Uterine exteriorization compared with *in situ* repair for Cesarean delivery: a systematic review and meta-analysis

Extériorisation de l'utérus vs. réparation *in situ* lors de césarienne: revue systématique et méta-analyse

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Abstract

Purpose To compare perioperative outcomes following uterine exteriorization vs *in situ* repair after Cesarean delivery.

Source We searched CENTRAL, MEDLINE®, EMBASE™, CINAHL, and ClinicalTrials.gov for randomized clinical trials that included any of our primary outcomes (blood loss, intraoperative nausea, vomiting, and pain), or secondary outcomes.

Principal findings Sixteen studies were included. In total, 9,736 subjects underwent exteriorization, 9,703 had *in situ* uterine repair. Estimated blood loss was not statistically different between the two methods of uterine repair (mean difference [MD], -61.03 mL; 95%

confidence interval [CI], -127.34 to 5.28); however, exteriorization reduced the decrease in hemoglobin (MD, -0.14 g·dL $^{-1}$; 95% CI, -0.22 to -0.07). Estimated blood loss was reduced with exteriorization in a sensitivity analysis that excluded an outlier study. There was no statistically significant difference in intraoperative nausea (odds ratio [OR], 0.99; 95% CI, 0.74 to 1.34), vomiting (OR, 0.94; 95% CI, 0.66 to 1.35), or pain (OR, 1.52; 95% CI, 0.86 to 2.71) between the two repair techniques. *In situ* repair was associated with faster return of bowel function (MD, 3.09 hr; 95% CI, 2.21 to 3.97). An association between exteriorization and endometritis did not reach statistical significance (OR, 1.25; 95% CI, 0.96 to 1.62).

Conclusion Uterine repair by exteriorization may reduce blood loss and the associated decrease in hemoglobin, but the difference may not be clinically relevant. There was no statistically significant difference between the two repair techniques for intraoperative nausea, vomiting, or pain. *In situ* repair may be associated with a faster return of bowel function.

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Résumé

Objectif Notre objectif était de comparer les résultats périopératoires suivant une extériorisation de l'utérus vs. une réparation *in situ* lors de césarienne.

Source Nous avons mené des recherches dans les bases de données CENTRAL, MEDLINE®, EMBASE™, CINAHL et ClinicalTrials.gov afin d'en extraire les études cliniques incluant un ou plusieurs de nos critères d'évaluation principaux (pertes sanguines, nausées, vomissements et douleurs péroperatoires) ou secondaires.

Constatations principales Seize études ont répondu à nos critères. Au total, 9736 patientes ont subi une extériorisation, et 9703 ont subi une réparation utérine

in situ. Aucune différence significative d'un point de vue statistique n'a été rapportée en matière de pertes sanguines estimées entre les deux méthodes de réparation utérine (différence moyenne [DM], $-61,03$ mL; intervalle de confiance [IC] 95 %, $-127,34$ à $5,28$); toutefois, l'extériorisation a réduit la baisse du taux d'hémoglobine (DM, $-0,14$ g·dL⁻¹; IC 95 %, $-0,22$ à $-0,07$). Lors d'une analyse de sensibilité excluant une étude aberrante, les pertes sanguines estimées étaient réduites lors des interventions d'extériorisation. Aucune différence significative d'un point de vue statistique n'a été observée en matière de nausées (rapport de cotes [RC], 0,99; IC 95 %, 0,74 à 1,34), de vomissements (RC, 0,94; IC 95 %, 0,66 à 1,35) ou de douleurs (RC, 1,52; IC 95 %, 0,86 à 2,71) peropératoires entre les deux techniques de réparation. La réparation *in situ* a été associée à un rétablissement plus rapide du transit intestinal (DM, 3,09 h; IC 95 %, 2,21 à 3,97). Une association entre l'extériorisation et l'endométrite ne s'est pas montrée statistiquement significative (RC, 1,25; IC 95 %, 0,96 à 1,62).

Conclusion La réparation de l'utérus par extériorisation pourrait réduire les pertes sanguines et la réduction associée du taux d'hémoglobine, mais la différence pourrait ne pas avoir de pertinence clinique. Il n'y a eu aucune différence significative d'un point de vue statistique entre les deux techniques de réparation en matière de nausées, de vomissements et de douleurs peropératoires. La réparation *in situ* pourrait être associée à un rétablissement plus rapide du transit intestinal.

Cesarean delivery (CD) is one of the most common surgeries performed throughout the world. In 2013, the CD rate in the United States was 32.7%, with an increase of nearly 60% from 1996-2009.¹ Similar statistics exist in Canada, with stable rates since 2007 (26.9% in 2010).² Many surgical techniques exist to perform CD, but the most optimal technique to limit maternal morbidity is still subject to debate.

