Operative technique at caesarean delivery and risk of complete uterine rupture in a subsequent trial of labour at term. A registry case-control study
Thisted, Dorthe L. A.; Mortensen, Laust Hvas; Hvidman, Lone; Krebs, Lone

Published in:
PLOS ONE

DOI:
10.1371/journal.pone.0187850

Publication date:
2017

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (APA):
Thisted, D. L. A., Mortensen, L. H., Hvidman, L., & Krebs, L. (2017). Operative technique at caesarean delivery and risk of complete uterine rupture in a subsequent trial of labour at term. A registry case-control study. DOI: 10.1371/journal.pone.0187850
Abstract

Objective
To estimate the relation of single-layer closure at previous caesarean delivery, and other pre-labour and intra-partum risk factors for complete uterine rupture in trial of vaginal birth after a caesarean (TOLAC) at term.

Study design
Population-based case-control study. We identified all women (n = 39 742) recorded in the Danish Medical Birth Registry (DMBR) during a 12-year period (1997–2008) with a singleton pregnancy at term and TOLAC. Among these, all women with a complete uterine rupture were identified (cases). Information from the registry was validated against medical records. Controls were selected in the DMBR as the following two births with TOLAC at term and no uterine rupture. Detailed information from cases and controls was collected from manual review of medical records. Main outcome measure was complete uterine rupture during TOLAC at term.

Results
Upon validation, 175 cases and 272 controls met the above criteria. After adjustment for possible confounding factors there was no association between single layer closure and uterine rupture (aOR 1.38, CI: 0.88–2.17). Significant risk factors were: Induction with an unfavourable cervix (aOR 2.10 CI: 1.19–3.71), epidural (aOR 2.17 CI 1.31–3.57), augmentation by oxytocin for more than one hour (aOR 2.03 CI: 1.20–3.44), and birth weight ≥ 4000g (aOR 2.65 CI 1.05–6.64). Previous vaginal delivery (aOR 0.41 CI: 0.25–0.68) and
inter-delivery interval of more than 24 months (aOR 0.38 CI: 0.18–0.78) reduced the risk of uterine rupture.

**Conclusion**

Single-layer uterine closure did not remain significantly associated to uterine rupture during TOLAC at term after adjustment for confounding factors. Induction of labour with an unfavourable cervix, birth weight ≥ 4000g and indicators of prolonged labour were all major risk factors for uterine rupture.

**Introduction**

Rupture of the pregnant uterus almost exclusively occurs among women who attempt a trial of labour after a caesarean delivery (TOLAC) [1]. A complete uterine rupture is associated with a very high perinatal mortality and a substantial perinatal and maternal morbidity. The complete uterine rupture is uniquely described as a complete rupture of the myometrium and rupture of the fetal membranes leading to a direct communication between the uterine cavity and the peritoneum [2–5]. The incidence of complete uterine rupture in TOLAC in high-income countries varies from 0.22% to 0.74% [6–8].

In 1998, the Danish Society of Obstetrics and Gynaecology recommended a new operative technique for caesarean delivery. The most important changes was to suture the uterus in a single layer, instead of two layers as previously done and to leave the visceral and parietal peritoneal layers of peritoneum open [9].

Many studies have investigated the impact of single layer closure and the risk of uterine rupture in TOLAC. Results have been conflicting, and given the rare occurrence of uterine rupture, many studies have been underpowered [10]. Other studies included both complete and partial uterine ruptures [1,10–15].

The primary aim of this study was to estimate the risk of complete uterine rupture in singleton term pregnancies attempting a TOLAC when the uterus was initially closed in one layer compared to two layers in a previous caesarean delivery. The secondary aim of the study was to identify other possible risk factors for complete uterine rupture related to the actual TOLAC.

**Materials and methods**

The Danish Medical Birth Registry (DMBR) contains data on all deliveries in Denmark [16].

Pre-pregnancy risk factors, medical diseases, and complications and interventions during pregnancy and delivery are recorded by codes according to the International Classification of Diseases and Related Health Problems 10th Revision [17] and the Nordic Medico-statistical Committee classification of surgical procedures [18]. A 10-digit personal identification is assigned to all Danish citizens, making it possible to link registries and medical records.

This study was based on data from the DMBR from January 1, 1997 to December 31, 2008. During the study period, 705,871 women had a singleton birth at hospital, of these 62,475 women had previous caesarean delivery (8.85%), and among these 39,472 (63.2%) attempted a vaginal delivery.

Cases were identified in the DMBR (1997–2008) among all women with a singleton term pregnancy, with TOLAC, who were recorded in the DMBR with uterine rupture during labour (n = 763). A complete uterine rupture is associated with a high perinatal mortality and
morbidity, and knowing that the recording of uterine rupture in the DMBR may be incomplete, we furthermore identified all cases (n = 1076) with TOLAC and where the perinatal outcome was severe perinatal asphyxia or death. The review of these medical records, were performed in order to comply with a possible underreporting of complete uterine ruptures to the DMBR. Altogether 1839 medical records were reviewed (Fig 1).

Medical records with information on both the current labour and all previous pregnancies were retrieved from various gynaecologic and obstetric departments in Denmark. Data were validated by review of medical records, and only cases with one previous caesarean delivery performed in Denmark, a singleton pregnancy and a complete uterine rupture during TOLAC at term were included. Our intention was to study the uterine ruptures occurring during TOLAC and the not the few ones that occur before onset of labour. In our study, labour was defined as a woman with contractions or induction of labour, but not necessarily having an orificium dilated to 4 cm or more. We did not include women with pre-labour emergency CS without induction or contractions.

