Balkan Med J 2026;43:115-24

Comparison of Tocolytic Agents for Successful External Cephalic Version: A Bayesian Network Meta-Analysis of Sixteen Randomized Controlled Trials

Yunyun Xiao[1], Jinhe Shi[2], Yan Dong[1], Lu Han[1]

[1]Department of Gynecology and Obstetrics, Dalian Maternal and Children's Medical Group, Liaoning, China
[2]Graduate School of Dalian Medical University, Liaoning, China

Background: Cesarean section is frequently performed for breech presentation; however, external cephalic version (ECV) is recommended as an alternative strategy to increase the likelihood of vaginal birth. Tocolytic agents are commonly administrated to improve ECV success, yet the comparative effectiveness of different regimens remains inadequately characterized.

Aims: To systematically evaluate and compare the efficacy and safety of various tocolytic agents in facilitating successful ECV through a Bayesian network meta-analysis.

Study Design: Bayesian network meta-analysis.

Methods: Bayesian network meta-analysis was performed using the "gemtc" package in R 4.1.1. Treatment effects were quantified by calculating odds ratios (ORs) with corresponding 95% credible intervals (CrIs). Surface under the cumulative ranking curve values were used to rank tocolytic agents according to ECV success rates, maternal outcomes, and adverse events.

Results: A total of sixteen RCTs encompassing 2,817 participants and six distinct tocolytic agents met the inclusion criteria. Compared with placebo, terbutaline (OR: 2.7, 95% CrI: 1.1–6.4) and ritodrine (OR: 2.2, 95% CrI: 1.4–3.9) were associated with significantly higher ECV success rates. Additionally, terbutaline was linked to an increased likelihood of vaginal delivery (OR: 2.0, 95% CrI: 1.0–2.9). Maternal adverse effects, including tachycardia, palpitations, hypotension, nausea, dizziness, and flushing, were more frequently reported with terbutaline, nifedipine, and nitroglycerin than with placebo. No statistically significant differences in fetal heart rate abnormalities were detected among the elevated interventions.

Conclusion: Terbutaline and ritodrine appear to offer superior efficacy in improving ECV success compared with alternative tocolytic agents, albeit with a higher incidence of maternal side effects. Consequently, clinical decision-making regarding tocolytic use should be informed by a comprehensive assessment of the associated benefits and potential risks.

INTRODUCTION

Breech presentation occurs in approximately 3–4% of term pregnancies[1] and constitutes the third most common indication for cesarean section (CS). In some regions, CS rates for breech delivery exceeds 93%.[2-5] Worldwide, the prevalence of CS increased markedly between 1990 and 2014, rising by 12.4% from 6.7% to 19.1%, with an average annual growth rate of 4.4% across 121 countries. This upward trend has been particularly pronounced in China.[6,7] The growing reliance on CS is concerning because it is associated with significant risks, including uterine injury, severe maternal morbidity, adverse perinatal outcomes, and an increased probability of repeat CS in subsequent pregnancies.[5-8]

External cephalic version (ECV) is a manual obstetric procedure in which the fetus is rotated from a breech to a cephalic presentation through transabdominal manipulation. Evidence indicates that ECV can reduce cesarean delivery rates by approximately 40%

Corresponding author: Yan Dong, Department of Gynecology and Obstetrics, Dalian Maternal and Children's Medical Group, Liaoning, China, Lu Han, Department of Gynecology and Obstetrics, Dalian Maternal and Children's Medical Group, Liaoning, China

e-mail: dlfcdy@126.com/13940801858@163.com

Received: October 28, 2025 **Accepted:** December 18, 2025 **Available Online Date:** March 02, 2026 • **DOI:** 10.4274/balkanmedj.galenos.2025.2025-10-205

Available at www.balkanmedicaljournal.org

ORCID iDs of the authors: Y.X. 0000-0002-3824-3716; J.S. 0009-0003-7082-9180; Y.D. 0000-0002-7358-7899; L.H. 0000-0003-4715-5512.

Cite this article as: Xiao Y, Shi J, Dong Y, Han L. Comparison of Tocolytic Agents for Successful External Cephalic Version: A Bayesian Network Meta-Analysis of Sixteen Randomized Controlled Trials. Balkan Med J.; 2026; 43(3): 115-24

while substantially increasing the likelihood of vaginal birth.[8,9] Consequently, major obstetrical organizations—including the American College of Obstetricians and Gynecologists (ACOG), the Society for Maternal-Fetal Medicine, the Royal College of Obstetricians and Gynecologists (RCOG), and the Royal Australian and New Zealand College of Obstetricians and Gynecologists, recommend the use of ECV for uncomplicated term breech pregnancies.[5,10,11] Economic evaluations further support its implementation, demonstrating that ECV is cost-effective when the probability of success exceeds 32% compared with planned cesarean delivery.[12]

Several adjunctive strategies have been investigated to improve ECV success rates, including the use of tocolytic agents, neuraxial anesthesia, vibroacoustic stimulation, moxibustion, and amnioinfusion.[13-18] A meta-analysis by Cluver et al.[9] demonstrated the effectiveness of β-adrenergic agonists in facilitating ECV; however, evidence supporting other adjunctive interventions remains limited. Current guidelines from ACOG and RCOG recommend the use of tocolytics during ECV, with RCOG specifically endorsing β-adrenergic agonists.[11] Despite these recommendations, direct comparative evidence regarding the relative efficacy and safety profiles of different tocolytic agents remains insufficient.[9] To address this knowledge gap, the present Bayesian network meta-analysis systematically evaluates the effects of six tocolytic agents on ECV success rates and maternal adverse outcomes.