One aspect of this debate relates to the method of uterine repair following delivery and its potential impact on maternal morbidity. Surgeons who favour repair of the uterus by exteriorization claim better surgical visualization and faster and simpler repair. Although the effect of exteriorization on the control of hemostasis is controversial,^{3,4} opponents to exteriorization are concerned about the side effects of uterine traction, including nausea and vomiting, pain, hemodynamic instability, trauma to the fallopian tubes, infection, and rupture or reduced flow of the utero-ovarian veins with consequent thrombosis or embolism.⁵⁻⁸

A recent meta-analysis⁴ published in 2009 compared the two methods of uterine repair in over 3,000 women, and results showed no difference in outcomes between the two repair techniques. Since the 2009 publication, three large randomized controlled trials and two smaller trials have been published,⁹⁻¹³ increasing the number of women studied to over 16,000. In addition, four of these five new trials^{9,10,12,13} included return of bowel function, an outcome that was lacking in previously analyzed trials. Therefore, we performed a systematic review and meta-analysis of randomized controlled trials to compare perioperative outcomes with uterine exteriorization vs *in situ* repair following CD.

Methods

The current meta-analysis adhered to the PRISMA guidelines for reporting meta-analyses.¹⁴ The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE® (PubMed), EMBASE™, CINAHL, and ClinicalTrials.gov were searched. The date of the last search was May 3, 2015. The MeSH term “cesarean section” and its different spellings were combined with text searches for “repair”, “uterus”, “exteriorization” and their different spellings and synonyms. The results of these searches were combined with a sensitive methodological filter for randomized trials, meta-analyses, and systematic reviews. Our PubMed search strategy is available in Appendix A (available as Electronic Supplementary Material).

No restrictions were placed on the dates of publication other than those intrinsic to the database being searched. The reference lists from retrieved randomized trials were screened to identify additional trials, as were recent tables of contents of major obstetric journals.^A No restrictions with respect to language were included. Unpublished meeting abstracts were not searched; only published randomized controlled trials were sought. An attempt was made to contact authors regarding any clarification of primary outcome measures.

We included randomized controlled trials comparing *in situ* uterine repair with extra-abdominal uterine repair

^A January 1, 2013 - September 30, 2014 - Acta Obstetrica et Gynecologica Scandinavica, Archives of Gynecology and Obstetrics, British Journal of Obstetrics and Gynaecology, Clinical & Experimental Obstetrics & Gynecology, International Journal of Obstetric Anesthesia, Infection Disease in Obstetrics and Gynecology, International Journal of Gynecology & Obstetrics, Journal of the American College of Surgeons, Obstetrics & Gynecology, Surgery, Gynecology & Obstetrics, West African Journal of Medicine.

during CD. The primary outcomes for this review were blood loss (blood transfusion, reduction in hemoglobin, estimated blood loss) and the incidence of intraoperative complications (nausea, vomiting, and pain). Secondary outcomes included return of bowel function, postoperative infection (endometritis, wound infection), operative time, length of hospital stay, fever, postoperative pain, use of postoperative analgesics, and hemodynamic instability. Studies were included if they reported any of our primary or secondary outcomes.

Data extraction and assessment

Data were extracted independently by two authors (V.Z., J.C.B.). An initial data sheet with a list of possible outcomes was created by one author (A.H.), and the list was modified during data extraction. The data extracted included number of patients, type of anesthesia, antibiotic prophylaxis, and outcomes, including intraoperative complications (nausea, vomiting, pain, hypotension, tachycardia), blood loss (drop in hemoglobin, estimated blood loss, blood transfusion, decrease in hematocrit), return of bowel function, operative time, length of hospital stay, and postoperative infections and pain. When data were presented as medians, ranges, and confidence intervals (CI), the mean and standard deviation (SD) were calculated as per Hozo *et al.*¹⁵ Two reviewers (V.Z., J.C.B.) independently assessed risk of bias of the included studies using the Cochrane Collaboration tool for assessing risk of bias.¹⁶ The six criteria for judging risk of bias were scored separately as high, low, or unclear. In the event that agreement could not be reached between the two reviewers, the opinion of a third reviewer (R.G.) was required. A sensitivity analysis was performed on studies that scored unclear or high risk of bias on all risk of bias elements.

All data pertaining to the predetermined outcome measures were transcribed to RevMan version 5.3.5 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for meta-analysis. The data were presented qualitatively if meta-analytic methods were not possible. All data were analyzed using the DerSimonian and Laird random-effects model.¹⁷ Continuous variables were reported as mean difference (MD) with 95% CI, while dichotomous data were reported as odds ratio (OR) with 95% CI. Heterogeneity was assessed with the I^2 statistic that describes the percentage variation across studies due to heterogeneity rather than chance.¹⁸ $I^2 > 50\%$ was considered to indicate significant heterogeneity. For outcomes with significant heterogeneity, we visually inspected forest plots for outliers and examined those study protocols for potential methodological differences that could explain the discrepancies. If we perceived an outlier with a significant methodological difference that might explain the heterogeneity, we performed a sensitivity

analysis excluding this outlier study. Publication bias was formally assessed with Egger's test¹⁹ for all outcomes included in at least ten studies²⁰⁻²² using the comprehensive meta-analysis software, version 2.0.

