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Review

Discontinuing Oxytocin Infusion in the Active Phase of Labor

A Systematic Review and Meta-analysis

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OBJECTIVE: To evaluate the benefits and harms of discontinuation of oxytocin after the active phase of labor is reached.

DATA SOURCES: Electronic databases (ie, MEDLINE, Scopus, ClinicalTrials.gov, EMBASE, ScienceDirect, the Cochrane Library at the CENTRAL Register of Controlled Trials, Scielo) were searched from their inception until April 2017.

METHODS OF STUDY SELECTION: We included all randomized controlled trials comparing discontinuation (ie, intervention group) and continuation (ie, control group) of oxytocin infusion after the active phase of labor is reached, either after induction or augmentation of labor. Discontinuation of oxytocin infusion was defined as discontinuing oxytocin infusion when the active phase of labor was achieved. Continuation of oxytocin infusion was defined as continuing oxytocin infusion until delivery. Only trials in singleton gestations with vertex presentation at term were included. The primary outcome was the incidence of cesarean delivery.

TABULATION, INTEGRATION, AND RESULTS: Nine randomized controlled trials, including 1,538 singleton gestations, were identified as relevant and included in the meta-analysis. All nine trials included only women undergoing induction of labor. In the discontinuation group, if arrest of labor occurred, usually defined as no cervical dilation in 2 hours or inadequate uterine contractions for 2 hours or more, oxytocin infusion was restarted. Women in the control group had oxytocin continued until delivery usually at the same dose used at the time the active phase was reached. Women who were randomized to have discontinuation of oxytocin infusion after the active phase of labor was reached had a significantly lower risk of cesarean delivery (9.3% compared with 14.7%; relative risk 0.64, 95% CI 0.48–0.87) and of uterine tachysystole (6.2% compared with 13.1%; relative risk 0.53, 95% CI 0.33–0.84) compared with those who were randomized to have continuation of oxytocin infusion until delivery. Discontinuation of oxytocin infusion was associated with an increase in the duration of the active phase of labor (mean difference 27.65 minutes, 95% CI 3.94–51.36).

CONCLUSION: In singleton gestations with cephalic presentation at term undergoing induction, discontinuation of oxytocin infusion after the active phase of labor at approximately 5 cm is reached reduces the risk of cesarean delivery and of uterine tachysystole compared with continuous oxytocin infusion. Given this evidence, discontinuation of oxytocin infusion once the active stage of labor is established in women being induced should be considered as an alternative management plan.

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Each author has indicated that he or she has met the journal's requirements for authorship.

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Since it was first synthesized in the 1953, oxytocin has become one of the most widely used medications in obstetrics to induce or to augment labor,

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utilized in up to 50% of deliveries in many countries.[1] Different oxytocin regimens and protocols have been described.[2] Moreover, there are various studies looking at optimal duration of oxytocin administration. However, so far there is no consensus regarding whether discontinuation of oxytocin, once the active phase of labor is reached, may be an alternative management to continuous oxytocin infusion either after induction or after augmentation of labor.

The aim of this study was to evaluate benefits and harms of discontinuation compared with continuation of oxytocin infusion after the active phase of labor is reached. This review was performed according to a protocol designed a priori and recommended for systematic reviews.[3] Electronic databases (ie, MEDLINE, Scopus, ClinicalTrials.gov, EMBASE, ScienceDirect, the Cochrane Library at the CENTRAL Register of Controlled Trials, Scielo) were searched from their inception until April 2017. Search terms used were the following text words: "labor," "labour," "randomised," "second stage," "randomized," "oxytocin," "continuation," "discontinuation," "infusion," "active phase," "vaginal delivery," "effectiveness," and "clinical trial." No restrictions for language or geographic location were applied. In addition, the reference lists of all identified articles were examined to identify studies not captured by electronic searches. The electronic search and the eligibility of the studies were independently assessed by two authors (G.S., V.B.). Differences were discussed and consensus reached.

