS Scoring SF Anxiety 4a, 6a, 8a.pdf, https://www.assessmentcenter.net/documents/PROMIS Depression Scoring Manual.pdf). This distribution has been established such that the mean value for the healthy US population is 50 and variation of 10 represents a standard deviation (SD). PCL-C is a standardised 17-item self-report rating scale for post-traumatic stress disorder, with each item response options ranging from 1 to 5. A total symptom severity score was calculated by summing the values of response to each item with lowest and highest possible total raw scores of 17 and 85, respectively. Baseline health-related quality of life assessment was performed using RAND 36 Item Health Survey 1.0 (SF-36; http://www.rand.org/health/surveys_tools/mos/36-item-short-form/survey-instrument.html). The SF-36 consists of 36 items that measure the following eight scales: physical functioning, role limitations because of physical health, role limitations because of emotional problems, energy or fatigue, emotional well-being, social functioning, pain, and general health. The numeric response value of each item was recoded to a score ranging from 0 to 100 according to the scoring manual. The score for each subscale was transformed to create standardised T-score for each scale, and physical and mental health composite T-scores with a mean of 50 and a SD of 10 as described by Hays and colleagues (http://www2.sas.com/proceedings/sugi22/POSTERS/PAPER244.PDF).

Study endpoint

Time to 'pain and opioid-free functional recovery', the primary outcome variable, was defined a priori at study registration as the time from delivery until the first day a woman met all of the following three endpoints: (1) the first day the postpartum woman reported functionally recovery to predelivery level; (2) the first of 5 consecutive days of zero average pain ('pain-free'); and (3) the first of 5 consecutive days of no opioid use ('opioid cessation'). Secondary endpoints evaluated were the three individual components of primary composite endpoint described above. Further, time to complete analgesic cessation, defined by time from delivery until the first day of no requirement for any analgesic drugs including non-steroidal anti-inflammatory drugs and paracetamol was added as a secondary endpoint as all patients had stopped taking all analgesics by the time they attained the planned primary composite endpoint.

Statistical analysis

Statistical analyses were performed using the R statistical software package, version 3.1 (The R Foundation for Statistical Computing, Vienna, Austria), and SAS Enterprise Guide, version 6.1 (SAS, Cary, NC, USA). The Shapiro–Wilk test was used to assess for normal distribution of continuous variables. As none of continuous variables were normally distributed, all continuous variables were expressed as medians, 25 (Q1), 75 (Q3) percentiles and ranges. Pain burden was calculated as area under the daily pain level curve (AUC), and was computed for subjects who attained the 'pain-free' endpoint, using the trapezoid rule ($AUC=AUC+(X[i]-X[i-1])\times((Y[i]+Y[i-1])/2)$, where X is the number of days since delivery and Y is the reported pain NRS score.

