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Journal:

Am J Obstet Gynecol 1999

Double-blind comparison of carbetocin versus oxytocin in prevention of uterine atony after cesarean section

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OBJECTIVE: The goal of this study was to compare carbetocin, a long-acting oxytocin analog, with oxytocin in the prevention of uterine atony after cesarean section.
STUDY DESIGN: We enrolled 694 patients undergoing elective cesarean section in a Canadian multicenter, double-blind, randomized clinical trial. We compared the effect of a single 100 μg dose of carbetocin with that of a standard 8-hour infusion of oxytocin. The primary outcome was the proportion of patients requiring additional oxytocic intervention for uterine atony. A variable sample size, sequential design was used.
RESULTS: The overall oxytocic intervention rate was 7.4%. The odds of treatment failure requiring oxytocic intervention was 2.03 (95% confidence interval 1.1 to 2.8) times higher in the oxytocin group compared with the carbetocin group, respectively, 32 of 318 (10.1%) versus 15 of 317 (4.7%), $P < .05$.
CONCLUSIONS: Carbetocin, a new drug for the prevention of uterine atony, appears to be more effective than a continuous infusion of oxytocin and has a similar safety profile. (Am J Obstet Gynecol 1999; 180:670-6.)

Key words: Uterine contraction, obstetric hemorrhage, oxytocics, oxytocin, uterotonic activity, cesarean section

Postpartum hemorrhage resulting from uterine atony is the main cause of maternal death in developing countries[1, 2] and remains a major cause of maternal death in North America.[3] Current literature supports an active management of the third stage of labor to decrease the incidence of postpartum hemorrhage.[4, 5] Which uterotonic drug is preferable for prophylactic use is still being debated.[6-12] Ergonovine alone or in association with oxytocin has been associated with too many side effects, including serious cardiovascular and gastrointestinal effects.[6-8, 10, 12] Prostaglandins have been used mostly as a second- or third-line therapy but also appear to have serious side effects, making them inappropriate for routine prophylactic therapy.[5, 9, 11] In North America oxytocin remains the preferred drug for the prevention of uterine atony.[13]

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Supported by a clinical research grant from Ferring Inc., Canada.
Received for publication March 2, 1998; revised March 28, 1998; accepted November 30, 1998.
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0002-9378/99 $8.00 + 0 ***6/1/96264***

Carbetocin is a synthetic analog of oxytocin with a half-life 4 to 10 times longer than that of oxytocin. It is used as a single-dose injection instead of an infusion and can be given intravenously or intramuscularly.[14] Preliminary studies, although of small size, showed that it is a well-tolerated and promising drug.[14, 15]

The current study is the first large-scale clinical trial to compare the efficacy and safety of a single 100 μg intravenous dose of carbetocin with 8 hours of oxytocin infusion in the prevention of uterine atony after cesarean section.

Methods

Patients. From February 1992 to December 1994, 694 patients were enrolled from 7 hospitals in Canada. This represents approximately 20% of all elective cesarean sections performed during the same period. In those centers the cesarean section rate varies between 18% and 26%. Patients were eligible if they were scheduled for an elective cesarean section through a lower-segment transverse incision under regional anesthesia. They were excluded if they had a current or previous history of significant disease including heart disease; chronic hypertension requiring treatment; liver, renal, or endocrine disorders (other than gestational diabetes); or known coagulopathy. Diagnosed placenta previa or abruptio placentae, use of general anesthesia, and classic uterine incision were also exclusion criteria. Although

not among the exclusion criteria, the following risk factors for excessive bleeding were recorded: previous history of uterine atony and postpartum bleeding, twin gestation, number of previous cesarean sections, and grand multiparity (>5 previous deliveries). All other coexisting medical conditions not meeting the exclusion criteria were also recorded.

Study design and statistical analysis. After informed consent was obtained and eligibility confirmed, patients were randomized to receive either carbetocin or oxytocin according to the computer-generated randomization code, stratified by center and with use of random blocks of 2. The study was supervised by local investigators in each center and performed by local nurses hired as research assistants who entered the data on standard forms. Regular site visits were made by the study monitor from the sponsoring company, who collected and double-entered all data. The database was then managed, validated, and analyzed by the statistician. All physicians and nurses involved, all investigators and their staff, and all sponsor representatives were kept blinded to the treatment codes at all time.