Subsequently, controls were identified in the DMBR (1997–2008). For each case two controls were selected as the two subsequent chronological deliveries in the DMBR among all the women with a singleton term pregnancy, a planned TOLAC, an available medical record, and no uterine rupture. Their medical records were requested, and all data were validated as described above. Only controls with one previous caesarean delivery performed in Denmark, a singleton pregnancy, TOLAC at term and no uterine rupture were included. We reviewed 1839 medical records in order to identify and validate cases and included 175. After selection of controls in the DMBR we reviewed further 392 medical records and included 272 controls (Fig 1). The review was performed by D. Thisted and validated by L. Krebs.

Information on pre-pregnancy risk factors and complications during the current and previous pregnancies and deliveries was collected by a thorough manual review of each medical record from cases and controls. The review included the labour with a planned TOLAC as well as all previous labours. The previous caesarean sections in both cases and controls were performed in the time period of 1982 to 2007. In Denmark, the surgeon performing the procedure is responsible for preparing the operative report in the medical record. During the period from 1982 to 2007 medical records were mostly paper-based and operative notes were either; dictated, handwritten or generated from a pre-printed form completed by the surgeon. We obtained the information regarding the surgical technique from manual review of each medical record. If there was no specific information regarding outcome measures such as closure in one or two layers, use of angle sutures or use of locked sutures, data were recorded as missing values. If information regarding birth weight was missing in the medical record we used the information recorded in the DMBR. All data were entered into a database and analysed using STATA 12.1. Data were entered into the database by the corresponding author D. Thisted; L. Krebs performed validation of the database.

Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated by use of chi2 test in marginal two-by-two contingency tables. Adjusted odds ratios (aOR) were estimated using logistic regression analysis in which uterine rupture was the outcome. The explanatory variables were selected based on both the uni-variable analysis and if pre-existing evidence have suggested an association to uterine rupture. Except for uterine closure, in which missing values were treated as a variable, missing values were omitted in the regression analysis.

No experiments on human or nonhuman animals or other species was performed. Reporting of the study followed the STROBE guidelines. This study was approved by the Danish Data Protection Agency ((Journal number: 2008-41-2256), initial approval on May 23, 2008, extended approval on July 21, 2014 (Journal number: 2014-41-3289)), and the Danish Health and Medicines Authority (Journal number: 3-3013-168/1, approval date September 7, 2012).
According to DMBR (1997-2008) population of 39,472 women with singleton term pregnancy and planned TOLAC

Review of medical records from all cases with
- ICD10 code for uterine rupture (n=763)
- TOLAC and severe neonatal asphyxia or death (n=1076)

196 cases with complete uterine rupture

After secondary review of medical records further 15 cases were excluded due to:
- Preterm delivery (n=11)*
- Previous caesarean performed outside DK (n=4)**
- Planned repeat caesarean (n=4)
- Two previous caesareans (n=2)

392 controls

After review of medical records 121 controls were excluded due to:
- Multiple pregnancy (n=35)
- Planned repeat caesarean (n=27)
- Preterm delivery (n=23)
- Unavailable medical record (n=10)
- Previous Caesarean performed outside DK (n=9)
- No previous caesarean section. (n=6)
- Partial uterine rupture (n=4)
- Control for two cases (n=3)
- Two previous caesareans (n=3)
- Complete uterine rupture (n=1)**

175 cases included

272 controls included
Results

Altogether, 175 cases and 272 controls were included in the study. Since both cases and controls had to meet the above-defined criteria, we were not able to include two controls per case as initially planned (Fig 1). In no cases and in two controls, chromic catgut was used for suturing the uterus. The remaining cases and controls were sutured with a monofilament polyglyconate suture, a polyglycolic acid suture, or a polyglactin suture.

Maternal characteristics in cases and controls are presented in Table 1. Women with uterine rupture were more often non-smokers. Maternal age, height, BMI and ethnicity did not differ between cases and controls (Table 1).

Characteristics from the previous pregnancy and labour in which a caesarean had been performed are presented in Table 2. A uni-variate analysis revealed that use of single layer compared to double layer closure of the uterotomy (OR 1.72 CI:1.12–2.64), absence of angle sutures (OR 2.52 CI:1.48–4.31) and birth weight ≥ 4000g (OR 1.91 CI 1.04–3.48) were associated with an increased risk of uterine rupture. Gestational age at delivery or cervical dilatation at the time of caesarean was not associated with uterine rupture (Table 2). Due to the large number of missing data regarding use of locked sutures in the first layer closure, we were not able to estimate the possible effect on uterine rupture (Table 2).

Characteristics from the pregnancy with TOLAC are presented in Table 3. The unadjusted analysis revealed that at least one previous vaginal delivery was associated with a decreased

Table 1. Maternal characteristics at trial of labour after caesarean (TOLAC) and their association to complete uterine rupture. (Denmark 1997–2008).