MATERIALS AND METHODS

Ethical approval

All data used in this study were derived from previously published research. Therefore, ethical approval and written informed consent were not required.

Search strategy

A Bayesian network meta-analysis was conducted to compare the success rates and adverse effects of commonly used tocolytic agents during ECV based on eligible randomized controlled trials (RCTs). This study was prospectively registered in the International Prospective Register of Systematic Reviews under registration number CRD 42022217842. A comprehensive literature search was performed in PubMed (http://www.ncbi.nlm.nih.gov/pubmed), the Cochrane Library (http://www.cochranelibrary.com), Embase (http://www.embase.com), and Web of Science (http://isiknowledge.com/) to identify relevant studies published up to October 31, 2024. No restrictions were imposed on the start date. The search strategy incorporated both MeSH terms and free-text words, including "Breech presentation," "Breech," "External cephalic version," "ECV," "Version fetal," "Tocolytic agent," "Tocolysis," "Tocolytic," "Uterine relaxation."

Selection criteria and data extraction

Studies were considered eligible if they met the following inclusion criteria: (1) Participants had a breech presentation and underwent ECV at or near term (gestational age ≥ 36 weeks). (2) Interventions involved the use of different tocolytic agents, with or without placebo. (3) Reasons for exclusion of patients in the study were almost consistent with the ACOGs recommendations on ECV. (ACOG practice bulletin 2021) (4) The study should at least provide the success rate of ECV. 5) The study design was a RCT. (6) The published language was English. Studies were excluded if: (1) More than one type of tocolytic agent was administered during a single ECV procedure. (2) Patients received anesthesia. (3) The study was incomplete. (4) Full-text articles or duplicate studies were identified. The following data were extracted from each included study: author, year of publication, sample size, type of tocolytic agent used, number of successful ECVs, vaginal delivery outcomes, and reported maternal side effects associated with tocolysis. The primary outcome was the ECV success rate, defined as confirmation of cephalic presentation by ultrasound at the conclusion of the procedure.

Risk of bias assessment

The methodologically quality of the included RCTs was independently assessed using the Cochrane Collaboration's risk-of-bias tool. The following domains were evaluated as potential sources of bias: (1) Random sequence generation (selection bias); (2) Allocation concealment (selection bias); (3) Blinding of participants and personnel (performance bias); (4) Blinding of outcome assessment (detection bias); (5) Incomplete outcome data (attrition bias); (6) Selective reporting (reporting bias); (7) Other potential sources of bias. Each trial received a total score out of 12 points. Studies scoring 10–12 points were classified as having a low-risk of bias, whereas those scoring 6 points or fewer were considered to have a high-risk of bias. Data extraction and quality assessment were performed independently by two investigators, with disagreements resolved through consultation with a third investigator.

Statistical analysis

The network meta-analysis was conducted within a Bayesian framework using the "gemtc" package in R software (version 4.1.1; R Foundation, https://www.r-project.org), which interfaces with JAGS (Version 4.3.0). Odds ratios (ORs) and corresponding 95% credible intervals (CrIs) were calculated to compare the efficacy and safety of different tocolytic agents. The mtc.run function was used to generate posterior samples, with a "burn-in" period of 20,000 iterations per chain followed by 50,000 sampling iterations across four simultaneously run Markov chain Monte Carlo chains. Model convergence was assessed using the Brooks–Gelman–Rubin diagnostic by calculating the potential scale reduction factor (R-hat), along with visual inspection of trace plots and density plots. Treatment ranking probabilities were estimated, and the surface under the cumulative ranking curve (SUCRA) was calculated to facilitate comparative evaluation of tocolytic efficacy. Consistency between direct and indirect evidence was examined using the node-splitting method. Inconsistency was assessed using a Bayesian p value, with values below 0.05 indicating statistically significant inconsistency. This Bayesian p value represents a posterior predictive check, assessing whether discrepancies between direct and indirect evidence are plausible under the assumption of consistency, and differs conceptually from frequentist p values, which estimates the

probability of observing the data (or more extreme data) assuming the null hypothesis is true. Statistical heterogeneity was evaluated using the mtc.anohe command based on the I^2 statistic. An I^2 value greater than 50% was considered indicative of substantial heterogeneity, prompting subgroup analyses to explore potential sources. Risk-of-bias summary graphs were generated using RevMan software (version 5.30).