We used a variable sample size, sequential design, and analysis, with use of the double triangular test[16] to evaluate the null hypothesis that the treatments are equivalent in terms of the primary outcome (need for further oxytocic) or that one treatment is superior. This design minimizes the sample size necessary to demonstrate a predetermined difference. It requires assessment of the primary outcome variable at regular intervals (Fig 1) until definitive evidence accumulates to declare the superiority of one of the treatments or their equivalence. At each inspection estimates of the parameter *Z*, which is a function of treatment outcome, and *V*, which is a function of the sample size are plotted on the double-triangular graph (Fig 1). When either of the 4 boundaries of significance is crossed, the enrollment is stopped. The boundaries and sample size were set to detect an odds ratio of 3 between the 2 groups, assuming an overall intervention rate of 8% on the basis of a chart audit before the study started, with type I and II errors rates defined at 0.05. Wilcoxon rank-sum test, χ^2, or Fisher's exact test and analysis of variance were used, as appropriate, to test secondary outcome variables. All analyses were done by a statistician who was independent of the sponsoring company. Similarly, all investigators and research assistants were independent of the sponsoring company.

Maneuver. The investigator injected dose 1 (1 mL) as an intravenous bolus and injected dose 2 (2 mL) into 1 L of lactated Ringer's solution, which was infused at a rate of 125 mL/h over 8 hours immediately after delivery of the infant (87% of cases) or after delivery of the placenta (13% of cases). For patients in the carbetocin group dose 1 was 100 μg of carbetocin, and dose 2 was 2 mL of normal saline solution. For patients in the oxytocin group

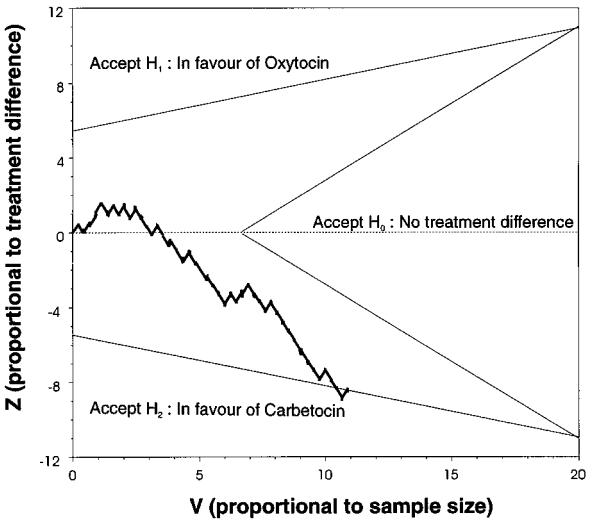

Fig 1. Sequential analysis with use of double triangular test.

dose 1 was 5 units of oxytocin, and dose 2 was 20 units of oxytocin. The study drugs were prepared by the hospital pharmacist and had identical appearances.

Infusion of study drug could be stopped at any time and additional oxytocic therapy instituted if the surgeon considered uterine tone to be inadequate; these patients were considered as treatment failures and subsequently managed as deemed appropriate by the surgeon. The protocol encouraged the use of additional oxytocic therapy whenever it would have been given under normal clinical practice.

Outcomes. The primary outcome was defined by the need for additional oxytocic intervention in the 48 hours after delivery to maintain the uterus well contracted, as judged by the attending surgeon, as would be done under usual clinical practice.

Secondary outcomes included position of the fundus and tone of the uterus, amount of lochia, vital signs, drop in hemoglobin level by postoperative day 2 (compared with preoperative value), side effects, delay between drug administration and adequate uterine contraction, delay before need for additional oxytocic, and difference in postoperative blood chemistry. The number of patients with major complications or requiring transfusions was also monitored, although the study was not designed to have the power to detect a difference in these rare complications.

Monitoring

In the operating room. Uterine tone assessed by the surgeon and vital signs were monitored at 0, 1, 2, 3, 4, 5, and 10 minutes and every 10 minutes thereafter until the end of the procedure.

In the recovery room. Uterine tone, lochia, fundal height, and vital signs were monitored at 0, 15, and 30 minutes and every 30 minutes thereafter until the patient was transferred to the postpartum ward.