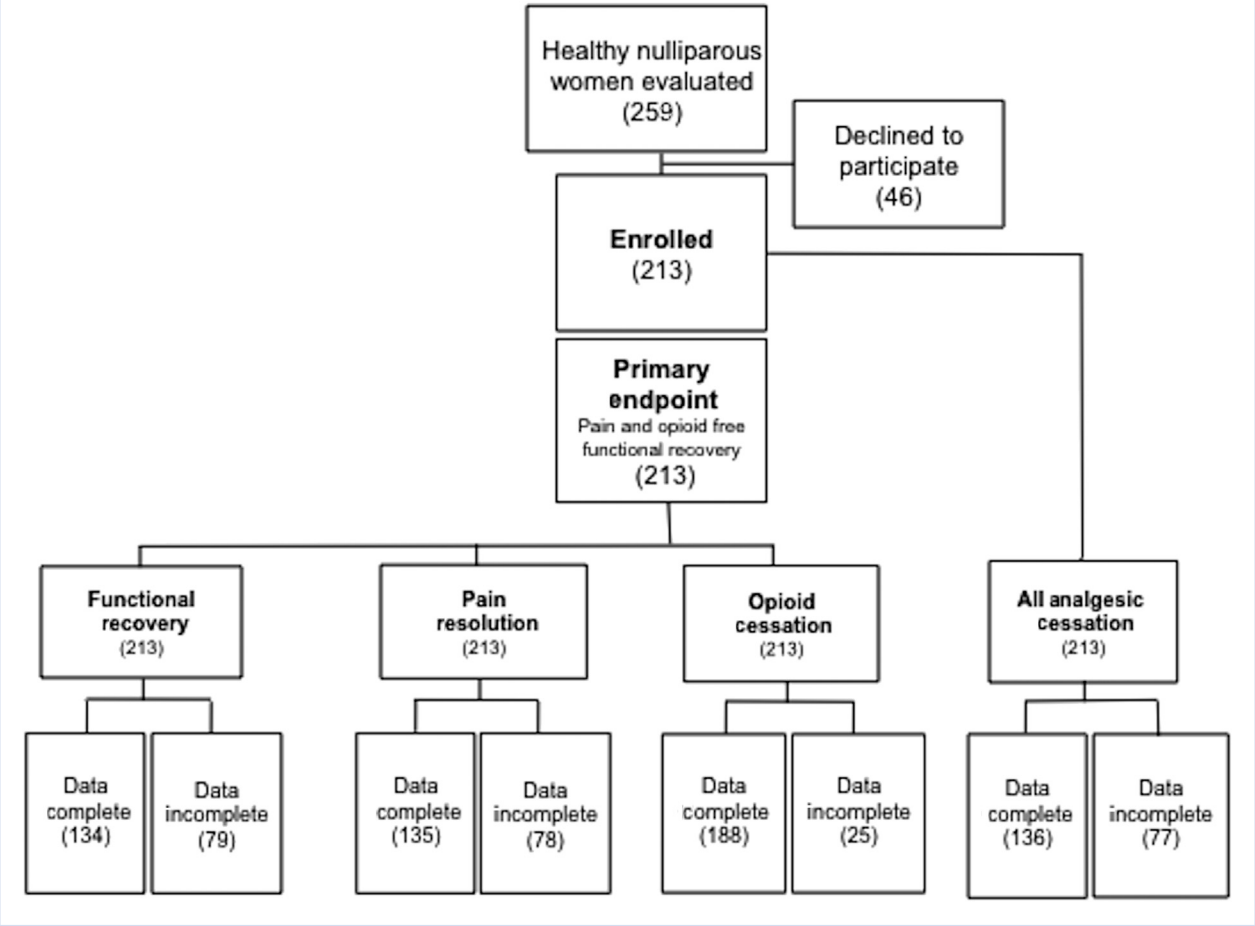

Fig 1. Flow diagram for participant's inclusion and data completion. Among 213 women enrolled in the study, 134 completed the primary endpoint, while 79 lost to follow-up before completing the primary endpoint. The numbers of participants who completed (data complete) and did not complete (data incomplete) each secondary endpoint (that are components of the composite primary outcome) are shown in the boxes labelled 'Data complete' and 'Data incomplete', respectively.

The sample size for the descriptive study was based on a previous study using similar methodology that investigated pain resolution and opioid cessation after non-obstetric surgery with the sample size of 134 (with 109 useable for analysis),[7] in which time to opioid cessation was successfully separated between the surgical types. We therefore enrolled 134 patients with successful completion of all study endpoints,[1] and the predictive modelling analysis was applied to this sample size.

On the days we failed to reach a patient during the follow-up process, we assumed the patient took same pain medications as the previous day that the patient was contacted and assumed the same status in terms of pain resolution and functional recovery (last observation carried forward).

To identify poorly preforming individuals for each of the study outcomes, the study subjects were divided into two categories (i.e. those who were in the worst 20 percentile *vs* the rest of those in the top 80 percentile) for the primary and secondary outcomes (i.e. time to pain and opioid-free functional recovery, time to pain resolution, time to opioid cessation, time to functional recovery, time to all analgesic drug cessation). We chose the 20th percentile cut-off to define poor outcomes in line with previous studies that investigated predictors for acute pain after Caesarean delivery.[8,9] This cut-off would allow for direct comparison between studies. Screening of potential predictors for being in the worst 20th percentile for primary and secondary outcomes and pain burden (AUC) were performed with univariate logistic regression modelling. Delivery type and degree of perineal laceration were highly correlated (i.e. no patients with Caesarean delivery had perineal laceration), and as the majority (73%) of patients who had vaginal delivery had second degree laceration, consideration of perineal laceration as a predictor variable would have created a situation of model overfitting. The level of neonatal care and postpartum day 1 breast feeding success were strongly correlated (i.e. breast feeding may not be feasible for neonates who required higher level of care). Therefore, degree of perineal laceration and level of neonatal care were not included in candidate predictor variables.

Multivariate logistic regressions were constructed using stepwise variable selection, initially with all potential predictive variables available for inclusion. Criteria for entry into the multivariate model was $P<0.2$ and a $P<0.05$ was required for retention in the multivariate model. Internal validation and

assessment for overfitting was performed by bootstrapping with 200 iterations. Optimism for the multivariate model was assessed by the difference in the AUC for the receiver operating characteristic (ROC) of the best model fitted in the training dataset and that of the bootstrap validation. The overall model performance was assessed with a Brier score. The Brier score measures the total difference between the event (being in the worst 20th percentile for outcome) and the forecast probability of that event as an average squared difference. As a bench mark, a perfect forecaster would have a Brier score of 0, and a perfect misforecaster would have a Brier score of 1. The smaller the Brier score, the better the model's performance.