RESULTS

Basic information

The descriptive literature search initially identified 559 records. After screening titles and abstracts, 480 studies were excluded due to irrelevant content, case reports, reviews, meta-analysis, or duplicates publications. Full-text review of the remaining articles led to the exclusion of an additional 49 studies because they were case-control studies, cohort studies, or did not involve comparisons of tocolytic agents during the ECV procedure. Furthermore, 13 studies were excluded because multiple tocolytic agents were administered to the same patient during a single procedure. Ultimately, 16 RCTs,[19-34] encompassing a total of 2,817 patients, met the inclusion criteria and were included in the analysis. The study selection process is illustrated in Figure 1, key characteristics of the included trials are summarized in Table 1. All eligible studies were RCTs. Methodological quality was evaluated using the Cochrane Handbook risk-of-bias tool, and potential sources of bias were classified as low, high, or unclear. The detailed results of the risk-of-bias assessment are presented in Figure 2a and Figure 2b. Network meta-analyses were performed for ECV success rates, vaginal delivery outcomes, common maternal adverse effects, and abnormal fetal heart rate. The incidence of adverse effects and fetal heart rate abnormalities associated with each tocolytic agent is summarized in Table 2.

The 16 included trials evaluated four major classes of tocolytic agents: β-adrenergic agonists (terbutaline, fenoterol, and ritodrine), selective oxytocin receptor antagonists (atosiban), calcium channel blockers (nifedipine), and nitric oxide donors (nitroglycerine). These agents were compared either directly with one another or against placebo. Network plots were generated according to the specific outcomes assessed, as shown in Figure 3. The thickness of the connecting lines reflect the number of direct comparisons, with corresponding numerical values displayed on each link.

Success rate of ECV

All 16 included studies reported both successful and failed ECV attempts (Table 1), with observed success rates ranging from 8.1% to 68%. Compared with placebo, terbutaline (OR = 2.7, 95% CrI: 1.1 to 6.4) and ritodrine (OR = 2.2, 95% CrI: 1.4 to 3.9) demonstrated statistically significant positive improvements in ECV success. In contrast, no significant benefit was observed for fenoterol (OR = 2.5, 95% CrI: 0.63 to 11), atosiban (OR = 1.9, 95% CrI: 0.68 to 6.0), nifedipine (OR = 1.2, 95% CrI: 0.5 to 2.6), or nitroglycerin (OR = 0.86, 95% CrI: 0.44 to 1.7) when compared with placebo (Figure 4a). Based on SUCRA values, treatment were ranked in descending order of effectiveness as follows: terbutaline (0.809), fenoterol (0.766), ritodrine (0.721), atosiban (0.582), nifedipine (0.306), placebo (0.198), and nitroglycerin (0.117) (Figure 5a). Model convergence was confirmed using the Brooks–Gelman–Rubin diagnostic. The potential scale reduction factor (R-hat) for all parameters, including treatment comparisons and the heterogeneity parameter (sd.d), ranged from 1.000 to 1.003 for both point estimates and 97.5% upper confidence limits (Supplementary Table 1, Supplementary Figure 1), well below the predefined threshold of 1.05. These results indicate excellent chain mixing and convergence, supporting the reliability of the posterior estimates. Trace plots further demonstrated

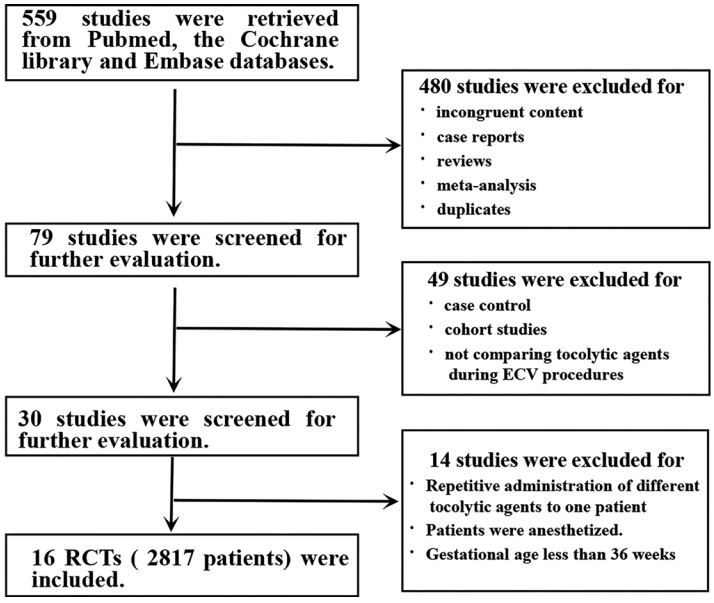

FIG. 1. Workflow of the research inclusion.
ECV, external cephalic version; RCTs, randomized controlled trials.

TABLE 1. Major Characteristics of Eligible Studies Included in the Network Meta-Analysis.

