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Title page

Severe maternal morbidities in women with a prior caesarean delivery planning vaginal birth or elective repeat caesarean section: a retrospective cohort analysis using data from the UK Obstetric Surveillance System

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ABSTRACT

Objective: To conduct a secondary analysis of data from the UK Obstetric Surveillance System (UKOSS) to estimate the rates of specific maternal risks associated with planned Vaginal Birth after Caesarean (VBAC) and Elective Repeat Caesarean Section (ERCS).

Design: A retrospective cohort analysis using UKOSS data.

Setting: All hospitals with consultant led maternity units in the UK.

Population: Pregnant women who had a previous caesarean section.

Method: Women who had undergone a previous caesarean section were divided into two exposure groups: planned VBAC and ERCS. We calculated the incidence of each of the four outcomes of interest with 95% confidence intervals (CI) for the two exposure groups using proxy denominators (total estimated VBAC and ERCS maternities in a given year). Incidences were compared between groups using chi squared or Fisher's exact tests and risk ratios with exact 95% CI.

Main outcome measures: Severe maternal morbidities: peripartum hysterectomy, severe sepsis, peripartum haemorrhage and failed tracheal intubation.

Results: The risks of all complications examined in both groups were low. The rates of peripartum hysterectomy, severe sepsis, peripartum haemorrhage and failed tracheal intubation were not significantly different between the two groups in absolute or relative terms.

Conclusion: While the risk of uterine rupture in VBAC and ERCS groups is well understood, this national study did not demonstrate any other clear differences in the outcomes we examined. The absolute and relative risks of maternal complications were small in both groups. Large epidemiological studies could further help to assess whether the incidence of these rare outcomes would significantly differ between VBAC and ERCS groups if a larger number of cases were to be examined. In the interim, this study provides important information to help pregnant women in their decision making process.

ARTICLE SUMMARY

Strengths and limitations of the study

- While the risk of uterine rupture associated with VBAC is known, this study estimated the rates of other specific maternal risks (peripartum hysterectomy, severe sepsis, peripartum haemorrhage and failed tracheal intubation) associated with VBAC and ERCS using existing national data from the UK Obstetrics Surveillance System (UKOSS).

- Low incidence of severe maternal morbidities in the UK makes it difficult to compare their risks between VBAC and ERCS groups. The UKOSS database of research data on rare and potentially life threatening conditions in pregnancy provided a unique opportunity to estimate the risk of the four adverse maternal outcomes between the two groups in a cost-effective manner.

- The method used to generate the exposure groups (planned VBAC and ERCS) could have misclassified some women who were planning ERCS, but went into spontaneous labour and were thus included under the VBAC group. However, we do not anticipate a large proportion of such women.

- Cases which could not be grouped into VBAC or ERCS due to missing information could have biased the study results, mainly for the sepsis group. We have thus reported the results of a sensitivity analysis.

- A large epidemiological study with a greater number of cases would improve the power and possibly show significant differences in the outcomes, however, this study intended to take advantage of existing secondary data and the results could pave way for further studies.

Key words: Vaginal Birth after Caesarean, Elective Repeat Caesarean Section, peripartum hysterectomy, severe sepsis, peripartum haemorrhage, failed tracheal intubation.

Word count: 2250

INTRODUCTION

Current UK guidelines[1 2] advise that women who have undergone a prior delivery by caesarean section should be informed of the risks and benefits of Elective Repeat Caesarean Section (ERCS) as well as the risks and benefits of planned Vaginal Birth after Caesarean (VBAC). Such a discussion requires comprehensive evidence of the risks associated with ERCS compared to VBAC. Several studies have examined the risk of uterine rupture following VBAC,[3-5] but robust data comparing a wider range of complications of VBAC and ERCS are limited and the few randomised controlled studies[6 7] have limitations.

A previous study in the UK demonstrated uterine rupture to be associated with VBAC.[8] Uterine rupture is a rare and serious complication of VBAC, but when comparing ERCS and VBAC it is important to consider other maternal complications. The aim of this study was therefore to estimate the rates of other specific maternal risks associated with VBAC and ERCS using available national data from the UK Obstetric Surveillance System (UKOSS).

METHODS

Study Design

We conducted a retrospective cohort analysis using data from the UKOSS. Details of the UKOSS methodology are described elsewhere.[9 10] UKOSS was set up in 2005 to investigate uncommon disorders of pregnancy and 'near-miss' conditions.[10] Case notification cards are sent to all consultant-led obstetric units in the UK every month. An approach of 'nil-reporting' together with rigorous follow-up of non-responders ensures good case ascertainment. For every case reported, details are completed in a data collection form by the clinician responsible for managing the case. Further details of the UKOSS methodology are provided elsewhere.[9 10]

Exposure groups were planned vaginal birth after caesarean (VBAC) and elective repeat caesarean section (ERCS). Women who had a history of caesarean section and underwent elective caesarean section during the current pregnancy were included in the ERCS group. Women who had a previous caesarean section, but planned vaginal delivery during current pregnancy were included in the planned VBAC group irrespective of whether they actually had a vaginal delivery.

Outcomes of interest were the maternal complications peripartum hysterectomy, severe sepsis, peripartum haemorrhage and failed tracheal intubation, which are suggested to be related to VBAC or ERCS in other studies.[6 11 12] We had national datasets within UKOSS for the outcomes (peripartum hysterectomy,[13] severe sepsis,[14] peripartum haemorrhage,[15 16] and failed tracheal intubation[17]) and thus case definitions were based on the standard case definitions used in the UKOSS (provided in Table-1).