| Maternal characteristics at TOLAC | Cases | Controls | OR (95% CI) | P |
|----------------------------------|-------|----------|-------------|---|
|                                  | n = 175 | n = 272  |             |   |
| Maternal height–cm               |        |          |             |   |
| > 165 cm                         | 88 (50.3) | 150 (55.2) | Ref         |   |
| ≤ 165 cm                         | 68 (38.8) | 101 (37.1) | 1.15 (0.77–1.72) | 0.505 |
| Missing data height              | 19 (10.9) | 21 (7.7)  |             |   |
| Maternal BMI                     |        |          |             |   |
| ≤ 30                             | 130 (74.3) | 219 (80.5) | Ref         |   |
| > 30                             | 26 (14.9) | 31 (11.4)  | 1.41 (0.80–2.48) | 0.229 |
| Missing data BMI                 | 19 (10.8) | 22 (8.1)   |             |   |
| Maternal age–years               |        |          |             |   |
| < 38                             | 160 (91.4) | 243 (89.3) | Ref         |   |
| ≥ 38                             | 15 (8.6) | 29 (10.7)  | 0.79 (0.41–1.51) | 0.469 |
| Ethnicity                        |        |          |             |   |
| Caucasian                        | 152 (86.8) | 244 (89.7) | Ref         |   |
| Non-caucasian                    | 22 (12.6) | 26 (9.6)   | 1.36 (0.74–2.48) | 0.318 |
| Missing data                      | 1 (0.6)  | 2 (0.7)    |             |   |
| Smoking                          |        |          |             |   |
| Non-smoking                      | 128 (73.1) | 189 (69.5) | Ref         |   |
| Smoking                          | 20 (11.5) | 55 (20.2)  | 0.54 (0.31–0.93) | 0.028 |
| Missing data–smoking              | 27 (15.4) | 28 (10.3)  |             |   |

https://doi.org/10.1371/journal.pone.0187850.t001
risk of uterine rupture (OR 0.36 CI:0.22–0.57). An inter-delivery interval of more than 24 months reduced the risk of uterine rupture (OR 0.32 CI:0.32–0.62) but no significant association was found considering an inter-delivery interval between 18–24 months. Induction of labour, especially when the cervix was unfavourable, deduced by the use of prostaglandins or double balloon catheter (OR 2.34 CI: 1.48–3.72) increased the risk of uterine rupture. Use of epidural (OR 3.16 CI: 2.10–4.76), augmentation by oxytocin for more than one hour (OR 2.82

Table 2. Characteristics assessed from the caesarean delivery (CD) prior to the trial of labour after caesarean (TOLAC) and their association to complete uterine rupture. (Denmark 1997–2008).

| Obstetric history            | Cases | Controls | OR (95% CI) | P     |
|------------------------------|-------|----------|-------------|-------|
| (At CD prior to TOLAC)       | n = 175 | n = 272  |             |       |
| Gestational age (GA)         |       |          |             |       |
| 37+0–42+0                    | 140 (80.0) | 212 (77.9) | Ref         |       |
| < 37+0                       | 15 (8.6)  | 34 (12.5) | 0.67 (0.35–1.27) | 0.217 |
| > 42+0                       | 19 (10.8) | 22 (8.1)  | 1.31 (0.68–2.50) | 0.417 |
| GA missing                   | 1 (0.6)   | 4 (1.5)   |             |       |
| Birth weight–grams (g)       |       |          |             |       |
| < 3000g                      | 32 (18.3) | 85 (31.3) | Ref         |       |
| 3000–3900g                   | 108 (61.7) | 141 (51.8) | 2.03 (1.27–3.27) | 0.003 |
| > 4000g                      | 33 (18.9) | 46 (16.9) | 1.91 (1.04–3.48) | 0.035 |
| Birth weight missing         | 2 (1.1)   | 0         |             |       |
| Fetal position               |       |          |             |       |
| Vertex                       | 123 (70.3) | 176 (64.7) | Ref         |       |
| Non-vertex                   | 51 (29.1) | 92 (33.8) | 0.79 (0.53–1.20) | 0.271 |
| Missing data                 | 1 (0.6)   | 4 (1.5)   |             |       |
| Induction of labour          |       |          |             |       |
| No induction                 | 131 (74.8) | 207 (76.1) | Ref         |       |
| Induction                    | 39 (22.3) | 53 (19.5) | 1.16 (0.73–1.86) | 0.527 |
| Missing data                 | 5 (2.9)   | 12 (4.4)  |             |       |
| Cervical dilatation          |       |          |             |       |
| No dilatation– 0 cm          | 44 (25.1) | 72 (26.5) | Ref         |       |
| Cervix dilated 0–5 cm        | 70 (40.0) | 96 (35.3) | 1.19 (0.73–1.94) | 0.476 |
| Cervix dilated 6–9 cm        | 38 (21.8) | 41 (15.1) | 1.52 (0.85–2.71) | 0.158 |
| Fully dilated– 10 cm         | 13 (7.4)  | 32 (11.7) | 0.66 (0.32–1.40) | 0.282 |
| Missing cervical dilatation  | 10 (5.7)  | 31 (11.4) |             |       |
| Mode of delivery             |       |          |             |       |
| Planned CS and CS before active labour | 100 (56.4) | 159 (58.0) | Ref         |       |
| Emergency CS during labour   | 75 (43.1) | 113 (41.7) | 1.06 (0.72–1.55) | 0.784 |
| Uterine closure              |       |          |             |       |
| 2-layer closure              | 52 (29.7) | 101 (37.1) | Ref         |       |
| 1-layer closure              | 101 (57.7) | 114 (41.9) | 1.72 (1.12–2.64) | 0.013 |
| Missing data—layers          | 22 (12.6) | 57 (21.0) | 0.75 (0.41–1.36) | 0.342 |
| Angle sutures                | 57 (32.6) | 115 (42.3) | Ref         |       |
| No angle sutures             | 45 (25.7) | 36 (13.2) | 2.52 (1.48–4.31) | <0.001 |
| Missing data–angle sutures   | 73 (41.7) | 121 (44.5) |            |       |
| Locked sutures in 1st layer  | 29 (16.6) | 28 (10.3) | Ref         |       |
| Unlocked sutures             | 59 (33.7) | 88 (32.4) | 0.65 (0.35–1.20) | 0.165 |
| Missing data–locked sutures  | 87 (49.7) | 156 (57.3) |            |       |

https://doi.org/10.1371/journal.pone.0187850.t002
Table 3. Characteristics assessed from pregnancy and birth with trial of labour after caesarean (TOLAC), and their association to complete uterine rupture. (Denmark 1997–2008).