Results

The results of the literature search are outlined in Fig. 1. After screening and excluding articles that were not related to our topic, 17 manuscripts were selected for in-depth

Fig. 1 PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of literature search and article selection

Table 1 Study characteristics of included studies

Study	Specialty of primary author	Patients		Primary Outcome	General Anesthesia (GA) vs Regional Anesthesia (RA)		Antibiotic Prophylaxis
		Exteriorized	In Situ		Exteriorized	In Situ	
Abalos <i>et al.</i> ¹¹ 2013	Unclear	4,899	4,896	Composite of death, maternal infectious morbidity, further operative procedures, or blood transfusion	GA: 487 RA: 4,412	GA: 461 RA: 4,434	Anesthesiologists choice
Baksu <i>et al.</i> ²⁵ 2005	Obstetrics	424	416	Postoperative hemoglobin and hematocrit	Not reported	Not reported	1 g cefazolin after cord clamping
Coutinho <i>et al.</i> ³¹ 2008	Unclear	325	312	None declared	RA: 325	RA: 312	1 g cefazolin after cord clamping
Doğanay <i>et al.</i> ¹² 2010	Unclear	2,463	2,462	Hemoglobin concentration	RA: 2,463	RA: 2,462	1 g cefazolin after cord clamping
Edi-Osagie <i>et al.</i> ²⁹ 1998	Obstetrics	100	94	Intraoperative pulse rate, mean arterial blood pressure and oxygen saturation, hemoglobin concentration, incidence of intraoperative vomiting, pain, intra- and postoperative complications, febrile and infectious morbidity, immediate and late puerperal pain, satisfaction	GA: 46 RA: 54	GA: 31 RA: 63	1.5 g cefuroxime and 500 mg metronidazole after cord clamping
El-Khayat <i>et al.</i> ¹³ 2014	Obstetrics	500	500	Operative time	RA: 500	RA: 500	ceftriaxone 1 g after cord clamping
Ezechi <i>et al.</i> ³² 2005	Unclear	65	62	Operative time	Not reported	Not reported	ampicillin, gentamicin, and metronidazole for 5 days
Hershey <i>et al.</i> ²⁴ 1978	Obstetrics	159	149	Number of febrile days, hospital stay	GA: not reported RA: 42	Not reported	Surgeon's preference
Magann <i>et al.</i> ²⁶ 1993a	Obstetrics	50	50	Blood loss	GA: 24 RA: 27	GA: 24 RA: 26	Not reported
Magann <i>et al.</i> ²⁷ 1993b	Obstetrics	53	55	Infectious morbidity	Not reported	Not reported	Not used
Magann <i>et al.</i> ²⁸ 1995	Obstetrics	142	142	Infectious morbidity	GA: 71 RA: 71	GA: 55 RA: 87	2 g cefazolin
Nafisi ⁸ 2007	Anesthesia	102	104	Postoperative pain	GA: 102	GA: 104	1 g cefazolin after cord clamping
Orji <i>et al.</i> ⁹ 2008	Obstetrics	105	105	Blood loss	GA: 84 RA: 21	GA: 78 RA: 27	Not reported
Ozbay ¹⁰ 2011	Obstetrics	171	167	Blood loss	GA: 171	GA: 167	1 g cefazolin after cord clamping
Siddiqui <i>et al.</i> ⁷ 2007	Anesthesia	39	40	Post-delivery nausea and vomiting	RA: 39	RA: 40	1 g cefazolin after cord clamping
Wahab <i>et al.</i> ³⁰ 1999	Obstetrics	139	149	Blood loss	GA: 8 RA: 131	GA: 10 RA: 139	Not reported

Table 2 The Cochrane Collaboration tool for assessing risk of bias¹⁶

	El-Khayat ¹³ 2014	Abalos ¹¹ 2013	Ozbay ¹⁰ 2011	Doganay ¹² 2010	Coutinho ³¹ 2008	Orji ⁹ 2008	Nafisi ⁸ 2007	Siddiqui ⁷ 2007	Ezechi ³² 2005	Baksu ²⁵ 2005	Wahab ³⁰ 1999	Edi-Osagie ²⁹ 1998	Magann ²⁸ 1995	Magann ²⁶ 1993a	Magann ²⁷ 1993b	Hershey ²⁴ 1978
Randomization sequence generation	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Unclear
Allocation concealment	Low	High	Low	Low	Low	Low	Low	Low	Unclear	Low	Low	Low	Low	Unclear	Low	Unclear
Blinding of participants	Low	High	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear
Blinding of outcome assessment	Unclear	High	Unclear	Unclear	High	Low	Unclear	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear	Unclear	Unclear
Incomplete outcome data	Low	Low	Low	Low	Low	High	High	Low	Low	Low	Low	Unclear	High	High	Low	High
Selective reporting	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	High

full-text review, and 16 of these were deemed eligible for inclusion in this systematic review (Table 1). One study could not be included because there was insufficient data in the article for analysis.²³ Our attempts to access additional data directly from these authors and through our research library over several occasions were unsuccessful. Risk of bias of the included studies is presented in Table 2. The criteria in one study²⁴ were deemed unclear or high risk of bias in all categories. In total, 9,736 subjects underwent exteriorization for uterine repair, while 9,703 subjects had *in situ* repair. Four studies subdivided the exteriorization and *in situ* repair groups by distinguishing between manual and spontaneous removal of the placenta.²⁵⁻²⁸ For the purpose of this meta-analysis, the results of these subgroups were combined to compare results solely for exteriorization and *in situ* uterine repair. A summary of pooled results for all outcomes is presented in Table 3.