We included all randomized controlled trials (RCTs) comparing discontinuation (ie, intervention group) and continuation (ie, control group) of oxytocin infusion after the active phase of labor is reached, either after induction or after augmentation of labor. Discontinuation of oxytocin infusion was defined as discontinuing oxytocin infusion when the active phase of labor was achieved. Continuation of oxytocin infusion during the active phase of labor was defined as continuing oxytocin infusion until delivery. Active phase of labor was defined as per the original trial. Only trials in singleton gestations with vertex presentation at term were included. Quasirandomized trials (ie, trials in which allocation was done on the basis of a pseudorandom sequence, eg, odd and even hospital number or date of birth, alternation) were not included. Trials in multiple gestations were also excluded.

The risk of bias in each included study was assessed by using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions*. Seven domains related to risk of bias were assessed in each included trial because there is evidence that these issues are associated with biased estimates of treatment effect: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective reporting, and 7) other bias. Review authors' judgments were categorized as "low risk," "high risk," or "unclear risk" of bias.[3]

Two authors (G.S., A.C.) independently assessed inclusion criteria, risk of bias, and data extraction. Disagreements were resolved by discussion with a third reviewer (V.B.).

All analyses were done using an intention-to-treat approach, evaluating women according to the treatment group to which they were randomly allocated in the original trials. Primary and secondary outcomes were defined before data extraction. The primary outcome was the incidence of cesarean delivery. The secondary outcomes were mean duration of the active phase, and of the second stage of labor, incidence of vaginal delivery, operative vaginal delivery, indications for cesarean delivery, epidural analgesia, uterine tachysystole, postpartum hemorrhage, chorioamnionitis, abnormal fetal heart rate, and neonatal outcomes, including birth weight, admission to the neonatal intensive care unit, and Apgar score less than 7 at 5 minutes. All authors were contacted for missing data, if possible. Trials on oxytocin for induction of labor and trials on oxytocin for augmentation of labor were analyzed separately.

Subgroup analysis in nulliparous compared with multiparous women was planned. We also performed sensitivity analysis[3] excluding trials with a high risk of bias (ie, trials with more than one "high risk of bias" in the Cochrane risk of bias tools)[3] for the primary outcome (ie, cesarean delivery).

The data analysis was completed independently by two authors (G.S., V.B.) using Review Manager 5.3.[3] The completed analyses were then compared, and any difference was resolved by discussion. The summary measures were reported as summary relative risk (RR) or as summary mean difference with 95% CI using the random-effects model of DerSimonian and Laird. Higgins I^2 was used to identify heterogeneity.

Data from each eligible study were extracted without modification of original data onto custom-made data collection forms. A two-by-two table was assessed for RR; for continuous outcomes, means±SD were extracted and imported into Review Manager 5.3.

Potential publication bias was assessed statistically by using Begg's and Egger's tests. P values $<.05$ were considered statistically significant.

The meta-analysis was reported following the Preferred Reporting Item for Systematic Reviews

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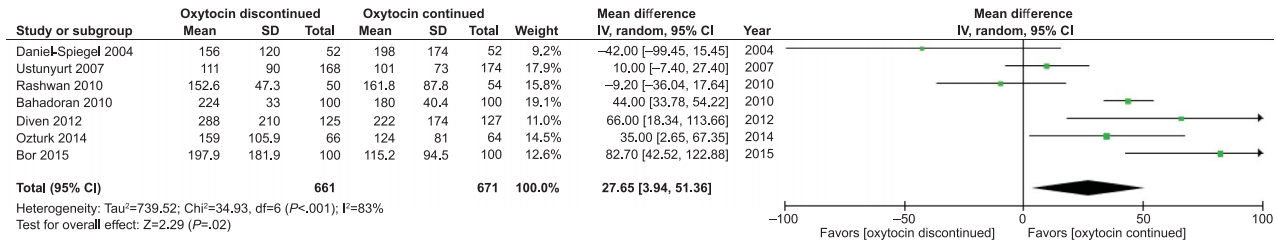

Fig. 1. Forest plot for the mean difference in duration of the active phase of labor in minutes, which was shorter by more than 27 minutes in the oxytocin continuation group. IV, independent variable; df, degrees of freedom.

Saccone. Discontinuing Oxytocin During Labor. Obstet Gynecol 2017.

and Meta-analyses (PRISMA) statement.[4] The review was registered with the PROSPERO International Prospective Register of Systematic Reviews (registration No. CRD42017065683).