| TOLAC characteristics | Cases (n = 175) | Controls (n = 272) | OR (95% CI) | P |
|------------------------|----------------|-------------------|-------------|---|
| **Parity (Vaginal deliveries prior to TOLAC)** | | | | |
| No vaginal deliveries | 148 (84.6) | 180 (66.2) | Ref | |
| ≥ 1 vaginal delivery | 27 (15.4) | 92 (33.8) | 0.36 (0.22–0.57) | < 0.001 |
| Vaginal delivery after last CD* | 12 (6.9) | 66 (24.3) | 0.22 (0.12–0.41) | < 0.001 |
| **Interval from last CD*** | | | | |
| Interval < 18 months | 24 (13.7) | 14 (5.1) | Ref | |
| Interval ≥ 18 – < 24 months | 25 (14.3) | 26 (9.6) | 0.56 (0.24–1.32) | 0.185 |
| Interval ≥ 24 months | 126 (72) | 232 (85.3) | 0.32 (0.16–0.62) | 0.001 |
| **Gestational age (GA)** | | | | |
| 37+0–42+0 | 158 (90.3) | 249 (91.5) | Ref | |
| > 42+0 | 17 (9.7) | 23 (8.5) | 1.16 (0.60–2.25) | 0.649 |
| **Birth weight–grams (g)** | | | | |
| < 3000 g | 8 (4.6) | 31 (11.4) | Ref | |
| 3000–3999g | 114 (65.1) | 179 (65.8) | 2.47 (1.12–5.45) | 0.025 |
| ≥ 4000g | 45 (25.7) | 59 (21.7) | 2.96 (1.26–6.91) | 0.012 |
| Birth weight missing | 8 (4.6) | 3 (1.1) | | |
| **Induction of labour** | | | | |
| No induction | 112 (64.0) | 216 (79.4) | Ref | |
| Induction (all methods) | 61 (34.9) | 53 (19.5) | 2.22 (1.45–3.41) | < 0.001 |
| - By Prostaglandins or | | | | |
| Double Balloon Catheter | 51 (29.1) | 42 (15.4) | 2.34 (1.48–3.72) | < 0.001 |
| - Prostaglandins | 41 (23.4) | 35 (12.9) | 2.26 (1.37–3.72) | 0.001 |
| - Double balloon catheter | 10 (5.7) | 7 (2.6) | 2.76 (1.06–7.19) | 0.038 |
| - By amniotomy or Oxytocin | 10 (5.7) | 11 (4.0) | 1.75 (0.72–4.22) | 0.209 |
| Missing data | 2 (1.1) | 3 (1.1) | | |
| **Analgesia** | | | | |
| No Epidural | 94 (53.7) | 213 (77.5) | Ref | |
| Epidural | 81 (46.3) | 58 (22.1) | 3.16 (2.10–4.76) | < 0.001 |
| Missing data | 0 | 1 (0.4) | | |
| **Augmentation** | | | | |
| No augmentation (Oxytocin) | 81 (46.3) | 184 (67.6) | Ref | |
| Augmentation | 94 (53.7) | 87 (32.0) | 2.45 (1.66–3.62) | < 0.001 |
| Augmentation: 0–1 hour | 16 (9.1) | 32 (11.8) | 1.14 (0.59–2.19) | 0.703 |
| Augmentation: 1–3 hours | 36 (20.6) | 29 (10.6) | 2.82 (1.64–4.85) | < 0.001 |
| Augmentation: > 3 hours | 42 (24.0) | 26 (9.6) | 3.67 (2.15–6.28) | < 0.001 |
| Missing data | 0 | 1 (0.4) | | |
| **Surveillance of labour** | | | | |
| Continuous CTG | 153 (87.4) | 205 (75.4) | | |
| No scalp pH | 143 (81.7) | 242 (88.9) | Ref | |
| ≥ 1 scalp pH | 31 (17.7) | 29 (10.7) | 1.81 (1.05–3.11) | 0.032 |
| Missing data | 1 (0.6) | 0 | | |
| **Duration of labour** | | | | |
| Arrival to birth < 10 hours | 89 (50.9) | 183 (67.3) | Ref | |
| Arrival to birth ≥ 10 hours | 86 (49.1) | 83 (30.5) | 2.13 (1.44–3.15) | < 0.001 |

(Continued)
CI: 1.64–4.85), birth weight ≥ 4000g (OR 2.96 CI 1.26–6.91) and signs of fetal asphyxia,
deduced by the need of a fetal scalp pH (OR 1.81 CI: 1.05–3.11) also imposed an increased
risk of uterine rupture (Table 3).

Two logistic regression analyses were performed. The first analysis, regarding the risk factors
to be taken into consideration before the decision of TOLAC, adjusted for previous vaginal deliv-
eries, birth weight at the caesarean prior to TOLAC, inter-delivery interval and uterine closure.
The second analysis, regarding the risk factors that can be considered during TOLAC, adjusted
for uterine closure, induction of labour by either prostaglandins or double balloon catheter, aug-
mentation for more than 1 hour, use of epidural, time at labour ward, and birth weight.