Study	Country	Year	Treatment allocation		ECV success rate		Vaginal delivery rate	
			Treatment	Control	Treatment	Control	Treatment	Control
Couceiro Naveira et al.[19]	Spain	2020	Atosiban (6.75 mg, intravenously)	Ritodrine (0.05 mg/min, intravenously)	99/215 (46.0%)	107/215 (50.0%)	75/215 (34.9%)	82/215 (38.1%)
Velzel et al.[20]	Netherlands	2017	Atosiban (6.75 mg, intravenouly)	Fenoterol (40 ug, intravenously)	140/416 (33.7%)	166/414 (40.1%)	163/416 (39.2%)	180/416 (43.3%)
Hilton et al.[21]	Canada	2009	Nitroglycerin (1 mg, intravenously)	Placebo	20/65 (31.0%)	12/61 (19.7%)	21/65 (32.3%)	12/61 (19.7%)
Collaris and Tan[22]	Malaysia	2009	Nifedipine (10 mg, orally)	Terbutaline (0.25 mg, subcutaneously)	15/44 (34.1%)	24/46 (52.2%)	10/44 (22.7%)	20/46 (43.4%)
Mohamed Ismail et al.[23]	Malaysia	2008	Nifedipine (20 mg, orally)	Terbutaline (0.05 mg, intravenously)	17/43 (39.5%)	25/43 (58.1%)	37/43 (86.0%)	38/42 (90.5%)
Kok et al.[24]	Netherlands	2008	Nifedipine (20 mg, orally)	Placebo	64/154 (41.6%)	58/156 (37.2%)	75/154 (48.7%)	84/156 (53.8%)
Nor Azlin et al.[25]	Malaysia	2005	Ritodrine (0.4 mg/mL, intravenously)	Placebo	15/30 (50.0%)	7/30 (23.3%)	13/30 (43.3%)	7/30 (23.3%)
Impey and Pandit[26]	United Kingdom	2005	Ritodrine (3 mg/mL,1mL/h, intravenously)	Placebo	17/62 (27.4%)	5/62 (8.1%)	21/62 (33.9%)	9/62 (14.5%)
El-Sayed et al.[27]	United States	2004	Nitroglycerin (0.2 mg, introvenously)	Terbutaline (0.25 mg, subcutaneously)	7/30 (23.3%)	16/29 (55.2%)	10/30 (33.3%)	11/29 (37.9%)
Bujold et al.[28]	United States	2003	Nitroglycerin (0.4 mg, sublingually)	Placebo	24/50 (48.0%)	31/49 (63.3%)	19/50 (38%)	24/49 (49.0%)
Bujold et al.[29]	Canada	2003	Ritodrine (111 ug/min, intravenously)	Nitroglycerin (0.4 mg, sublingually)	17/38 (44.7%)	9/36 (25%)	11/38 (28.9%)	7/36 (19.4%)
Fernandez et al.[30]	New Jersey	1997	Terbutaline (0.25 mg, subcutaneously)	Placebo	27/52 (51.9%)	14/51 (27.5%)	22/52 (42.3%)	12/51 (23.5%)
Marquette et al.[31]	Canada	1996	Ritodrine (111 ug/min, intravenously)	Placebo	72/138 (52.2%)	61/145 (42.1%)	62/138 (44.9%)	51/145 (35.2%)
Chung et al.[32]	Hong Kong	1996	Ritodrine (0.4 mg/mL, intravenously)	Placebo	17/25 (68.0%)	7/25 (28%)	NR	NR
Stock et al.[33]	Hong Kong	1993	Ritodrine (0.3 mg/min, intravenously)	Placebo	14/21 (66.7%)	9/21 (42.9%)	NR	NR
Robertson et al.[34]	United States	1987	Ritodrine (0.2 mg/min, intravenously)	Placebo	20/30 (66.7%)	19/28 (67.9%)	22/30 (73.3%)	23/28 (82.1%)

NR, not reached; ECV, external cephalic version.

satisfactory convergence after 50,000 iterations (Supplementary Figure 2). Heterogeneity testing identified substantial inconsistency ($I^2 > 50\%$) for the nitroglycerin versus placebo comparison between the studies by Hilton et al.[21] and Bujold et al.[28] (Supplementary Figure 3). Consequently, a subgroup analysis stratified by route of administration was conducted. The resulting ORs and CrIs are presented in Figure 4c. SUCRA rankings in this subgroup analysis were as follows: subcutaneous terbutaline (0.842), intravenous terbutaline (0.720), intravenous fenoterol (0.712), intravenous ritodrine (0.670), intravenous atosiban (0.548), intravenous nitroglycerin (0.389), oral nifedipine (0.334), placebo (0.216), and oral nitroglycerin (0.067) (Figure 5c). No statistically significant inconsistency or qualitative differences ($p > 0.05$) were detected across studies (Supplementary Figures 4-6).

Vaginal delivery rate

Fourteen studies reported delivery outcomes, with vaginal delivery rates ranging from 14.57% to 82.14%. Compared with placebo,

terbutaline was associated with a significantly higher rate of vaginal delivery (OR = 2.0, 95% CrI: 1.0 to 2.9). No statistically significant differences were observed for fenoterol (OR = 1.4, 95% CrI: 0.44 to 4.9), ritodrine (OR = 1.4, 95% CrI: 0.89 to 2.2), atosiban (OR = 1.2, 95% CrI: 0.48 to 3.1), nifedipine (OR = 0.85, 95% CrI: 0.44 to 1.6), or nitroglycerin (OR = 1.4, 95% CrI: 0.83 to 2.6) (Figure 4b). According to SUCRA values, treatments were ranked as follows: terbutaline (0.870), nitroglycerin (0.615), fenoterol (0.608), ritodrine (0.602), atosiban (0.424), placebo (0.243), and nifedipine (0.138) (Figure 5b). The potential scale reduction factor (R-hat) for all parameters ranged from 1.000 to 1.003 (point estimate and 97.5% upper confidence interval), falling below the 1.05 threshold (Supplementary Table 1, Supplementary Figure 7), which confirms excellent chain mixing and supports the reliability of the posterior estimates. The trace plot was shown in Supplementary Figure 8, also showed satisfactory convergence after 50,000 iterations. Significant heterogeneity (I^2 > 50%) was detected for the nitroglycerin versus placebo comparison between the Hilton et al.[21] and Bujold et al.[28] studies (Supplementary Figure 9). Subgroup analysis by administration route was therefore conducted. ORs are shown in Figure 4d, with corresponding SUCRA rankings as follows: subcutaneous terbutaline (0.804), intravenous terbutaline (0.778), intravenous nitroglycerin (0.730), intravenous fenoterol (0.594), intravenous ritodrine (0.581), intravenous atosiban (0.437), placebo (0.262), oral nifedipine (0.179), and oral nitroglycerin (0.136) (Figure 5d). No significant inconsistency was identified in either the overall analysis or subgroup analyses (p > 0.05) (Supplementary Figures 10-12).

