Am J Transl Res 2022;14(3):1934-1951
www.ajtr.org /ISSN:1943-8141/AJTR0139967

Review Article

Side-effects of oxytocin in postpartum hemorrhage: a systematic review and meta-analysis

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Received October 21, 2021; Accepted March 3, 2022; Epub March 15, 2022; Published March 30, 2022

Abstract: Objective: To evaluate the side-effects of oxytocin for the prevention of postpartum hemorrhage (PPH) in randomized controlled trials (RCTs). Methods: Electronic databases (Web of Science, Embase, PubMed, Elsevier ScienceDirect, the Cochrane Library, and ClinicalTrials.gov) were searched from the beginning of indexing to Sep 2021. RCTs comparing oxytocin with non-oxytocin uterotonic agent(s) or non-pharmacologic interventions for the prevention of PPH were eligible. Results: Overall, sixty-one RCTs meeting the inclusion criteria were included, involving 68834 participants. Twenty-seven types of side-effects were reported in this study. There were 24, 35, or 2 trials assessed as high medium and low quality, respectively. Compared with non-oxytocin, oxytocin had significantly lower risk for shivering (RR=0.31, 95% CI=0.23-0.41, n=36680), fever (RR=0.27, 95% CI=0.20-0.37, n=34031), and diarrhea (RR=0.48, 95% CI=0.35-0.66, n=30883). Other side-effects were not found associated with oxytocin. Conclusion: Oxytocin use was association with a significantly lower incidence of shivering, fever, and diarrhea events and did not increase risk of other side-effects during the third stage of labor. These observations may aid obstetricians and gynecologists in weighing up the benefits and risks associated with oxytocin in prevention and treatment of PPH during the third stage of labor.

Keywords: Oxytocin, side-effects, postpartum hemorrhage, meta-analysis, systematic review, randomized controlled trials

Introduction

Approximately 300,000 women and adolescent girls die as a result of pregnancy and childbirth-related complications around the world, and over one quarter of all maternal deaths are attributable to postpartum hemorrhage (PPH) every year [1]. Abnormal uterine tone can cause PPH-related maternal mortality and it remains the most common etiology of severe PPH worldwide [2]. Prophylactic uterotonic drugs, such as oxytocin, could decrease excessive blood loss and reduce the incidence of PPH. They are routinely recommended as a choice for prevention and treatment of PPH during the third stage of labor [3].

Oxytocin is almost universally accepted as the first-line agent in the management and prevention of abnormal uterine tone after cesarean and vaginal delivery [4]. Many studies have shown that oxytocin is associated with a substantial reduction in PPH, blood transfusion and the use of additional uterotonics [5-8]. Meanwhile, a number of trials and observational studies have shown that the side-effects of oxytocin include nausea, vomiting, headache, and hemodynamic instability [9-12]. Recently, numerous system review and meta-analysis studies researched the efficacy of oxytocin, but few data have intentionally concentrated on side-effects in clinical trials of oxytocin. Hence, evidence about the safety of oxytocin is needed.

To help inform clinical practice and address this gap, we specifically focused on randomized control trials (RCTs) that examined the side-

effects of oxytocin for the prevention of PPH during the third stage of labor in this systematic review and meta-analysis. The primary objective was to characterize side-effects occurring in clinical trials of oxytocin, compared to any non-oxytocin uterotonic agent(s) and non-pharmacologic interventions. Further objectives were to explore the possible confounding risk factors of side-effects for oxytocin.

Materials and methods

The PRISMA Statement and Checklist have been followed in this systematic review and meta-analysis [13]. The protocol was registered in advance in PROSPERO (Identifier: CRD420-19119768) [14].

Search strategy

An academic librarian developed the search strategies (Supplementary File 1). Searched databases included Web of Science, Embase, PubMed, Elsevier ScienceDirect, the Cochrane Library, and ClinicalTrials.gov from the earliest available online indexing year until January 1, 2019, and updated on Sep 1, 2021. There were no language restrictions. Additional eligible bibliographies of included studies were also identified and authors were contacted to obtain unpublished data.

Eligibility criteria

The inclusion criteria included: (1) RCTs comparing oxytocin with non-oxytocin uterotonic agent(s) (misoprostol, carbetocin, ergometrine/methylergometrine, prostaglandins, placebo, or no treatment), non-pharmacologic interventions (uterine massage, controlled cord traction, cord clamping); (2) trials enrolling women in cesarean section or vaginal birth; and (3) trials providing adverse events or side effects data. Exclusion criteria were: (1) RCTs without oxytocin group; (2) RCTs comparing oxytocin with syntometrine (oxytocin plus ergometrine) or misoprostol plus oxytocin group; and (3) quasi-randomised trials. Using a standardized form, reviewers screened titles, abstracts, and full-text articles to assess their eligibility. Any disagreements were resolved by consensus.

Data extraction

A blank electronic form was created on Microsoft Excel to extract the eligible studies' data. From each included RCT, the information of the first author, year of publication, country of origin, clinical trial registration number, trial duration, funding source, participant characteristics (age, route of delivery, risk of PPH, and number of participants in each group), oxytocin characteristics (dosage and route of administration), and the types and frequency of side-effects, was extracted from each included study.

Risk of bias assessment

The methodological quality was stated based on the Cochrane handbook [15]. Each quality item in the included study was assessed and classified as high-, unclear-, or low-risk of bias. The studies included were defined as high-, medium-, or low-quality. Regardless of the results of other items, if random sequence generation or allocation concealment was defined as high-risk of bias, the studies were graded as low-quality. If random sequence generation and allocation concealment were all defined as low-risk of bias, while all other items were not defined as high-risk of bias, the studies were graded as high-quality. Other included studies were graded as unclear-quality.

Data analysis

Data analysis was performed by using R software 3.0.3 and Review Manager 5.3. The dichotomous outcome was shown as the risk ratios (RRs) and 95% confidence intervals (CIs). Based on the Cochrane Handbook, 0.5 was added to each cell in the fourfold table if one group reported zero event; studies were excluded if both groups reported zero event [15].

Fixed- or random-effect was used to pool the results. Random-effect was presented given heterogeneity among studies. Tau^2 and I^2 statistics were used to calculate the statistical heterogeneity. We planned to perform subgroup analysis when ten or more studies were included in the side-effects. Subgroup analysis was performed in route of administration (intramuscular [i.m.] or intravenous [i.v.]), dose (standard dose [10 iu], high dose, or low dose), mode of delivery (cesarean section [CS] or vaginal birth [VD]), risk of PPH (low risk, high and low risk, or high risk), controlled-intervention (misoprostol, carbetocin, ergometrine, prostaglandins, or placebo), trial registration

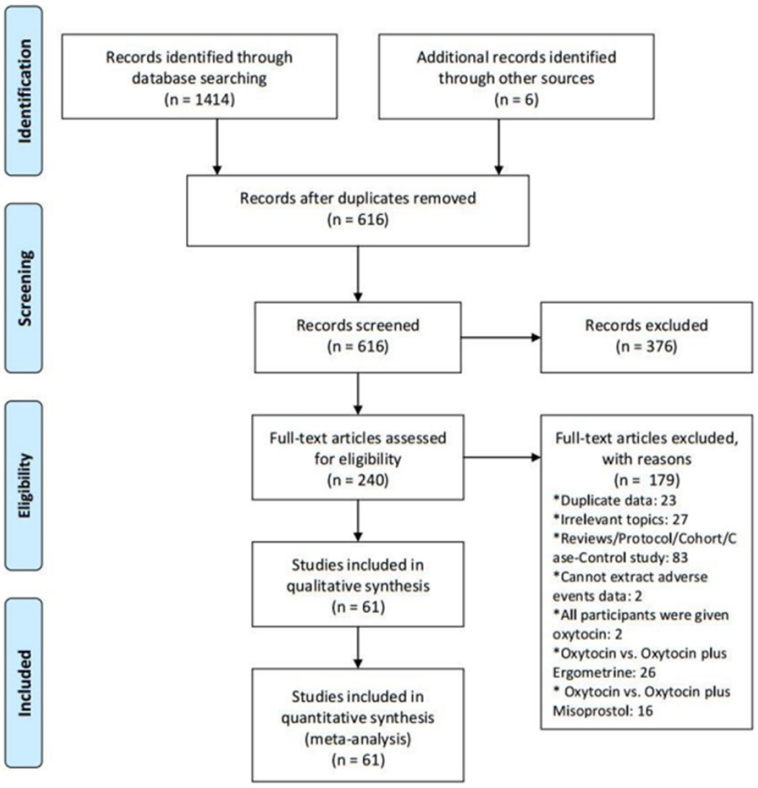

Figure 1. Flow chart of systematic review and meta-analysis.

(yes or no), funding source (public institution, drug company, or none), published year (before-2000, 2000-2010, or 2011-present) and region (Africa, America, Asia, Europe, or Mixed). Meanwhile, we also performed a cumulative meta-analysis ranked by year published to examine the stability and sufficiency of evidence as it was accumulated over time. Publications bias was evaluated using Begg and Egger tests. Funnel plot was also provided if ten or more studies were included.

Results

Study selection and characteristics

There are 1420 records through the initial search. Six hundred and sixteen records were screened for full-text review after removing duplicates and 555 were excluded. Overall, sixty-one RCTs meeting the inclusion criteria were included, involving 68834 participants (**Figure 1**).

Table 1 showed the clinical and methodological characteristics of the included studies. These studies were published between 1979 and 2018. The median number of sample sizes per study was 220 (range, 30-29497). Totally, twenty-seven types of side-effects were reported in this study. Eight side-effects, including vomiting, shivering, nausea, fever, headache, diarrhea, flushing, and dizziness, were reported in more than ten trials. Only one study reported serious adverse event [12], leukocytosis [16], wheezing [17], arm pain [17] and xerostomia [6] (**Figure 2**).

Participants received oxytocin via intramuscular injection in twenty-two trials, and underwent vaginal birth in thirty-nine trials. Twenty trials provided the trial registration number. Twenty-five trials comprised women at low risk for PPH, 17 trials comprised women at high and low risk, and 34 trials comprised women at high risk. Twenty-three trials stated that their funding came from public institution, 4 trials from drug company, and 34 trials did not state the source of the funds. Thirty-four trials used standard dose, 10 trials used low dose, and 17 trials reported high dose. Fifty-eight trials were identified as two-arms, including oxytocin vs. misoprostol (38 trials) [18-55], carbetocin (14 trials) [11, 12, 16, 17, 56-65], ergometrine (4 trials) [66-69], prostaglandins (1 trial) [70], and placebo (1 trial) [71]; and three trials were identified as three-arms, including oxytocin vs. misoprostol vs. ergometrine (2 trials) [72, 73], and oxytocin vs. carbetocin vs. placebo (1 trial) [6].

Risk of bias

Figures 3 and **4** showed the detailed risk of bias of the included studies. Fifty RCTs were randomized, and 37 of them underwent an adequate allocation and setting blinding. Thirty-five trials blinded outcome assessors and 44 RCTs described the incomplete outcome data or provided the complete outcome data. There were 24, 35, or 2 trials assessed as high, medium and low quality, respectively.

Table 1. General characteristics of included studies

First author	Publish Year	Trial Phase	Trail No.	Funded	Country	Risk for PPH	Delivery Mode	Interventions (sample size; dose; adm)	Side effects
Mannaerts D [56]	2018	NA	ISRCTN95504420	NA	Belgium	L	CS	Oxytocin (26; 20 iu, i.v.) vs. Carbetocin (32; 100 ug, i.v.)	Nausea Flushing Hypotension Vomiting
Taheripanah R [11]	2018	II	NCT02079558	Shahid Beheshti University of Medical Sciences	Iran	H	CS	Oxytocin (110; 30 iu, i.v.) vs. Carbetocin (110; 100 ug, i.v.)	Vomiting Headache Nausea Tremor Dizziness Pruritus
Widmer M [12]	2018	III	Australian New Zealand Clinical Trials Registry number, ACTRN12614000870651; EudraCT number, 2014-004445-26; and Clinical Trials Registry-India number, CTRI/2016/05/006969	Merch Sharpe & Dohme	Argentina; Egypt; India; Kenya; Nigeria; Singapore; South Africa; Thailand; Uganda; the United Kingdom	L	VD	Oxytocin (14743; 10 iu, i.m.) vs. Carbetocin (14754; 100 ug, i.m.)	Chest pain Flushing Abdominal pain Vomiting
Shady NW [55]	2017	NA	NA	NA	Egypt	L	VD	Oxytocin (120; 10 iu, i.v.) vs. Misoprostol (120; 600 ug, oral) vs. Tranexamic acid + Misoprostol (120; 1000 mg + 600 ug, oral)	Vomiting Nausea Diarrhea
El Behery MM [57]	2016	NA	NA	NA	Egypt	H	CS	Oxytocin (90; 20 iu, i.v.) vs. Carbetocin (90; 100 ug, i.v.)	Headache Nausea Vomiting Sweating Palpitation Fever
Gavilanes P [18]	2016	NA	NA	NA	Ecuador	H	CS	Oxytocin (50; 10 iu, i.v.) vs. Misoprostol (50; 400 ug, s.l.)	Shivering Nausea Vomiting Headache
Maged AM [59]	2016	NA	NA	NA	Egypt	H	VD	Oxytocin (100; 100 ug, i.m.) vs. Carbetocin (100; 100 ug, i.m.)	Nausea Vomiting Tachycardia Flushing Dizziness Headache Shivering Anemia Metallic taste Dyspnea Palpitations Itching