RESULTS

Nine RCTs, including 1,538 singleton gestations who underwent induction of labor, were identified as relevant and included in the meta-analysis (Appendix 1, available online at http://links.lww.com/AOG/B22).[5–13] Publication bias, assessed using Begg's and Egger's tests, was not significant (P=.75 and .84, respectively). Statistical heterogeneity between the trials ranged from low (I^2=0%) to high (I^2=96%) with no inconsistency in risk estimates (I^2=0%) for the primary outcome (ie, cesarean delivery) and most of the secondary outcomes. Two authors kindly provided additional unpublished data from their trials.[7,9]

The quality of the RCTs included in our meta-analysis was assessed by using the seven criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions.*[3] All the included studies had "low risk" of bias in "random sequence generation," except for two in which details on methods used for randomization were not reported. Adequate methods for allocation of women were used in five trials, whereas in four RCTs, details on methods used to conceal allocation were not reported (Appendix 2, available online at http://links.lww.com/AOG/B22). Three trials[5,8,13] used a placebo in the control group (500 mL of 0.9% of NaCl solution). In four studies, randomization was performed by using a computer-generated random number sequence with sealed opaque envelopes opened before dividing the women into the two groups.[6,7,9,12]

The included trials came from both high-income and low-income countries (Appendix 3, available online at http://links.lww.com/AOG/B22). Years of publication ranged from 2004 to 2015. Most of the studies (seven of nine) were published in 2010 or after. Only one trial came from the United States[9] and only one from Europe.[7] Of the 1,538 women included, 764 (49.7%) were randomized in the intervention group (ie, discontinuation of oxytocin infusion after the active phase of labor was reached), and 774 (50.3%) were randomized in the comparison group (ie, continuation of oxytocin infusion even after the active phase of labor was reached and until delivery). All trials included only singleton gestations with vertex presentation at 36 or more weeks of gestation who underwent induction of labor. Women with "fetal distress" at the time of randomization were excluded (Appendix 3, http://links.lww.com/AOG/B22).

The definition of active phase was different among the included trials, but in most of them, it was defined as 5 cm or greater cervical dilation (Appendix 4, available online at http://links.lww.com/AOG/B22). Women in the intervention group

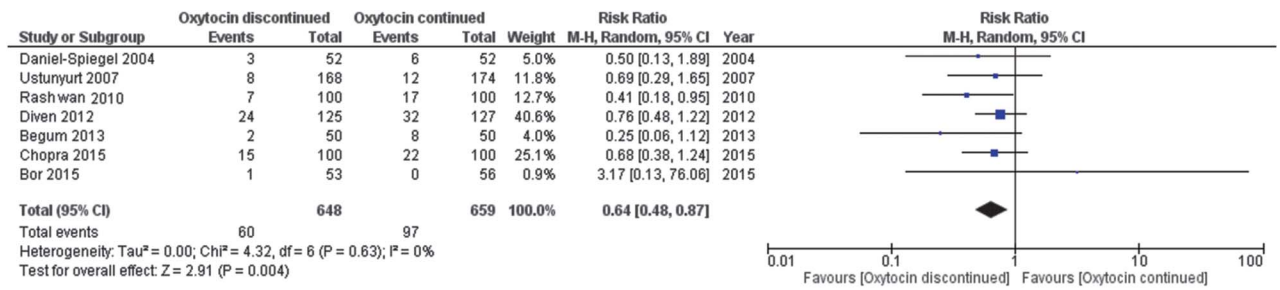

Fig. 2. Forest plot for the risk of cesarean delivery. M-H, Mantel-Haenszel test; df, degrees of freedom.