Side effects of tocolytic agents

Seven studies reported data on common maternal adverse effects associated with tocolysis (Table 2). Six of these studies were included in the network meta-analysis, while Velzel et al.[20] was excluded due to the absence of a shared active comparator. Abnormal fetal heart rate outcomes were reported in seven studies. The estimated ORs and corresponding CrIs are presented in Figure 4e (maternal adverse effects) and Figure 4f (fetal heart rate abnormalities). Compare with placebo, significantly higher odds of maternal adverse effects were observed for terbutaline (OR: 11, 95% CrI: 1.7 to 71), nifedipine (OR: 5.1, 95% CrI: 1.0 to 29), and nitroglycerin (OR: 4.1, 95% CrI: 1.1 to 16). Ritodrine showed a non-significant trend toward adverse effects (OR: 4.3, 95% CrI: 0.38 to 54) (Figure 4e). No statistically significant differences in abnormal fetal heart rate were detected for ant tocolytic agent compared with placebo (Figure 4f). Analyses of these outcomes revealed no substantial inconsistency or heterogeneity actross studies (Supplementary Figures 13-16).

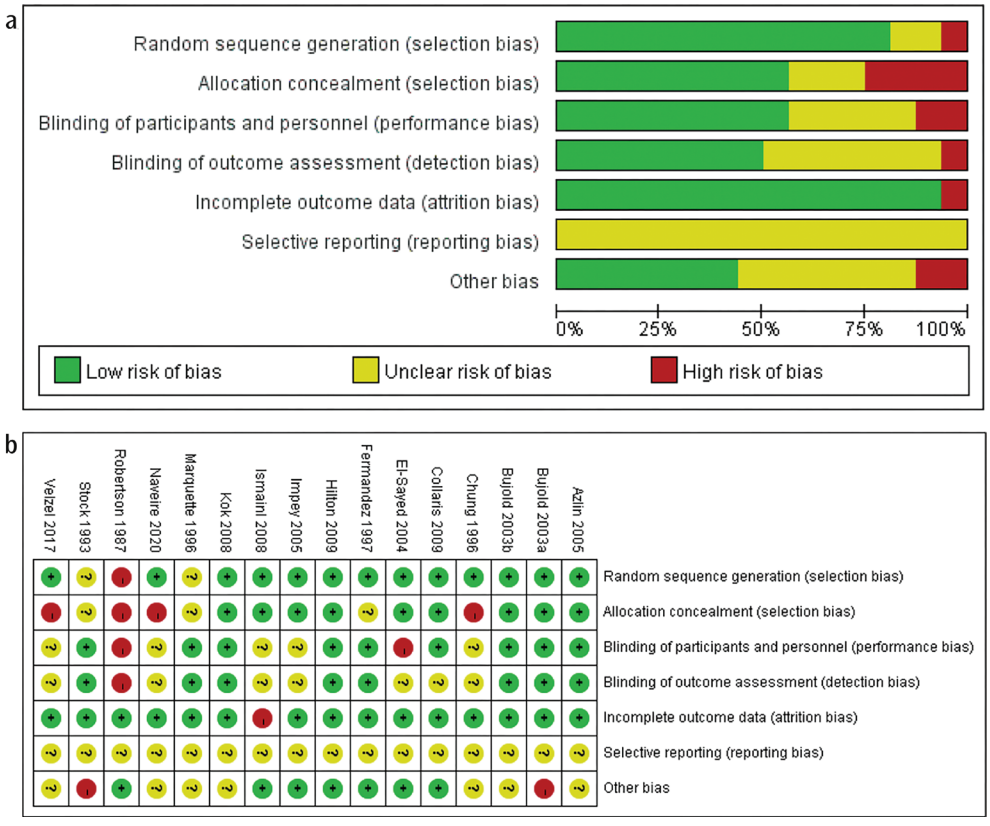

FIG. 2. Risk-of-bias summary. (a) Review the author's judgement for each risk-of-bias item for the included studies. (b) Review author's judgement for each risk-of-bias item presented as percentages of all included studies.

TABLE 2. Common Side Effects of the Applied Tocolytic Agents.