To demonstrate the accuracy of the multivariate models over the range of predicted probabilities in the models that only had labour type (induction or no induction) as predictor, we stratified the study subjects by labour type (induction *vs* non-induction), and the predicted and actual probabilities of being in the worst 20th percentile for the outcome for each labour type. For the multivariate models that had more than two predictors, the subjects were stratified into quartiles of predicted probability, and the predicted and actual probabilities of being in the worst 20th percentile for the outcome were demonstrated for each quartile. The final models were assessed for multicollinearity by performing a linear regression with the same variables and obtaining the variance inflation factor for each variable. The variance inflation factor values ranged from 1.008 to 1.065, all below the threshold of 10, which indicates a low risk of multicollinearity.

Results

The study flow diagram is shown in Fig. 1. We made a total of 3343 daily phone call attempts to the 213 enrolled patients, and successfully reached patients 1610 times (48% overall success rate). Among 213 women enrolled in the study, 134 women continued to complete the composite primary outcome of 'pain and opioid-free functional recovery' while 79 did not complete the primary endpoint (i.e. lost to follow-up before completing the composite primary endpoint; Fig. 1). For secondary endpoints, 135, 188, 134, and 136 subjects remained in the study to report pain resolution, opioid cessation, functional recovery, and complete analgesic cessation, respectively. Demographic, obstetric, neonatal characteristics, results of the psychological assessments, and SF-36 results for all participants are reported in Table 1. Subjects who did not complete the study differed from completers with respect to race (Asian 58 *vs* 31%, Caucasian 29 *vs* 55%), and being shorter (160 *vs* 163 cm, $P=0.05$), lighter (72 *vs* 77 kg, $P=0.03$) and less likely to have ever smoked tobacco (4% *vs* 14%, $P=0.02$). There was no difference in other reported factors.[1] Among all enrolled patients, 97% received neuraxial analgesia, and all patients who underwent Caesarean delivery received neuraxial morphine for postoperative analgesia purpose. Among 81 patients whose labour was induced, 91% were medically indicated rather than elective induction.

The primary endpoint of 'pain and opioid-free functional recovery' was attained after {median (Q1, Q3) [range]} 21 (13, 31) [3–85] days after delivery. Pain resolution was reported after 17 (9, 26) [0–85] days. Opioid cessation was reported at 0 (0, 4) [0–39] days, complete analgesic cessation at 11 (7, 18) [0–77] days, and functional recovery at 21 (13, 31) [3–85] days postpartum. Pain burden (AUC, NRS×days) among those who reported pain resolution was 29.0 (14.0, 47.0) [0.5–140.0] NRS×days.

Table 1 Demographic, obstetric, psychological, and neonatal characteristics. Summary statistics were presented as number (% of patients), or median [interquartile range; range]. Data may not add up to total number of patients because of missing values. Data may not add up to 100% because of rounding.

Characteristic	*n*=213
Age (yr)	32 [29–34; 20–44]
BMI (kg m^{-2})	28 [26–30; 19–43]
Gravidity (%)	
1	179 (84)
≥2	34 (16)
Ethnicity (%)	
Caucasian	97 (46)
Asian	87 (41)
Others	29 (14)
Educational status (%)	
Graduate degree	121 (57)
Four-year college degree or less	90 (43)
Labour type (%)	
Induced	81 (38)
Not induced*	132 (62)
Delivery type (%)	
Vaginal delivery	157 (74)
Caesarean delivery	56 (26)
Degree of perineal laceration (%)	
None and first degree	85 (40)
Second degree or higher	128 (60)
Neonatal outcome	
Level of neonatal care (%)	
Well baby nursery	181 (85)
Intermediate care nursery/neonatal ICU	32 (15)
Psychological profile	
PROMIS Anxiety-8a T-score†	52 [48–56; 37–67]
PROMIS Depression-8a T-score‡	38 [38–48; 38–60]
PCL-C total score¶	21 [18–25; 17–47]
SF-36§	
Physical health composite T-score	39[32–47; 17–63]
Mental health composite T-score	54 [42–59; 20–68]
Postpartum outcomes	
Day 1 pain-NRS (0–10)‖	3 [2–5, 0–10]
Day 1 breast feeding success (%)#	
Less than half	18 (10)
More than half	160 (90)

BMI, body mass index; ICU, intensive care unit.

* Spontaneous labour with and without labour augmentation;

† Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety Scale 8a short form. T-score was calculated by transformation of sum score into *t* values suggested by the scoring manual (http://www.assessmentcenter.net/documents/PROMIS Scoring SF Anxiety 4a, 6a, 8a.pdf).

‡ PROMIS Depression Scale 8a short form. T-score is transformation of sum score into *t* values suggested by the scoring manual (https://www.assessmentcenter.net/documents/PROMIS Depression Scoring Manual.pdf).

¶ Post-traumatic Stress Disorder Checklist—Civilian version.

§ RAND 36 Item Health Survey 1.0. Physical and mental health composite T-scores were calculated as shown by Hays and colleagues (http://www2.sas.com/proceedings/sugi22/POSTERS/PAPER244.PDF).