Primary outcomes

Blood transfusion

Pooled results from ten studies (17,568 patients)^{9,11-13,27-32} did not show a significant difference between groups for blood transfusion (OR, 1.07; 95% CI, 0.48 to 2.41; $I^2 = 51\%$) (Table 3, Fig. 2A). The funnel plot for blood transfusion is available in Appendix B (available as Electronic Supplementary Material).

Reduction in hemoglobin

Six studies including 7,585 patients reported a reduction in hemoglobin data.^{10,12,13,25,29,30} Pooled results showed a statistically significant higher drop in hemoglobin with *in situ* repair (MD, -0.14 g.dL^{-1} ; 95% CI, -0.22 to -0.07) (Table 3, Fig. 2B). Significant heterogeneity was observed among studies for this outcome ($I^2 = 82\%$); however, no outliers with methodological differences accounted for this heterogeneity, and therefore, a sensitivity analysis was not conducted. A seventh study reported preoperative and 48-hr postoperative hemoglobin but did not report the standard deviation for the drop in hemoglobin for the two groups; therefore, the study could not be included in the analysis.⁸ This study reported that the drop in hemoglobin did not differ significantly between the groups.

Estimated blood loss

Pooled results for estimated blood loss from six studies (908 patients)^{7,9,26-28,32} showed no statistically significant difference between the two repair techniques (MD, -61.03 mL ; 95% CI, -127.34 to 5.28 ; $I^2 = 76\%$) (Table 3,

Table 3 Primary and secondary outcomes and sensitivity analysis of two outcomes that exclude data from a study²⁴ with possible high risk of bias

Primary Outcomes	Definition	# of studies	# of patients	OR or MD	95% CI	I ²	Egger's test
Blood Transfusions	Any transfusion of blood. ^{9,12,13,27-32} Transfusion of more than 1 unit of blood. ¹¹	10 ^{9,11-13,27-32}	17,568	OR 1.07	0.48 to 2.41	51%	<i>P</i> = 0.75
Drop in hemoglobin	(pre-op Hg) - (48 hr PO Hg). ^{10,12,25,30} (pre-op Hg) - (24 hr PO Hg). ¹³ (pre-op Hg) - (3 day PO Hg). ²⁹	6 ^{10,12,13,25,29,30}	7,585	MD -0.14 g·dL⁻¹	-0.22 to -0.07	82%	N/A
Estimated blood loss	Blood in the suction before irrigation + weight of sponges, lap pads, drapes. ^{7,9,26-28,32} Calculation using a formula including pre-op Hct, PO Hct, and blood volume. ⁷ Evaluation by blinded anesthesiologist. ³²	6 ^{7,9,26-28,32}	908	MD -61.03 mL	-127.34 to 5.28	76%	N/A
Intraoperative nausea	N/A	5 ^{7,13,29-31}	2,071	OR 0.99	0.74 to 1.34	36%	N/A
Intraoperative vomiting	N/A	5 ^{7,13,29-31}	2,075	OR 0.94	0.66 to 1.35	22%	N/A
Intraoperative pain	N/A	3 ^{7,29,30}	439	OR 1.52	0.86 to 2.71	0%	N/A
Secondary Outcomes	Definition	# of studies	# of patients	OR or MD	95% CI	I ²	Egger's test
Return of bowel function	Time (hr) to auscultate bowel sounds. ^{9,12,13} Time (hr) to intestinal gas evacuation. ¹⁰	4 ^{9,10,12,13}	6,473	MD 3.09 hr	2.21 to 3.97	95%	N/A
Endometritis	Fever >38°C × 2 separate occasions ± uterine tenderness or foul smelling lochia. ^{12,13,25,27,28,31}	9 ^{11-13,24,25,27,28,31,32}	17,968	OR 1.25	0.96 to 1.62	52%	N/A
Endometritis (Sensitivity analysis)	No fever in definition. ³² Antibiotic treatment. ¹¹ No definition. ²⁴	8 ^{11-13,25,27,28,31,32}	17,660	OR 1.35	1.06 to 1.73	41%	N/A
Wound infection	N/A	10 ^{8,9,11-13,24,29-32}	17,496	OR 0.96	0.59 to 1.56	87%	<i>P</i> = 0.51
Wound infection (Sensitivity analysis)		9 ^{8,9,11-13,29-32}	17,188	OR 1.03	0.62 to 1.70	88%	N/A
Operative time	Mean time in minutes	13 ^{7,9-13,26-32}	18,085	MD 1.45 min	-0.80 to 3.71	99%	<i>P</i> = 0.76
Hospital stay	Mean number of days	9 ^{9-13,28-30,32}	17,161	MD 0.13 days	-0.10 to 0.37	99%	N/A
Fever	Temperature >38°C × > 24 hr, not on PO day 1. ^{8,9,29} Temperature >38.5°C × > 6 hr. ³⁰ Antibiotic treatment. ¹¹	5 ^{8,11,29,30,32}	10,610	OR 1.03	0.73 to 1.44	0%	N/A

CI= confidence interval; Hct = hematocrit; Hg = hemoglobin; MD = mean difference; N/A = not applicable; OR = odds ratio; PO = postoperative; pre-op = preoperative

Statistically significant differences are presented in **bold**

Fig. 2C). Visual inspection of the forest plot revealed a potential outlier study²⁸ in which the authors had divided the study population into four groups, further differentiating between manual and spontaneous removal of the placenta. Removal of data from this study eliminated heterogeneity for this outcome ($I^2 = 0\%$) and resulted in a statistically significant difference of the pooled results

favouring exteriorization (MD, -89.33 mL; 95% CI, -119.86 to -58.79).