		Tachycardia		Palpitations		Hypotension		Nausea/dizziness		Flushes		Abnormal FHR	
Study	year	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control	Treatment	Control
Couceiro Naveira et al.[19]	2020	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	35	28
Velzel et al.[20]	2017	NR	NR	15	209	NR	NR	25	55	17	99	NR	NR
Vani et al.[35]	2009	3	0	2	0	0	0	NR	NR	NR	NR	2	0
Hilton et al.[21]	2009	4	0	1	2	3	2	16	8	12	4	3	4
Collaris and Tan[22]	2009	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Mohamed Ismail et al.[23]	2008	0	0	4	5	0	0	NR	NR	NR	NR	NR	NR
Kok et al.[24]	2008	0	0	0	0	0	0	5	5	11	0	12	11
Nor Azlin et al.[25]	2005	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Impey and Pandit[26]	2005	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
El-Sayed et al.[27]	2004	NR	NR	0	5	NR	NR	2	1	3	6	8	3
Bujold et al.[28]	2003a	NR	NR	0	0	6	1	NR	NR	NR	NR	2	5
Bujold et al.[29]	2003b	NR	NR	4	2	1	3	NR	NR	NR	NR	2	2
Fernandez et al.[30]	1997	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Marquette et al.[31]	1996	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Chung et al.[32]	1996	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Stock et al.[33]	1993	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Tan et al.[36]	1989	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Robertson et al.[34]	1987	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	2	5

NR, not reached; ECV, external cephalic version; FHR, fetal heart rate.

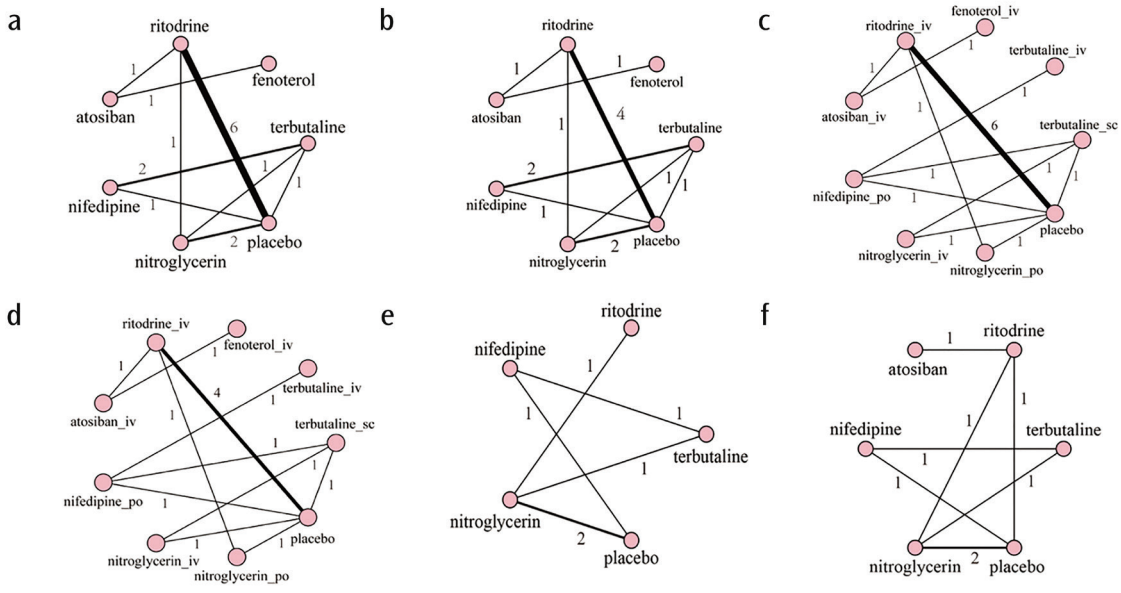

FIG. 3. Network structure diagrams. (a) Success rate of external cephalic version (ECV) under various tocolytic agents. (b) Vaginal delivery rate of patients with different tocolytic agents. (c) Success rate of ECV according to administration of tocolytic agents. (d) Vaginal delivery rate of patients according to administration of tocolytic agents. (e) Incidence of common adverse effects of tocolytic agents. (f) Abnormal condition of the fetal heart rate under various tocolytic agents. The thicknesses of the connected lines were proportional to the number of comparisons.

iv, intravenously; sc, subcutaneously; po, peros.