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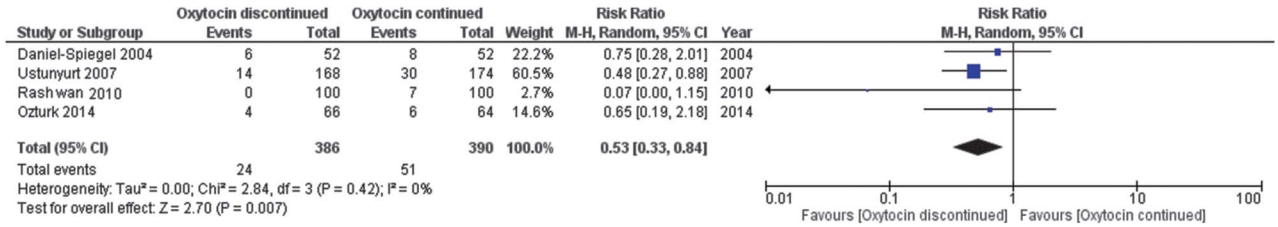

Fig. 3. Forest plot for the risk of uterine tachysystole. M-H, Mantel-Haenszel test; df, degrees of freedom.
Saccone. Discontinuing Oxytocin During Labor. Obstet Gynecol 2017.

had infusion of oxytocin discontinued when the active phase was reached. In this group, if arrest of labor occurred, usually defined as no cervical dilation in 2 hours or inadequate uterine contractions for 2 hours or more, the oxytocin infusion was restarted (Appendix 5, available online at http://links.lww.com/AOG/B22). The percentages of women in the intervention group who had oxytocin restarted ranged from 0% to 46.4% with a mean of 30% (140/461). In one study, 31 of 125 (24.8%) women in the intervention group did not had oxytocin discontinued despite being randomized to the discontinuation group. Women in the control group had the infusion of oxytocin continued until delivery usually at the same dose used at the time the active phase reached, unless there was an indication to stop the infusion or to reduce the dosage, for example, nonreassuring fetal heart rate tracing. The percentages of women in the control group who had oxytocin discontinued ranged from 0% to 7.7% with a mean of 2% (15/567) (Appendix 5, http://links.lww.com/AOG/B22).

In most of the included trials (Appendix 6, available online at http://links.lww.com/AOG/B22), induction of labor was started by oxytocin infusion of 1–2 milli-international units/min (5 international units of oxytocin diluted was usually diluted in 500 mL of 0.9 NaCl or of Ringer's solution). The dose was increased every 15–20 minutes by 1–2 milli-international units/min until regular contractions at a rate of three to five per 10 minutes were reached. In most of the included trials, the maximum dose allowed was 20 milli-international units/min (Appendix 6, http://links.lww.com/AOG/B22). In case of an unfavorable Bishop score, cervical ripening was used before or at the time of oxytocin induction of labor, usually with misoprostol, or a Foley balloon (Appendix 7, available online at http://links.lww.com/AOG/B22).

By using an intention-to-treat approach, we found that women who were randomized to have discontinuation of oxytocin infusion after the active phase of labor was reached had a longer length of active phase of labor (mean difference 27.65 minutes, 95% CI 3.94–51.36; Fig. 1), but similar duration of the second stage of labor (Appendix 8, available online at http://links.lww.com/AOG/B22), compared with those who were randomized to have continuation of oxytocin infusion until

Table 1. Labor Outcomes

	Duration of Active Phase of Labor (min)	Duration of Second Stage (min)
Daniel-Spiegel, 2004[12]	156±120 vs 198±174	31.8±3.6 vs 30±3.6
Ustunyurt, 2007[13]	111±90 vs 101±73	21.4±35.6 vs 18.6±15.9
Bahadoran, 2010[5]	152.6±47.3 vs 161.8±87.7	47±30 vs 43±30.3
Rashwan, 2010[11]	224±33 vs 180±40.4	45.16±14.13 vs 36.2±9.86
Diven, 2012[9]	288±210 vs 222±174*	30 (0–390) vs 30 (0–402)†
Begum, 2013[6]	Not reported	Not reported
Ozturk, 2014[10]	159±105.9 vs 124±81.0	Not reported
Bor, 2015[7]	197.8±181.9 vs 115.2±94.5	Not reported
Chopra, 2015[8]	510 vs 426‡	Not reported
I^2	83%	80%
MD (95% CI)†	**27.65 min (3.94–51.36)**	4.46 min (−0.08 to 9.01)

MD, mean difference.
Data are mean±SD or median (range) for number in the intervention group vs number in the control group unless otherwise specified. Bold indicates statistical significance.
* Additional unpublished data kindly provided by the authors of the original trials.
† Data not included in the meta-analysis because mean and SD were not reported.
‡ Mean without SD was not included in the meta-analysis.