Intraoperative nausea and vomiting

Four studies reported intraoperative nausea and vomiting as separate outcomes.^{13,29-31} We contacted one of the

Fig. 2 Forest plots describing effect of uterine exteriorization on A) Likelihood of blood transfusion B) Pre- to post-operative fall in hemoglobin ($\text{g} \cdot \text{L}^{-1}$), and C) Estimated blood loss (mL)

authors of a fifth study (Dr. J.C. Carvalho) to retrieve their unpublished data on nausea and vomiting separately.⁷ Intraoperative nausea and vomiting was a primary outcome in only one study,⁷ which reported a statistically significant increased risk of intraoperative nausea in the exteriorization group (OR, 2.95; 95% CI, 1.04 to 8.34). Nevertheless, pooled results of the two repair techniques did not show a statistically significant difference in intraoperative nausea for 2,071 patients (OR, 0.99; 95% CI, 0.74 to 1.34; $I^2 = 36\%$) (Table 3, Fig. 3A) or in intraoperative vomiting for 2,075 patients (OR, 0.94; 95% CI, 0.66 to 1.35; $I^2 = 22\%$) (Table 3, Fig. 3B). A sixth study reported incomplete data regarding intraoperative

nausea and vomiting and could not be included in the analysis.²⁴

Intraoperative pain

Overall pooled results from three studies (439 patients)^{7,29,30} did not show a statistically significant difference in the incidence of intraoperative pain between the two repair techniques (OR, 1.52; 95% CI, 0.86 to 2.71; $I^2 = 0\%$) (Table 3, Fig. 4), but the confidence intervals were wide, suggesting that our data are insufficient to draw definitive conclusions about this outcome.

Fig. 3 Forest plots describing the effect of uterine exteriorization on the likelihood of intraoperative A) Nausea and B) Vomiting

Secondary outcomes

Return of bowel function

Pooled results for return of bowel function from four studies^{9,10,12,13} including 3,234 patients showed considerable heterogeneity for this outcome (MD, 3.09 hr; 95% CI, 2.21 to 3.97; $I^2 = 95\%$) (Table 3, Fig. 5). Nevertheless, while the heterogeneity was significant, no outlier studies with methodological differences were identified, and therefore, we did not conduct a sensitivity analysis. Three of the four studies strongly favoured *in situ* repair with statistically significant differences reported,^{9,12,13} whereas the fourth study showed a trend favouring *in situ* repair.¹⁰ Two of the four studies reporting this outcome accounted for over 90% of the patients and showed statistically significant results favouring *in situ* repair (MD, 3.9 hr; 95% CI, 3.87 to 3.93¹² and MD, 3.0 hr; 95% CI, 2.71 to 3.29).¹³

Additional outcomes

Pooled results and definitions for the outcomes of endometritis, wound infection, operative time, hospital stay, and fever are presented in Table 3. Funnel plots for operative time and wound infection are available in Appendix B (available as Electronic Supplementary

Material). One study reported data for operative time, hospital stay, blood transfusions, and fever that could not be included in the analysis of these outcomes due to lack of reporting mean, standard deviation, or number of patients with the outcome of interest.²⁴ This same study was evaluated to have unclear or high risk of bias in all of the risk of bias criteria, and thus, a sensitivity analysis was performed for the two outcomes that included data from this study, i.e., endometritis and wound infection (Table 3).

Many studies reported postoperative pain outcomes (including pain at six hours,^{13,31} ten hours,⁸ 24 hr,^{29,31} 34 hr,⁸ or 36 hr³¹ postoperatively), the number of analgesic doses,^{9,31,32} the need for postoperative rescue analgesics,^{8,11-13,31} and opioid consumption.¹⁰ A detailed summary of these results for postoperative pain outcome is presented in Table 4. The heterogeneous presentation of postoperative analgesia regimens and postoperative pain measures prevented us from conducting a formal meta-analysis on these outcomes.

Three studies reported outcomes involving heart rate and blood pressure during uterine repair.^{7,13,29} One study⁷ reported a significant difference in tachycardia occurring in 18% of the exteriorization group vs 3% of the *in situ* group (OR, 8.53; 95% CI, 0.99 to 394.12). A second study¹³ that defined tachycardia as a pulse > 90 beats·min⁻¹ and a third study²⁹ that measured the pulse difference during uterine repair found no significant difference between groups. Due

Fig. 4 Forest plot describing the effect of uterine exteriorization on the likelihood of patient report of intraoperative pain

Fig. 5 Forest plot describing the effect of uterine exteriorization of the days until return of bowel function following delivery

to the different presentation of heart rate outcomes, we could not conduct a meta-analysis. None of the three studies found a significant difference in the incidence of hypotension^{7,13} or mean arterial pressure²⁹ between groups.