The adjusted analysis showed that neither single layer closure (1st analysis aOR 1.38
CI:0.88–2.17) (2nd analysis aOR 1.61 CI:0.99–2.59) nor prolonged labour (aOR 1.07 CI:0.63–
1.82) remained significantly related to uterine rupture (Table 4).

Complications related to the first caesarean delivery such as infection (endometritis, wound
infection, or fever), post partum haemorrhage, or placental abnormalities (previa or placenta
accrete) were not associated with uterine rupture in a subsequent TOLAC (data not shown).
Also, there was no association between previous dilatation and curettage or other previous
genital surgery (other than a caesarean delivery) and uterine rupture (data not shown).
Pregnancy complications such as preeclampsia or hypertension in pregnancy and pre-preg-
nancy medical disorders (diabetes, thyroid disorders, rheumatoid arthritis, asthma, or inflam-
matory bowel diseases) were not associated with uterine rupture in a subsequent TOLAC (data
not shown).

A missing value analysis, in which information on single or double layer closure was
regrouped into either “missing” or “non-missing” was performed. We found that information
on single or double layer closure were more often missing in women who were non-caucasian,
had BMI above 30 or were below 165 cm high.

Discussion
In the present population-based case-control study we found no significant association
between single layer uterine closure and complete uterine rupture in a subsequent TOLAC

Table 3. (Continued)

| TOLAC characteristics          | Cases | Controls | OR (95% CI) | P     |
|---------------------------------|-------|----------|-------------|-------|
| **Missing values (arrival to birth)** | 0     | 6 (2.2)  |             |       |
| Stage I (cervix ≥ 4 cm) *****    | 118 (67.4) | 255 (93.8) |             |       |
| Stage I < 6 hours               | 71 (40.6)  | 199 (73.2) | Ref         |       |
| Stage I ≥ 6 hours               | 44 (25.1)  | 44 (16.2)  | 2.80 (1.72–4.57) | < 0.001 |
| Missing value (Stage I)         | 3 (1.7)    | 12 (4.4)   |             |       |
| Stage II                        | 62 (35.4)  | 226 (83.1) |             |       |
| Stage II < 1 hour               | 32 (18.3)  | 161 (59.2) | Ref         |       |
| Stage II ≥ 1 hour               | 27 (15.4)  | 55 (20.2)  | 2.47 (1.37–4.45) | 0.003  |
| Missing value (Stage II)        | 3 (1.7)    | 10 (3.7)   |             |       |

* CD: Caesarean Delivery
** The interdelivery interval is calculated and reported by months with zero decimals
*** Even though only 67.4% of cases and 93.8% of the controls reached stage I (defined strict as cervix ≥ 4 cm) all women had contractions or had the labour induced.

https://doi.org/10.1371/journal.pone.0187850.t003
after adjusting for previous vaginal deliveries, Birth weight \( \geq 4000g \) at previous caesarean, inter-delivery interval, and induction of labour (by either prostaglandins or double balloon catheter), augmentation by oxytocin (for more than one hour), use of epidural actual birth weight \( \geq 4000g \) and prolonged labour.

Induction of labour with an unfavourable cervix, augmentation by oxytocin for more than one hour, high birth weight use of epidural and measurement of fetal scalp pH indicating a cardiotocography with signs of fetal asphyxia, all increased the risk of a uterine rupture. In contrast, at least one previous vaginal delivery reduced the risk of a subsequent uterine rupture. An inter-delivery interval of 24 months or more decreased the risk of uterine rupture.

| Risk factors                      | Cases     | Controls  | OR (95% CI)   | P   | aOR* (95% CI) |
|-----------------------------------|-----------|-----------|---------------|-----|---------------|
| 2-layer closure                   | 52 (29.7) | 101 (37.1)| Ref           |     |               |
| 1-layer closure                   | 101 (57.7)| 114 (41.9)| 1.72 (1.12–2.64) | 0.013| 1.38 (0.88–2.17) | 0.160 |
| Missing data—layers               | 22 (12.6) | 57 (21.0) | 0.75 (0.41–1.36) | 0.342| 0.65 (0.35–1.21) | 0.174 |
| No vaginal deliveries             | 148 (84.6)| 180 (66.2)| Ref           |     |               |
| \( \geq 1 \) vaginal delivery     | 27 (15.4) | 92 (33.8) | 0.36 (0.22–0.57) | < 0.001 | 0.41 (0.25–0.68) | 0.001 |
| Birth weight < 3000g              | 32 (18.3) | 85 (31.3) | Ref           |     |               |
| Birth weight 3000-3900g           | 108 (61.7)| 141 (51.8)| 2.03 (1.27–3.27) | 0.003| 1.93 (1.18–3.16) | 0.009 |
| Birth weight \( \geq 4000g \)     | 33 (18.9) | 46 (16.9) | 1.91 (1.04–3.48) | 0.035| 2.02 (1.08–3.78) | 0.028 |
| Interdelivery interval < 18 months| 24 (13.7) | 14 (5.1)  | Ref           |     |               |
| Interdelivery interval \( > 18 \) < 24 months | 25 (14.3)| 26 (9.6)  | 0.56 (0.24–1.32) | 0.185| 0.51 (0.21–1.27) | 0.148 |
| Interdelivery interval \( \geq 24 \) months | 126 (72.0)| 232 (85.3)| 0.32 (0.16–0.62) | 0.001| 0.38 (0.18–0.78) | 0.009 |

Table 4. Adjusted odds ratios (aOR) for risk factors for complete uterine rupture from previous and present delivery Denmark 1997–2000.

after adjusting for previous vaginal deliveries, Birth weight \( \geq 4000g \) at previous caesarean, inter-delivery interval, and induction of labour (by either prostaglandins or double balloon catheter), augmentation by oxytocin (for more than one hour), use of epidural actual birth weight \( \geq 4000g \) and prolonged labour.