Table-1: Definitions of outcomes included from the UKOSS national studies

Condition	Definition
Peripartum hysterectomy	Any woman giving birth to an infant and having a hysterectomy during the same clinical episode.
Peripartum haemorrhage	Cases were pregnant women of 20 weeks gestation or more identified as having ≥8 units of red blood cell transfusion within a 24 hour period.
Failed tracheal intubation	A case of failed intubation was defined as failure to achieve tracheal intubation during a rapid sequence induction for obstetric anaesthesia, thereby initiating a failed intubation drill.
Severe sepsis	Any pregnant woman (up to six weeks postpartum) diagnosed with severe sepsis (irrespective of the source of infection). A severe sepsis case would be expected to include women in one of the following groups: 1. Death related to infection or suspected infection 2. Any women requiring level 2 or level 3 critical care (or obstetric HDU type care) due to severe sepsis or suspected severe sepsis 3. A clinical diagnosis of severe sepsis – based on 2 or more the following – a. Temperature > 38^0C or <36^0C measured on 2 occasions at least 4 hours apart b. Heart rate >100 beats/minute measured on 2 occasions at least 4 hours apart c. Respiratory rate >20/minute measured on 2 occasions at least 4 hours apart d. White cell count >17X10^9/L or <4 X10^9/L or with >10% immature band forms, measured on 2 occasions

Study sample

For each of the four maternal outcomes, for which a national dataset was available, we used the total reported cases. Among the cases, those without a previous history of caesarean section were excluded. We also excluded women with placenta praevia/accreta/percreta diagnosed before delivery to exclude known confounding due to these conditions which would be regarded as an absolute indication for ERCS. The final sample of cases that remained was divided into planned VBAC and ERCS groups based on planned mode of delivery. If a dataset did not include information on 'planned mode of delivery', we investigated two other variables – 'woman underwent induction of labour with or without prostaglandins and/or oxytocin' and 'woman went into labour'. If either of these were 'true', we categorised the woman as planned VBAC (irrespective of her actual mode of delivery - vaginal or caesarean), otherwise ERCS. If information on any of these criteria was not available, we grouped the cases into a missing category. A schematic diagram of the process of derivation of the study samples for peripartum hysterectomy, severe sepsis, peripartum haemorrhage and failed intubation is provided in figure-1.

Statistical analyses

We calculated the incidence of each of the outcomes of interest with 95% confidence intervals (CI) for the two exposure groups, VBAC and ERCS, using the denominators - total expected VBAC and ERCS maternities in a given year. The method of calculating proxy denominators was similar to that used by Fitzpatrick et al. to report the incidence of uterine rupture in VBAC and ERCS groups.[8] Total

maternities for the UK in the study period for each of the outcomes were calculated from the annually reported birth data for England and Wales,[18] Scotland[19] and Northern Ireland.[20] From these, we calculated the estimated number of maternities likely to have undergone previous caesarean section, which was 13% of the total maternities, derived from a group of population based controls comprised of women giving birth in the UK in 2012-13. Based on proportions observed in the control group of the UKOSS uterine rupture study,[8] we further divided the maternities with previous caesarean section into women undergoing planned VBAC (44% of the total maternities with previous caesarean section) and women undergoing planned ERCS (56% of the total maternities with previous caesarean section) which gave the required proxy denominators.

In addition, we also tested whether the calculated rates in the exposure groups were significantly different from each other using chi square test or Fisher's exact test. We estimated the risk ratios and exact 95% confidence intervals (CI) to ascertain the relative risk of severe maternal morbidities in the planned VBAC compared to ERCS group. We also used descriptive statistics to compare the two exposures groups. In order to account for any differences in known and potential confounding factors, we conducted multivariable logistic regression analyses for the outcomes for which we had a control group: peripartum hysterectomy, sepsis and failed intubation. The multivariable logistic regression analysis results for uterine rupture have been published previously.[8]

In the sample for sepsis, 11 cases could not be classified into VBAC or ERCS due to missing information, and peripartum haemorrhage and hysterectomy each had one case with missing information (Figure-1). We conducted a sensitivity analysis by calculating incidence rates assuming extreme scenarios and accordingly including the missing numbers under each of the two exposure groups.

RESULTS

A total of 83 confirmed cases of peripartum haemorrhage, 66 cases of hysterectomy, 49 cases of severe sepsis and 7 cases of failed tracheal intubation were included in the study (Figure-1). The exposure groups, ERCS and planned VBAC, for each of the outcomes were not significantly different in terms of maternal age, body mass index (BMI), parity, history of previous pregnancy problems and socioeconomic status. The calculated incidence rates of the maternal complications were low and were not found to be significantly different between the two groups (Table-2). The relative risk of the severe maternal morbidities was not different between the VBAC and ERCS groups (Table-2).