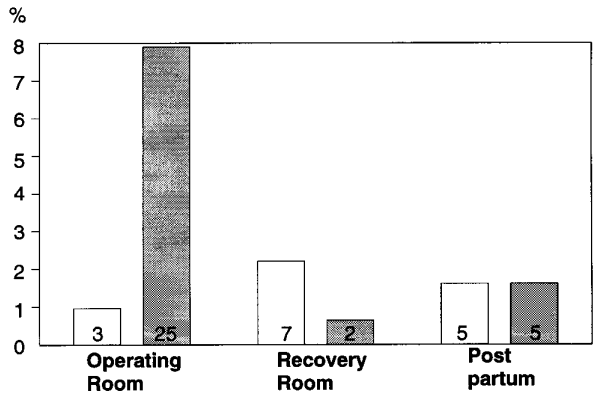

Fig 2. Location where additional oxytocin was given. *Numbers* inside *bars* represent number of patients. Height of *bar* represents proportion in each group. *Open bars,* Carbetocin; *stippled bars,* oxytocin.

On the postpartum ward. Patients received routine care and monitoring. On postoperative day 2 blood was drawn for complete blood cell count, serum creatinine, γ-glutamyl transferase, aspartate aminotransferase, alkaline phosphatase, and serum sodium levels as a routine safety measure to detect any unexpected toxic effects on renal and hepatic functions.

Signs, symptoms, and side effects. At the end of surgery and before transfer to the postpartum ward, the patient was questioned for side effects and specifically for abdominal pain, back pain, headache, nausea, feeling of warmth, and metallic taste because these symptoms had been previously reported with both drugs.[14, 15] The severity of these symptoms was rated from 0 to 100 with use of a visual analog scale. The patient was also monitored for signs of flushing, sweating, tremor, and vomiting. Any other symptoms volunteered or signs observed by the primary nurse were also recorded. Comments made by the surgeon, if recorded, were classified in a blinded fashion as positive or negative.

Ethics. Each participating center received approval of the study from its own ethics review board. All patients gave informed consent. Interim safety analyses were performed after 200 and 400 patients had been enrolled and were reviewed by the study statistician and an independent perinatalogy consultant. No safety concerns were found and the study was allowed to continue.

Results

Disposition of patients. Informed consent was obtained from 694 patients. Thirty-five patients were withdrawn from the study before they received study drug, leaving a total of 659 patients who received study drug and were included in the safety analysis. Major protocol violations that confounded the primary efficacy outcome variable were identified in a total of 24 patients, 12 in each treatment group. This includes 10 patients withdrawn from analysis after they received additional oxytocin on a routine basis rather than for clinical indications. This left a total of 635 patients who completed the study as per the protocol, 317 in the carbetocin arm and 318 in the oxytocin arm, who were included in the primary efficacy analysis (Table I). The decision to withdraw a patient from the analysis was always done blindly in regard to the study group.

Table I. Disposition of patients

	Carbetocin	*Oxytocin*
Enrolled in study	348	346
Withdrawn before study drug administered		
Withdrew consent	3	2
General anesthesia administered	11	7
Other reason	5	7
Included in safety analysis	329	330
Withdrawn after study drug administration		
Unnecessary intervention*	7	3
Intravenous port access problems	2	2
Adverse event	1	3
General anesthesia	1	1
Other	1	3
Included in efficacy analysis	317	318

*No need for further oxytocic therapy.

Baseline characteristics. Table II shows the baseline characteristics of all randomized patients. As expected when multiple variables are assessed between 2 groups of patients, a few differences were detected. More twin gestations appeared in the oxytocin group (12 vs 4, $P < .05$). Gestational diabetes was also more common in the oxytocin group (28 vs 11, $P < .05$). Only 7 patients had a history of postpartum hemorrhage, 2 in the carbetocin group and 5 in the oxytocin group ($P > .05$). The preoperative platelet count was slightly lower in the carbetocin group (232 vs 219, $P < .001$). None of the patients met the criteria for grand multiparity. No other differences were detected in 17 other baseline characteristics.

Primary outcome. Fig 1 highlights the progress of the sequential trial. Enrollment was stopped when the lower boundary of the triangular region was crossed, proving the hypothesis that carbetocin has a lower intervention rate than oxytocin.

A total of 47 of the 635 patients evaluable for the primary outcome variable (7.4%) required additional oxytocic intervention, 15 of 317 (4.7%) in the carbetocin group and 32 of 318 (10.1%) in the oxytocin group. The odds of intervention was 2.03 times higher in the oxytocin group ($P < .05$). The 95% confidence limits of the odds ratio were 1.1 and 2.8.