### Table 4. Adjusted odds ratios (aOR) for risk factors for complete uterine rupture from previous and present delivery Denmark 1997–2000.

| Risk factors                      | Cases     | Controls  | OR (95% CI)   | P   | aOR* (95% CI) |
|-----------------------------------|-----------|-----------|---------------|-----|---------------|
| 2-layer closure                   | 52 (29.7) | 101 (37.1)| Ref           |     |               |
| 1-layer closure                   | 101 (57.7)| 114 (41.9)| 1.72 (1.12–2.64) | 0.013| 1.61 (0.99–2.59) | 0.052 |
| Missing data—layers               | 22 (12.6) | 57 (21.0) | 0.75 (0.41–1.36) | 0.342| 0.71 (0.37–1.37) | 0.310 |
| No induction with unfavorable cervix** | 122 (69.7)| 227 (83.5)| Ref           |     |               |
| Induction with unfavorable cervix**** | 51 (29.1)| 42 (15.4) | 2.26 (1.43–3.57) | < 0.001| 2.10 (1.19–3.71) | 0.010 |
| No Epidural                       | 94 (53.7) | 213 (77.5)| Ref           |     |               |
| Epidural                          | 81 (46.3) | 58 (22.1) | 3.16 (2.10–4.76) | < 0.001| 2.17 (1.31–3.57) | 0.002 |
| No augmentation (Oxytocin) < 1 hour | 97 (54.4)| 216 (79.4)| Ref           |     |               |
| Augmentation (Oxytocin) > 1 hour | 78 (44.6) | 55 (20.2) | 3.16 (2.09–4.77) | < 0.001| 2.03 (1.20–3.44) | 0.008 |
| Time from arrival to birth < 10 hours | 89 (50.9)| 183 (67.3)| Ref           |     |               |
| Time from arrival to birth > 10 hours | 86 (49.2)| 83 (30.5) | 2.13 (1.44–3.15) | < 0.001| 1.07 (0.63–1.82) | 0.790 |
| Birth weight < 3000g              | 8 (4.6)   | 31 (11.4) | Ref           |     |               |
| Birth weight 3000-3900g           | 114 (65.1)| 179 (65.8)| 2.47 (1.12–5.45) | 0.025| 2.49 (1.06–5.85) | 0.037 |
| Birth weight \( \geq 4000g \)     | 45 (25.7) | 59 (21.7) | 2.96 (1.26–6.91) | 0.012| 2.65 (1.05–6.64) | 0.038 |

*Adjusted for: previous vaginal deliveries, inter-delivery interval, birth weight at caesarean prior to TOLAC and uterine closure (2 cases were omitted from the analysis due to missing data of birth weight)

** Adjusted for uterine closure, induction, augmentation, use of epidural and time at labour ward (10 cases and 12 controls were omitted from the analysis due to missing data)

*** No induction by Prostaglandins or a double balloon catheter.

**** Induction by Prostaglandins or a double balloon catheter

https://doi.org/10.1371/journal.pone.0187850.t004
The strengths of this study are the use of validated data, the number of cases included, the strict definition of uterine rupture, and inclusion of only complete uterine ruptures. Thus we avoided the risk of including the less well-defined partial uterine ruptures [6], which are often without medical complications and incidentally diagnosed at repeat caesarean delivery [2,3].

Previous case-control or cohort studies have investigated the impact of single layer closure and the risk of uterine rupture with conflicting results [11,13,19]. Obviously, a randomized controlled study comparing single-layer to double-layer closure in caesarean delivery would be the gold standard when estimating the impact of the operative technique on the risk of uterine rupture. The CEASAR and CORONIS studies [10, 20] may answer the question; however, as illustrated in the CORONIS study [10] it takes many years of follow-up before the impact of an operative technique on future pregnancies can be estimated. In Denmark, the change in suture technique was a consequence of a change in a national guideline in 1998. The study period 1997–2008 with the previous caesarean sections performed during the period from 1982 to 2007 was selected in order to obtain a material with equal distribution of cesareans with uterine closure in one and two-layer.

In our study information on single or double layer closure was missing in 12.6% of cases and 21% of controls. In order to evaluate this potential bias we repeated the logistic regression analysis with all missing data recoded as single layer closure, which did not change the results. When recoding all missing data as double layer closure we found a shift towards an association between uterine rupture and single layer closure.

The limitations of this study are the large amount of missing data regarding use of angle sutures and locked versus un-locked sutures. A few studies have found an increased risk of uterine rupture when the single layer or the inner layer of a double layer closure is performed using a locked suture [21]. No previous studies have estimated the association between use of angle sutures, defined as the application of one or two single sutures at the uterine angles before closure of the uterotomy, and risk of uterine rupture in a subsequent TOLAC. Most bleeding takes place from the angles of the incision. Applying an angle suture should, in theory, secure both haemostasis and sufficient closure of the lateral angle of the uterotomy. In the operative technique introduced in Denmark in 1998 neither use of angle sutures nor use of locked or unlocked sutures was addressed [9]. Thus, the use or non-use of angle sutures or locked sutures was not routinely addressed in the operative record, and un-recorded angle sutures or locked sutures can disguise the fact that they have actually been there. With regard to information on both angle sutures and locked sutures, the present study is underpowered to make a valid conclusion.