Discussion

In our review, we analyzed 16 randomized controlled trials evaluating uterine repair by exteriorization *vs in situ* repair. Exteriorization may be associated with a smaller decrease in hemoglobin and less estimated blood loss. There was no statistically significant difference in the need for blood transfusion. There were no significant differences between the two repair techniques in the primary outcomes of intraoperative nausea, vomiting, or pain. Regarding secondary outcomes, *in situ* repair may be associated with less endometritis and a faster return of bowel function.

A Cochrane review comparing the two methods of uterine repair was published in 2004 and was subsequently updated in 2011 without a change in conclusions.³ The updated review included six randomized controlled trials comparing exteriorization of the uterus with *in situ* repair. The authors found no statistically significant difference in complications, except for reduced febrile morbidity with uterine exteriorization and a shorter hospital stay with *in situ* repair. No definitive conclusions could be made, however, due to the available studies being too few and too limited in scope.³ In 2009, a systematic review and

meta-analysis that included 11 randomized controlled trials was published.⁴ The primary endpoints included intraoperative nausea, vomiting, hypotension, and pain as well as blood transfusion and infectious complications. The authors found no difference in complication rates between exteriorized and *in situ* uterine repair. Nevertheless, they included a study that failed all five quality indicators they assessed,²⁴ signifying poor quality, and they did not perform a sensitivity analysis similar to those we performed in this updated meta-analysis.

Better control of hemostasis is among the reasons why some surgeons favour uterine repair by exteriorization. With the exception of three of the 16 included studies,^{11,24,31} blood loss was reported by either a reduction in hemoglobin or estimated blood loss, although the method of estimating blood loss varied greatly between studies. It should be emphasized that, in all but one study³² reporting estimated blood loss, the difference in blood loss between groups was less than 100 mL. This minimal clinical impact is shown by the lack of a difference in blood transfusions between repair groups.

The primary concerns of opponents of uterine exteriorization are intraoperative nausea, vomiting, pain, and hemodynamic instability, yet few randomized controlled trials have measured these outcomes and only one measured these as primary outcomes.⁷ Three studies included patients who underwent emergent CDs but did not report a standardized anesthetic technique that might impact the occurrence of intraoperative nausea and vomiting.²⁹⁻³¹ Therefore, the results of those studies

Table 4 Postoperative pain outcomes

Study	Outcome	Measure	Results
El-Khayat <i>et al.</i> ¹³	Need for post-op rescue analgesic	# of patients requiring rescue pethidine 50 mg	Ext: 100 (20%) In: 50 (10%), $P < 0.001$
	Pain 6 hr post-op	Visual analogue scale rating $>5/10$	Ext: 165 (33%) In: 115 (23%), $P = 0.001$
Abalos <i>et al.</i> ¹¹	Need for post-op rescue analgesic	# of patients requiring rescue analgesia, type/dose not reported	Ext: 204 (4%), In: 188 (4%), RR: 1.08, 99% CI: 0.84 to 1.40
Ozbay ¹⁰	Opioid consumption	Pethidine consumed, either 50 or 100 mg IM given if pain $>6/10$	Ext: 62.3 (21.6), In: 64.4 (22.7), $P = 0.385$
Doganay <i>et al.</i> ¹²	Need for post-op rescue analgesic	# of patients who required rescue tenoxicam, 20 mg doses	Ext: 859 (34.8%), In: 428 (17.4%), $P = 0.002$
Coutinho <i>et al.</i> ³¹	Number of analgesic doses	# of patients who used > 2 doses of dipyron	Ext: 103 (31.7%), In: 95 (30.4%), $P = 0.73$
	Need for post-op rescue analgesic	# of patients requiring rescue codeine (30 mg) and paracetamol	Ext: 10 (3.1%), In: 6 (1.9%), $P = 0.35$
	Pain 6 hr post-op	Visual analogue scale rating $>5/10$	Ext: 106 (32.6%), In: 72 (23.1%), $P = 0.026$
	Pain 24 hr post-op	Visual analogue scale rating $>5/10$	Ext: 62 (19.1%), In: 72 (23.1%), $P = 0.22$
	Pain 36 hr post-op	Visual analogue scale rating $>5/10$	Ext: 47 (14.5%), In: 47 (15.1%), $P = 0.83$
Orji <i>et al.</i> ⁹	Number of analgesic doses	# of patients requiring rescue analgesia, type/dose not reported	Ext: 4.2 (0.8), In: 4.7 (1.2), $P = 0.004$
Nafisi ⁸	Need for post-op rescue analgesic	# of patients requiring rescue opioids, type/dose not reported	Ext: 64 (62%), In: 15 (14%), $P < 0.001$
	Pain 10 hr post-op	Visual analogue scale (mm)	Ext: 66.7 (11.3), In: 43.5 (13.2), $P < 0.001$
	Pain 34 hr post-op	Visual analogue scale (mm)	Ext: 44.6 (10.5), In: 23.9 (10.2), $P < 0.001$
Ezechi <i>et al.</i> ³²	Number of analgesic doses	Analgesia consumed, type/dose not reported	Ext: 5.7 (1.2), In: 5.6 (1.4), $P = 0.799$
Edi-Osagie <i>et al.</i> ²⁹	Pain 24 hr post-op	Likert scale from 1-10, increasing with severity of pain	Ext: 5.9 (5.2 to 6.5), In: 5.2 (4.6 to 5.7), $P = 0.082$