Maged AM [58]	2016	III	NCT02304055	Cairo University	Egypt	H	VD	Oxytocin (50; 5 iu, i.v.) vs. Carbetocin (50; 100 ug, i.v.)	Nausea Vomiting Tachycardia Flushing Dizziness Headache Shivering Metallic taste Dyspnea Palpitations Itching
Othman ER [20]	2016	II	NCT02562300	Assiut University	Egypt	L	CS	Oxytocin (60; 20 iu, i.v.) vs. Misoprostol (60; 400 ug, sub)	Pyrexia Shivering Vomiting Headache Metallic taste Giddiness
Razali N [61]	2016	NA	ISRCTN18976822	the University of Malaya	Malaysia	L	CS	Oxytocin (271; 10 iu, i.v.) vs. Carbetocin (276; 100 ug, i.v.)	Arrhythmias
Sunil Kumar KS [60]	2016	NA	NA	NA	India	L	VD	Oxytocin (100; 10 iu, i.m.) vs. Carbetocin (100; 125 ug, i.m.)	Nausea Vomiting Shivering Diarrhea Fever
Musa AO [19]	2015	NA	PACTR201407000825227	University of Ilorin Teaching Hospital	Nigeria	L	VD	Oxytocin (100; 10 iu, i.m.) vs. Misoprostol (100; 600 ug, p.o.)	Nausea Diarhea Shivering Pyrexia
Pakniat H [21]	2015	II	NCT01571323 and AC-TRN12612000095864	Qazvin University Of Medical Sciences	Iran	L	CS	Oxytocin (50; 20 iu, i.v.) vs. Misoprostol (50; 400 ug, sub)	Nausea Vomiting Dyspnea Shivering Fever Chest pain
Priya GP [22]	2015	NA	NA	NA	India	L	VD	Oxytocin (250; 10 iu, i.m.) vs. Misoprostol (250; 400 ug, sub)	Nausea Vomiting Diarrhea Fever Shivering
Atukunda EC [23]	2014	III	NCT01866241	the Father Bash Foundation and Divine Mercy Hospital scholar-ship awards to ECA	Uganda	HL	VD	Oxytocin (570; 10 iu, i.m.) vs. Misoprostol (570; 600 ug, s.l.)	Vomiting Nausea Headache Fever Shivering Diarrhea Afterpains
Ezeama CO [66]	2014	NA	Pan African Clinical Trial Registry: 201105000292708	NA	Nigeria	HL	VD	Oxytocin (151; 10 iu, i.m.) vs. Ergometrine (149; 500 ug, i.m.)	Nausea Vomiting Headache Hypertension

Rajaei M [24]	2014	I	NCT01863706	Hormozgan University of Medical Sciences	Iran	HL	VD	Oxytocin (200; 20 iu, i.v.) vs. Misoprostol (200; 400 ug, p.o.)	Hypotension Fever Chills
Tewatia R [25]	2014	NA	NA	NA	India	L	VD	Oxytocin (50; 10 iu, i.v.) vs. Misoprostol (50; 600 ug, s.l.)	Fever Shivering Nausea Vomiting Diarrhea
Fazel MR [26]	2013	NA	NA	Kashan University of Medical Sciences	Iran	H	CS	Oxytocin (50; 10 iu, i.v.) vs. Misoprostol (50; 400 ug, i.v.)	Nausea Vomiting Shivering Hyperpyrexia Chest pain
Mukta M [27]	2013	NA	NA	NA	India	HL	VD	Oxytocin (100; 10 iu, i.m.) vs. Misoprostol (100; 600 ug, p.o.)	Shivering Pyrexia Abdominal pain Diarrhea Nausea Vomiting
Rosseland LA [6]	2013	IV	NCT00977769	Ferring Pharmaceutical	Norway	H	CS	Oxytocin (26; 5 iu, i.v.) vs. Carbetocin (25; 100 ug, i.v.) vs. placebo	Metallic taste Xerostomia Nasal congestion Headache Flushing Palpitations Shortness of breath Chest pain Feeling of warmth
Adanikin AI [28]	2012	NA	NA	NA	Nigeria	H	CS	Oxytocin (109; 20 iu, i.v.) vs. Misoprostol (109; 600 ug, rec)	Nausea Vomiting Shivering Pyrexia
Badejoko OO [29]	2012	NA	ERC/2009/03/04	NA	Nigeria	HL	VD	Oxytocin (132; 20 iu, i.v.) vs. Misoprostol (132; 600 ug, rec)	Vomiting Pyrexia Shivering
Bellad MB [31]	2012	III	NCT01373359	Jawaharlal Nehru Medical College	India	L	VD	Oxytocin (331; 10 iu, i.m.) vs. Misoprostol (321; 400 ug, s.l.)	Nausea Vomiting Shivering Fever
Chaudhuri P [30]	2012	NA	CTRI/2009/091/000672	NA	India	L	VD	Oxytocin (265; 10 iu, i.m.) vs. Misoprostol (265; 400 ug, s.l.)	Shivering Fever Vomiting Nausea Diarrhea
Moertl MG [63]	2011	NA	EudraCT number: 2007-005498-78; NCT01277978	Medical University of Graz	Austria	H	CS	Oxytocin (28; 5 iu, i.v.) vs. Carbetocin (28; 100 ug, i.v.)	Nausea Flushing Headache Tachycardia Shortness of breath Feeling warm

Owonikoko KM [32]	2011	NA	NA	NA	Nigeria	H	CS	Oxytocin (50; 20 iu, i.v.) vs. Misoprostol (50; 400 ug, s.l.)	Nausea Vomiting Headache Shivering Hypotension
Reyes OA [62]	2011	NA	NA	NA	Panama	H	VD	Oxytocin (29; 20 iu, i.v.) vs. Carbetocin (26; 100 ug, i.v.)	Headaches Palpitations Fever Nausea Vomiting Hot sensation Flushing Malaise
Shrestha A [33]	2011	NA	NA	NA	Nepal	L	VD	Oxytocin (100; 10 iu, i.m.) vs. Misoprostol (100; 1000 ug, p.r.)	Shivering Abdominal pain
Afolabi EO [34]	2010	NA	NA	NA	Nigeria	Low	VD	Oxytocin (100; 10 iu, i.m.) vs. Misoprostol (100; 400 ug, p.o.)	Nausea Shivering
Attilakos G [17]	2010	NA	EudraCT number: 2005-002812-94	Ferring UK funded the cost of preparation of the 'blinded'drug ampoules	UK	High	CS	Oxytocin (189; 5 iu, i.v.) vs. Carbetocin (188; 100 ug, i.v.)	Nausea Vomiting Headache Tachycardia Metallic taste Backache Abdominal pain Arm pain Trigeminy Flushed Shortness of breath Wheezing Tremors Hypotension Sweating Tightness throat ST depression Blurred vision
Blum J [35]	2010	NA	NCT00116350	The Bill & Melinda Gates Foundation	Burkina Faso; Egypt; Turkey; Vietnam	L	CS	Oxytocin (402; 40 iu, i.v.) vs. Misoprostol (407; 800 ug, sub)	Vomiting Nausea Shivering Fever Dizziness Diarrhoea
Butwick AJ [71]	2010	NA	NA	Stanford University School of Medicine	USA	H	CS	Oxytocin (15, 15, 14, 15; 0.5 iu, 1 iu, 3 iu, 5 iu, i.v.) vs. placebo	Hypotension Tachycardia Nausea
Chaudhuri P [36]	2010	NA	CTRI/2009/091/000075	NA	India	H	CS	Oxytocin (94; 40 iu, i.v.) vs. Misoprostol (96; 800 ug, p.r.)	Shivering Pyrexia Vomiting

Winikoff B [37]	2010	NA	NCT00116350	the Bill & Melinda Gates Foundation	Ecuador, Egypt, Vietnam	L	VD	Oxytocin (490; 40 iu, i.v.) vs. Misoprostol (488; 800 ug, sub)	Vomiting Nausea Shivering Fever Fainting Diarrhoea
Borruto F [64]	2009	NA	NA	NA	Italy	H	CS	Oxytocin (52; 10 iu, i.v.) vs. Carbetocin (52; 100 ug, i.v.)	Anemia Arrhythmias Abdominal pain Nausea Vomiting Metallic taste Heat sensation Back pain Headache Tremor Dizziness Difficulty in breathing Dyspnea Chest pain Pruritus Flushing Hypotension
Nasr A [38]	2009	NA	NA	NA	Egypt	L	VD	Oxytocin (257; 5 iu, i.m.) vs. Misoprostol (257; 800 ug, p.o.)	Nausea Vomiting Diarrhea Shivering Fever
Singh G [72]	2009	NA	NA	NA	India	L	VD	Oxytocin (75; 5 iu, i.v.) vs. Misoprostol (75, 75; 400 ug, 600 ug, s.l.) vs. Ergometrine (75; 200 ug, i.v.)	Fever Shivering
Orji E [67]	2008	NA	NA	NA	Nigeria	HL	VD	Oxytocin (297; 10 iu, i.v.) vs. Ergometrine (303; 250 ug, i.v.)	Nausea Vomiting Headaches Hypertension
Baskett TF [39]	2007	NA	NA	Nova Scotia Health Research Foundation	Canada	HL	VD	Oxytocin (311; 5 iu, i.v.) vs. Misoprostol (311; 400 ug, p.o.)	Shivering Fever
Parsons SM [40]	2007	NA	NA	MaterCare International and the Canadian Foundation for Women's Health	Ghana	HL	VD	Oxytocin (226; 10 iu, i.m.) vs. Misoprostol (224; 800 ug, p.r.)	Nausea Vomiting Shivering Fever Hypertension
Saito K [68]	2007	NA	NA	NA	Japan	L	VD	Oxytocin (156; 5 iu, i.m.) vs. Ergometrine (187; 200 ug, i.m.)	Nausea Headache Dyspnea Hypertension

Gupta B [41]	2006	NA	NA	NA	India	HL	VD	Oxytocin (100; 10 iu, i.m.) vs. Misoprostol (100; 600 ug, p.r.)	Shivering Nausea Fever
Parsons SM [42]	2006	NA	NA	Matercare International and the Society of Obstetricians and Gynaecologists of Canada	Ghana	HL	VD	Oxytocin (225; 10 iu, i.m.) vs. Misoprostol (225; 800 ug, p.o.)	Nausea Vomiting Diarrhea Shivering Fever Hypertension
Vimala N [43]	2006	NA	NA	Division of Reproductive Health and Nutrition, Indian Council of Medical Research (ICMR), New Delhi	India	H	CS	Oxytocin (50; 20 iu, i.v.) vs. Misoprostol (50; 400 ug, s.l.)	Pyrexia Shivering Vomiting Headache Metallic taste Giddiness
Zachariah ES [73]	2006	NA	NA	NA	India	HL	VD	Oxytocin (617; 10 iu, i.m.) vs. Misoprostol (730; 400 ug, p.o.) vs. Ergometrine (676; 2000 ug, i.v.)	Fever Nausea Vomiting Shivering Diarrhea Headache
Boucher M [16]	2004	NA	NA	NA	Canada	H	VD	Oxytocin (77; 10 iu, i.v.) vs. Carbetocin (83; 100 ug, i.m.)	Headache Chills Abdominal pain Dizziness Tremor Vasodilatation Leukocytosis Nausea Vomiting Pruritis
Caliskan E [44]	2003	NA	NA	NA	Turkey	HL	VD	Oxytocin (384; 10 iu, i.v.) vs. Misoprostol (388; 600 ug, p.o.)	Shivering Vomiting Diarrhea Fever
Oboro VO [45]	2003	NA	NA	NA	Nigeria	L	VD	Oxytocin (249; 10 iu, i.m.) vs. Misoprostol (247; 600 ug, p.o.)	Nausea Vomiting Diarrhoea Dizziness Shivering Fever
Calişkan E [47]	2002	NA	NA	NA	Turkey	HL	VD	Oxytocin (407; 10 iu, i.v.) vs. Misoprostol (396; 600 ug, p.r.)	Shivering Vomiting Diarrhea Fever
Karkanis SG [46]	2002	NA	NA	The Physicians Services Incorporated Foundation	Canada	L	VD	Oxytocin (110; 10 iu, i.m.) vs. Misoprostol (105; 400 ug, p.r.)	Nausea Vomiting Headache Shivering Abdominal pain Fever

Acharya G [48]	2001	NA	NA	NA	UK	High	CS	Oxytocin (30; 10 iu, i.v.) vs. Misoprostol (30; 400 ug, p.o.)	Vomiting Headache
Bugalho A [49]	2001	NA	NA	Maputo Central Hospital and the Special Program on Research and Research Training in Human Reproduction of WHO	Mozambique	HL	VD	Oxytocin (339; 10 iu, i.m.) vs. Misoprostol (324; 400 ug, p.r.)	Vomiting Diarrhea Shivering
Gerstenfeld TS [50]	2001	NA	NA	NA	USA	HL	VD	Oxytocin (166; 20 iu, i.v.) vs. Misoprostol (159; 400 ug, p.r.)	Shivering
Gülmezoglu AM [51]	2001	NA	NA	UNDP/UNFPA/WHO/ World Bank Special Programme of Research	Argentina; China; Egypt; Ireland; Nigeria; South Africa; Switzerland; Thailand; Vietnam	HL	VD	Oxytocin (9266; 10 iu, i.v./i.m.) vs. Misoprostol (9264; 600 ug, p.o.)	Shivering Fever Nausea Vomiting Diarrhoea
Kundodyiwa TW [52]	2001	NA	NA	NA	Zimbabwe	L	VD	Oxytocin (256; 10 iu, i.m.) vs. Misoprostol (243; 400 ug, p.o)	Shivering Vomiting Nausea Diarrhea Fever Hypertension
Lokugamage AU [53]	2001	NA	NA	NA	UK	H	CS	Oxytocin (20; 10 iu, i.v.) vs. Misoprostol (20; 500 ug, p.o.)	Shivering
Walley RL [54]	2000	NA	NA	MaterCare International and the Canadian International Development Agency	Ghana	L	VD	Oxytocin (198; 10 iu, i.m.) vs. Misoprostol (203; 400 ug, p.o.)	Nausea Vomiting Diarrhoea Shivering Fever
Dansereau J [65]	1999	NA	NA	A Clinical Research Grant from Ferring Inc., Canada	Canada	H	CS	Oxytocin (330; 25 iu, i.v.) vs. Carbetocin (329; 100 ug, i.v.)	Abdominal pain Back pain Headache Nausea Metallic taste Flushing Sweating Tremors Vomiting Feeling of warmth
Chou MM [70]	1994	NA	NA	Tachung Veterans General Hospital	China	HL	CS	Oxytocin (30; 20 iu, i.v.) vs. Prostaglandin (30; 125 ug, i.m.)	Vomiting Diarrhea Flushing Dizziness Pyrexia
Moir DD [69]	1979	NA	NA	NA	UK	L	VD	Oxytocin (44; 10 iu, i.v.) vs. Ergometrine (44; 500 ug, i.v.)	Vomiting

CS: cesarean section; H: high risk for PPH; HL: high and low risk for PPH; L: low risk for PPH; NA: none; PPH: postpartum hemorrhage; VD: vaginal birth.

