Inter-pregnancy interval and uterine rupture following a trial of labour after caesarean among women with one previous caesarean section and no previous vaginal births: Study protocol for a population-based cohort study.

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Introduction:

In the United States (U.S) and Australia, 32% to 37% of all mothers give birth by caesarean section.[1,2] However, only 12% to 14% of women with a previous caesarean section had a vaginal birth.[1,2] Recently, 'previous caesarean section' has become the most common indication for caesarean delivery.[3,4] Assuming vaginal birth is not otherwise contraindicated, suitability to attempt a vaginal birth after a previous caesarean section is commonly determined by assessing risk factors for uterine rupture, with a trial of labour after caesarean (TOLAC) being considered a safe option for most women.[5,6] The primary risk associated with a TOLAC is uterine rupture,[5] commonly defined as any full thickness separation of the myometrial layer, typically at the site of the previous caesarean scar. Risk factors for uterine rupture include shorter interdelivery interval (IDI, the time from the index caesarean section to the next birth) or interpregnancy interval (IPI, the time from the index caesarean section to conception), post-dates pregnancy, fetal macrosomia, and lower pre-labour Bishop score.[6] Of these, the interval elapsed since the index caesarean section (IDI or IPI) is perhaps the most controllable risk factor for uterine rupture.

Data around the significance of IPI as a risk factor for uterine rupture is conflicting, both with respect to the relative risk and to length of the interval required to reduce the risk of rupture. Several studies have shown shorter IPIs to be associated with an increased risk of uterine rupture.[7-13] Within these studies the proposed interval which conveys a significant risk reduction varies between an IPI of 6 months,[9] an IDI of 18 months (IPI approximately 9 months),[8] IPI of 12 months,[12,13] and an IDI of 24 months (IPI approximately 15 months).[14] In contrast, several other studies have not shown any difference in uterine rupture rates for shorter compared to longer IPIs.[14,15]

Using a large U.S population-based dataset, this study aimed to evaluate the nature and strength of the relationship between IPI and the risk of uterine rupture and other complications in a future pregnancy among women with one previous caesarean section and no previous vaginal deliveries.

Study design: This will be a retrospective cohort study examining the relationship between IPI and uterine rupture.

Study setting: The study will include all eligible births recorded in the United States in the 12-year period from 2011 to 2021.

Participants:

Eligibility criteria:

- Planned vaginal birth
- At least 17 weeks gestational age
- Singleton or twin pregnancy
- One previous livebirth
- One previous caesarean delivery

Exclusion criteria:

- Planned prelabour caesarean delivery
- Fetal congenital abnormalities
- Triplets or higher order pregnancies
- More than one previous livebirth
- More than one previous caesarean delivery

Note that including one previous caesarean delivery and one previous livebirth will include almost exclusively women with only one birth in the past, where that birth was a caesarean delivery. There are rare exceptions, such as women with two previous births, one of which was by caesarean delivery and one of which was a stillbirth. These rare events are not expected to impact the estimates of rates of uterine rupture in this study.

Primary study factor: The primary study factor will be IPI, the number of months from the last live birth to the calculated date of the last menstrual period in the current pregnancy.

Primary Outcome: The primary outcome will be uterine rupture. Uterine rupture is defined in the dataset as:

"(Tearing of the uterine wall). A full-thickness disruption of the uterine wall that also involves the overlaying visceral peritoneum (uterine serosa). Does not include uterine dehiscence in which the fetus, placenta and umbilical cord remain contained with the uterine cavity. Does not include a silent or incomplete rupture or an asymptomatic separation."

Other outcomes: These will include relevant clinical outcomes available in the data. These are all categorical outcomes and will be expressed as numbers and percentages (n %)

Maternal:

- Unplanned hysterectomy
- Blood transfusion
- Intensive care unit admission

Fetal/neonatal:

- Intrapartum fetal death or neonatal death (combined outcome)
- 5-minute Apgar score < 4
- Neonatal seizures
- Admission to the neonatal intensive care unit
- Neonatal ventilation immediately after birth (as part of resuscitation)
- Neonatal ventilation for more than six hours

Explanatory Variables:

Mean and standard deviation (SD) will be used to describe continuous variables if they are normally distributed, otherwise median and interquartile range (IQR) will be used.

Categorical variables will be reported as numbers and percentages. Demographic and clinical characteristics will be reported as follows:

- IPI in months
- Maternal body mass index (BMI)
- Maternal height in cm
- Maternal age in years
- Gestational age at birth in weeks
- Race (to be categorised as the dataset allows)
- Maternal cigarette smoking
- Year of delivery (birth of the baby)
- Payment type (public/private)
- Education (to be categorised as the dataset allows)
- Diabetes in pregnancy (to be categorised as the dataset allows)
- Hypertension in pregnancy (to be categorised as the dataset allows)
- Birthweight in grams
- Labour type (spontaneous onset, induced, augmented)
- Plurality (twin v singleton pregnancies)

Sample-size:

No sample size calculation will be performed. The maximum amount of available data will be used with the aim of narrowing confidence intervals around the association between IPI and uterine rupture, as uterine rupture is a rare outcome.

Data collection and methods:

Publicly available data from the Center for Disease Control (CDC) will be used and can be downloaded from https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm.

Variables that are a planned part of the analysis will be interrogated to describe any missingness and extreme outliers.

Analysis plan:

Data will be downloaded from the CDC website (https://www.cdc.gov/nchs/data_access/vitalstatsonline.htm) for birth years 2011 to 2021.