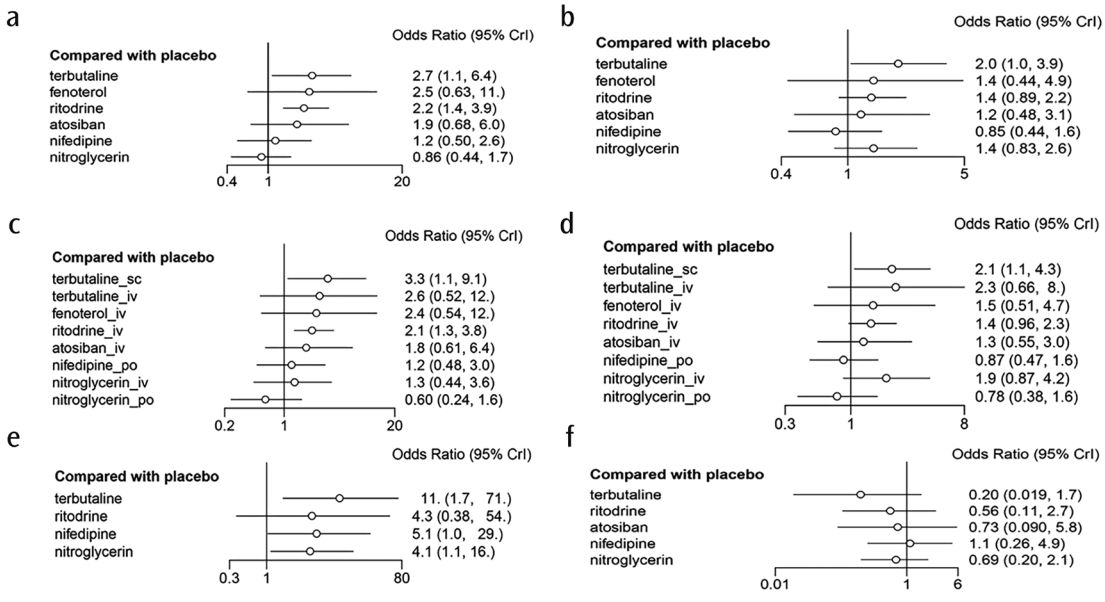

FIG. 4. The efficacy of different tocolytics. (a) The effectiveness of tocolysis compared with placebo on the success rate of external cephalic version (ECV). (b) The effectiveness of tocolysis compared with placebo on vaginal delivery of ECV. (c) The efficiency of tocolysis according to different administrations compared with placebo on success rate of ECV. (d) The efficiency of tocolysis according to different administrations compared with placebo on vaginal delivery of ECV. (e) The incidence of common adverse effects of tocolysis compared with placebo. (f) The incidence of abnormal fetal heart rate of different tocolysis compared with placebo.

iv, intravenously; sc, subcutaneously; po, peros; CrI, credible interval.

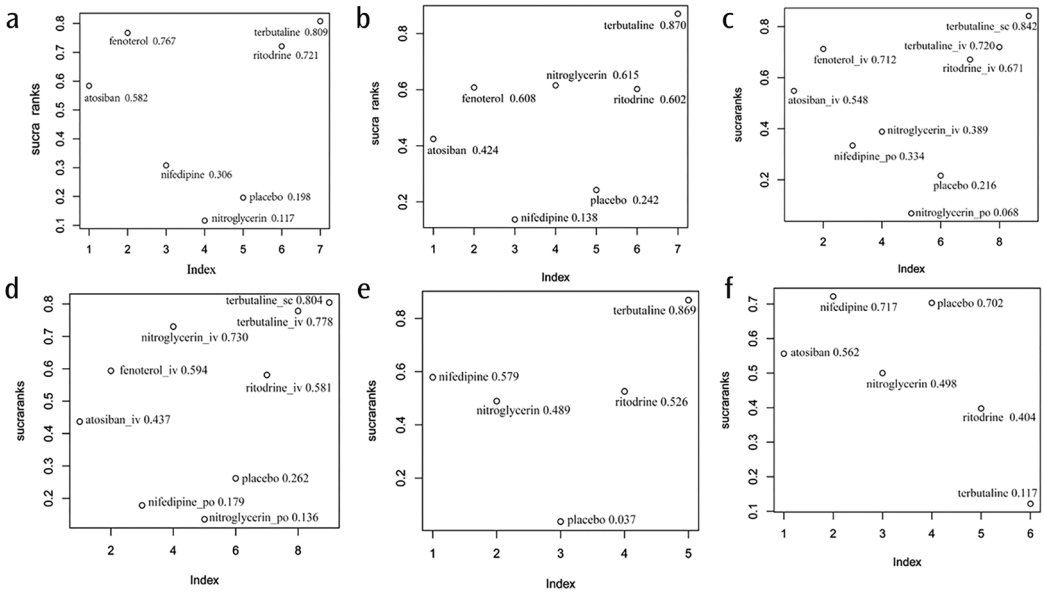

FIG. 5. The surface under the cumulative probability ranking (SUCRA) value of different tocolytics. (a) SUCRA of different tocolytic agents and placebo on success rate of external cephalic version (ECV). (b) SUCRA of tocolysis and placebo on vaginal delivery of ECV. (c) SUCRA of tocolysis according to different administration and placebo on success rate of ECV. (d) SUCRA of tocolysis according to different administration and placebo on vaginal delivery of ECV. (e) SUCRA of tocolysis and placebo on the incidence of common adverse effects. (f) SUCRA of different tocolysis and placebo on the incidence of abnormal fetal heart rate.

iv, intravenously; sc, subcutaneously; po, peros.

DISCUSSION

ECV has been practiced since the time of Hippocrates.[37,38] Prior to the mid-1970s, ECV was commonly attempted before term, based on the prevailing belief that the procedure was rarely successful at term gestation.[39-41] However, the use of preterm ECV declined after the mid-1970s because of concerns regarding perinatal complications, including preterm rupture of membranes, preterm labor, placental abruption, and fetomaternal transfusion.[39] Since the 1980s, accumulating evidence has demonstrated that ECV can be safely and effectively performed in term breech pregnancies, with a relatively low incidence of complications.[36,42,43] Subsequent RCTs further confirmed that ECV performed at or near term significantly reduces the rate of non-cephalic presentation at birth and cesarean delivery attributable to malpresentation.[40,41] In line with this evidence, contemporary clinical practice guidelines recommend ECV at or near term.[6,41] Accordingly, all participants included in the present study underwent ECV at a gestational age beyond 36 weeks.