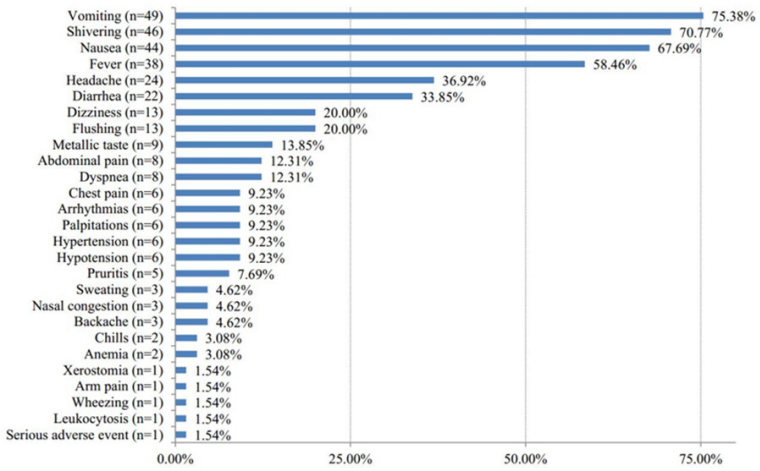

Figure 2. Number and proportions of each side-effect in this study.

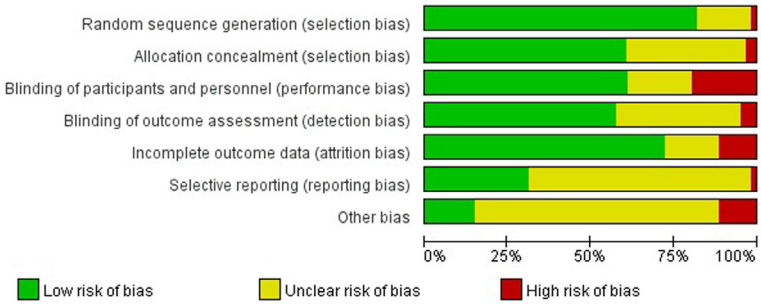

Figure 3. Proportions of trials that met each criterion for risk of bias across the 61 included randomized clinical trials.

Outcomes

Figure 5 showed pooled RRs for side-effects. Compared with non-oxytocin, oxytocin had significantly lower risk for shivering (RR=0.31, 95% CI=0.23-0.41, n=36680), fever (RR=0.27, 95% CI=0.20-0.37, n=34031), and diarrhea (RR=0.48, 95% CI=0.35-0.66, n=30883). However, other side-effects, such as vomiting, nausea, headache, flushing, dizziness, etc., were not associated with oxytocin.

Subgroup analysis showed that oxytocin was associated with lower risk for vomiting in i.m. group (RR=0.65, 95% CI=0.54-0.80, n=39041) and VD group (RR=0.50, 95% CI=0.36-0.69, n=62493), low risk in PPH group (RR=0.69, 95% CI=0.53-0.90, n=36624), high risk in PPH group (RR=0.42, 95% CI=0.25-0.71, n=26874), misoprostol group (RR=0.59, 95% CI=0.50-0.69, n=31887), ergometrine group (RR=0.12, 95% CI=0.07-0.19, n=2283), and public institution funding group (RR=0.62, 95% CI=0.45-0.85, n=25094), slightly lower risk in trial registration group (RR=0.65, 95% CI=0.43-0.99, n=35341), and higher risk for headache in CS group (RR=1.81, 95% CI=1.16-2.82, n=2184) (Supplementary File 2).

However, oxytocin was not associated with lower risk for shivering in drug company funding group (RR=1.35, 95% CI=0.92-1.99, n=1036), carbetocin group (RR=1.29, 95% CI=0.92-1.81, n=2024), and ergometrine group (RR=0.59, 95% CI=0.31-1.12, n=1293); high risk for fever in PPH group (RR=0.67, 95% CI=0.36-1.23, n=949), drug company funding group (RR=1.26, 95% CI=0.29-5.47, n=102), carbetocin group (RR=0.57, 95% CI=0.17-1.91, n=490), ergometrine group (RR=0.34, 95% CI=0.11-1.03, n=1293), prostaglandins group (RR=2.00, 95% CI=0.19-20.90, n=60), and placebo group (RR=1.92, 95% CI=0.19-19.90, n=51); for diarrhea in low dose group (RR=0.83, 95% CI=0.26-2.70, n=514) and high dose group (RR=0.85, 95% CI=0.29-2.51, n=1849), CS group (RR=0.80, 95% CI=0.22-2.92, n=871), ergometrine group (RR=0.22, 95% CI=0.01-4.55, n=1295), and placebo group (RR=3.00, 95% CI=0.13-70.83, n=62) (Supplementary File 2).

Supplementary File 3 showed the results of cumulative meta-analysis. Cumulative meta-analysis showed that oxytocin use was association with a significantly lower incidence of shivering, fever, and diarrhea events since 2001 (Supplementary File 3, Figures S2, S4 and S6). However, other side-effects were not associated with oxytocin use (Supplementary File 3, Figures S1, S3, S5, S7 and S8).

Publication bias

Begg and Egger tests found that there was no publication bias for side-effects (Supplementary File 2). Meanwhile, funnel plots also

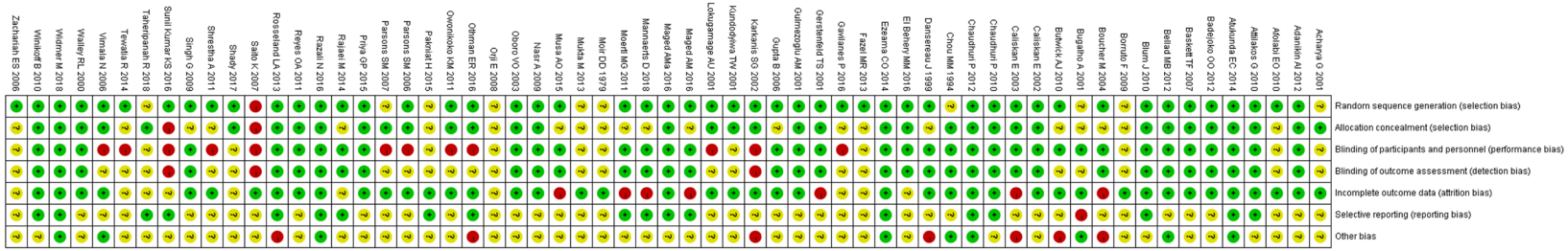

Figure 4. Results of the risk of bias for 61 included randomized clinical trials. Green means low risk; yellow means unclear risk; red means high risk.

Outcome	No. of Studies	No. of Events	No. of Participants	RR (95%CI)	*p* Heterogeneity	*p* Begger	*p* Egger
Vomiting	49	989	66054	0.74 (0.54-1.01)	0.0001	0.9450	0.4991
Shivering	46	5135	36680	0.31 (0.23-0.41)	0.0001	0.1160	0.0035
Nausea	44	1292	34458	0.92 (0.68-1.23)	0.0001	0.7249	0.5403
Fever	38	1629	34031	0.27 (0.20-0.37)	0.0001	0.8222	0.7689
Headache	24	384	7943	1.19 (0.82-1.74)	0.0054	0.6723	0.3670
Diarrhea	22	208	30883	0.48 (0.35-0.66)	0.3575	0.3665	0.2431
Flushing	13	364	31438	0.85 (0.72-1.01)	0.5039	0.2044	0.3047
Dizziness	13	289	3787	1.00 (0.80-1.25)	0.2413	0.4354	0.6398
Metallic taste	9	86	1776	0.76 (0.45-1.27)	0.1038	0.9161	0.0473
Abdominal pain	8	513	31414	0.94 (0.81-1.09)	0.9028	0.2751	0.4029
Dyspnea	8	28	1341	0.83 (0.38-1.81)	0.8910	0.9008	0.9250
Chest pain	6	43	29907	0.84 (0.43-1.65)	0.1678	0.7194	0.1582
Arrhythmias	6	77	873	1.24 (0.32-4.76)	0.0295	0.9999	0.3275
Palpitations	6	22	842	1.66 (0.01-4.06)	0.4430	0.9999	0.9420
Hypertension	6	93	2652	0.23 (0.05-1.05)	0.0407	0.7194	0.6916
Hypotension	6	59	1071	1.22 (0.74-2.01)	0.2542	0.7194	0.1414
Pruritis	5	55	792	0.84 (0.10-6.86)	0.0113	0.4833	0.7813
Nasal congestion	3	6	483	0.98 (0.17-5.53)	0.6397	0.9999	0.9631
Sweating	3	50	1226	2.80 (0.34-22.90)	0.0139	0.9999	0.8601
Backache	3	34	1144	1.16 (0.59-2.30)	0.4344	0.9999	0.6804

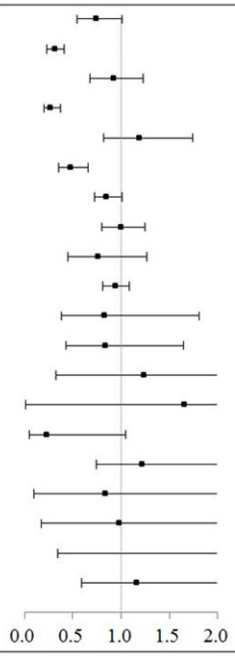

Figure 5. Results of side-effects in this meta-analysis.

observed symmetry for vomiting, shivering, nausea, fever, headache, diarrhea, flushing and dizziness (Supplementary File 4, Figures S9, S10, S11, S12, S13, S14, S15 and S16).

Discussion

This is the first large systematic review and meta-analysis, to our knowledge, to intentionally assess the side-effects of oxytocin for the prevention of PPH during the third stage of labor. Sixty-one RCTs based on 68834 participants reported 27 types of side-effects. Results showed that oxytocin could decrease the risk of shivering, fever, and diarrhea, and did not show evidence of an increased risk of other side-effects.

Oxytocin is currently regarded as the gold standard for prevention and treatment of PPH during the third stage of labor. Observational articles and RCTs indicated that vomiting, nausea, shivering and fever are the most frequent side-effects encountered when oxytocin is used for the prevention of PPH. Other side-effects include gastro-intestinal disorders (diarrhea, metallic taste, and abdominal pain), heart disorders (arrhythmias and palpitations), blood system disorders (anemia and leukocytosis), vascular disorders (flushing, hypotension, and hypertension), respiratory disorder (dyspnea, wheezing, and nasal congestion), nervous system disorders (headache, and dizziness) and other general disorders (pruritis, sweating, backache, chills, xerostomia, chest pain and arm pain). These side-effects are generally related to the maternal condition, mode of delivery, dose, and route of administration.

As a secondary outcome, the side-effects of oxytocin use have been mentioned in previous studies. There is difference between our finding and previous studies for the side-effects after using oxytocin for preventing PPH during the third stage of labor. Many guidelines, including Royal College of Obstetricians and Gynaecologists [74] and World Health Organization [3], recommend oxytocin 10 iu intramuscularly or intravenously. Interestingly, it was found that recommended dose of oxytocin (10 iu) could reduce the risk of diarrhea in this meta-analysis. However, this phenomenon was not found in the low- and high-groups. However, it needs to be cautious to interpret this finding because data for low- or high-dose group were rare. Small sample size could lead to false neg-

atives in clinical trials. The meta-analysis by Zhou et al. [75] found no significant differences between the intramuscular and intravenous groups. RCTs [76-78] and systematic review [79, 80] also demonstrated that intravenous and intramuscular routes have a similar efficacy and side-effects. In this side-effects focused study, although the route administration did not have significant effect on the side-effects, the risk of vomiting was significantly reduced via IM injection. The main reason for this difference is that previous studies mostly grouped all sided-effects into only one indicator, while our study analyzed the effect of each side-effect in a more detailed way.

Compared with other several different uterotonics, oxytocin is the most widely recommended and used as the main intervention for preventing PPH during the third stage of labor. However, despite its widespread use, there is no consensus with clear evidence on the side-effects of oxytocin for the prevention of PPH. This study involved a large number of RCT articles and all side-effects. Sufficient sample size could improve the precision and comprehension of risk estimates, especially for rare side-effects. And, the results more closely reflect the real clinical practice than the rigorous single clinical trial. Through these results, obstetricians and gynaecologists could weigh up the benefits and risks associated with oxytocin in the prevention and treatment of PPH during the third stage of labor, and further help inform best practice in clinical care.

This meta-analysis has several strengths. The major strength of this study is the large number of included studies, sufficient sample size, and all side-effects. This can improve the precision and comprehension of risk estimates. Given that side-effect is a rare outcome, the relatively large number of participants is necessary to obtain reliable conclusions. A further strength is the data from multiple studies and centers, including participants with different conditions. It more closely reflects the real clinical practice than the rigorous single clinical trial. In addition, most of the included trials had high and moderate quality. Only two trials [60, 68] had low quality base on Cochrane handbook tool assessment. This could ensure the quality of the results in meta-analysis.