Table-2: Rate of severe maternal morbidities in VBAC and ERCS groups

Conditions	Study period	Total Maternities for the study period	Maternities with previous Caesarean deliveries*	VBAC			ERCS			P-value of χ^2 test[¥] for outcome difference between VBAC & ERCS	Risk ratios (VBAC to ERCS) (Exact 95% CI)
				Maternities with previous CS with VBAC[ɨ]	Cases	Estimated rate per 100,000 maternities (95% CI)	Maternities with previous CS with ERCS[ƒ]	Cases	Estimated rate per 100,000 maternities (95% CI)		
Uterine rupture[8]	01/04/2009 to 30/04/2010	852206	127831	56246	116	206.7 (170.5 -247.3)	71585	20	27.9 (17.1 - 43.2)	<0.001	7.39 (4.58 - 12.55)
Peripartum hysterectomy	01/02/2005 to 29/02/2006	839785	109172	48036	35	72.9 (50.8 - 101.3)	61136	30	49.1 (33.1 - 70.0)	0.110	1.49 (0.89 - 2.50)
Sepsis	01/06/2011 to 31/05/2012	801770	104231	45861	23	50.1 (31.7 - 75.2)	58370	18	30.8 (18.3 - 48.7)	0.119	1.63 (0.84 - 3.19)
Peripartum haemorrhage	01/09/2007 to 31/03/2009[$]	1176025	152884	67269	31	46.0 (31.3 - 65.4)	85616	51	59.5 (44.3 - 78.3)	0.259	0.77 (0.48 - 1.23)
Failed intubation	01/04/2008 to 31/03/2010	1504593	195597	86062	2	2.3 (0.2 - 8.3)	109535	5	4.5 (1.4 - 10.6)	0.476	0.51 (0.05 - 3.11)

*Proportion of maternities likely to have undergone previous caesarean section (based on 13% calculated from the Sepsis controls, 2012-13, drawn from the general population); [ɨ] Proportion of maternities with previous caesarean section (CS) likely to undergo VBAC (based on 44% calculated from UKOSS-uterine rupture controls as was done by Fitzpatrick et al (8)); [ƒ] Proportion of maternities with previous caesarean section (CS) likely to undergo ERCS (based on 56% calculated from UKOSS-uterine rupture controls as was done by Fitzpatrick et al (8)); VBAC – Vaginal birth after caesarean; ERCS – Elective Repeat Caesarean section; CI – Confidence Interval; [¥] For counts <5 Fisher's Exact test was done instead of Pearson's chi squared test, [$] The total maternities for this 18 month study were calculated as: Total maternities in 2008 + half of the maternities in 2009, as the number of maternities found for 2007 (from the same sources) did not appear to be in complete agreement with the 2005-2012 trend. Owing to this uncertainty in the 2007 numbers, the 2008 and 2009 maternities have been used here.

The unadjusted odds ratios for the adverse outcomes, for which we had a control group, were not significantly different between the VBAC and ERCS groups (data not shown). The odds of peripartum hysterectomy (adjusted odds ratio=0.92; 95%CI=0.45 to 1.91) and sepsis (adjusted odds ratio =0.51; 95% CI=0.22 to 1.19) in the ERCS group were not significantly different from that of the VBAC group after controlling for current and previous pregnancy problems, number of previous caesarean sections, pre-existing medical problems, parity, smoking status, socioeconomic status, ethnic background, marital status, BMI and maternal age. The adjusted odds ratio was not meaningful for failed intubation which had a total sample size of 15.

Sensitivity analysis for cases with missing information showed that although the rates changed slightly in the planned VBAC and ERCS groups for peripartum haemorrhage and hysterectomy, it did not result in a significant difference in the risk of the adverse outcome between the two exposure groups in either scenario. However, for severe sepsis, when all the 11 cases with missing information were included in the planned VBAC group, the rate in the VBAC group was found to be significantly higher than the rate in the ERCS group (p-value for chi square test=0.002). When these cases were included in the ERCS group, the rates of sepsis in the two exposure groups were equal (50 per 100,000 maternities).

DISCUSSION

This study using the UKOSS data and a nested retrospective cohort design did not find a significant difference in the incidence and relative risk of adverse maternal outcomes between the VBAC and ERCS groups. However, the incidence rates of these outcomes were low.

Strengths and Limitations

Low incidence of severe maternal morbidities in the UK makes it difficult to compare their risks between VBAC and ERCS groups. The UKOSS database of research data on rare and potentially life threatening conditions in pregnancy provided a unique opportunity to estimate the risk of four adverse maternal outcomes between the two groups in a cost-effective manner. The method used to generate the exposure groups (planned VBAC and ERCS) could have misclassified some women who were planning ERCS, but went into spontaneous labour and were thus included under the VBAC group. However, we do not anticipate a large proportion of such women. Cases which could not be grouped into VBAC or ERCS due to missing information could have biased the study results, mainly for the sepsis group. We have thus reported the results of a sensitivity analysis. Although we accounted for known confounders for each outcome in the multivariable logistic regression analyses, the results cannot be interpreted with certainty due to the small sample sizes. A longer term study with a greater number of cases would improve the power and possibly show significant differences in the outcomes, however, this study intended to take advantage of existing secondary data and the

results could pave the way for further studies. Furthermore, the adverse outcomes presented in this study are immediate risks associated with the current pregnancy in the ERCS and VBAC groups and we cannot comment on the risk of morbidity in future pregnancies.