A post-hoc sequential analysis was carried out in all 659 patients who received study drug, including the 24 protocol violations. When these 24 patients were considered

Table II. Baseline characteristics of study patients

Characteristic	*Carbetocin*	*Oxytocin*
Age (y)	31 (5)	31 (5)
Weight (kg)	79 (21)	81 (19)
Height (cm)	159 (8)	160 (9)
Gravidity	2.7 (1.3)	2.8 (1.2)
Parity	1.2 (0.8)	1.2 (0.9)
No. of previous cesarean sections	1.0 (0.8)	1.0 (0.8)
Pulse	82 (9)	82 (9)
Respiratory rate	19 (2)	19 (2)
Systolic blood pressure (mm Hg)	113 (12)	114 (13)
Diastolic blood pressure (mm Hg)	71 (9)	71 (10)
Preoperative hemoglobin (g/L)	122 (11)	121 (11)
Preoperative platelet count (10^9/L)	219 (59)	232 (64)*
Twin gestation†	4 (1)	12 (4)*
Previous history of postpartum hemorrhage†	2 (0.6)	5 (1.5)
Gestational diabetes†	11 (3.3)	28 (8.5)*

Values are mean and SD except as noted.
*$P < .05$.
†Number and percent.

as treatment successes (ie, no need for further oxytocic therapy), the same result was obtained.

Post-hoc analyses. More post-hoc analyses were performed with use of a fixed sample size analysis approach. Because there were significantly more patients in the oxytocin group with twin gestations and gestational diabetes, a post-hoc evaluation of these potential confounders was performed. Only 1 of the patients with a twin gestation in the oxytocin group required oxytocic intervention. However, patients with gestational diabetes had a higher oxytocic intervention rate compared with those without diabetes (16.2% vs 6.9%, respectively; odds ratio 2.63, 95% confidence interval 1.04-6.66). After correction for this imbalance in distribution of gestational diabetic patients between the groups, the odds of intervention remained higher in the oxytocin group than in the carbetocin group (odds ratio 1.97, 95% confidence interval 1.07-3.63).

Even when all 694 patients randomized to the study and all oxytocic interventions were included (together with the 35 patients who did not receive any treatment drug and the 10 patients who received additional oxytocic without clinical indications), oxytocin was still associated with more intervention than carbetocin but with a mild diluting effect on the odds ratio (oxytocin group 10.1% vs carbetocin group 6.3%, odds ratio 1.72, 95% confidence interval 0.99 to 2.99).

Characteristics of additional oxytocic therapy. The mean dose of additional oxytocin required in nonresponders to carbetocin and oxytocin was identical (48 ± 28 IU, range 5 to 120 IU). Seven patients also received other oxytocics; 3 patients in the oxytocin group and 2 in the carbetocin group received 0.125 to 0.25 mg of methylergonovine maleate. Two patients in the carbetocin group received prostaglandin $F_{2\alpha}$, which was combined with vasopressin in 1 case.

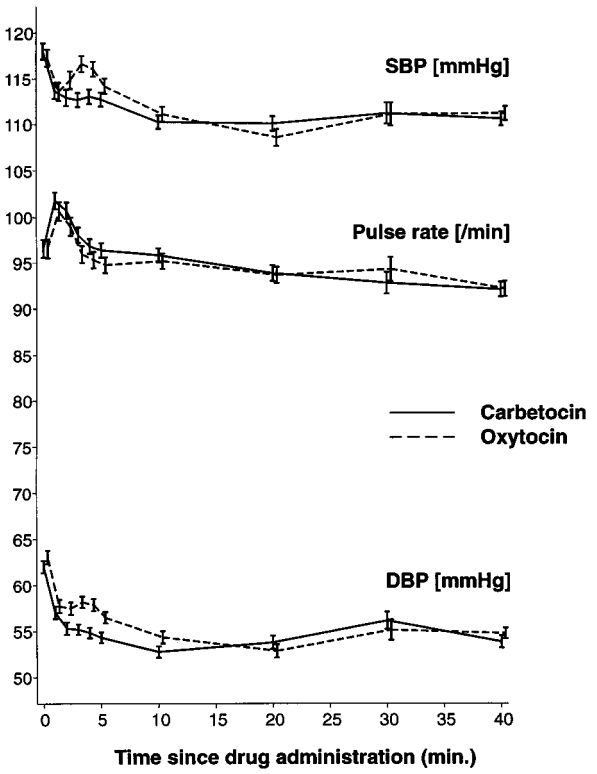

Fig 3. Variation of vital signs in operating room. *Vertical bars,* SEM. *SBP,* Systolic blood pressure; *DPB,* diastolic blood pressure.