Meanwhile, several limitations of this study should be mentioned. First, some low incidence of certain side-effects was not reported in one or two groups in some articles. The continuity correction of adding 0.5 to each cell in the fourfold table was applied in the studies with zero events for one group to improve the analysis and they were excluded for trials with double zero events in both groups from the analysis. This implies that there is a certain error between the pooled RR and the true value. Second, these sixty-one included RCTs ranged nearly 40 years from 45 countries and regions. Although subgroup and cumulative analyses were performed, there could have been inconsistency in the definition and diagnosis of the side-effects in different time, researchers and countries and regions, resulting in difficulty in comparison of studies. These could result in a bias of reported incidence rates in the clinical trials. Third, side-effects were reported, but no data were provided in two trials [5, 81], and we excluded them in these studies. Although no publication bias was found, this could increase the publication bias risk. Fourth, heterogeneity was found in some side-effects. Subgroup analysis could partially explain the existence of heterogeneity, but not completely. Some findings might be statistically significant by chance.

In brief, oxytocin use was associated with a significantly lower incidence of shivering, fever, and diarrhea events and did not increase the risk of other side-effects during the third stage of labor. These observations may aid obstetricians and gynaecologists in weighing up the benefits and risks associated with oxytocin in the prevention and treatment of PPH during the third stage of labor.

Acknowledgements

We appreciate the efforts of all the researchers whose articles were included in this study. And, no funding or sponsorship was received for this study or publication of this article.

Disclosure of conflict of interest

None.

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Supplementary File 1. Appendix_1_Search strategies

((randomized controlled trial [Publication Type]) OR (controlled clinical trial [Publication Type]) OR randomized [Title/Abstract] OR placebo [Title/Abstract] OR drug therapy [subheading] OR randomly [Title/Abstract] OR trial [Title/Abstract] OR groups [Title/Abstract]) AND ((third stage [All Fields]) AND (labor [All Fields] OR labour [All Fields]) AND Oxytocin [All Fields] AND (haemorrhage [All Fields] OR hemorrhage [All Fields]) AND postpartum [All Fields]).

Supplementary File 2. Results

Side-effects	Outcome	No of Studies	No of Done	No of Participants	RR (95%CI)	R/F	Heterogeneity			Begger		Egger	
							tau^2	I^2	p	Kendall's tau	p	z	p
Vomiting	Overall	49	989	66054	0.74 (0.54 to 1.01)	R	0.5888	68.93	0.0001	-0.0068	0.9450	0.6759	0.4991
	Type												
	IV	31	604	27013	0.81 (0.52 to 1.26)	R	0.9303	75.04	0.0001	0.0517	0.6833	0.9330	0.3508
	IM	18	385	39041	0.65 (0.54 to 0.80)	F	0.0000	0.00	0.8484	-0.0658	0.7045	-0.0573	0.9543
	Dose												
	Low dose	4	29	1195	0.98 (0.46 to 2.09)	F	0.0000	0.00	0.5078	-0.6667	0.3333	-1.3161	0.1881
	Standard dose	30	702	60740	0.68 (0.46 to 1.00)	R	0.5585	68.62	0.0001	-0.0529	0.6972	0.6585	0.5102
	High dose	15	258	4119	0.87 (0.47 to 1.61)	R	0.9064	74.40	0.0001	0.1429	0.4951	0.8175	0.4137
	Delivery												
	VD	32	742	62493	0.50 (0.36 to 0.69)	R	0.3108	54.74	0.0002	-0.0101	0.9354	1.0751	0.2823
	CS	17	247	3561	1.35 (0.82 to 2.22)	R	0.5575	61.70	0.0015	0.1912	0.3081	0.2627	0.7928
	Risk												
	L	20	253	36624	0.69 (0.53 to 0.90)	F	0.0455	10.05	0.1360	0.0316	0.8728	0.1785	0.8584
	HL	14	545	26874	0.42 (0.25 to 0.71)	R	0.4552	70.69	0.0001	0.1429	0.5183	1.2630	0.2066
	H	15	191	2556	1.37 (0.80 to 2.37)	R	0.5059	55.19	0.0110	0.0574	0.7662	-0.5546	0.5791
	Drug												
	Misoprostol	32	608	31887	0.59 (0.50 to 0.69)	F	0.0876	24.05	0.1364	0.2339	0.0618	1.7753	0.0758
	Carbetocin	12	216	31822	1.51 (0.80 to 2.85)	R	0.5996	66.31	0.0032	0.1385	0.5352	-0.6095	0.5422
	Ergometrine	4	161	2283	0.12 (0.07 to 0.19)	F	0.5498	44.53	0.1569	0.0001	0.9999	1.4073	0.1593
	Prostaglandins	1	4	62	0.14 (0.01 to 2.65)								
	Trial registration												
	no	34	532	30713	0.78 (0.52 to 1.17)	R	0.6977	64.38	0.0001	-0.0679	0.5731	0.3527	0.7243
	yes	15	457	35341	0.65 (0.43 to 0.99)	R	0.2927	60.04	0.0096	0.0286	0.9226	0.5209	0.6024
	Fund												
	Reseach	17	473	25094	0.62 (0.45 to 0.85)	R	0.1002	31.89	0.0439	0.0147	0.9677	1.1899	0.2341
	Company	3	132	30533	0.94 (0.67 to 1.31)	F	0.0000	0.00	0.5555	0.3333	0.9999	0.9570	0.3385
	None	29	384	10427	0.73 (0.45 to 1.18)	R	0.9160	63.31	0.0001	0.0321	0.8073	0.5519	0.5810
	Year												
	before-2000	4	79	1212	0.85 (0.54 to 1.33)	F	0.0628	10.46	0.2190	-0.6667	0.3333	-1.9295	0.0537
	2001-2010	21	452	29412	0.79 (0.49 to 1.25)	R	0.7105	71.25	0.0010	0.2381	0.1403	2.4562	0.0140
	2011-present	24	458	35430	0.74 (0.46 to 1.19)	R	0.5940	63.82	0.0032	0.1384	0.3455	-0.0322	0.9743

	Region											
	Africa	19	538	7181	0.73 (0.39 to 1.34)	R	1.1360	80.61	0.0001	-0.0235	0.8889	1.0871	0.2770
	America	5	81	1193	0.93 (0.60 to 1.44)	F	0.0001	0.00	0.3317	-0.2000	0.8167	0.1195	0.9049
	Asia	16	100	7175	0.73 (0.48 to 1.10)	F	0.0000	0.00	0.8630	-0.0833	0.6901	-0.9528	0.3407
	Europe	5	59	691	1.84 (0.75 to 4.50)	R	0.4583	48.79	0.0687	0.0001	0.9999	-1.2539	0.2099
	Mixed	4	211	49814	0.29 (0.13 to 0.67)	R	0.1127	54.22	0.0826	0.0001	0.9999	-0.5747	0.5655
Shivering	Overall	46	5135	36680	0.31 (0.23 to 0.41)	R	0.7033	93.27	0.0001	-0.1605	0.1160	-2.9175	0.0035
	Type												
	IV	26	3244	26642	0.33 (0.21 to 0.53)	R	0.9222	93.26	0.0001	-0.2554	0.0704	-3.0106	0.0026
	IM	20	1891	10038	0.27 (0.19 to 0.40)	R	0.5876	91.53	0.0001	-0.1111	0.4952	-1.2365	0.2163
	Dose												
	Low dose	6	134	2046	0.14 (0.02 to 0.89)	R	3.7200	68.83	0.0035	-0.3333	0.4694	-1.6734	0.0943
	Standard dose	28	4191	30549	0.28 (0.20 to 0.39)	R	0.5151	92.58	0.0001	-0.1777	0.1854	-2.3169	0.0205
	High dose	12	810	4085	0.46 (0.25 to 0.84)	R	0.8107	91.43	0.0001	0.0606	0.8406	-1.3653	0.1721
	Delivery												
	VD	32	4624	33439	0.29 (0.22 to 0.39)	R	0.5001	92.42	0.0001	-0.1596	0.2000	-2.4141	0.0158
	CS	14	511	3241	0.35 (0.17 to 0.73)	R	1.4518	89.94	0.0001	-0.0110	0.9999	-2.0814	0.0374
	Risk												
	L	19	1499	7324	0.27 (0.18 to 0.40)	R	0.4656	87.26	0.0001	-0.1294	0.4409	-2.0918	0.0365
	HL	14	3377	27061	0.32 (0.21 to 0.48)	R	0.5198	94.67	0.0001	-0.1648	0.4506	-1.5975	0.1101
	H	13	259	2295	0.35 (0.15 to 0.82)	R	1.6357	83.41	0.0001	-0.1795	0.4354	-2.4034	0.0162
	Drug												
	Misoprostol	37	4959	33363	0.26 (0.20 to 0.35)	R	0.5175	92.33	0.0001	-0.2372	0.0394	-4.1753	0.0001
	Carbetocin	8	136	2024	1.29 (0.92 to 1.81)	F	0.2778	37.56	0.1219	-0.5000	0.1087	-1.2923	0.1962
	Ergometrine	1	40	1293	0.59 (0.31 to 1.12)								
	Trial registration												
	no	33	3693	30998	0.30 (0.21 to 0.41)	R	0.6252	90.23	0.0337	-0.2600	0.0337	-3.6899	0.0002
	yes	13	1442	5682	0.36 (0.19 to 0.68)	R	1.0741	95.87	0.0001	-0.0513	0.8577	0.1096	0.9127
	Fund												
	Reseach	18	3925	25854	0.27 (0.17 to 0.44)	R	0.7664	96.36	0.0001	-0.2026	0.2599	-0.7978	0.4250
	Company	2	92	1036	1.35 (0.92 to 1.99)	F	0.0000	0.00	0.6427	1.0000	0.9999	0.4640	0.6427
	None	26	1118	9790	0.31 (0.22 to 0.44)	R	0.4881	79.04	0.0001	-0.2160	0.1227	-3.7638	0.0002
	Year												
	before-2000	2	135	1060	0.60 (0.12 to 2.93)	R	1.2238	93.97	0.0001	-1.0000	0.9999	-4.0727	0.0001
	2001-2010	25	3876	30370	0.34 (0.24 to 0.47)	R	0.4463	91.23	0.0001	-0.1333	0.3662	-2.2616	0.0237
	2011-present	19	1124	5250	0.25 (0.14 to 0.43)	R	1.0536	89.12	0.0001	-0.0292	0.8903	-1.2506	0.2111
	Region												
	Africa	14	1565	5717	0.27 (0.17 to 0.44)	R	0.6575	93.66	0.0001	-0.3626	0.0795	-2.8267	0.0047
	America	6	206	2083	0.39 (0.12 to 1.30)	R	1.8067	90.44	0.0002	-0.6000	0.1361	-3.0584	0.0022
	Asia	20	722	8040	0.27 (0.16 to 0.44)	R	0.8297	79.85	0.0001	-0.1053	0.5424	-1.0745	0.2826
	Europe	3	34	523	0.65 (0.36 to 1.15)	F	0.2535	28.78	0.1441	-0.3333	0.9999	-0.6554	0.5122
	Mixed	3	2608	20317	0.33 (0.27 to 0.40)	R	0.0198	68.10	0.0341	1.0000	0.3333	2.5985	0.0094

Nausea	Overall	44	1292	34458	0.92 (0.68 to 1.23)	R	0.4996	76.81	0.0001	-0.0381	0.7249	0.6123	0.5403
	Type												
	IV	24	882	24634	0.93 (0.61 to 1.41)	R	0.6485	83.96	0.0001	-0.0217	0.9024	1.1061	0.2687
	IM	20	410	9824	0.92 (0.64 to 1.33)	R	0.2059	39.35	0.0090	-0.0842	0.6308	-0.3706	0.7110
	Dose												
	Low dose	7	43	1622	0.84 (0.46 to 1.55)	F	0.0000	0.00	0.8294	0.1429	0.7726	0.1896	0.8497
	Standard dose	27	746	29455	0.85 (0.56 to 1.28)	R	0.6960	77.56	0.0001	-0.0199	0.9014	0.7271	0.4671
	High dose	10	503	3381	1.08 (0.92 to 1.27)	F	0.0000	0.00	0.0196	0.0222	0.9999	0.5121	0.6086
	Delivery												
	VD	30	802	31343	0.73 (0.50 to 1.08)	R	0.5771	73.71	0.0001	-0.1126	0.3950	0.3309	0.7407
	CS	14	490	3115	1.18 (1.00 to 1.38)	F	0.0000	0.00	0.0826	0.3407	0.1010	1.4848	0.1376
	Risk												
	L	20	394	7658	0.94 (0.77 to 1.14)	F	0.0355	12.41	0.0461	0.0632	0.7246	-1.0509	0.2933
	HL	10	557	24512	0.74 (0.36 to 1.51)	R	0.9629	89.31	0.0001	0.1111	0.7275	0.9878	0.3232
	H	14	341	2288	1.20 (0.90 to 1.46)	F	0.0381	15.06	0.1043	0.0330	0.9145	0.7730	0.4395
	Drug												
	Misoprostol	27	770	29519	0.86 (0.64 to 1.14)	R	0.1818	52.16	0.0003	0.0712	0.6201	0.7774	0.4370
	Carbetocin	12	337	2371	1.20 (0.97 to 1.47)	F	0.0038	2.06	0.1880	-0.1212	0.6384	-0.2659	0.7903
	Ergometrine	4	182	2536	0.44 (0.12 to 1.60)	R	1.4000	84.42	0.0001	0.3333	0.7500	0.7014	0.4830
	Placebo	1	3	32	5.00 (0.26 to 96.13)								
	Trial registration												
	no	31	725	28934	1.01 (0.67 to 1.52)	R	0.7391	76.61	0.0001	-0.0796	0.5437	0.7059	0.4803
	yes	13	567	5524	0.80 (0.69 to 0.94)	F	0.0581	35.89	0.0247	0.0000	0.9999	-0.1390	0.8894
	Fund												
	Reseach	16	684	24437	0.84 (0.64 to 1.11)	R	0.1037	49.90	0.0044	0.1667	0.3984	1.2547	0.2096
	Company	2	203	1036	1.08 (0.85 to 1.36)	F	0.0000	0.00	0.5009	-1.0000	0.9999	-0.6731	0.5009
	None	26	405	8985	0.92 (0.56 to 1.50)	R	0.9652	70.88	0.0001	-0.1077	0.4574	-0.0023	0.9982
	Year												
	before-2000	2	196	1060	1.10 (0.87 to 1.40)	F	0.0000	0.00	0.8532	1.0000	0.9999	0.1851	0.8532
	2001-2010	19	646	27601	0.87 (0.57 to 1.35)	R	0.5465	78.89	0.0001	-0.1111	0.5340	0.5712	0.5678
	2011-present	23	450	5797	0.94 (0.59 to 1.51)	R	0.6542	67.45	0.0003	0.0909	0.5653	0.2852	0.7755
	Region												
	Africa	18	512	6534	0.73 (0.40 to 1.35)	R	1.0516	79.49	0.0001	-0.0327	0.8814	0.9779	0.3281
	America	6	220	1223	1.10 (0.88 to 1.39)	F	0.0000	0.00	0.4704	0.2000	0.7194	0.4287	0.6681
	Asia	13	166	5789	1.13 (0.77 to 1.65)	R	0.0870	18.80	0.0485	-0.0769	0.7650	-0.9302	0.3523
	Europe	4	65	595	1.29 (0.83 to 2.00)	F	0.0000	0.00	0.6085	0.3333	0.7500	0.1821	0.8555
	Mixed	3	329	20317	0.77 (0.43 to 1.35)	R	0.2149	85.73	0.0008	-1.0000	0.3333	-1.4626	0.1436
Fever	Overall	38	1629	34031	0.27 (0.20 to 0.37)	R	0.4633	69.23	0.0001	-0.0270	0.8222	-0.2939	0.7689
	Type												
	IV	22	1334	25250	0.30 (0.18 to 0.50)	R	0.8898	84.66	0.0001	0.0649	0.6964	0.5535	0.5799
	IM	16	295	8781	0.28 (0.21 to 0.38)	F	0.1392	25.23	0.2450	-0.1833	0.3502	-1.7482	0.0804