While the higher risk of uterine rupture associated with planned VBAC is known,[4 8 21 22] studies from different parts of the world have reported variable relative and absolute risks of other maternal complications in ERCS versus VBAC groups. Similar to the findings of this study, a multicentre prospective cohort study in the USA,[4] a Canadian study[11] and a meta-analysis of literature published between 2000 and 2007[22] did not find any difference in the risk of hysterectomy between those that underwent a trial of labour and those that had an elective caesarean section. However, a decision model analysis conducted by Paré et al. suggested that the decision to undergo VBAC or ERCS among women with one prior caesarean section should be guided by the number of planned subsequent pregnancies.[23] Based on an analysis of risk of hysterectomy, the authors suggested that ERCS should be the strategy of choice for women planning one additional pregnancy, but for women who desire two or more subsequent pregnancies VBAC should be attempted to minimise morbidity associated with multiple caesarean sections.[23]

In contrast to our findings, a study in Australia found a 63% lower risk of peripartum haemorrhage in the planned ERCS compared to planned VBAC group [6] and the multicentre study from the USA demonstrated a higher odds of transfusion in the VBAC group compared with the ERCS.[4] However, a meta-analysis suggested a lower risk of peripartum haemorrhage in the VBAC group[21] and other studies did not show any difference.[11 22] A prospective cohort study of obese women using data collected through the UKOSS did not find any difference in anaesthetic complications between ERCS and planned VBAC groups,[24] but this finding cannot be generalised to non-obese women.

Conclusion

While the risk of uterine rupture in VBAC and ERCS groups is well understood, this national study did not demonstrate any other clear differences in the outcomes we examined. The absolute and relative risks of maternal complications were small in both groups which is important information to help pregnant women in their decision making process. Large epidemiological studies with a longer time-period for data collection are required to assess whether the incidence of these rare outcomes would significantly differ between VBAC and ERCS groups if a larger number of cases were to be examined. In the interim, this study contributes additional information to the process of individualised decision-making about mode of delivery by women who have had a previous delivery by caesarean section, as recommended in current guidance.

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Caption for the figure

Figure 1: Schematic diagram of derivation of study sample

Competing interest: The authors declare that they have no competing interests.

Ethics statement: The London Multi-centre Research Ethics Committee approved the UK Obstetric Surveillance System (UKOSS) general methodology (04/MRE02/45) and the surveillance of individual near-miss maternal morbidities using UKOSS (04/MRE02/73, 10/H0717/20, 08/H0781/1, 07/MRE02/24).

Contributions to authorship: MN coded the data, carried out the analysis, and wrote the first draft of the article. KS contributed to the writing of the article. NN contributed to the analysis. MK designed the study, supervised the data collection and analysis, and contributed to writing the article. MG developed the research question, contributed to the design of the study and writing the article.

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Data sharing statement: Data sharing is governed by the National Perinatal Epidemiology Unit Data Sharing policy, available on request from Prof. Marian Knight.

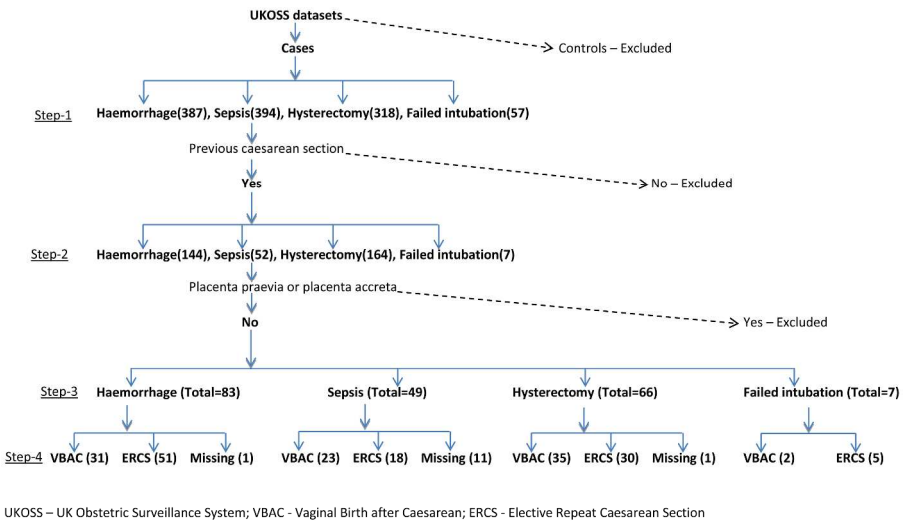

Figure 1: Schematic diagram of derivation of study sample
275x181mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page number/s
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 & 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4 & 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5 (methods of follow-up – not applicable because it is a retrospective cohort analysis)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4 & 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4 & 5
Bias	9	Describe any efforts to address potential sources of bias	5 & 6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5 & 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5 & 6
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5 & Figure-1
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Figure-1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	6

		confounders	
		(b) Indicate number of participants with missing data for each variable of interest	6, 7, 8 & Figure-1
		(c) Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures over time	6, 7 & 8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8 & 9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for exposed and unexposed groups.

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Title page

Selected maternal morbidities in women with a prior caesarean delivery planning vaginal birth or elective repeat caesarean section: a retrospective cohort analysis using data from the UK Obstetric Surveillance System

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ABSTRACT

Objective: To conduct a secondary analysis of data from the UK Obstetric Surveillance System (UKOSS) to estimate the rates of specific maternal risks associated with planned Vaginal Birth after Caesarean (VBAC) and Elective Repeat Caesarean Section (ERCS).

Design: A retrospective cohort analysis using UKOSS data from four studies conducted between 2005 and 2012.

Setting: All hospitals with consultant led maternity units in the UK.

Population: Pregnant women who had a previous caesarean section.

Method: Women who had undergone a previous caesarean section were divided into two exposure groups: planned VBAC and ERCS. We calculated the incidence of each of the four outcomes of interest with 95% confidence intervals (CI) for the two exposure groups using proxy denominators (total estimated VBAC and ERCS maternities in a given year). Incidences were compared between groups using chi squared or Fisher's exact tests and risk ratios with exact 95% CI.