Secondary outcomes. The median time to intervention was 2 hours in the carbetocin group and 11 minutes in the oxytocin group ($P < .001$). This difference is explained by the more frequent need to intervene in the operating room for the patients receiving oxytocin (Fig 2).

Uterine tone increased rapidly after study drug administration, with 88% and 84% in carbetocin and oxytocin treatment groups, respectively, having a firm uterus by 1 minute after injection. Maximum tone was reached by 3 to 4 minutes after drug administration, and during the remainder of the operative procedure 92% to 100% of all patients had a firm uterus at all times. After transfer to the recovery room, uterine tone remained firm in 98% to 100% of all patients at all time points evaluated. There were no significant differences in uterine tone between treatment groups.

There were no significant differences between the 2 treatment groups in fundal position over time in the recovery room, which was at or below the umbilicus in 78% to 84% of all patients. Lochia was considered normal in amount and type in 93% to 100% of all patients in both treatment groups.

Table III. Postoperative blood parameters

Blood parameter	*Carbetocin*	*Oxytocin*
Postoperative hemoglobin change(g/L)	–7.5 (10)	–8.3 (10)
Postoperative platelet count change (10^9/L)	5.1 (34)	–1 (32)*
Creatinine (μmol/L)	69 (11)	69 (12)
γ-Glutamyl transferase	15 (9)	16 (11)
Aspartate aminotransferase	24 (9)	23 (9)
Alkaline phosphatase	137 (50)	132 (47)
Sodium	139 (2)	139 (2)

Values are mean and SD.
*$P < .01$.

Table IV. Frequency of symptoms and signs*

Symptom or sign	*Carbetocin*	*Oxytocin*
Symptom		
Abdominal pain	131 (40)	127 (38)
Back pain	13 (4)	16 (5)
Headache	46 (14)	43 (13)
Nausea	88 (27)	97 (29)
Feeling of warmth	65 (20)	56 (17)
Metallic taste	20 (6)	21 (6)
Other symptoms	84 (26)	90 (27)
Sign		
Flushing	86 (26)	76 (23)
Sweating	10 (3)	10 (3)
Tremors	37 (11)	49 (15)
Vomiting	30 (9)	29 (9)
Other signs	9 (3)	8 (2)

None of these differences are statistically significant. Values are number and percent.
*Includes all patients with symptom or sign at any time in operating room or recovery room.

The difference between the 2 groups in terms of hemoglobin drop and platelet count postoperatively was trivial and is of no clinical importance (Table III). There were otherwise no differences in blood chemistry drawn postoperatively between the 2 groups.

There was no difference in pulse and respiratory rate between the 2 groups. There was a minimal and transient difference in blood pressure between 2 and 5 minutes after drug injection, never exceeding 4 mm Hg, also of no clinical importance (Fig 3).

There was no difference in severity and frequency of symptoms and no difference in frequency of signs between the 2 groups (Table IV). Two patients in each group had a postpartum hemorrhage. In each patient a risk factor was identified. All patients recovered and none of these were considered to be the result of either of the 2 drugs.

Nonoxytocic intervention. In addition to requiring additional oxytocic, some patients required uterine massage: 9 of 317 (2.8%) and 24 of 318 (7.5%), respectively, in the carbetocin and oxytocin groups. Other patients had negative comments made by the surgeon regarding uterine tone: 9 of 317 (2.8%) and 22 of 318 (7.0%), respectively, in the carbetocin and oxytocin groups. This is an underestimation of the true incidence of massage and negative comments because these events were not consistently recorded. However, those observations made by clinicians unaware of the study group are consistent with the primary outcome. In total, 32 of 317 (10.1%) and 61 of 318 (19.2%) patients, respectively, in the carbetocin and oxytocin groups, had 1 or more of the 3 events of additional intervention, uterine massage, or negative comments (odds ratio 2.11, 95% confidence interval 1.33 to 3.35, $P = .001$).