‖ Postpartum day 1 pain level numeric rating scale.

Postpartum day 1 breast feeding success was assessed by proportion of breast milk in relation to total daily nutrition of the neonate.

The median (Q1, Q3) of the time to the primary endpoint, pain resolution, opioid cessation, complete analgesic cessation, and functional recovery for the subjects in the worst 20th percentile were 45 (40, 47), 38 (31, 47), 10 (8, 12), 30 (24, 39), and 45 (40, 47) days, respectively. The median (Q1, Q3) of the time

Table 2 Univariate prediction of outcomes. Odds ratio and 95% confidence interval (CI) of univariate logistic regression between each predictor and outcome variable is shown. Odds ratios for continuous predictor variables represent odds ratios associated with 1 unit increase in the variables.

Predictors	Outcomes					
	Time to pain and opioid-free functional recovery	Time to pain resolution	Time to opioid cessation	Time to functional recovery	Time to all analgesic cessation	Pain burden—AUC
Age	1.05 (0.94—1.18)	1.03 (0.91—1.16)	1.02 (0.93—1.13)	1.05 (0.94—1.18)	1.11 (0.99—1.25)*	1.09 (0.97—1.22)*
BMI	0.98 (0.87—1.11)	1.05 (0.93—1.18)	1.11 (1.01—1.22)*	0.98 (0.86—1.11)	1.05 (0.94—1.18)	1.06 (0.95—1.19)
Gravidity (*vs* 1)						
≥2	0.32 (0.04—2.57)	0.84 (0.17—4.09)	0.86 (0.27—2.74)	0.32 (0.04—2.57)	1.52 (0.45—5.20)	1.38 (0.35—5.44)
Ethnicity (*vs* Caucasian)						
Asian	0.72 (0.25—2.07)	1.19 (0.42—3.38)	0.48 (0.19—1.18)	0.72 (0.25—2.07)	0.81 (0.29—2.22)	1.19 (0.42—3.38)
Others	0.55 (0.11—2.71)	0.75 (0.15—3.79)	0.50 (0.13—1.87)	0.55 (0.11—2.71)	0.69 (0.14—3.48)	1.22 (0.30—4.99)
Educational status (*vs* ≤4-year college degree)						
Graduate degree	1.57 (0.56—4.35)	1.31 (0.46—3.69)	1.20 (0.53—2.71)	1.57 (0.56—4.35)	0.48 (0.19—1.22)*	0.85 (0.32—2.24)
Labour type (*vs* not induced)						
Induced	3.65 (1.36—9.77)*	2.36 (0.89—6.29)*	4.44 (1.91—10.32)*	4.74 (1.70—13.19)*	2.33 (0.91—5.97)*	3.37 (1.25—9.08)*
Delivery type (*vs* VD)						
CD	1.91 (0.71—5.13)*	0.99 (0.33—2.98)	15.78 (6.21—40.10)*	2.46 (0.93—6.49)*	1.96 (0.73—5.26)*	2.11 (0.78—5.71)*
PROMIS Anxiety-8a T-score†	1.02 (0.95—1.10)	1.01 (0.94—1.09)	1.06 (0.99—1.13)*	1.03 (0.95—1.10)	1.07 (0.99—1.16)*	0.98 (0.91—1.05)
PROMIS Depression-8a T-score‡	0.98 (0.91—1.06)	0.96 (0.87—1.05)	0.96 (0.89—1.03)	0.98 (0.91—1.06)	1.02 (0.95—1.10)	0.97 (0.89—1.06)
PCL-C total score¶	0.96 (0.87—1.06)	0.97 (0.89—1.07)	0.99 (0.92—1.07)	0.96 (0.87—1.06)	1.05 (0.97—1.13)	0.99 (0.90—1.08)
SF-36 Physical health composite T-score§	0.97 (0.92—1.02)*	0.97 (0.93—1.02)	0.96 (0.92—1.00)*	0.98 (0.93—1.03)	1.00 (0.95—1.04)	1.00 (0.96—1.05)
SF-36 Mental health composite T-score§	0.99 (0.95—1.02)	1.04 (0.99—1.08)*	0.99 (0.96—1.02)	0.99 (0.95—1.02)	1.04 (0.99—1.08)*	1.03 (0.98—1.07)
Day 1 pain-NRS (0—10)‖	1.29 (1.01—1.64)*	1.26 (0.98—1.61)*	1.17 (0.95—1.45)*	1.35 (1.05—1.72)*	1.13 (0.90—1.43)	1.76 (1.31—2.37)*
Day 1 breast feeding success (*vs* less than half)#						
More than half	0.86 (0.22—3.36)	0.75 (0.19—2.93)	0.36 (0.12—1.08)	0.86 (0.22—3.36)	0.84 (0.22—3.29)	0.80 (0.21—3.13)

* Univariate associations with P<0.20; AUC, area under the curve; BMI, body mass index; VD, vaginal delivery; CD, caesarean delivery.

† Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety Scale 8a short form. T-score was calculated by transformation of sum score into t values suggested by the scoring manual (http://www.assessmentcenter.net/documents/PROMIS Scoring SF Anxiety 4a, 6a, 8a.pdf).

‡ PROMIS Depression Scale 8a short form. T-score is transformation of sum score into t values suggested by the scoring manual (https://www.assessmentcenter.net/documents/PROMIS Depression Scoring Manual.pdf).

¶ Posttraumatic Stress Disorder Checklist—Civilian version.

§ RAND 36 Item Health Survey 1.0. Physical and mental health composite T-scores were calculated as shown by Hays and colleagues (http://www2.sas.com/proceedings/sugi22/POSTERS/PAPER244.PDF).

‖ Postpartum day 1 pain level numeric rating scale.

Postpartum day 1 breast feeding success was assessed by proportion of breast milk in relation to total daily nutrition of the neonate.

to the primary endpoint, pain resolution, opioid cessation, complete analgesic cessation, and functional recovery for the rest of subjects (top 80th percentile) were 18 (11, 24), 14 (7, 20), 0 (0, 2), 9 (5, 14), and 19 (11, 24) days, respectively. The median (Q1, Q3) of the pain burden (AUC, NRS×days) for the subjects in the worst 20th percentile, and the rest of subjects (top 80th percentile) were 72.0 (57.0, 118.0) and 25.5 (11.5, 38.5), respectively.

Prediction model development

Univariate predictors for being in the worst 20th percentile for the outcomes identified by univariate logistic regressions are shown in Table 2. The predictors that describe the final multivariate logistic regression models, their beta coefficients, multivariate odds ratios, 95% confidence intervals (CIs), and *P*-values are shown in Table 3.

Performance of prediction model

The AUC for the ROC, the AUC for the ROC after bootstrapping, and the Brier score for the prediction model for each outcome are reported in Table 4. Overall, the AUCs for the ROC were 0.66 or larger, and the Brier scores were 0.14 or less, that suggest moderate to good performance of the probability model. The optimism of developed models was ≤0.02, suggesting that the predictions are not overly optimistic.

The predicted and actual probabilities of being in the worst 20th percentile for the primary composite outcome among subjects with induced labour were 28.8% and 28.9%, and amongst subjects with non-induced labour were 10.0% and 10.0%, respectively. For the time to opioid cessation, functional recovery, and pain burden (AUC) outcomes, mean predicted probability for being in the worst 20th percentile among subjects in each predicted probability stratum, and the actual probability of are demonstrated in Table 5.

Discussion

Labour induction (*vs* spontaneous onset of labour) was a strong predictor for being in the worst 20th percentile in the primary composite endpoint, pain burden (AUC), opioid cessation, and functional recovery. Labour induction has been found to be a risk factor for Caesarean delivery.[10] Importantly, adjustment for delivery type in our final multivariate prediction models did not the change the odds ratio for labour type by >10% suggesting that confounding by delivery did not mediate the association between labour induction and

Table 3 Multivariate prediction of outcomes. β-coefficients, odds ratios with 95% confidence intervals (CI), and *P*-values of multivariate logistic regression model for each outcome variable are shown. Predictive variables not left in any of multivariate models are not shown in the table. No predictors are left in the final models for time to pain resolution outcome and time to all analgesic cessation outcome. The constants (intercepts) of multivariate logistic regression models for pain and opioid-free functional recovery, pain resolution, opioid cessation, functional recovery, all analgesic cessation, and pain burden AUC were −1.506, −1.599, −4.565, −2.628, −1.484, and −3.987, respectively.

Predictors		Outcomes			
		Time to pain and opioid-free functional recovery	Time to opioid cessation	Time to functional recovery	Pain burden—AUC
Labour type					
Induced *vs* not induced	β coefficient	0.659	0.887	0.759	0.611
	Odds ratio (95% CI)	3.74 (1.39—10.04)	5.89 (1.84—18.88)	4.56 (1.60—12.98)	3.39 (1.14—10.09)
	P-value	0.009	0.003	0.004	0.028
Delivery type					
Caesarean *vs* vaginal delivery	β coefficient		1.523		
	Odds ratio (95% CI)		21.02 (6.50—67.96)		
	P-value		<0.001		
PROMIS Anxiety-8a T-score*	β coefficient		0.13		
	Odds ratio (95% CI)		1.14 (1.04—1.25)		
	P-value		0.007		
SF-36 Physical health composite T-score†	β coefficient		−0.063		
	Odds ratio (95% CI)		0.94 (0.88—0.99)		
	P-value		0.043		
Day 1 pain-NRS (0—10)‡	β coefficient			0.269	0.565
	Odds ratio (95% CI)			1.31 (1.01—1.70)	1.76 (1.29—2.41)
	P-value			0.046	<0.001
Day 1 breast feeding success¶					
More than half *vs* less than half	β coefficient		−1.239		
	Odds ratio (95% CI)		0.08 (0.02—0.47)		
	P-value		0.005		

AUC, area under the curve; CI, confidence interval.

*Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety Scale 8a short form. T-score was calculated by transformation of sum score into *t* values suggested by the scoring manual (http://www.assessmentcenter.net/documents/PROMIS Scoring SF Anxiety 4a, 6a, 8a.pdf).

†RAND 36 Item Health Survey 1.0. Physical health composite T-scores were calculated as shown by Hays and colleagues (http://www2.sas.com/proceedings/sugi22/POSTERS/PAPER244.PDF).

‡Postpartum day 1 pain level numeric rating scale (NRS).

¶Postpartum day 1 breast feeding success was assessed by proportion of breast milk in relation to total daily nutrition of the neonate.

Table 4 Receiver operating characteristic area under the curve data for the performance of multivariate prediction models for the outcomes.

	AUC for model (95% CI)	Bootstrap validation	Brier score
Time to pain and opioid-free functional recovery	0.66 (0.55–0.77)	0.65	0.14
Time to opioid cessation	0.90 (0.85–0.96)	0.88	0.09
Time to functional recovery	0.76 (0.63–0.89)	0.75	0.13
Pain burden–AUC	0.80 (0.70–0.90)	0.79	0.12

AUC, area under the curve. CI, confidence interval.

Table 5 Performance of multivariate prediction models for the worst 20th percentile of outcomes. Probabilities are expressed as %. Predicted probability is shown as mean of predicted probability for each quartile stratum. Thresholds for the worst 20th percentile: time to opioid cessation >5 days, time to functional recovery >36 days, and pain burden AUC >51 NRS×days.

Predicted probability stratum (quartile)	Time to opioid cessation		Time to functional recovery		Pain burden–AUC	
	Predicted	Observed	Predicted	Observed	Predicted	Observed
1st	1.0	0.0	4.4	9.1	2.2	4.4
2nd	3.7	2.6	8.7	2.6	7.4	5.0
3rd	13.3	18.0	17.7	16.7	18.6	20.5
4th	60.5	57.9	33.6	37.2	48.9	47.6

AUC, area under the curve.

recovery (i.e. associations between labour induction and outcomes were independent of increased rate of Caesarean delivery in labour induction patients). Proinflammatory cytokines and prostaglandins cause sensitisation of nociceptors leading to hyperalgesia.[11] As prostaglandin E_2 is often used for labour induction, the inflammatory process may be accentuated in induced compared with spontaneous labour. Greater labour pain has been reported after labour induction compared with spontaneous onset of labour.[12] However, mediation of prolonged poor recovery by cytokines and prostaglandins after labour remains speculative and merits replication and future study.

Studies assessing persistent pain after 2–3 months (corresponding to the duration of follow-up in our study) have identified lower body weight,[13] omission of intrathecal morphine for Caesarean delivery,[13] preoperative depression,[14] longer duration of surgery,[14] pre-existing pain problems,[15] non-private insurance status,[15] and severe acute postpartum pain[5,14,15] to be predictive of persistent post-Caesarean delivery pain. In our study, all Caesarean delivery patients received neuraxial morphine, and the vast majority of patients had private insurance. Postpartum day 1 pain NRS score was an independent predictor for being in the worst 20th percentile for pain burden (AUC), and for every one-point increase in the 0–10 pain NRS on day 1 the odds of being in the worst 20th percentile increased by 76%. These results are consistent with previous studies,[5,14,15] where every point increase in acute pain NRS increased the odds of having pain at 2–3 months after the delivery by 13–140%.

Few studies have evaluated psychological factors as predictors for recovery after childbirth. Jin and colleagues[14] demonstrated that depression defined by Edinburgh Depression Scale ≥12 increased the odds of persistent pain at 3 months after Caesarean delivery by 360%, while anxiety assessed by the State Trait Anxiety Inventory was not predictive. In our study, depression and anxiety were evaluated as continuous variables with the PROMIS Depression Scale 8a short form and the Anxiety Scale 8a short form scores. Anxiety was predictive of delayed opioid cessation but not for being in the worst 20th percentile for pain burden (AUC) or time to pain resolution. A larger proportion of patients who had vaginal deliveries (74%), and different instruments used for depression evaluation may explain discordant results between our study and the study by Jin and colleagues.[14] We specifically excluded patients with depression and anxiety that required treatment, and may have missed a relationship driven by more severe psychological disease.