Main outcome measures: Severe maternal morbidities: peripartum hysterectomy, severe sepsis, peripartum haemorrhage and failed tracheal intubation.

Results: The risks of all complications examined in both groups were low. The rates of peripartum hysterectomy, severe sepsis, peripartum haemorrhage and failed tracheal intubation were not significantly different between the two groups in absolute or relative terms.

Conclusion: While the risk of uterine rupture in VBAC and ERCS groups is well understood, this national study did not demonstrate any other clear differences in the outcomes we examined. The absolute and relative risks of maternal complications were small in both groups. Large epidemiological studies could further help to assess whether the incidence of these rare outcomes would significantly differ between VBAC and ERCS groups if a larger number of cases were to be examined. In the interim, this study provides important information to help pregnant women in their decision making process.

ARTICLE SUMMARY

Strengths and limitations of the study

- While the risk of uterine rupture associated with VBAC is known, this study estimated the rates of other specific maternal risks (peripartum hysterectomy, severe sepsis, peripartum haemorrhage and failed tracheal intubation) associated with VBAC and ERCS using existing national data from the UK Obstetrics Surveillance System (UKOSS).

- Low incidence of severe maternal morbidities in the UK makes it difficult to compare their risks between VBAC and ERCS groups. The UKOSS database of research data on rare and potentially life threatening conditions in pregnancy provided a unique opportunity to

estimate the risk of the four adverse maternal outcomes between the two groups in a cost-effective manner.

- The method used to generate the exposure groups (planned VBAC and ERCS) could have misclassified some women who were planning ERCS, but went into spontaneous labour and were thus included under the VBAC group. However, we do not anticipate a large proportion of such women.

- Cases which could not be grouped into VBAC or ERCS due to missing information could have biased the study results, mainly for the sepsis group. We have thus reported the results of a sensitivity analysis.

- A large epidemiological study with a greater number of cases would improve the power and possibly show significant differences in the outcomes, however, this study intended to take advantage of existing secondary data and the results could pave way for further studies.

Key words: Vaginal Birth after Caesarean, Elective Repeat Caesarean Section, peripartum hysterectomy, severe sepsis, peripartum haemorrhage, failed tracheal intubation.

Word count: 2413

INTRODUCTION

Current UK guidelines[1 2] advise that women who have undergone a prior delivery by caesarean section should be informed of the risks and benefits of Elective Repeat Caesarean Section (ERCS) as well as the risks and benefits of planned Vaginal Birth after Caesarean (VBAC). Such a discussion requires comprehensive evidence of the risks associated with ERCS compared to VBAC. Several studies have examined the risk of uterine rupture following VBAC,[3-5] but robust data comparing a wider range of complications of VBAC and ERCS are limited and the few randomised controlled studies[6 7] have limitations.

A previous study in the UK demonstrated uterine rupture to be associated with VBAC.[8] Uterine rupture is a rare and serious complication of VBAC, but when comparing ERCS and VBAC it is important to consider other maternal complications. The aim of this study was therefore to estimate the rates of other specific maternal risks associated with VBAC and ERCS using available national data from the UK Obstetric Surveillance System (UKOSS).

METHODS

Study Design

We conducted a retrospective cohort analysis using data from the UKOSS. Details of the UKOSS methodology are described elsewhere.[9 10] UKOSS was set up in 2005 to investigate uncommon disorders of pregnancy and 'near-miss' conditions.[10] Case notification cards are sent to all consultant-led obstetric units in the UK every month. An approach of 'nil-reporting' together with rigorous follow-up of non-responders ensures good case ascertainment. For every case reported, details are completed in a data collection form by the clinician responsible for managing the case.

Exposure groups were planned vaginal birth after caesarean (VBAC) and elective repeat caesarean section (ERCS). Women who had a history of caesarean section and underwent elective caesarean section during the current pregnancy were included in the ERCS group. Women who had a previous caesarean section, but planned vaginal delivery during current pregnancy were included in the planned VBAC group irrespective of whether they actually had a vaginal delivery.

Outcomes of interest were the maternal complications peripartum hysterectomy, severe sepsis, peripartum haemorrhage and failed tracheal intubation, which are suggested to be related to VBAC or ERCS in other studies.[6 11 12] We had national datasets within UKOSS for the outcomes (peripartum hysterectomy,[13] severe sepsis,[14] peripartum haemorrhage,[15 16] and failed tracheal intubation[17]) and thus case definitions were based on the standard case definitions used in the UKOSS (provided in Table-1).