	Dose											
	Low dose	5	123	1465	0.15 (0.03 to 0.86)	R	2.9464	74.34	0.0042	0.4000	0.4833	0.2502	0.8024
	Standard dose	21	995	29088	0.24 (0.17 to 0.33)	R	0.1659	39.64	0.0186	-0.2571	0.1101	-1.0439	0.2965
	High dose	12	511	3478	0.45 (0.23 to 0.87)	R	0.8178	81.60	0.0001	0.0606	0.8406	1.3875	0.1653
	Delivery											
	VD	27	1420	32050	0.20 (0.15 to 0.27)	R	0.2227	51.53	0.0020	-0.0712	0.6201	-1.0112	0.3119
	CS	11	209	1981	0.69 (0.53 to 0.91)	F	0.0000	0.00	0.3262	0.0182	0.9999	0.2806	0.7790
	Risk											
	L	16	602	6547	0.24 (0.13 to 0.44)	R	0.7376	76.32	0.0001	-0.1500	0.4503	-1.0727	0.2823
	HL	14	974	26535	0.21 (0.15 to 0.28)	R	0.1063	35.11	0.0245	0.0549	0.8299	0.2667	0.7897
	H	8	53	949	0.67 (0.36 to 1.23)	F	0.0271	3.06	0.2741	0.0000	0.9999	-0.1839	0.8541
	Drug											
	Misoprostol	31	1588	32137	0.24 (0.17 to 0.34)	R	0.4723	72.96	0.0001	-0.1011	0.4375	-1.2760	0.2020
	Carbetocin	4	18	490	0.57 (0.17 to 1.91)	F	0.0095	0.59	0.2956	0.0000	0.9999	-0.4029	0.6870
	Ergometrine	1	17	1293	0.34 (0.11 to 1.03)								
	Prostaglandins	1	3	60	2.00 (0.19 to 20.9)								
	Placebo	1	3	51	1.92 (0.19 to 19.9)								
	Trial registration											
	no	25	1052	28542	0.23 (0.15 to 0.35)	R	0.4300	57.14	0.0001	-0.1267	0.3914	-1.0591	0.2896
	yes	13	577	5489	0.36 (0.20 to 0.64)	R	0.6247	78.65	0.0001	0.1026	0.6754	1.1506	0.2499
	Fund											
	Reseach	17	1303	25331	0.27 (0.17 to 0.43)	R	0.5029	80.94	0.0001	0.0147	0.9677	-0.0064	0.9949
	Company	2	7	102	1.26 (0.29 to 5.47)	F	0.0000	0.00	0.6507	1.0000	0.9999	0.4528	0.6507
	None	19	319	8598	0.24 (0.15 to 0.39)	R	0.4451	44.50	0.0273	-0.0526	0.7825	-0.8734	0.3825
	Year											
	before-2000	2	20	461	0.55 (0.21 to 1.40)	F	0.3381	28.38	0.2374	1.0000	0.9999	1.1816	0.2374
	2001-2010	18	1368	28499	0.21 (0.13 to 0.35)	R	0.7065	84.55	0.0001	-0.1111	0.5498	-1.5066	0.1319
	2011-present	18	241	5071	0.29 (0.21 to 0.40)	F	0.1086	16.66	0.1517	0.0458	0.8228	0.9181	0.3586
	Region											
	Africa	12	275	4936	0.25 (0.14 to 0.46)	R	0.6011	61.87	0.0072	-0.1212	0.6384	-1.0276	0.3041
	America	3	74	894	0.30 (0.02 to 3.62)	R	3.8105	82.28	0.0075	-0.3333	0.9999	0.2398	0.8105
	Asia	18	245	7782	0.25 (0.18 to 0.36)	F	0.1136	15.15	0.2777	-0.1373	0.4543	-0.0881	0.9298
	Europe	2	7	102	1.26 (0.29 to 5.47)	F	0.0000	0.00	0.6507	1.0000	0.9999	0.4528	0.6507
	Mixed	3	1028	20317	0.23 (0.08 to 0.67)	R	0.8767	97.41	0.0001	0.3333	0.9999	-0.1220	0.9029
Headache	Overall	24	384	7943	1.19 (0.82 to 1.74)	R	0.3221	50.01	0.0054	-0.0617	0.6723	-0.9021	0.3670
	Type											
	IV	17	319	3105	1.53 (0.98 to 2.39)	R	0.3106	51.16	0.0040	-0.1255	0.4834	-0.9050	0.3654
	IM	7	65	4838	0.68 (0.41 to 1.13)	F	0.0000	0.00	0.7576	0.2381	0.5619	-0.2438	0.8074
	Dose											
	Low dose	7	29	1182	0.89 (0.41 to 1.93)	F	0.0000	0.00	0.7302	-0.0476	0.9999	0.4592	0.6461
	Standard dose	10	153	5325	0.92 (0.47 to 1.77)	R	0.5192	54.13	0.0117	-0.1111	0.7275	-0.9499	0.3422
	High dose	7	202	1436	1.78 (0.88 to 3.59)	R	0.5274	75.39	0.0061	0.1429	0.7726	0.0257	0.9795

	Delivery											
	VD	11	143	5759	0.60 (0.32 to 1.12)	R	0.4098	41.92	0.0435	-0.2727	0.2830	-2.3510	0.0187
	CS	13	241	2184	1.81 (1.16 to 2.82)	R	0.2244	46.92	0.0928	0.1282	0.5900	1.9302	0.0536
	Risk												
	L	4	43	1055	1.24 (0.31 to 5.06)	R	1.3577	69.46	0.0084	0.0000	0.9999	-0.4918	0.6228
	HL	5	97	4682	0.48 (0.13 to 1.79)	R	1.4718	72.25	0.0219	-0.4000	0.4833	-1.5252	0.1272
	H	15	244	2206	1.26 (0.99 to 1.60)	F	0.0603	17.87	0.2467	-0.0574	0.7662	0.9572	0.3384
	Drug												
	Misoprostol	8	83	3186	1.57 (0.75 to 3.28)	R	0.4930	49.76	0.0897	0.2857	0.3988	0.6894	0.4906
	Carbetocin	11	222	2166	1.21 (0.94 to 1.55)	F	0.0693	23.58	0.1442	-0.2364	0.3587	-0.0663	0.9471
	Ergometrine	4	75	2538	0.28 (0.05 to 1.68)	R	2.2393	69.63	0.0432	-0.3333	0.7500	-0.9824	0.3259
	Placebo	1	4	53	6.74 (0.37 to 124.21)								
	Trial registration												
	no	15	293	5524	1.09 (0.79 to 1.49)	R	0.0609	18.37	0.0367	-0.1619	0.4351	-1.3504	0.1769
	yes	9	91	2419	1.65 (0.77 to 3.56)	R	0.6732	54.16	0.0276	0.0000	0.9999	-0.1066	0.9151
	Fund												
	Reseach	7	92	1953	1.55 (0.67 to 3.60)	R	0.7809	65.77	0.0114	-0.0476	0.9999	-0.5058	0.6130
	Company	4	102	1140	0.98 (0.68 to 1.42)	F	0.0000	0.00	0.5839	0.6667	0.3333	1.0943	0.2738
	None	13	190	4850	0.97 (0.55 to 6.55)	R	0.4044	47.99	0.0242	-0.1538	0.5098	-1.5542	0.1201
	Year												
	before-2000	1	89	659	0.93 (0.63 to 1.37)	F	0.0000	0.00	0.9999				
	2001-2010	10	138	4603	1.00 (0.53 to 1.89)	R	0.4023	44.40	0.0285	-0.3778	0.1557	-1.9810	0.0476
	2011-present	13	157	2681	1.41 (0.76 to 2.60)	R	0.5527	55.50	0.0277	-0.0129	0.9513	-0.2224	0.8240
	Region												
	Africa	8	178	2744	0.77 (0.25 to 2.36)	R	1.8801	84.76	0.0005	-0.2143	0.5484	-1.5432	0.1228
	America	5	125	1193	0.95 (0.67 to 1.32)	F	0.1762	37.07	0.1634	0.0000	0.9999	-0.3875	0.6984
	Asia	5	40	3303	1.69 (0.86 to 3.31)	F	0.3791	17.49	0.3415	-0.2000	0.8167	-0.4141	0.6788
	Europe	6	41	703	1.85 (1.00 to 3.43)	F	0.0000	0.00	0.8693	0.0667	0.9999	-0.0276	0.9780
Diarrhea	Overall	22	208	30883	0.48 (0.35 to 0.66)	F	0.0998	13.84	0.3575	-0.1391	0.3665	-1.1673	0.2431
	Type												
	IV	9	131	22948	0.59 (0.40 to 0.85)	F	0.1196	26.09	0.3605	0.1111	0.7614	1.3022	0.1929
	IM	13	77	7935	0.27 (0.14 to 0.51)	F	0.0000	0.00	0.6505	0.0909	0.6682	-0.6023	0.5470
	Dose												
	Low dose	1	11	514	0.83 (0.26 to 2.70)								
	Standard dose	18	183	28520	0.43 (0.31 to 0.61)	F	0.1569	20.18	0.2935	-0.1053	0.5439	-1.6429	0.1004
	High dose	3	14	1849	0.85 (0.29 to 2.51)	F	0.0000	0.00	0.6538	1.0000	0.3333	0.9219	0.3566
	Delivery												
	VD	20	198	30012	0.47 (0.34 to 0.65)	F	0.1245	17.05	0.3191	-0.1958	0.2295	-1.5423	0.1230
	CS	2	10	871	0.80 (0.22 to 2.92)	F	0.0000	0.00	0.3667	1.0000	0.9999	0.9026	0.3667
	Risk												
	L	12	83	5613	0.48 (0.29 to 0.79)	F	0.0000	0.00	0.6981	-0.4242	0.0629	-1.8838	0.0596
	HL	10	125	25270	0.48 (0.32 to 0.73)	F	0.2830	35.17	0.1031	0.0222	0.9999	-0.3819	0.7025

	Drug												
	Misoprostol	19	194	29326	0.49 (0.36 to 0.68)	F	0.0954	14.47	0.3594	-0.2118	0.2073	-1.2255	0.2204
	Carbetocin	1	9	200	0.13 (0.02 to 0.98)								
	Ergometrine	1	3	1295	0.22 (0.01 to 4.55)								
	Prostaglandins	1	2	62	3.00 (0.13 to 70.83)								
	Trial registration												
	no	17	174	27222	0.49 (0.35 to 0.70)	F	0.1352	19.19	0.2694	-0.1029	0.5976	-0.7631	0.4454
	yes	5	34	3661	0.41 (0.17 to 0.96)	F	0.0000	0.00	0.4633	-0.4000	0.4833	-1.2357	0.2166
	Fund												
	Reseach	9	89	23239	0.37 (0.22 to 0.62)	F	0.1998	19.88	0.1812	0.3889	0.1802	1.4133	0.1576
	None	13	119	7644	0.56 (0.38 to 0.84)	F	0.0000	0.00	0.6344	-0.4615	0.0305	-2.5833	0.0098
	Year												
	before-2000	2	6	463	1.38 (0.26 to 7.25)	F	0.0000	0.00	0.5711	1.0000	0.9999	0.5665	0.5711
	2001-2010	12	140	27162	0.53 (0.37 to 0.76)	F	0.1374	22.70	0.3403	-0.1818	0.4590	-0.1517	0.8794
	2011-present	8	62	3258	0.29 (0.15 to 0.58)	F	0.0000	0.00	0.5052	-0.4074	0.1670	-2.1179	0.0342
	Region												
	Africa	10	72	4849	0.50 (0.29 to 0.87)	F	0.0000	0.00	0.4768	-0.2000	0.4843	-0.9098	0.3629
	Asia	9	81	5717	0.59 (0.36 to 0.98)	F	0.2023	20.99	0.3232	0.1111	0.7614	-1.9341	0.0531
	Mixed	3	55	20317	0.56 (0.38 to 0.84)	F	0.2351	34.16	0.2456	1.0000	0.3333	1.6665	0.0956
Dizziness	Overall	13	289	3787	1.00 (0.80 to 1.25)	F	0.0000	0.00	0.2413	-0.1795	0.4354	0.4680	0.6398
	Type												
	IV	11	192	3089	1.07 (0.80 to 1.43)	F	0.0000	0.00	0.1998	-0.1273	0.6481	0.6784	0.4975
	IM	2	97	698	0.89 (0.62 to 1.28)	F	0.0000	0.00	0.3292	-1.0000	0.9999	-0.9757	0.3292
	Dose												
	Low dose	3	12	679	0.91 (0.26 to 3.19)	F	0.1696	10.96	0.3611	-1.0000	0.3333	-1.4206	0.1554
	Standard dose	3	110	762	0.89 (0.64 to 1.26)	F	0.0000	0.00	0.6178	-1.0000	0.3333	-0.7798	0.4355
	High dose	7	167	2346	1.09 (0.81 to 1.49)	F	0.0674	12.23	0.0812	0.1429	0.7726	1.3656	0.1721
	Delivery												
	VD	6	123	1993	0.88 (0.63 to 1.22)	F	0.0000	0.00	0.8938	-0.7333	0.0556	-0.9861	0.3241
	CS	7	166	1794	1.12 (0.82 to 1.52)	F	0.3766	41.70	0.0563	0.2381	0.5619	1.5087	0.1314
	Risk												
	L	5	244	2782	1.01 (0.79 to 1.28)	F	0.0000	0.00	0.1098	0.6000	0.2333	2.0893	0.0367
	HL	1	3	60	0.50 (0.05 to 5.22)								
	H	7	42	945	0.98 (0.51 to 1.91)	F	0.0000	0.00	0.3099	-0.4286	0.2389	-1.0159	0.3097
	Drug												
	Misoprostol	5	247	2505	1.00 (0.79 to 1.27)	F	0.0000	0.01	0.1345	0.4000	0.4833	1.8824	0.0598
	Carbetocin	7	39	1222	1.03 (0.51 to 2.09)	F	0.0818	7.10	0.2662	-0.4286	0.2389	-0.9444	0.3449
	Prostaglandins	1	3	60	0.50 (0.05 to 5.22)								
	Trial registration												
	no	7	127	1181	0.88 (0.64 to 1.21)	F	0.0000	0.00	0.8257	-0.5238	0.1361	-1.2156	0.2241
	yes	6	162	2606	1.81 (0.74 to 4.44)	R	0.5849	53.81	0.8677	0.6000	0.1361	1.6116	0.1071