Comment

This is the first large clinical study assessing the effects of carbetocin, a long-acting synthetic oxytocin analog. Ideally, an exact estimation of blood loss at surgery would be the preferred method of evaluating an oxytocic drug. Boucher et al,[17] with use of a hemoglobin extraction technique, reported that patients treated with oxytocin did bleed approximately 30 mL more than did patients given carbetocin. This degree of blood loss difference is clinically trivial. Furthermore, this is a cumbersome measurement, impractical on a large scale. Instead we chose the more pragmatic "need to give additional oxytocin," a clinically relevant and unbiased end point because the surgeon was blinded to the study group. This blinding of all people involved when subjective assessments had to be made, as well as, in general, the careful design and method of this study, was a key point in protecting from biases.[18]

Carbetocin appears well tolerated in this healthy population, with no safety concerns as judged by the assessment of symptoms, vital signs, or other serious adverse events. There was no concern regarding a possible "wearing off" of a single injection of carbetocin, as judged by the reassuring low incidence of late oxytocic interventions or postpartum hemorrhages.

In nonpregnant women an intravenous dose of carbetocin 4 to 8 times higher than the one used in the current study produced a mild transient decrease in diastolic blood pressure.[14] In this study it was not seen, presumably because of the lower dosage used. Rather, we observed a mild increase in blood pressure of no clinical importance.

Some adverse events occurring during this study, namely, headache, flushing, feeling of warmth, metallic taste, and abdominal pain, were observed previously during clinical pharmacology studies with carbetocin[14, 15] and probably represent true side effects of the drug. Other adverse events, however, are more likely to be the

result of concomitant medications. For example, pruritus, nausea, and vomiting are typical side effects of opiates that were routinely used as analgesics.

Although it remains to be shown in proper clinical trials, it seems reasonable to predict that similar results would also be obtained after vaginal delivery. In that situation, the long action of carbetocin and its good bioavailability when given intramuscularly[14, 15] would make it an attractive option in clinical settings where an intravenous line is not easily available. Studies aimed at fine-tuning the dose of carbetocin for vaginal delivery without regional anesthesia are under way.[19]

Establishing the exact place of carbetocin among the short list of useful oxytocic drugs requires more than the simple demonstration of its efficacy. It has to be determined in each clinical situation, with patient safety, convenience, and economic constraints in mind. Oxytocin has a good track record, proving inferior to carbetocin mainly in the early postoperative period when patients can be monitored closely and action taken immediately. In this study this did not result in a decreased hemoglobin level or in more transfusions. On the other hand, the additional number of interventions, massage, and negative comments in the group of patients receiving oxytocin, as well as the convenience and safety of carbetocin observed in this study, establish carbetocin as a better drug to maintain uterine contractility after elective cesarean section.

Carbetocin combines the safety of oxytocin with the longer duration of action of ergot preparations and as such has the potential to become the drug of choice in the prevention of postpartum uterine atony.

The following persons and institutions participated in this multicenter study: British Columbia Women's/Grace Hospital/University of British Columbia: J. Dansereau, (local investigator), D.R. Gambling (coinvestigator), L. Jenkins, M. MacIntosh, E. Nickel, B. Wiebe (research assistants); St Mary's Hospital/McGill University: A.K. Joshi (local investigator), I. Ross, M. Lynn, A. Alcok (research assistants); St Boniface Hospital/University of Manitoba: M.E. Helewa (local investigator), S. Lucy, P.F. Hall (coinvestigators), S. Paddon (research assistant); Toronto Hospital/University of Toronto: T.A. Doran (local investigator), R.A. Livingstone (coinvestigator), M. Bailey, J. Hillier (research assistants); Foothills Provincial General Hospital/University of Calgary: I.R. Lange (local investigator), J. Jarrell (coinvestigator), B. Ingleson, I. DeBruyn (research assistants); Grace Maternity Hospital/Victoria General Hospital/Dalhousie University: E.R. Luther (local investigator), R.C. Shukla, R. Liston (coinvestigators), K. Phalen-Kelly, L. Lauzon (research assistants); Mount Sinai Hospital/University of Toronto: D. Farine (local investigator), S. Lye (coinvestigator), M. Oskamp (research assistant); Scian Clinical: M.L. Schulz, S.C. Chung-Hun (statisticians); Ferring Inc: G.L.A. Horbay (study manager), P. Griffin, W. Wassenaar (development and coordination), L. Ferreira (data validation). We also thank H. Tsang for perinatology consultancy for the interim analysis and pharmacists in each of the hospitals for the valuable support: V. Cardeno (British Columbia Women's); M. Prevost (St Mary's Hospital); D. Sawatsky and A. Adamson (St Boniface Hospital); M. Lee and L. Duncan (Toronto Hospital); B. MacKenzie (Foothills Hospital); A. Yeull and J. Nape (Grace Maternity and Victoria General Hospital); A. Kosyrskys and C. Ho (Mount Sinai Hospital).

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