Table-1: Definitions of outcomes included from the UKOSS national studies

Condition	Definition
Peripartum hysterectomy	Any woman giving birth to an infant and having a hysterectomy during the same clinical episode.
Peripartum haemorrhage	Cases were pregnant women of 20 weeks gestation or more identified as having ≥8 units of red blood cell transfusion within a 24 hour period.
Failed tracheal intubation	A case of failed intubation was defined as failure to achieve tracheal intubation during a rapid sequence induction for obstetric anaesthesia, thereby initiating a failed intubation drill.
Severe sepsis	Any pregnant woman (up to six weeks postpartum) diagnosed with severe sepsis (irrespective of the source of infection). A severe sepsis case would be expected to include women in one of the following groups: 1. Death related to infection or suspected infection 2. Any women requiring level 2 or level 3 critical care (or obstetric HDU type care) due to severe sepsis or suspected severe sepsis 3. A clinical diagnosis of severe sepsis – based on 2 or more of the following – a. Temperature > 38^0C or <36^0C measured on 2 occasions at least 4 hours apart b. Heart rate >100 beats/minute measured on 2 occasions at least 4 hours apart c. Respiratory rate >20/minute measured on 2 occasions at least 4 hours apart d. White cell count >$17X10^9$/L or <4 $X10^9$/L or with >10% immature band forms, measured on 2 occasions

Study sample

For each of the four maternal outcomes, for which a national dataset was available, we used the total reported cases. The datasets were from four different UKOSS studies, thus the data included were from different time-periods corresponding to the data collection period for each study (Table-2). Among the cases, those without a previous history of caesarean section were excluded. We also excluded women with placenta praevia/accreta/percreta diagnosed before delivery to exclude known confounding due to these conditions which would be regarded as an absolute indication for ERCS. The final sample of cases that remained were women with any previous caesarean sections and were further divided into planned VBAC and ERCS groups based on planned mode of delivery. If a dataset did not include information on 'planned mode of delivery', we investigated two other variables – 'woman underwent induction of labour with or without prostaglandins and/or oxytocin' and 'woman went into labour'. If either of these were 'true', we categorised the woman as planned VBAC (irrespective of her actual mode of delivery - vaginal or caesarean), otherwise ERCS. If information on any of these criteria was not available, we grouped the cases into a missing category. A schematic diagram of the process of derivation of the study samples for peripartum hysterectomy, severe sepsis, peripartum haemorrhage and failed intubation is provided in figure-1.

Statistical analyses

We calculated the incidence of each of the outcomes of interest with 95% confidence intervals (CI) for the two exposure groups, VBAC and ERCS, using the denominators - total expected VBAC and

ERCS maternities in a given year. The method of calculating proxy denominators was similar to that used by Fitzpatrick et al. to report the incidence of uterine rupture in VBAC and ERCS groups.[8] Total maternities for the UK in the study period for each of the outcomes were calculated from the annually reported birth data for England and Wales,[18] Scotland[19] and Northern Ireland.[20] From these, we calculated the estimated number of maternities likely to have undergone previous caesarean section, which was 13% of the total maternities, derived from a group of population based controls comprised of women giving birth in the UK in 2012-13. Based on proportions observed in the control group of the UKOSS uterine rupture study,[8] we further divided the maternities with previous caesarean section into women undergoing planned VBAC (44% of the total maternities with previous caesarean section) and women undergoing planned ERCS (56% of the total maternities with previous caesarean section) which gave the required proxy denominators.

In addition, we also tested whether the calculated rates in the exposure groups were significantly different from each other using chi square test or Fisher's exact test. We estimated the risk ratios and exact 95% confidence intervals (CI) to ascertain the relative risk of severe maternal morbidities in the planned VBAC compared to ERCS group. We also used descriptive statistics to compare the two exposures groups. In order to account for any differences in known and potential confounding factors, we conducted multivariable logistic regression analyses for the outcomes for which we had a control group: peripartum hysterectomy, sepsis and failed intubation. The multivariable logistic regression analysis results for uterine rupture have been published previously.[8]

In the sample for sepsis, 11 cases could not be classified into VBAC or ERCS due to missing information, and peripartum haemorrhage and hysterectomy each had one case with missing information (Figure-1). We conducted a sensitivity analysis by calculating incidence rates assuming extreme scenarios and accordingly including the missing numbers under each of the two exposure groups.

RESULTS

A total of 83 confirmed cases of peripartum haemorrhage, 66 cases of hysterectomy, 49 cases of severe sepsis and 7 cases of failed tracheal intubation were included in the study (Figure-1). The exposure groups, ERCS and planned VBAC, for each of the outcomes were not significantly different in terms of maternal age, body mass index (BMI), parity, history of previous pregnancy problems and socioeconomic status. The calculated incidence rates of the maternal complications were low and were not found to be significantly different between the two groups (Table-2). The relative risk of the severe maternal morbidities was not different between the VBAC and ERCS groups (Table-2).

177 Table-2: Rate of severe maternal morbidities in VBAC and ERCS groups

Conditions	Study period	Total Maternities for the study period	Maternities with previous Caesarean deliveries*	VBAC			ERCS			P-value of χ^2 test[¥] for outcome difference between VBAC & ERCS	Risk ratios (VBAC to ERCS) (Exact 95% CI)
				Maternities with previous CS with VBAC[ɨ]	Cases	Estimated rate per 100,000 maternities (95% CI)	Maternities with previous CS with ERCS[ƒ]	Cases	Estimated rate per 100,000 maternities (95% CI)		
Uterine rupture[8]	01/04/2009 to 30/04/2010	852206	127831	56246	116	206.7 (170.5 -247.3)	71585	20	27.9 (17.1 - 43.2)	<0.001	7.39 (4.58 - 12.55)
Peripartum hysterectomy	01/02/2005 to 29/02/2006	839785	109172	48036	35	72.9 (50.8 - 101.3)	61136	30	49.1 (33.1 - 70.0)	0.110	1.49 (0.89 - 2.50)
Sepsis	01/06/2011 to 31/05/2012	801770	104231	45861	23	50.1 (31.7 - 75.2)	58370	18	30.8 (18.3 - 48.7)	0.119	1.63 (0.84 - 3.19)
Peripartum haemorrhage	01/09/2007 to 31/03/2009[$]	1176025	152884	67269	31	46.0 (31.3 - 65.4)	85616	51	59.5 (44.3 - 78.3)	0.259	0.77 (0.48 - 1.23)
Failed intubation	01/04/2008 to 31/03/2010	1504593	195597	86062	2	2.3 (0.2 - 8.3)	109535	5	4.5 (1.4 - 10.6)	0.476	0.51 (0.05 - 3.11)