	Fund											
	Reseach	7	168	2389	1.09 (0.81 to 1.49)	F	0.0341	6.83	0.0879	0.3333	0.3813	1.4743	0.1404
	Company	1	6	377	1.99 (0.37 to 10.73)								
	None	5	115	1021	0.87 (0.62 to 1.22)	F	0.0000	0.00	0.6747	-0.4000	0.4833	-1.3789	0.1679
	Year												
	before-2000	1	3	60	0.50 (0.05 to 5.22)	F	0.0000	0.00	0.9999				
	2001-2010	7	249	3026	0.98 (0.78 to 1.23)	F	0.0000	0.00	0.9109	0.0476	0.9999	-0.0285	0.9775
	2011-present	5	37	701	1.72 (0.24 to 12.44)	R	3.2342	64.50	0.0262	-0.2000	0.8167	-0.8063	0.4201
	Region												
	Africa	4	120	920	1.29 (0.19 to 8.65)	R	2.5502	72.41	0.0424	0.0000	0.9999	0.1937	0.8464
	America	2	15	217	0.83 (0.31 to 2.23)	F	0.0000	0.00	0.5075	-1.0000	0.9999	-0.6627	0.5075
	Asia	3	21	380	1.62 (0.61 to 4.29)	F	0.5502	38.18	0.1798	-0.3333	0.9999	0.2925	0.7699
	Europe	2	9	483	1.15 (0.26 to 5.01)	F	1.0879	41.23	0.1921	-1.0000	0.9999	-1.3044	0.1921
	Mixed	2	124	1787	1.01 (0.73 to 1.40)	F	0.0000	0.00	0.9819	-1.0000	0.9999	-0.0227	0.9819
Flushing	Overall	13	364	31438	0.85 (0.72 to 1.01)	F	0.0000	0.00	0.5039	-0.2821	0.2044	-1.0264	0.3047
	Type												
	IV	11	353	1739	0.86 (0.72 to 1.01)	F	0.0000	0.00	0.3614	-0.2000	0.4454	-0.9011	0.3675
	IM	2	11	29699	0.70 (0.21 to 2.38)	F	0.0000	0.00	0.6185	-1.0000	0.9999	-0.4979	0.6185
	Dose												
	Low dose	6	25	841	0.80 (0.35 to 1.80)	F	0.0000	0.00	0.7467	-0.0667	0.9999	0.3896	0.6968
	Standard dose	3	44	29763	0.35 (0.05 to 2.58)	R	2.3251	78.88	0.0446	-1.0000	0.3333	-2.4737	0.0134
	High dose	4	295	834	0.87 (0.73 to 1.03)	F	0.0000	0.00	0.6315	-0.3333	0.7500	-0.4406	0.6595
	Delivery												
	VD	5	27	30018	0.69 (0.32 to 1.50)	F	0.0000	0.00	0.8391	-0.4000	0.4833	-1.1322	0.2576
	CS	8	337	1420	0.86 (0.73 to 1.02)	F	0.0000	0.00	0.2151	0.2857	0.3988	-0.4706	0.6380
	Risk												
	L	3	22	29932	0.73 (0.31 to 1.69)	F	0.0000	0.00	0.9692	-1.0000	0.3333	-0.2365	0.8130
	HL	1	3	60	0.73 (0.31 to 1.69)								
	H	9	339	1446	0.85 (0.72 to 1.01)	F	0.0000	0.00	0.2260	-0.2778	0.3585	-1.2527	0.2103
	Drug												
	Carbetocin	11	358	31327	0.84 (0.71 to 1.00)	F	0.0000	0.00	0.4137	-0.4545	0.0602	-1.5622	0.1183
	Prostaglandins	1	3	60	2.00 (0.19 to 20.90)								
	Placebo	1	3	51	1.92 (0.19 to 19.90)								
	Trial registration												
	no	6	326	1244	0.86 (0.72 to 1.02)	F	0.0000	0.00	0.1200	-0.4667	0.2722	-1.5959	0.1105
	yes	7	38	30194	0.79 (0.41 to 1.52)	F	0.0000	0.00	0.8677	0.0476	0.9999	0.7439	0.4569
	Fund												
	Reseach	3	13	218	0.73 (0.24 to 2.15)	F	0.0000	0.00	0.5988	-0.3333	0.9999	0.1449	0.8848
	Company	5	305	30637	0.88 (0.74 to 1.04)	F	0.0000	0.00	0.7816	0.8000	0.0833	0.7623	0.4459
	None	5	46	583	0.49 (0.21 to 1.11)	R	0.7658	41.06	0.1619	-0.4000	0.4833	-1.9885	0.0468

	Year											
	before-2000	2	286	719	0.88 (0.73 to 1.04)	F	0.0000	0.00	0.4890	1.0000	0.9999	0.6919	0.4890
	2001-2010	3	42	643	0.34 (0.05 to 2.50)	R	2.2855	76.68	0.0469	-1.0000	0.3333	-2.3919	0.0168
	2011-present	8	36	30076	0.71 (0.36 to 1.42)	F	0.0000	0.00	0.8202	-0.2143	0.5484	-0.0309	0.9753
	Region												
	Africa	2	4	304	0.33 (0.04 to 3.16)	F	0.0000	0.00	0.9999	-1.0000	0.9999	0.0000	0.9999
	America	3	297	876	0.87 (0.73 to 1.03)	F	0.0000	0.00	0.5863	-1.0000	0.3333	-0.7342	0.4629
	Asia	1	3	60	2.00 (0.19 to 20.90)	F	0.0000	0.00	0.9999				
	Europe	6	51	701	0.64 (0.31 to 1.34)	F	0.0000	0.00	0.1338	0.3333	0.4694	-0.1549	0.8769
	Mixed	1	9	29497	0.80 (0.22 to 2.98)	F	0.0000	0.00	0.9999				
Metallic taste	Overall	9	86	1776	0.76 (0.45 to 1.27)	F	0.8420	39.57	0.1038	0.0286	0.9161	-1.9834	0.0473
Abdominal pain	Overall	8	513	31414	0.94 (0.81 to 1.09)	F	0.0000	0.00	0.9028	-0.3571	0.2751	-0.8364	0.4029
Dyspnea	Overall	8	28	1341	0.83 (0.38 to 1.81)	F	0.0000	0.00	0.8910	0.0364	0.9008	-0.0941	0.9250
Chest pain	Overall	6	43	29907	0.84 (0.43 to 1.65)	R	0.4400	34.56	0.1678	0.2000	0.7194	1.4110	0.1582
Arrhythmias	Overall	6	77	873	1.24 (0.32 to 4.76)	R	1.6556	68.73	0.0295	0.0667	0.9999	0.9792	0.3275
Palpitations	Overall	6	22	842	1.66 (0.01 to 4.06)	F	0.0000	0.00	0.4430	0.0000	0.9999	0.0728	0.9420
Hypertension	Overall	6	93	2652	0.23 (0.05 to 1.05)	R	1.9281	57.99	0.0407	0.2000	0.7194	-0.3966	0.6916
Hypotension	Overall	6	59	1071	1.22 (0.74 to 2.01)	F	0.0000	0.00	0.2542	0.2000	0.7194	1.4706	0.1414
Pruritis	Overall	5	55	792	0.84 (0.10 to 6.86)	R	3.9700	73.24	0.0113	-0.4000	0.4833	-0.2776	0.7813
Nasal congestion	Overall	3	6	483	0.98 (0.17 to 5.53)	F	0.0000	0.00	0.6397	-0.3333	0.9999	-0.0463	0.9631
Sweating	Overall	3	50	1226	2.80 (0.34 to 22.9)	R	2.5279	75.64	0.0139	0.3333	0.9999	0.1763	0.8601
Backache	Overall	3	34	1144	1.16 (0.59 to 2.30)	F	0.0000	0.00	0.4344	0.3333	0.9999	-0.4119	0.6804
Chills	Overall	2	19	560	0.95 (0.40 to 2.27)	F	0.0000	0.00	0.9580	1.0000	0.9999	0.0527	0.9580
Anemia	Overall	2	69	306	0.26 (0.01 to 5.43)	R	3.9062	78.86	0.0296	-1.0000	0.9999	-2.1751	0.0296
Xerostomia	Overall	1	2	54	0.33 (0.01 to 7.82)								
Serious adverse event	Overall	1	192	29497	0.86 (0.65 to 1.15)								
Arm pain	Overall	1	2	379	2.98 (0.12 to 72.79)								
Wheezing	Overall	1	2	379	0.33 (0.01 to 8.09)								
Leukocytosis	Overall	1	14	160	1.44 (0.52 to 3.95)								

Supplementary File 3. The results of cumulative meta-analysis

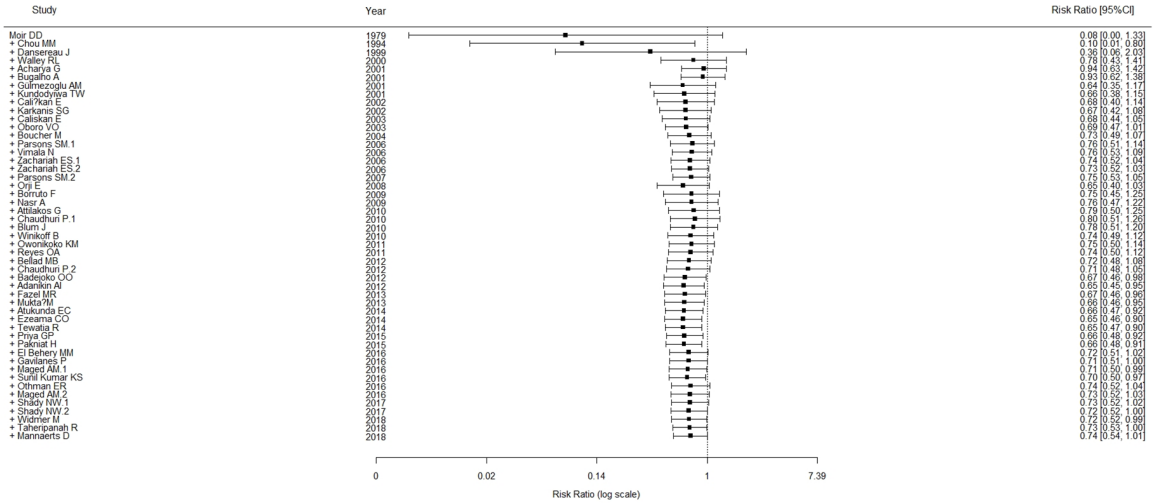

Figure S1. Cumulative meta-analysis of the association between vomiting and oxytocin use.

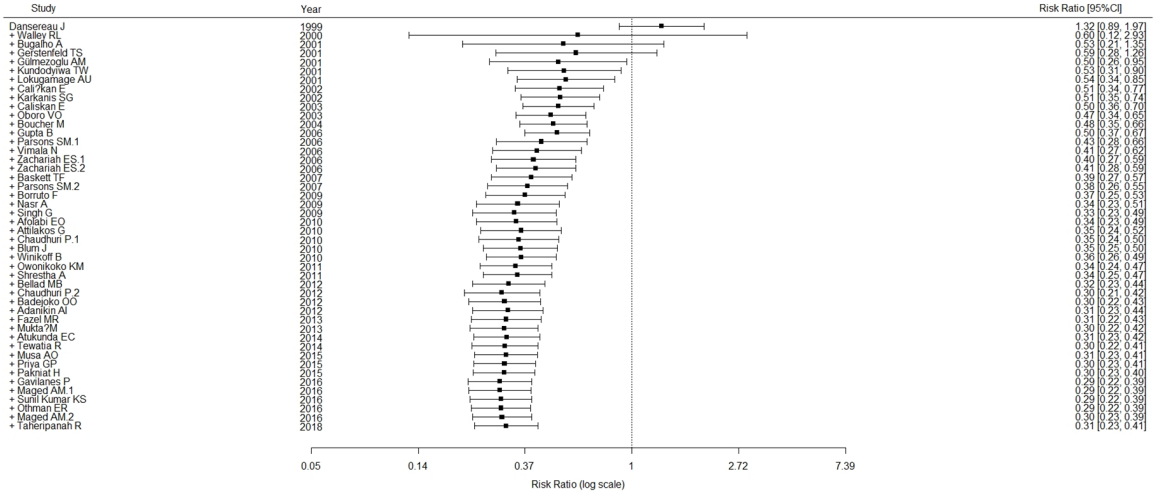

Figure S2. Cumulative meta-analysis of the association between shivering and oxytocin use.