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Table 2. Mode of Delivery and Rate of Analgesia

	Vaginal Delivery	Operative Vaginal Delivery	Cesarean Delivery*	Epidural Analgesia
Daniel-Spiegel, 2004[12]	47/52 (90.3) vs 44/52 (84.7)	2/52 (3.8) vs 3/52 (5.8)	3/52 (5.8) vs 6/52 (11.5)	29/52 (56.0) vs 29/52 (56.0)
Ustunyurt, 2007[13]	160/168 (95.2) vs 162/174 (93.1)	Not reported	8/168 (4.8) vs 12/174 (6.9)	Not reported
Bahadoran, 2010[5]	Not reported	Not reported	Not reported	Not reported
Rashwan, 2010[11]	93/100 (93.0) vs 83/100 (83.0)	Not reported	7/100 (7) vs 17/100 (17)	41/100 (41.0) vs 100/100 (100)
Diven, 2012[9]	96/125 (76.8) vs 94/127 (74.0)	5/125 (4.0) vs 1/127 (0.8)	24/125 (19.2) vs 32/127 (25.2)	118/125 (94.8) vs 122/127 (96.1)
Begum, 2013[6]	44/50 (88.0) vs 40/50 (80.0)	4/50 (8.0) vs 2/50 (4.0)	2/50 (4.0) vs 8/50 (16.0)	Not reported
Ozturk, 2014[10]	Not reported	Not reported	Not reported	Not reported
Bor, 2015[7]	85/100 (85.0) vs 78/100 (78.0)	11/100 (11.0) vs 8/100 (8.0)	15/100 (15.0) vs 22/100 (22.0)	51/100 (51.0) vs 41/100 (41.0)
Chopra, 2015[8]	46/53 (86.8) vs 45/53 (84.9)	6/53 (11.3) vs 8/53 (15.1)	1/53 (1.9) vs 0/56	Not reported
Total	571/648 (88.1) vs 546/656 (83.2)	28/380 (7.3) vs 22/382 (5.8)	60/648 (9.3) vs 97/659 (14.7)	239/377 (63.4) vs 292/379 (77.0)
I^2	0%	0%	0%	96%
RR (95% CI)	1.05 (1.00–1.09)	1.20 (0.69–2.09)	**0.64 (0.48–0.87)**	0.84 (0.49–1.44)

RR, relative risk.
Data are n/N (%) for number in the intervention group vs number in the control group unless otherwise specified.
Bold indicates statistical significance.
*Primary outcome.

delivery. Women in the intervention group had a significantly lower risk of cesarean delivery (9.3% compared with 14.7%; RR 0.64, 95% CI 0.48–0.87; Fig. 2) and of uterine tachysystole (6.2% compared with 13.1%; RR 0.53, 95% CI 0.33–0.84; Fig. 3). No differences were found in the incidence of abnormal fetal heart rate (Appendix 9, available online at http://links.lww.com/AOG/B22) and in the other secondary outcomes (Tables 1–3; Appendix 10 [Appendix 10 is available online at http://links.lww.com/AOG/B22]).

Sensitivity analysis for the primary outcome, including only RCTs with low risk of bias,[6,9,11–13]

Table 3. Maternal and Fetal Complications

	Uterine Tachysystole	PPH	Chorioamnionitis	Abnormal FHR
Daniel-Spiegel, 2004[12]	6/52 (12) vs 8/52 (16)	Not reported	Not reported	8/52 (15.4) vs 8/52 (15.4)
Ustunyurt, 2007[13]	14/168 (8.3) vs 30/174 (17.2)	Not reported	Not reported	4/168 (2.4) vs 6/174 (3.5)
Bahadoran, 2010[5]	Not reported	Not reported	Not reported	Not reported
Rashwan, 2010[11]	0/100 vs 7/100 (7.0)	Not reported	Not reported	6/100 (6.0) vs 16/100 (16.0)
Diven, 2012[9]	Not reported	8/125 (6.4) vs 8/127 (6.3)	16/125 (12.8) vs 7/127 (5.5)	7/125 (29.2) vs 8/127 (25.0)
Begum, 2013[6]	Not reported	0/50 vs 6/50 (12.0)	Not reported	4/50 (8.0) vs 6/50 (12.0)
Ozturk, 2014[10]	4/66 (6.1) vs 6/64 (9.4)	Not reported	Not reported	10/66 (15.2) vs 5/64 (7.8)
Bor, 2015[7]	Not reported	16/100 (16) vs 22/100 (22)	Not reported	93/100 (93.0) vs 89/100 (89.0)
Chopra, 2015[8]	Not reported	Not reported	Not reported	8/53 (15.1) vs 11/53 (20.7)
Total	24/386 (6.2) vs 51/390 (13.1)	8/175 (4.6) vs 14/177 (7.9)	16/125 (12.8) vs 7/127 (5.5)	140/714 (19.6) vs 149/720 (20.7)
I^2	0%	69%	Not applicable	44%
RR (95% CI)	**0.53 (0.33–0.84)**	0.39 (0.03–5.22)	2.32 (0.99–5.45)	0.87 (0.61–1.25)