The frequency of uterine rupture will be examined for IPIs grouped into three-monthly intervals ("categorised IPI") and visually examined for suitability for a linear spline logistic regression model. The fitted curve in the univariable regression will be plotted with uterine rupture rates and 95% confidence intervals for categorised IPIs.

If univariate regression supports a linear spline fit for IPI, a multivariate logistic regression model incorporating such a spline, as well as other explanatory variables, will be fitted. Model selection will be conducted by stepwise backward elimination.

If data missingness is present for the explanatory variables for more than 5% and less than 40% of eligible births then multiple imputation with fully conditional specification will be used, with five imputed datasets.

Multiple imputation will include all explanatory and outcome variables, all spline terms, and derived terms including body mass index, squared terms used to assess for linearity, and an interaction term. Interdependencies amongst variables will be handled with the passive imputation method.

Initial analysis described in the AJOG article (https://www.ajog.org/article/S0002-9378(23)00880-3/fulltext) informed our approach to multiple imputation and to determining the knot position for the linear spline of IPI in the regression. Simulation studies with purely random data helped to understand both the estimation uncertainty and computational requirements. Based on these, we pre-specified a procedure that minimises the number of regression models created, to reduce the risk of overfitting and Type I errors, while ensuring practicality for available hardware resources.

Procedure for Knot Position Identification

Objective: Identify a knot position representing a risk threshold for IPI in the region predicted by prior literature whose logistic regression model has the lowest Akaike Information Criterion (AIC)

A univariate single-knot linear spline logistic regression model (uterine rupture against IPI) will be fitted using a sequence of potential knot positions as described below. All cases in the augmented/induced cohort with available IPI and rupture outcome will be included. The higher uterine rupture rate in the augmented/induced cohort allows a more precise statistical estimate, while initial analysis and clinical considerations suggest that the knot position is not different between the cohorts. To start, knot positions of 12, 15 and 18 months will be searched. If the lowest AIC of these is at either end, the search will be expanded in that direction in 3-month steps. Once an interior minimum is found, further nearby knot positions at monthly intervals will be searched to find the local AIC-minimising knot position in months.

Once the best knot position is identified, subsequent multiple imputation can be conducted using a specification consistent with a linear spline form for the IPI response, with a single knot

at the identified position. The total number of models fitted in the above procedure will be reported to indicate the potential for over-fitting. A bootstrap analysis will also be conducted to estimate a confidence interval for the best knot position.

Linearity of continuous explanatory variables will be tested by adding a squared term for each continuous variable, and model formulation will be revisited if the squared term is not eliminated during backward stepwise elimination.

Backward stepwise elimination will be conducted using log-likelihood ratio tests on the contribution of each explanatory variable remaining in the model. Variables will be eliminated one at a time if (1) they have the highest p-value; and (2) the p-value is > 0.05. If multiple imputation has been used, p-values for the likelihood ratio test in each imputed dataset will be pooled using the median p-value rule.

The following variables will be included in the base model as potential predictors of uterine rupture:

- Interpregnancy interval as a linear spline with one knot (not eligible for exclusion in the stepwise elimination) (continuous, months)
- Labour induced or augmented versus spontaneous onset of labour (not eligible for exclusion in the stepwise elimination) (dichotomous)
- Maternal age (continuous) and maternal age squared
- Gestational age (continuous) and gestational age squared
- Maternal height (continuous) and maternal height squared
- Birthweight (continuous) and birthweight squared
- Maternal race (categorical)
- Cigarette smoking (dichotomous)
- Year of birth (11 categories from 2011 to 2021)
- Payment type (dichotomous, public v private)
- Trimester of onset of maternity care (4 categories: first, second or third trimester, or no antenatal care)
- An interaction term of IPI less than the knot in the linear spline regression x the augmented/induced dichotomous variable (continuous)
- Body Mass Index (continuous) and BMI squared
- Hypertension in pregnancy (dichotomous)
- Diabetes (3 categories: pre-pregnancy, gestational, none)
- Education (integer level, as available in the original dataset)
- Plurality (dichotomous: twins, singleton)

After stepwise elimination, the slope of the upper segment of the spline fit for IPI will be assessed and, if that slope is not statistically different from zero, the model will be fitted again with that slope fixed to zero to obtain the final primary analysis fit.

Using the final multivariate fitted model, predicted probabilities of uterine rupture and the upper limits of the 95% confidence intervals will be tabulated by months' IPI – the latter to give clinicians some certainty about the point estimates of probability.

Sensitivity analyses:

The final multivariate fitted model from the imputed datasets will be replicated in the complete data for comparison.

Secondary outcomes:

Among women with a ruptured uterus, secondary outcomes will be compared by short versus long IPI (IPI ≤ the knot position versus IPI > the knot position) using χ^2 tests for categorical variables and the Wilcoxon Rank Sum test for Apgar score. If there is no association between IPI and the secondary outcome, the outcome will be reported by uterine rupture and no uterine rupture. If the outcome is associated with IPI then it will be reported in four groups: (1) uterine rupture with a short IPI; (2) uterine rupture with a long IPI; (3) no uterine rupture with a short IPI; and (4) no uterine rupture with a long IPI.

Summary:

This study will utilise 11 years of all recorded US birth data to explore the risk factors for uterine rupture and secondary outcomes following a TOLAC among women with one previous caesarean section and no previous vaginal births. IPI will be the primary focus, particularly changes in the risk as IPI increases and whether a threshold level of IPI can be identified via a multivariate spline logistic regression model. Estimates for the probability of uterine rupture in given scenarios that incorporate all significant available risk factors will be computed from the fitted model to support clinical decision-making.

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