178 *Proportion of maternities likely to have undergone previous caesarean section (based on 13% calculated from the Sepsis controls, 2012-13, drawn from the general
179 population); [ɨ] Proportion of maternities with previous caesarean section (CS) likely to undergo VBAC (based on 44% calculated from UKOSS-uterine rupture controls as was
180 done by Fitzpatrick et al (8)); [ƒ] Proportion of maternities with previous caesarean section (CS) likely to undergo ERCS (based on 56% calculated from UKOSS-uterine rupture
181 controls as was done by Fitzpatrick et al (8)); VBAC – Vaginal birth after caesarean; ERCS – Elective Repeat Caesarean section; CI – Confidence Interval; [¥] For counts <5
182 Fisher's Exact test was done instead of Pearson's chi squared test, [$] The total maternities for this 18 month study were calculated as: Total maternities in 2008 + half of the
183 maternities in 2009, as the number of maternities found for 2007 (from the same sources) did not appear to be in complete agreement with the 2005-2012 trend. Owing to
184 this uncertainty in the 2007 numbers, the 2008 and 2009 maternities have been used here.

The unadjusted odds ratios for the adverse outcomes, for which we had a control group, were not significantly different between the VBAC and ERCS groups (peripartum hysterectomy: unadjusted odds ratio (uOR) = 0.86, 95% CI = 0.46 to 1.62; sepsis: uOR = 0.51, 95% CI = 0.24 to 1.07; failed intubation: uOR=0.36, 95% CI = 0.02 to 5.11). The adjusted odds of peripartum hysterectomy (adjusted odds ratio=0.92; 95%CI=0.45 to 1.91) and sepsis (adjusted odds ratio =0.51; 95% CI=0.22 to 1.19) in the ERCS group were not significantly different from that of the VBAC group after controlling for current and previous pregnancy problems, number of previous caesarean sections, pre-existing medical problems, parity, smoking status, socioeconomic status, ethnic background, marital status, BMI and maternal age. The adjusted odds ratio was not meaningful for failed intubation which had a total sample size of 15.

Sensitivity analysis for cases with missing information showed that although the rates changed slightly in the planned VBAC and ERCS groups for peripartum haemorrhage and hysterectomy, it did not result in a significant difference in the risk of the adverse outcome between the two exposure groups in either scenario. However, for severe sepsis, when all the 11 cases with missing information were included in the planned VBAC group, the rate in the VBAC group was found to be significantly higher than the rate in the ERCS group (p-value for chi square test=0.002). When these cases were included in the ERCS group, the rates of sepsis in the two exposure groups were equal (50 per 100,000 maternities).

DISCUSSION

This study using the UKOSS data and a nested retrospective cohort design did not find a significant difference in the incidence and relative risk of adverse maternal outcomes between the VBAC and ERCS groups. However, the incidence rates of these outcomes were low.

Strengths and Limitations

Low incidence of severe maternal morbidities in the UK makes it difficult to compare their risks between VBAC and ERCS groups. The UKOSS database of research data on rare and potentially life threatening conditions in pregnancy provided a unique opportunity to estimate the risk of four adverse maternal outcomes between the two groups in a cost-effective manner. The method used to generate the exposure groups (planned VBAC and ERCS) could have misclassified some women who were planning ERCS, but went into spontaneous labour and were thus included under the VBAC group. However, we do not anticipate a large proportion of such women. Cases which could not be grouped into VBAC or ERCS due to missing information could have biased the study results, mainly for the sepsis group. We have thus reported the results of a sensitivity analysis. Further, including a proxy denominator calculated from a control population comprising of women giving birth in 2012-13 assumes that the rate of caesarean sections and proportions of VBAC and ERCS did not

vary over a time-period between 2005-06 and 2012-13. Considering that population level caesarean section rates for the UK per year were not available from any source, we employed this alternative method used in a previous study by Fitzpatrick et al.[8] Although we accounted for known confounders for each outcome in the multivariable logistic regression analyses, the results cannot be interpreted with certainty due to the small sample sizes. While we excluded women diagnosed antenatally with placenta praevia/accreta/percreta, we did not have information on other potential absolute indications for ERCS, which could bias the study results. A longer term study with a greater number of cases would improve the power and possibly show significant differences in the outcomes, however, this study intended to take advantage of existing secondary data and the results could pave the way for further studies. Furthermore, the adverse outcomes presented in this study are immediate risks associated with the current pregnancy in the ERCS and VBAC groups and we cannot comment on the risk of morbidity in future pregnancies.