Data presented as mean (SD), n (%), or mean (95% confidence interval [CI]). Ext = exteriorization; IM = intramuscular; In = *in situ* repair, post-op = postoperative; RR = relative risk

regarding these outcomes must be interpreted with caution. It is noteworthy that studies with nausea and vomiting as primary outcomes favour *in situ* repair.^{7,33} Clearly, more randomized controlled trials examining nausea and vomiting as primary endpoints are necessary before a definite conclusion can be made regarding the impact of the repair technique on the risk of intraoperative nausea and vomiting.

Few randomized controlled trials on uterine repair have reported intraoperative pain. The three studies in our analysis that reported this outcome assessed pain with a numerical rating scale (0 to 10) but dichotomized the data into patients either experiencing or not experiencing pain.^{7,29,30} The term intraoperative pain is quite broad and therefore differentiation of the intensity, quality, and timing of intraoperative pain needs to be properly evaluated in order to adequately assess its relationship with a uterine repair technique. Regarding postoperative pain, we were unable to perform a meta-analysis due to the heterogeneous nature of the presented data, but results from several studies suggest improved postoperative pain outcomes with *in situ* repair.

Analysis of the nine studies measuring endometritis revealed results that tended to favour *in situ* repair, but the difference was not statistically significant. By excluding a study with a possible high risk of bias,²⁴ a sensitivity analysis favours *in situ* repair. The inclusion of this high risk of bias study in previous meta-analyses as well as the recent publication of very large studies that reported data on endometritis probably account for the difference in conclusions between our meta-analysis and earlier analyses regarding this outcome. Considering that no study specified administration of antibiotics before cord clamping, our results for endometritis may not reflect current North American practice, and therefore, no recommendations can be derived from this analysis.

This novel meta-analysis reports return of bowel function with respect to type of uterine repair. Our results show faster return of bowel function after *in situ* repair, with a mean difference of three hours; however, there was no statistically significant difference between groups in the duration of hospital stay.

Limitations

Our systematic review and meta-analysis may have several limitations. There was inconsistency among the studies with regard to reporting outcomes. Each of the included studies reported at least one primary outcome, but no study included all primary outcomes as defined in our systematic review. Despite the concerns of nausea, vomiting, pain, and hemodynamic instability with uterine exteriorization, few studies reported these outcomes. This resulted in wide confidence intervals for the pooled results of these outcomes and prevented us from making definitive conclusions. Many studies reported some type of postoperative pain, but we could not conduct a meta-analysis on this outcome due to the diverse postoperative analgesia regimens and reporting of postoperative pain. Furthermore, the method of measuring blood loss varied significantly between studies, and it was not possible to analyze these results together with the studies reporting only on a reduction in hemoglobin. The use of uterotonic medications might have been a surrogate for bleeding; however, the use of oxytocin and other uterotonics were not included results in any of the studies.

Finally, several outcomes can be influenced by many confounding variables such as emergent vs elective CD, length of labour, rupture of membranes, type of anesthetic, use and timing of antibiotics, use of vasopressors, and postoperative analgesia regimen. In general, those factors were balanced between the groups in the individual included studies. While we tested for publication bias, we were able to do so for only three outcomes. Statistical tests to identify this bias are unreliable in the presence of a small number of studies, as is the case with most of our outcomes.^{20–22} Lastly, systematically searching the literature is not a standardized undertaking. We attempted to complete an inclusive search strategy and identify all relevant articles by working with an expert in library sciences.

In conclusion, the ideal technique of uterine repair for CD continues to be a subject to debate. Uterine repair by exteriorization may reduce blood loss and the decrease in hemoglobin, but the difference is small and unlikely to be clinically relevant. Our results show no statistically significant difference in intraoperative nausea, vomiting, or pain between the two repair techniques. *In situ* repair may be associated with a faster return of bowel function. Additional well-conducted randomized controlled trials are needed that focus specifically on intraoperative complications such as nausea, vomiting, pain, and hemodynamic instability.

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Conflicts of interest None declared.