Our results are in agreement with a Swedish cohort study [15] and a recent meta-analysis [14] that concluded that single-layer closure was not a risk factor for uterine rupture. Performing a caesarean involves a number of different elements. We cannot exclude that other aspects of suturing the uterotomy could explain our findings [22]. During the same period as the new technique for caesarean delivery was recommended in Denmark many obstetricians changed to a practice where suturing of the uterotomy included the full uterine wall in contrast to the previous routine where inclusion of the endometrium was avoided as far as possible [9].

Augmentation by oxytocin is a well-known risk factor for uterine rupture. Cahill et al [23] found that the risk of uterine rupture was proportional to both the duration and the dose of oxytocin administered. Also, induction of labour is a well known risk factor for uterine rupture [1,24,25]. Studsgaard et al. found an association between induction of labour by a double balloon catheter and uterine rupture. However, the risk was not found significantly increased [25]. While, the same study found a significant association between uterine rupture and use of epidural for analgesia (OR 2.2, CI 1.1–4.9) [25], Weimer et al (a nested case-control study) found no association between uterine rupture and use of epidural [26]. Since the use of
epidural has no impact on the strength of the uterine wall, the need for epidural, especially when used in combination with augmentation by oxytocin, should be considered as an indicator of labour dystocia. Consequently, the lack of significance of prolonged labour in the adjusted analysis (Table 4) should be interpreted with caution.

Previously Bujold et al [27] found that an inter-delivery interval of less than 18 months increased the risk of uterine rupture. In our study we found that compared to an inter-delivery interval of 18 months, an interval between a caesarean delivery and a TOLAC of at least 24 months decreased the risk of uterine rupture.

In this study single-layer uterine closure did not remain significantly associated to uterine rupture during TOLAC at term after adjustment of confounding factors. Still, induction of labour with an unfavourable cervix, Birth weight $\geq$ 4000g and indicators of prolonged labour, such as use of epidural and augmentation by oxytocin for more than 1 hour, are major risk factors for uterine rupture.

Acknowledgments
The authors would like to acknowledge Steen C Rasmussen (Department of Gynaecology and Obstetrics, University of Copenhagen, Hvidovre Hospital, Hvidovre, Denmark) for assistance with data management. Mr. Rasmussen received no compensation for his contribution.

Also the authors would like to acknowledge secretaries and obstetricians at various departments of Gynaecology and Obstetrics in Denmark for generosity and support in collecting medical records.

Author Contributions
Conceptualization: Dorthe L. A. Thisted, Laust H. Mortensen, Lone Krebs.
Data curation: Lone Hvidman, Lone Krebs.
Formal analysis: Dorthe L. A. Thisted, Laust H. Mortensen.
Investigation: Dorthe L. A. Thisted, Lone Krebs.
Methodology: Laust H. Mortensen, Lone Krebs.
Project administration: Dorthe L. A. Thisted.
Supervision: Laust H. Mortensen, Lone Hvidman, Lone Krebs.
Validation: Dorthe L. A. Thisted, Lone Krebs.
Writing – original draft: Dorthe L. A. Thisted, Laust H. Mortensen, Lone Hvidman, Lone Krebs.
Writing – review & editing: Dorthe L. A. Thisted, Laust H. Mortensen, Lone Hvidman, Lone Krebs.

References
1. Fitzpatrick KE, Kurinczuk JJ, Alfivric Z, Spark P, Brocklehurst P, Knight M. Uterine rupture by intended mode of delivery in the UK: a national case-control study. PLoS Med. 2012 Jan; 9(3):e1001184. https://doi.org/10.1371/journal.pmed.1001184 PMID: 22427745
2. Kieser KE, Baskett TF. A 10-year population-based study of uterine rupture. Obstet Gynecol. 2002 Oct; 100(4):749–53. PMID: 12383544
3. Landon MB. Vaginal birth after cesarean delivery. Clin Perinatol. 2008 Sep; 35(3):491–504, ix–x. https://doi.org/10.1016/j.cclp.2008.07.004 PMID: 18952017
4. Turner MJA, Agnew G, Langan H. Uterine rupture and labour after a previous low transverse caesarean section. BJOG. 2006; 113:729–32. https://doi.org/10.1111/j.1471-0528.2006.00940.x PMID: 16709218

5. Spong CY, Landon MB, Gilbert S, Rouse DJ, Leveno KJ, Varner MW, et al. Risk of uterine rupture and adverse perinatal outcome at term after cesarean delivery. Obstet Gynecol. 2007; 110:801–7. https://doi.org/10.1097/AOG.0b013e3181a40c06 PMID: 17960612

6. Thisted DLA, Mortensen LH, Hvidman L, Rasmussen SC, Larsen T, Krebs L. Use of ICD-10 codes to monitor uterine rupture: Validation of a national birth registry. Eur J Obstet Gynecol Reprod Biol. 2014; 173:23–8. https://doi.org/10.1016/j.ejogrb.2013.10.033 PMID: 24278275

7. Zwart JJ, Richters JM, Ory F, de Vries JIP, Bloemenkamp KWM, van Roosmalen J. Uterine rupture in The Netherlands: a nationwide population-based cohort study. BJOG. 2009 Jul; 116(8):1069–78; discussion 1078–80. https://doi.org/10.1111/j.1471-0528.2009.02136.x PMID: 19515148