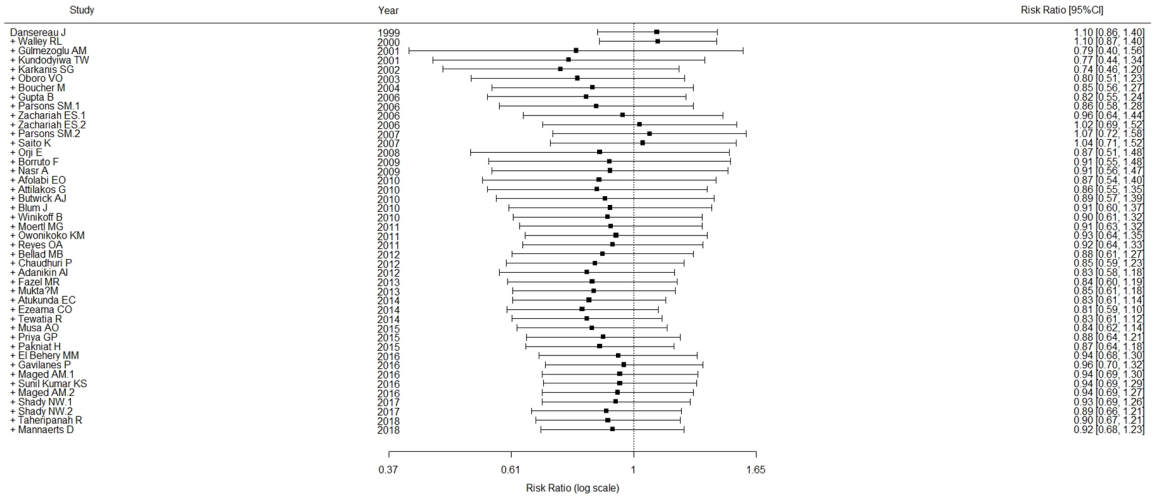

Figure S3. Cumulative meta-analysis of the association between nausea and oxytocin use.

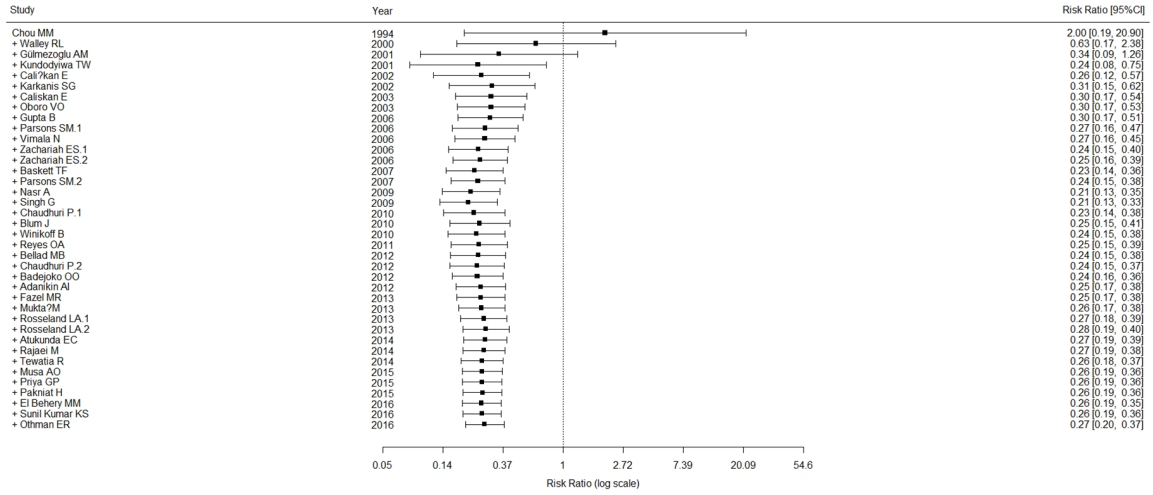

Figure S4. Cumulative meta-analysis of the association between fever and oxytocin use.

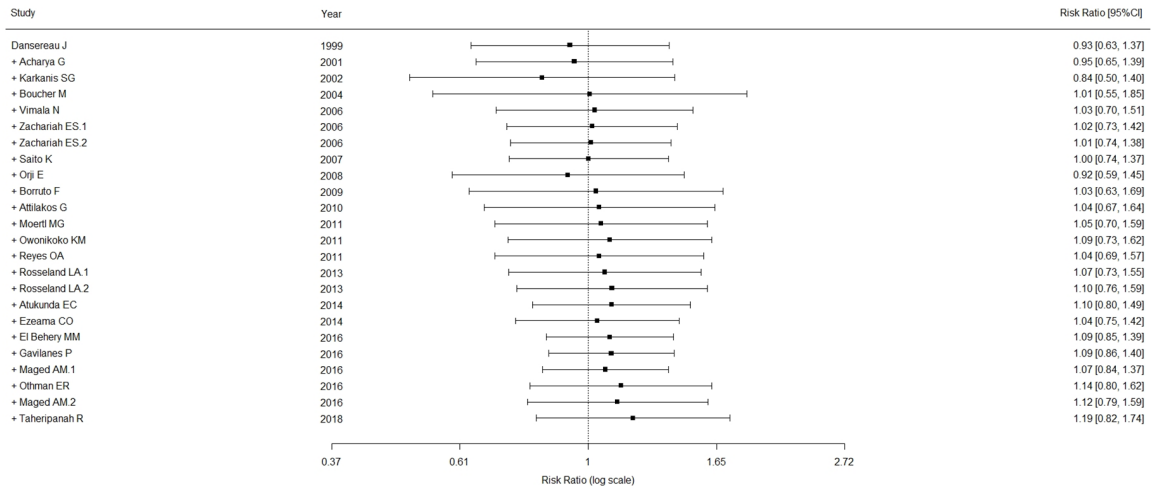

Figure S5. Cumulative meta-analysis of the association between headache and oxytocin use.

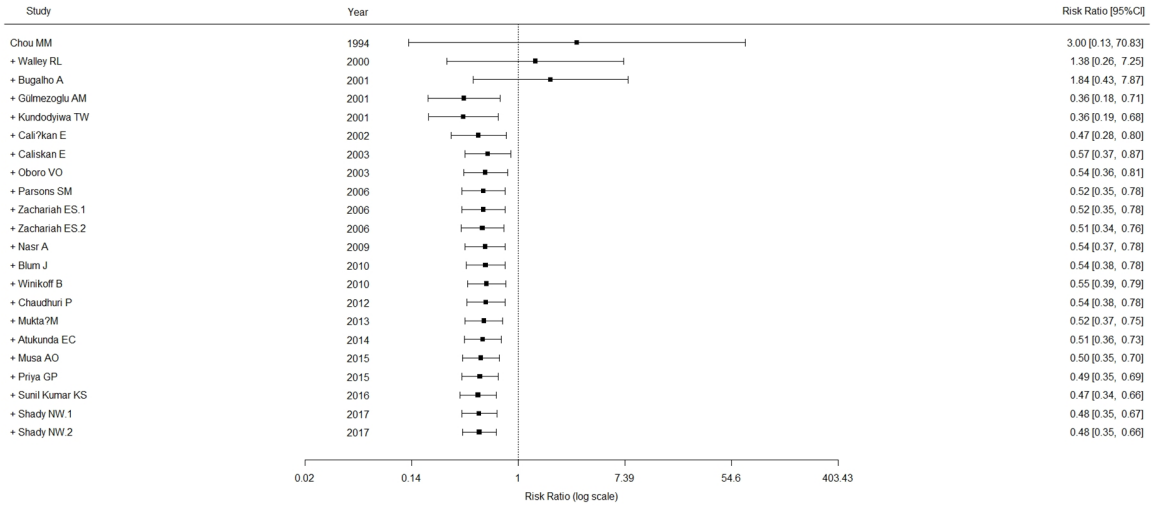

Figure S6. Cumulative meta-analysis of the association between diarrhea and oxytocin use.

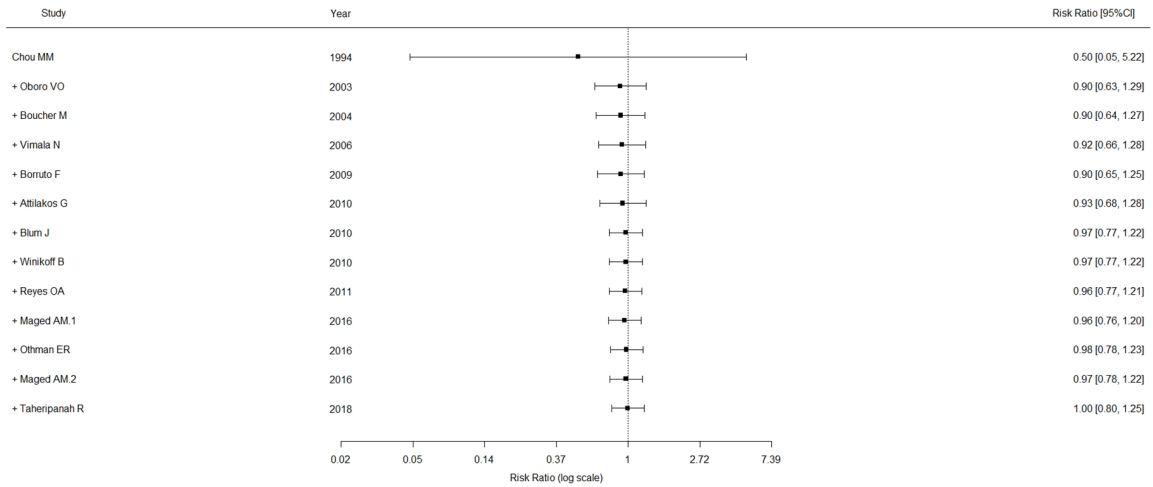

Figure S7. Cumulative meta-analysis of the association between dizziness and oxytocin use.

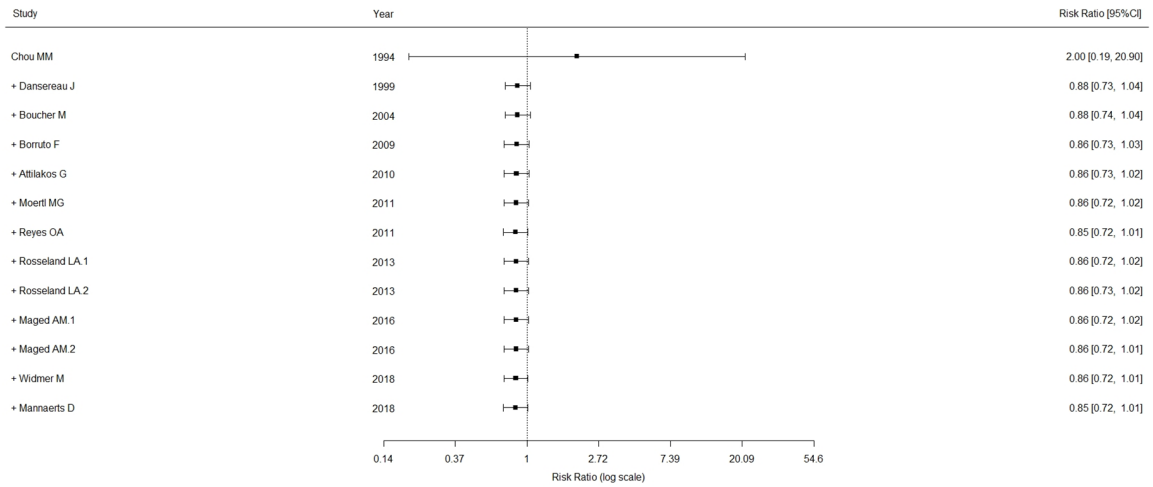

Figure S8. Cumulative meta-analysis of the association between flushing and oxytocin use.

Supplementary File 4. The results of funnel plots

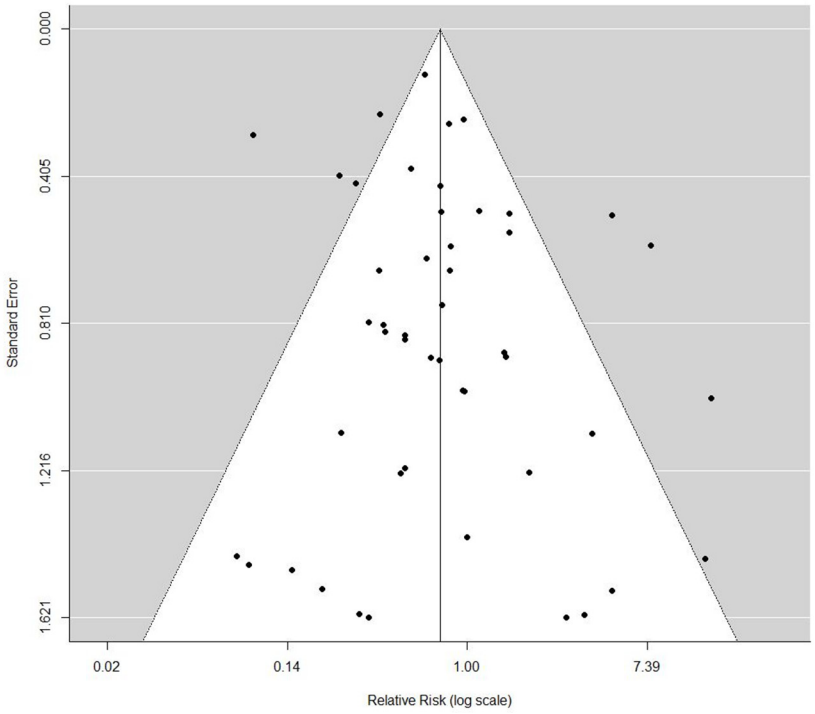

Figure S9. Funnel plot of included studies for side-effects (vomiting).