While the higher risk of uterine rupture associated with planned VBAC is known,[4 8 21 22] studies from different parts of the world have reported variable relative and absolute risks of other maternal complications in ERCS versus VBAC groups. Similar to the findings of this study, a multicentre prospective cohort study in the USA,[4] a Canadian study[11] and a meta-analysis of literature published between 2000 and 2007[22] did not find any difference in the risk of hysterectomy between those that underwent a trial of labour and those that had an elective caesarean section. However, a decision model analysis conducted by Paré et al. suggested that the decision to undergo VBAC or ERCS among women with one prior caesarean section should be guided by the number of planned subsequent pregnancies.[23] Based on an analysis of risk of hysterectomy, the authors suggested that ERCS should be the strategy of choice for women planning one additional pregnancy, but for women who desire two or more subsequent pregnancies VBAC should be attempted to minimise morbidity associated with multiple caesarean sections.[23]

In contrast to our findings, a study in Australia found a 63% lower risk of peripartum haemorrhage in the planned ERCS compared to planned VBAC group [6] and the multicentre study from the USA demonstrated a higher odds of transfusion in the VBAC group compared with the ERCS.[4] However, a meta-analysis suggested a lower risk of peripartum haemorrhage in the VBAC group[21] and other studies did not show any difference.[11 22] A prospective cohort study of obese women using data collected through the UKOSS did not find any difference in anaesthetic complications between ERCS and planned VBAC groups,[24] but this finding cannot be generalised to non-obese women.

Conclusion

While the risk of uterine rupture in VBAC and ERCS groups is well understood, this national study did not demonstrate any other clear differences in the outcomes we examined. The absolute and

relative risks of maternal complications were small in both groups which is important information to help pregnant women in their decision making process. Large epidemiological studies with a longer time-period for data collection are required to assess whether the incidence of these rare outcomes would significantly differ between VBAC and ERCS groups if a larger number of cases were to be examined. In the interim, this study contributes additional information to the process of individualised decision-making about mode of delivery by women who have had a previous delivery by caesarean section, as recommended in current guidance.

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Caption for the figure

Figure 1: Schematic diagram of derivation of study sample

Competing interest: The authors declare that they have no competing interests.

Ethics statement: The London Multi-centre Research Ethics Committee approved the UK Obstetric Surveillance System (UKOSS) general methodology (04/MRE02/45) and the surveillance of individual near-miss maternal morbidities using UKOSS (04/MRE02/73, 10/H0717/20, 08/H0781/1, 07/MRE02/24).

Contributions to authorship: MN coded the data, carried out the analysis, and wrote the first draft of the article. KS contributed to the writing of the article. NN contributed to the analysis. MK designed the study, supervised the data collection and analysis, and contributed to writing the article. MG developed the research question, contributed to the design of the study and writing the article.

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Data sharing statement: Data sharing is governed by the National Perinatal Epidemiology Unit Data Sharing policy, available on request from Prof. Marian Knight.

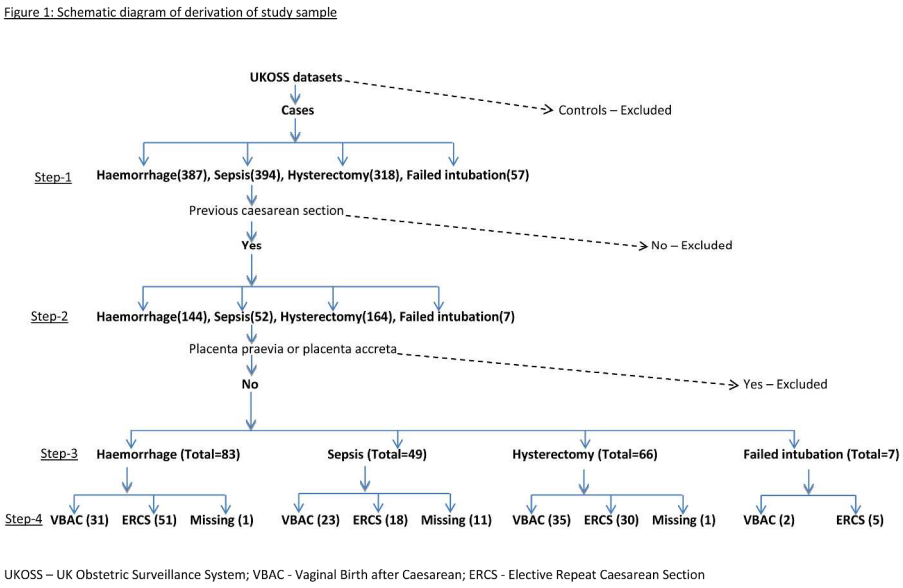

Figure 1: Schematic diagram of derivation of study sample
275x181mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page number/s
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1 & 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	4
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	4 & 5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	5 (methods of follow-up – not applicable because it is a retrospective cohort analysis)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Not applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4 & 5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	4 & 5
Bias	9	Describe any efforts to address potential sources of bias	5 & 6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5 & 6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5 & 6
		(*b*) Describe any methods used to examine subgroups and interactions	Not applicable
		(*c*) Explain how missing data were addressed	6
		(*d*) If applicable, explain how loss to follow-up was addressed	Not applicable
		(*e*) Describe any sensitivity analyses	6
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	5 & Figure-1
		(b) Give reasons for non-participation at each stage	Not applicable
		(c) Consider use of a flow diagram	Figure-1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential	6

		confounders	
		(b) Indicate number of participants with missing data for each variable of interest	6, 7, 8 & Figure-1
		(c) Summarise follow-up time (eg, average and total amount)	Not applicable
Outcome data	15*	Report numbers of outcome events or summary measures over time	6, 7 & 8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	8
		(*b*) Report category boundaries when continuous variables were categorized	Not applicable
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	8 & 9
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for exposed and unexposed groups.