8. Colmorn LB, Petersen KB, Jakobsen M, Lindqvist PG, Klungsoyr K, Källen K, et al. The Nordic Obstetric Surveillance Study: a study of complete uterine rupture, abnormally invasive placenta, peripartum hysterectomy, and severe blood loss at delivery. Acta Obstet Gynecol Scand. 2015 Jul; 94(7):734–44. DOI:10.1111/aogs.12639 PMID: 25828911

9. Lorentzen U, Philipson JP, Langhoff-Roos J, Hornes PJ. [Surgical technique in Cesarean section. Evidence or tradition?]. Ugeskr Laeger. DENMARK; 1998 Apr; 160(17):2517–20. PMID: 9599531

10. Brocklehurst P. Caesarean section surgical techniques: 3 year follow-up of the CORONIS fractional, factorial, unmasked, randomised controlled trial. The Lancet. 2016;

11. Bujold E, Bujold C, Hamilton EF, Harel F, Gauthier RJ. The impact of a single-layer or double-layer closure on uterine rupture. Am J Obstet Gynecol. Elsevier; 2002 Jun 1; 186(6):1326–30. PMID: 12066117

12. Gyamfi C, Juhasz G, Gyamfi P, Blumenfeld Y, Stone JL. Single- versus double-layer uterine incision closure and uterine rupture. J Matern Fetal Neonatal Med. 2006; 19(October):639–43.

13. Bujold E, Goyet M, Marcoux S, Brassard N, Cormier H, Hamilton E, et al. The role of uterine closure in the risk of uterine rupture. Obstet Gynecol. 2010; 116:43–50. https://doi.org/10.1097/AOG.0b013e1814e1be3 PMID: 20567166

14. Roberge S, Chaillet N, Boutin A, Moore L, Jastrow N, Brassard N, et al. Single- versus double-layer closure of the hysterotomy incision during cesarean delivery and risk of uterine rupture. Int J Gynaecol Obstet. International Federation of Gynecology and Obstetrics; 2011 Oct; 115(1):5–10.

15. Hesselman S, Högb erg U, Ekholm-Selling K, Råssjö E-B, Jonsson M. The risk of uterine rupture is not increased with single- compared with double-layer closure: a Swedish cohort study. BJOG. 2014 Aug 4;

16. Sørensen HT, Sabroe S, Olsen J, Sørensen HT. A framework for evaluation of secondary data sources for epidemiological research. Int J Epidemiol. 1996; 25:435–42. PMID: 9119571

17. World Health Organization. The ICD-10 Classification of Mental and Behavioural Disorders. Int Classif. 1992; 10:1–267.

18. Committee NM-S. NOMESCO classification of surgical procedures. Copenhagen: NOMESCO; 2007;

19. Dodd JM, Anderson ER, Gates S, Grivell RM. Surgical techniques for uterine incision and closure at the time of caesarean section. Cochrane database Syst Rev. 2014 Jan;7:CD004732. https://doi.org/10.1002/14651858.CD004732.pub3 PMID: 25048608

20. Perinatal N, Unit E. Caesarean section surgical techniques: a randomised factorial trial (CAESAR). BJOG. 2010 Oct; 117(11):1366–76. https://doi.org/10.1111/j.1471-0528.2010.02686.x PMID: 20840692

21. Roberge S, Demers S, Girard M, Vikhareva O, Markey S, Chaillet N, et al. Impact of uterine closure on residual myometrial thickness after cesarean: a randomized controlled trial. Am J Obstet Gynecol. 2015;

22. Roberge S, Demers S, Berghella V, Chaillet N, Moore L, Bujold E. Impact of single- vs double-layer closure on adverse outcomes and uterine scar defect: a systematic review and metaanalysis. Am J Obstet Gynecol. 2014 Jun 6;

23. Cahill AG, Waterman BM, Stamilio DM, Odibo AO, Allsworth JE, Evanoff B, et al. Higher maximum doses of oxytocin are associated with an unacceptably high risk for uterine rupture in patients attempting vaginal birth after cesarean delivery. Am J Obstet Gynecol. 2008 Jul; 199(1):32.e1–5.

24. Landon MB, Hauth JC, Leveno KJ, Spong CY, Leindecker S, Varner MW, et al. Maternal and perinatal outcomes associated with a trial of labor after prior cesarean delivery. N Engl J Med. 2004; 351:2581–9. https://doi.org/10.1056/NEJMoa040405 PMID: 15598960

25. Studsgaard A, Skorstengaard M, Glavind J, Hvidman L, Uldbjerg N. Trial of labor compared to repeat cesarean section in women with no other risk factors than a prior cesarean delivery. Acta Obstet Gynecol Scand. 2013 Nov; 92(11):1256–63. https://doi.org/10.1111/aogs.12240 PMID: 23962339
26. Weimar CHE, Lim a C, Bots ML, Bruinse HW, Kwee a. Risk factors for uterine rupture during a vaginal birth after one previous caesarean section: a case-control study. Eur J Obstet Gynecol Reprod Biol. Elsevier Ireland Ltd; 2010 Jul; 151(1):41–5. https://doi.org/10.1016/j.ejogrb.2010.03.023 PMID: 20427113

27. Bujold E, Gauthier RJ. Risk of uterine rupture associated with an interdelivery interval between 18 and 24 months. Obstet Gynecol. 2010 May; 115(5):1003–6. https://doi.org/10.1097/AOG.0b013e3181d992f
PMID: 20410775