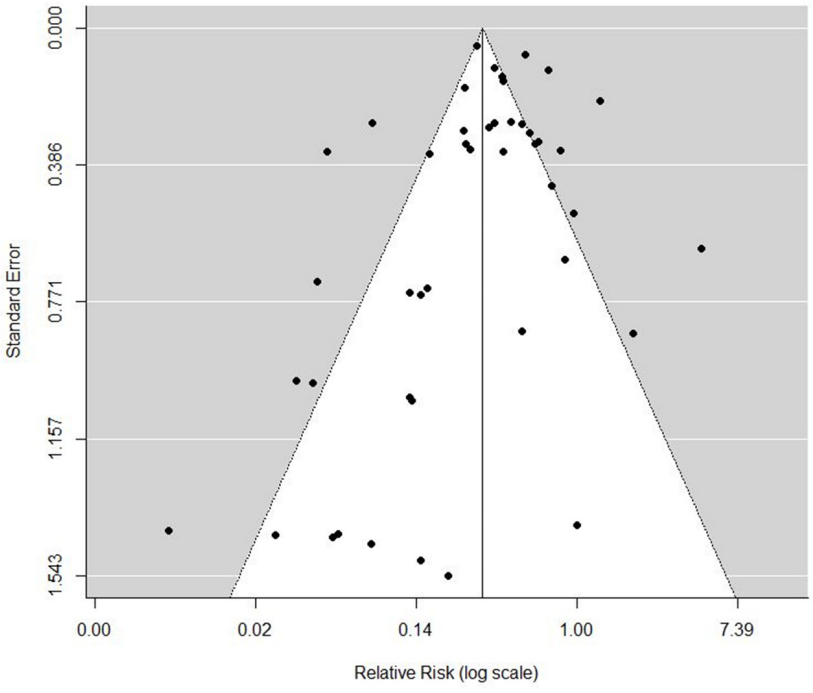

Figure S10. Funnel plot of included studies for side-effects (shivering).

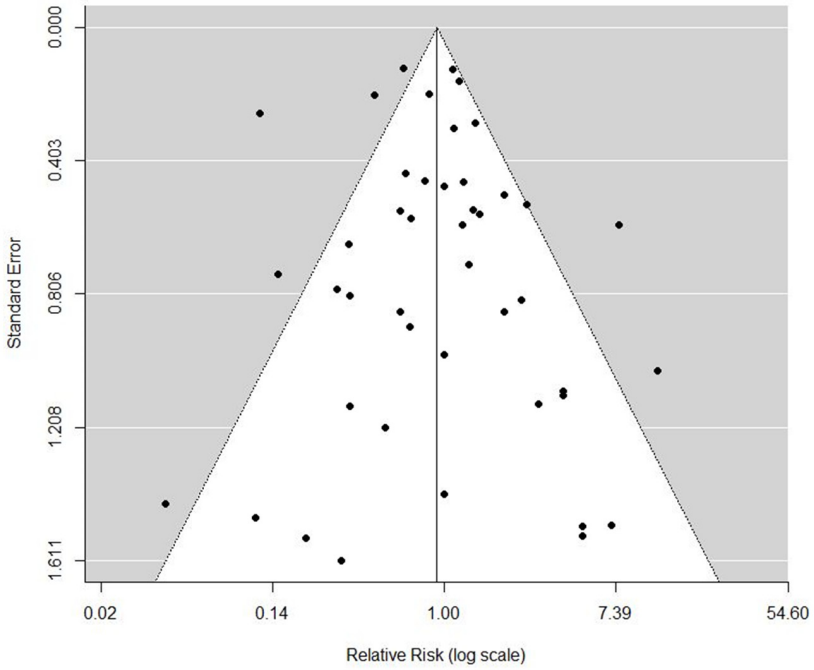

Figure S11. Funnel plot of included studies for side-effects (nausea).

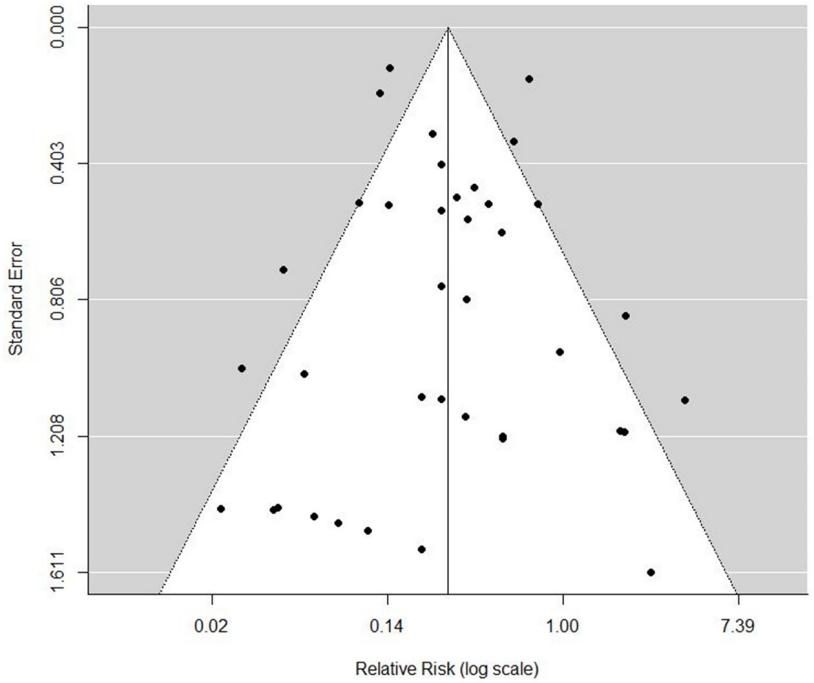

Figure S12. Funnel plot of included studies for side-effects (fever).

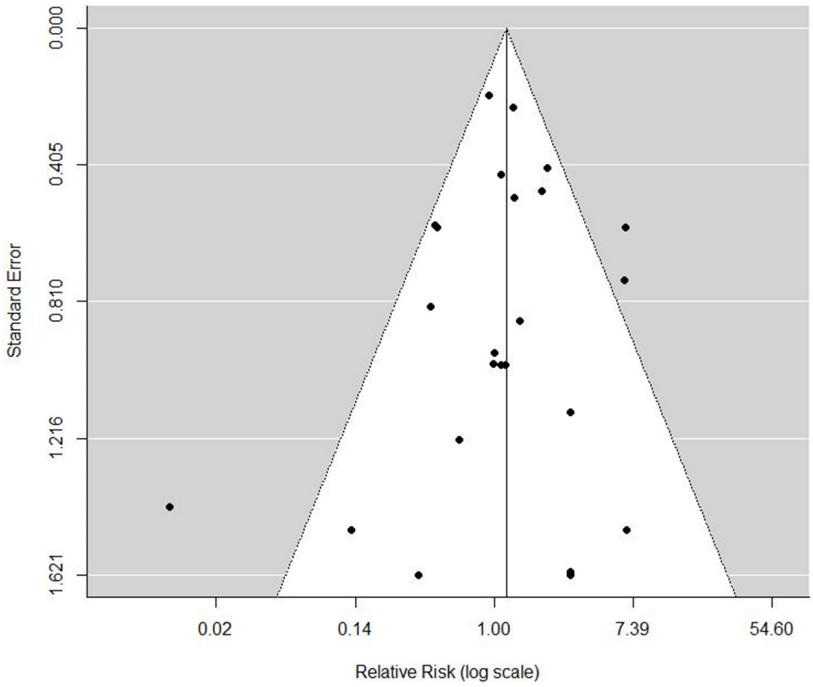

Figure S13. Funnel plot of included studies for side-effects (headache).

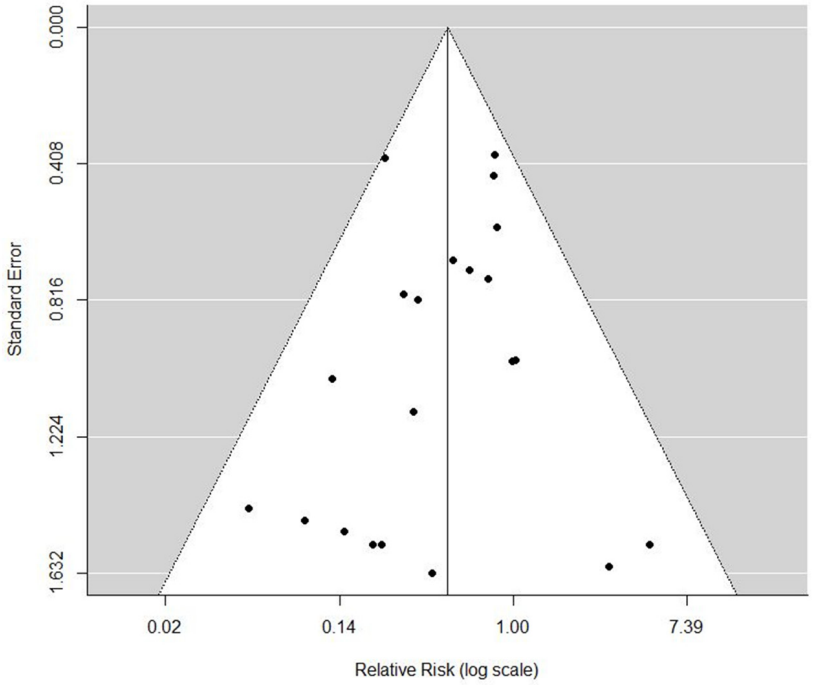

Figure S14. Funnel plot of included studies for side-effects (diarrhea).

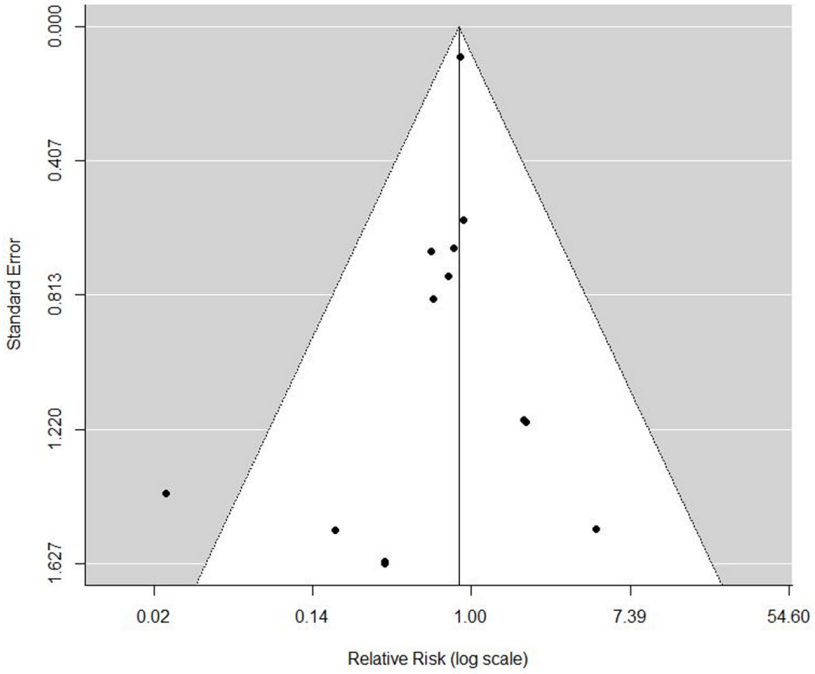

Figure S15. Funnel plot of included studies for side-effects (flushing).

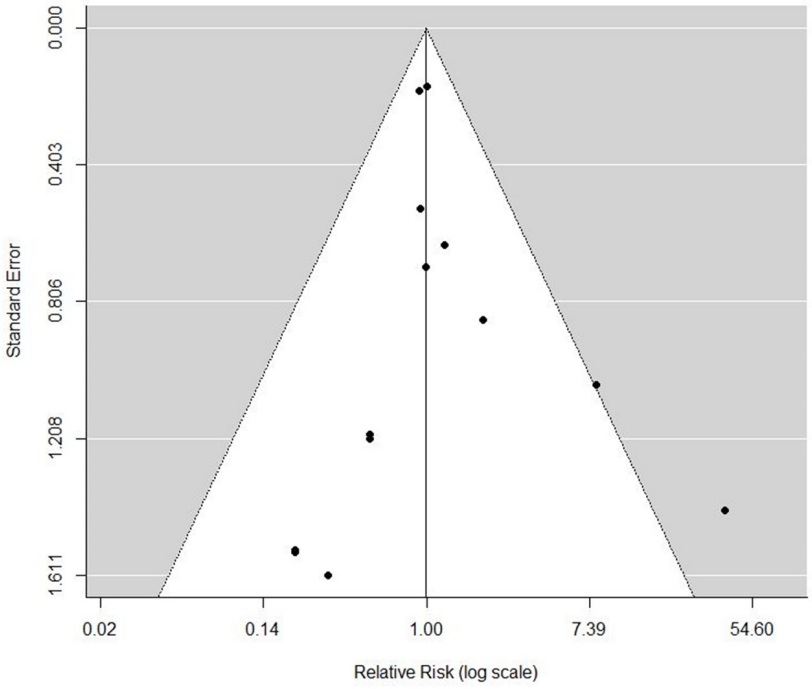

Figure S16. Funnel plot of included studies for side-effects (dizziness).

Supplementary File 5. PRISMA 2009 Checklist

Section/Topic	#	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	4
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2 for each meta-analysis).	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5

RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Figures 3, 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7
Synthesis of results	21	Present the main results of the review. If meta-analyses done, include for each, confidence intervals and measures of consistency.	7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	7
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	8
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	None

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097. For more information, visit: www.prisma-statement.org.