The greater degree of tissue injury accompanying Caesarean delivery compared with vaginal delivery has been identified as a predictor for acute postpartum pain, while delivery type (Caesarean *vs* vaginal) explained only 17% of variability in pain level at 24 h after the delivery.[16] Our results suggest that the contribution of delivery type to pain lasting months after the delivery is less significant than might be expected. Undergoing Caesarean delivery compared with vaginal delivery predicted opioid use postpartum, but not postpartum pain or functional recovery. This finding suggests that Caesarean and vaginal delivery both result in similar functional recovery profiles, and pain (at the expense of more opioid use) is managed as effectively after Caesarean compared with vaginal delivery in our study cohort. These findings are concordant with results reported by Eisenach and colleagues.[5]

Predictors for prolonged opioid use have been previously evaluated, however the analysis by Bateman and colleagues[2] used an administrative database and was limited to Caesarean delivery. In our study, we identified multiple predictors: delivery type, labour type, PROMIS Anxiety Scales T-scores, SF-36 physical health composite T-score, and postpartum day 1 breastfeeding success were found to be independent predictors for prolonged opioid use after the delivery. Caesarean delivery (*vs* vaginal delivery) was a strong predictor

of being in the worst 20th percentile for time to opioid cessation with odds ratio of 21, despite being non-predictive for other pain outcomes. This could be partially explained by a non-linear relationship between pain intensity and opioid requirement suggested in a non-obstetric surgical population.[17] It may also be explained by practitioner prescription practices, patient expectations, or both. Perception of vaginal delivery as a natural physiological phenomenon and Caesarean delivery an invasive traumatic procedure may impact practitioners' willingness to prescribe opioids and affect parturients' willingness to take opioids for pain relief after vaginal delivery.

Women who successfully breastfed (defined as more than half of the newborn's daily nutrition obtained from breastfeeding) on day one postpartum had a 92% decreased odds of delayed opioid cessation in comparison with those whose breast feeding was less successful (less than half of the newborn's daily nutrition obtained from breastfeeding). The mechanism underlying this association between early breastfeeding and remote opioid cessation is unclear and may not be direct. However, animal studies have shown that oxytocin administered intrathecally exerts analgesic effects.[18,19] In humans, oxytocin administered intrathecally resulted in improvement of chronic and acute back pain.[20] Nipple stimulation during breastfeeding causes release of endogenous oxytocin from the posterior pituitary gland leading to surges in oxytocin levels.[21,22] Therefore, the association between breastfeeding success and reduced opioid requirement is biologically plausible. Breastfeeding success failed to predict other metrics of pain (postpartum day 1 pain NRS was 3.8 with and 3.4 without reported breastfeeding success). One possible explanation is that women who successfully breastfeed avoided opioids for fear of sedating their infants.

There are several limitations intrinsic to our population and study design. We chose to study a healthy nulliparous cohort to limit the number of variables that require consideration. Our cohort was opioid-naïve without ongoing pain problems. The vast majority of our study participants had private insurance and >60% held a graduate degree. We acknowledge that results may differ in sicker, opioid-exposed, less educated, and under-resourced populations. With relatively the small sample size of the study, only robust predictor–outcome association could have been detected, and there remains a possibility that subtle, but clinically meaningful associations may have been missed. Further, as the reported incidence of chronic pain after childbirth is rare,[16,23] we may not have identified those cases because of small sample size, the generally healthy nature of our sample, and exclusion of patients with other chronic pain syndromes.

Thirty-seven percent of participants did not complete all endpoints of the study and only partially contributed to the outcome data. We do not know whether subjects with more or less difficult postpartum courses were more likely to drop out, and if dropouts had different pain, opioid use, or functional recovery to those who did not drop out. Furthermore, we only evaluated demographic, psychological, and health-related quality of life measures as candidate predictors, and did not evaluate genetic factors that have been shown to impact pain perception, including haplotypes of catecholamine-O-methyltransferase,[24] β 2 adrenergic receptor[25] and others.

In summary, we have identified several risk factors and have developed prediction models to identify parturients who will experience more severe postpartum pain, prolonged opioid use and delayed recovery after delivery that can be evaluated as future targets for intervention. Labour induction and severe postpartum day 1 pain were identified predictive risk factors that allow for early prophylactic intervention. Labour induction is a strong predictor of prolonged postpartum pain and protracted opioid requirement that has not been previously reported and requires further evaluation.

Authors' contributions

Study design: all authors.
Data collection: R.K.
Data analysis and interpretation: all authors.
Drafting manuscript: all authors.
Final approval of manuscript: all authors.

Acknowledgements

We would like to thank A. Aksamit, research assistant, Department of Anaesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine, Stanford, CA, for her role in helping to contact patients postpartum.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2018.04.033.

Disclosure of interests

None of the authors have any financial interest other than reported in the funding section.

Funding

Department of Anaesthesiology, Perioperative and Pain Medicine, Stanford University School of Medicine. R.K. acknowledges support from T32GM089626 from National Institute of General Medical Sciences (Bethesda MD, USA).