PPH, postpartum hemorrhage; FHR, fetal heart rate; RR, relative risk.
Data are n/N (%) for number in the intervention group vs number in the control group unless otherwise specified.
Bold indicates statistical significance.

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concurred with the primary analysis (Appendix 11, available online at http://links.lww.com/AOG/B22). Planned subgroup analysis in nulliparous and multiparous women could not be assessed as a result of the limited data available in these subsets of women.

DISCUSSION

This meta-analysis of nine RCTs, including 1,538 singleton gestations at term, showed that discontinuation of oxytocin infusion after the active phase of labor is reached reduces the risk of cesarean delivery and of uterine tachysystole but lengthens the active phase of labor. The rate of oxytocin restarted in the oxytocin discontinuation group was 30%.

One prior meta-analysis has been published on this issue. Vlachos et al[14] in their review found a significantly decreased rate of cesarean delivery among women who discontinued oxytocin as well as decreased rates of uterine tachysystole. This meta-analysis differs from ours in the fact that not all trials were included and statistics were different. Indeed, Vlachos et al performed a systematic review without a formal meta-analysis. Moreover, the two most recent RCTs were not included with approximately 25% less women included in the review.

Our study has several limitations. Only one of the included trials was from the United States, and none was large. We could not perform subgroup analysis by parity. We did not identify any trials on discontinuation of oxytocin after augmentation of labor, so the external validity of our data in this population is unknown. Trials were somewhat different in terms of oxytocin dosing and management and delivery protocol. Only three RCTs[5,8,13] used a placebo (500 mL of 0.9% of NaCl solution) in the control group. Data on parity, cervical ripening, and Bishop score were limited. At least half or more than half of the included women were nulliparous, when parity data were reported, but a separate analysis just on nulliparous or multiparous women was not possible.

Different strategies have been adopted in labor and delivery to improve the successful rate of induction, reduce the length of labor as well as reduce the risk of cesarean delivery.[14–30] Since 1954, when it was isolated and synthesized by Vincent du Vigneaud, oxytocin has become the most widely used obstetric agent for inducing or augmenting labor.[24] However, despite the widespread use, there is no consensus on its mode of administration.[24,25] Two preclinical studies have shown that after 10 hours of oxytocin use, the myometrium receptor concentration diminishes and further oxytocin administration has no or a negative effect on myometrial contractility.[26,27] Despite this evidence, continuous oxytocin infusion during labor has been broadly adopted by the international obstetric community and recommended by guidelines.[28,29] Our study shows no difference in the length of labor comparing discontinuing and discontinuing oxytocin infusion after the active phase of labor has been reached after induction of labor. This may suggest that oxytocin-induced desensitization of the oxytocin receptor, as shown in vitro,[26,27] may also occur in vivo. Once labor has entered the active phase (eg, approximately 5 cm cervical dilation in most included RCTs), further oxytocin seems not to be associated with any benefit other than a shorter labor, but indeed is associated with some harm.

In summary, in singleton gestations with cephalic presentation at term, discontinuation of oxytocin infusion after the active phase of labor is reached reduces the risk of cesarean delivery and of uterine tachysystole in women undergoing induction of labor. Given this evidence, discontinuation of oxytocin infusion once the active stage of labor is established in women being induced should be considered as an alternative and efficacious management plan.

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