References

1. Hamilton BE, Martin JA, Osterman MJ, Curtin SC. Births: Preliminary Data for 2013. National Vital Statistics Reports 2014; 1–20. Available from URL: <http://www.cdc.gov/nchs/products/nvsr.htm> (accessed June 2015).
2. Kelly S, Sprague A, Fell DB, et al. Examining caesarean section rates in Canada using the robson classification system. J Obstet Gynaecol Can 2013; 35: 206–14.
3. Jacobs-Jokhan D, Hofmeyr G. Extra-abdominal versus intra-abdominal repair of the uterine incision at caesarean section. Cochrane Database Syst Rev 2004; 4: CD000085.
4. Walsh CA, Walsh SR. Extraabdominal vs intraabdominal uterine repair at cesarean delivery: a metaanalysis. Am J Obstet Gynecol 2009; 200: 625.e1–8.
5. Epps SN, Robbins AJ, Marx GF. Complete recovery after near-fatal venous air embolism during cesarean section. Int J Obstet Anesth 1998; 7: 131–3.
6. Lowenwirt IP, Chi DS, Handwerker SM. Nonfatal venous air embolism during cesarean section: a case report and review of the literature. Obstet Gynecol Surv 1994; 49: 72–6.
7. Siddiqui M, Goldszmidt E, Fallah S, Kingdom J, Windrim R, Carvalho JC. Complications of exteriorized compared with in situ uterine repair at cesarean delivery under spinal anesthesia: a randomized controlled trial. Obstet Gynecol 2007; 110: 570–5.
8. Nafisi S. Influence of uterine exteriorization versus in situ repair on post-cesarean maternal pain: a randomized trial. Int J Obstet Anesth 2007; 16: 135–8.
9. Orji EO, Olaleye AO, Loto OM, Ogunniyi SO. A randomised controlled trial of uterine exteriorisation and non-exteriorisation at caesarean section. Aust N Z J Obstet Gynaecol 2008; 48: 570–4.
10. Ozbay K. Exteriorized versus in-situ repair of the uterine incision at cesarean delivery: a randomized controlled trial. Clin Exp Obstet Gynecol 2011; 38: 155–8.
11. The CORONIS Collaborative Group; Abalos E, Addo V, Brocklehurst P, et al. Caesarean section surgical techniques (CORONIS): a fractional, factorial, unmasked, randomised controlled trial. Lancet 2013; 382: 234–48.
12. Doganay M, Tonguc EA, Var T. Effects of method of uterine repair on surgical outcome of cesarean delivery. Int J Gynaecol Obstet 2010; 111: 175–8.
13. El-Khayat W, Elsharkawi M, Hassan A. A randomized controlled trial of uterine exteriorization versus in situ repair of the uterine incision during cesarean delivery. Int J Gynaecol Obstet 2014; 127(2): 163–6.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009; 151(264–9): W64.
15. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005; 5: 13.
16. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343: d5928.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177–88.
18. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539–58.
19. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629–34.
20. Terrin N, Schmid CH, Lau J, Olkin I. Adjusting for publication bias in the presence of heterogeneity. Stat Med 2003; 22: 2113–26.

21. Terrin N, Schmid CH, Lau J. In an empirical evaluation of the funnel plot, researchers could not visually identify publication bias. *J Clin Epidemiol* 2005; 58: 894-901.
22. Thornton A, Lee P. Publication bias in meta-analysis: its causes and consequences. *J Clin Epidemiol* 2000; 53: 207-16.
23. Yaqub U, Noreen S. Extra abdominal versus intra abdominal uterine repair: a randomized control trial. *Pak J Med Health Sci* 2012; 6: 470-1.
24. Hershey DW, Quilligan EJ. Extraabdominal uterine exteriorization at cesarean section. *Obstet Gynecol* 1978; 52: 189-92.
25. Baksu A, Kalan A, Ozkan A, Baksu B, Tekellioglu M, Goker N. The effect of placental removal method and site of uterine repair on postcesarean endometritis and operative blood loss. *Acta Obstet Gynecol Scand* 2005; 84: 266-9.
26. Magann EF, Dodson MK, Allbert JR, McCurdy CM Jr, Martin RW, Morrison JC. Blood loss at time of cesarean section by method of placental removal and exteriorization versus in situ repair of the uterine incision. *Surg Gynecol Obstet* 1993; 177: 389-92.
27. Magann EF, Dodson MK, Harris RL, Floyd RC, Martin RW, Morrison JC. Does method of placental removal or site of uterine incision repair alter endometritis after cesarean delivery? *Infect Dis Obstet Gynecol* 1993; 1: 65-70.
28. Magann EF, Washburne JF, Harris RL, Bass JD, Duff WP, Morrison JC. Infectious morbidity, operative blood loss, and length of the operative procedure after cesarean delivery by method of placental removal and site of uterine repair. *J Am Coll Surg* 1995; 181: 517-20.
29. Edi-Osagie EC, Hopkins RE, Ogbo V, et al. Uterine exteriorisation at caesarean section: influence on maternal morbidity. *Br J Obstet Gynaecol* 1998; 105: 1070-8.
30. Wahab MA, Karantzis P, Eccersley PS, Russell IF, Thompson JW, Lindow SW. A randomised, controlled study of uterine exteriorisation and repair at caesarean section. *Br J Obstet Gynaecol* 1999; 106: 913-6.
31. Coutinho IC, Ramos Amorim MM, Katz L, Bandeira Ferraz AA. Uterine exteriorization compared with in situ repair at cesarean delivery: a randomized controlled trial. *Obstet Gynecol* 2008; 111: 639-47.
32. Ezechi OC, Kalu BK, Njokanma FO, Nwokoro CA, Okeke GC. Uterine incision closure at caesarean section: a randomised comparative study of intraperitoneal closure and closure after temporary exteriorisation. *West Afr J Med* 2005; 24: 41-3.
33. Habib AS, George RB, McKeen DM, et al. Antiemetics added to phenylephrine infusion during cesarean delivery: a randomized controlled trial. *Obstet Gynecol* 2013; 121: 615-23.