References

1. Komatsu R, Carvalho B, Flood PD. Recovery after nulliparous birth: a detailed analysis of pain analgesia and recovery of function. *Anesthesiology* 2017; **127**: 684–94
2. Bateman BT, Franklin JM, Bykov K, et al. Persistent opioid use following cesarean delivery: patterns and predictors among opioid-naive women. *Am J Obstet Gynecol* 2016; **215**. 353 e1–18
3. Shah A, Hayes CJ, Martin BC. *Characteristics of initial prescription episodes and likelihood of long-term opioid use—United States, 2006–2015*. Atlanta, GA: Centers for Disease Control and Prevention; 2017
4. Kainu JP, Sarvela J, Tiippana E, Halmesmaki E, Korttila KT. Persistent pain after caesarean section and vaginal birth: a cohort study. *Int J Obstet Anesth* 2010; **19**: 4–9
5. Eisenach JC, Pan PH, Smiley R, Lavand'homme P, Landau R, Houle TT. Severity of acute pain after childbirth, but not type of delivery, predicts persistent pain and postpartum depression. *Pain* 2008; **140**: 87–94
6. Sunshine A, Olson NZ, Zighelboim I, De Castro A. Ketoprofen, acetaminophen plus oxycodone, and acetaminophen in the relief of postoperative pain. *Clin Pharmacol Ther* 1993; **54**: 546–55

7. Carroll I, Barelka P, Wang CK, et al. A pilot cohort study of the determinants of longitudinal opioid use after surgery. *Anesth Analg* 2012; **115**: 694–702
8. Pan PH, Coghill R, Houle TT, et al. Multifactorial preoperative predictors for postcesarean section pain and analgesic requirement. *Anesthesiology* 2006; **104**: 417–25
9. Pan PH, Tonidandel AM, Aschenbrenner CA, Houle TT, Harris LC, Eisenach JC. Predicting acute pain after cesarean delivery using three simple questions. *Anesthesiology* 2013; **118**: 1170–9
10. Muto H, Ishii K, Nakano T, Hayashi S, Okamoto Y, Mitsuda N. Rate of intrapartum cesarean section and related factors in older nulliparous women at term. *J Obstet Gynaecol Res* 2018; **44**: 217–22
11. Hucho T, Levine JD. Signaling pathways in sensitization: toward a nociceptor cell biology. *Neuron* 2007; **55**: 365–76
12. Dannenbring D, Stevens MJ, House AE. Predictors of childbirth pain and maternal satisfaction. *J Behav Med* 1997; **20**: 127–42
13. Moriyama K, Ohashi Y, Motoyasu A, Ando T, Moriyama K, Yorozu T. Intrathecal administration of morphine decreases persistent pain after cesarean section: a prospective observational study. *PLoS One* 2016; **11**, e0155114
14. Jin J, Peng L, Chen Q, et al. Prevalence and risk factors for chronic pain following cesarean section: a prospective study. *BMC Anesthesiol* 2016; **16**: 99
15. Sng BL, Sia AT, Quek K, Woo D, Lim Y. Incidence and risk factors for chronic pain after caesarean section under spinal anaesthesia. *Anaesth Intensive Care* 2009; **37**: 748–52
16. Eisenach JC, Pan P, Smiley RM, Lavand'homme P, Landau R, Houle TT. Resolution of pain after childbirth. *Anesthesiology* 2013; **118**: 143–51
17. Aubrun F, Langeron O, Quesnel C, Coriat P, Riou B. Relationships between measurement of pain using visual analog score and morphine requirements during postoperative intravenous morphine titration. *Anesthesiology* 2003; **98**: 1415–21
18. Yang J, Yang Y, Chen JM, Liu WY, Wang CH, Lin BC. Central oxytocin enhances antinociception in the rat. *Peptides* 2007; **28**: 1113–9
19. Yang J, Pan YJ, Zhao Y, et al. Oxytocin in the rat caudate nucleus influences pain modulation. *Peptides* 2011; **32**: 2104–7
20. Yang J. Intrathecal administration of oxytocin induces analgesia in low back pain involving the endogenous opiate peptide system. *Spine (Phila Pa 1976)* 1994; **19**: 867–71
21. Leake RD, Waters CB, Rubin RT, Buster JE, Fisher DA. Oxytocin and prolactin responses in long-term breast-feeding. *Obstet Gynecol* 1983; **62**: 565–8
22. Lee HJ, Macbeth AH, Pagani JH, Young 3rd WS. Oxytocin: the great facilitator of life. *Prog Neurobiol* 2009; **88**: 127–51
23. Weibel S, Neubert K, Jelting Y, et al. Incidence and severity of chronic pain after caesarean section: a systematic review with meta-analysis. *Eur J Anaesthesiol* 2016; **33**: 853–65
24. Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. *Hum Mol Genet* 2005; **14**: 135–43
25. Terkawi AS, Jackson WM, Hansoti S, Tabassum R, Flood P. Polymorphism in the ADRB2 gene explains a small portion of intersubject variability in pain relative to cervical dilation in the first stage of labor. *Anesthesiology* 2014; **121**: 140–8

Handling editor: L. Colvin