Although tocolysis is widely recommended to facilitate ECV, direct comparisons among different tocolytic agents remain limited, particularly with respect to safety profiles. The most recent meta-analysis by Cluver et al.[9] evaluated tocolytics as a broad category rather than comparing individual agents. Moreover, methodological heterogeneity across previous studies, such as repeated administration of multiple tocolytic,[36] inclusion of pregnancies before 36 weeks' gestation.[35] or the use of anesthesia[44] has further complicated interpretation of the evidence. To address these gaps, we conducted a Bayesian network meta-analysis of 16 RCTs to compare the effects of six commonly used tocolytic agents on ECV success, vaginal delivery rates, and associated complications. Although SUCRA rankings suggested that all tocolytics agents except nitroglycerin ranked higher than placebo in terms of ECV success, only terbutaline and ritodrine demonstrated statistically significantly improvements when ORs and CrIs were considered. Fenoterol, atosiban, nifedipine, and nitroglycerin did not show a significant advantage over placebo.

Because substantial heterogeneity was identified between the Hilton et al.[21] and Bujold et al.[28] studies for the comparison of nitroglycerin vs. placebo, a subgroup analysis stratified by route of administration was performed. This analysis demonstrated that subcutaneous terbutaline and intravenous ritodrine significantly improved ECV success rates. In contrast, intravenous terbutaline, intravenous fenoterol, intravenous atosiban, oral nifedipine were not associated with a significant benefit over placebo. Importantly, these subgroup findings were consistent with the primary analysis and did not alter the overall conclusions. Subcutaneous administration of terbutaline was associated with improvement in the ECV success rate. Based on SUCRA rankings, only orally administered nitroglycerin demonstrated a lower relative efficacy than placebo, although this difference did not reach statistical significance.

With respect to vaginal delivery outcomes, SUCRA rankings indicated that nitroglycerin, fenoterol, ritodrine, and atosiban ranked higher than placebo, whereas nifedipine ranked lowest. However, terbutaline was the only agent that demonstrated a statistically significant increase in vaginal delivery rates. The low SUCRA value observed for nifedipine in relation to successful ECV may be attributable to dosage differences across studies. Specifically, the

Collaris and Tan[22] trial employed a 10 mg dose, yielding a vaginal delivery rate of 22.7%, whereas other studies used a 20 mg dose and reported higher rates (48.7% and 86.0%). Although this difference did not reach statistical significance, it suggests a potential dose-response relationship and does not negate a possible beneficial effect of nifedipine. Subgroup analysis further reinforced the superior performance of subcutaneously administered terbutaline compared with other agents. Commonly reported maternal adverse effects associated with tocolytic use included tachycardia, palpitations, hypotension, nausea, dizziness, and flushing. Terbutaline, nifedipine, and nitroglycerin were consistently associated with higher incidences of these adverse events, whereas ritodrine did not demonstrate this pattern. In the study by Velzel et al.[20] palpitations occurred significantly more frequently in the fenoterol group than in the atosiban group; however, no other adverse events differed significantly between these two agents. Importantly, none of the evaluated tocolytics were associated with abnormal fetal heart rate patterns. Given the limited amount of studies and substantial variability in reporting, these safety findings should be interpreted cautiously and regarded as exploratory and potentially underpowered.

Overall, our results indicate that tocolytic agents can facilitate ECV, with terbutaline and ritodrine showing the most consistent and statistically significant improvements in success rate. Terbutaline was also associated with an increased likelihood of vaginal delivery. However, with the exception of ritodrine, most tocolytics were linked to higher incidence of maternal adverse effects. Importantly, no agent was associated with clinically significant fetal heart rate abnormalities.

Based on the available evidence, terbutaline and ritodrine appear to be the most effective agents for improving ECV success. When considering their use, clinicians must carefully evaluate the potential benefits against the risk of maternal side effects, a trade-off that should be discussed with patients as part of shared decision-making.[45] Whether uterine relaxants should be used routinely during ECV remains a matter of debate.[9,45] Given that ECV success is strongly influenced by fetal head palpability and uterine relaxation, the decision to administer tocolysis should be individualized and guided by the operator's clinical assessment.[46-51] Thus, uterine relaxants are not universally required but may be particularly beneficial in cases where excessive uterine tension limits effective manipulation.

Several limitations warrant consideration. First, the included studies span more than three decades (1987–2020), during which clinical practice has evolved substantially. This temporal variation may partly explain the wide ranges observed in ECV success (8.1–68%) and vaginal birth rates (14.57–82.14%). Second, dosage regimens and routes of administration for the same tocolytic agent were not uniform across studies. Third, other β-receptor agonists, such as salbutamol and hexoprenaline, were not included due to the absence of eligible RCTs. However, given their infrequent use in contemporary ECV practice within our clinical setting, their exclusion is unlikely to have materially influenced the results. Despite these limitations, none are considered to compromise the validity of the primary findings.

In conclusion, this network meta-analysis demonstrates that terbutaline is associated with a significant increase in cephalic presentation at delivery, while both terbutaline and ritodrine improve the likelihood of successful ECV. With the exception of ritodrine, most tocolytic agents were associated with increased maternal adverse effects, although none were linked to abnormal fetal heart rate outcomes. The route of administration may represent an important determinant of tocolytic efficacy and warrant further focused investigation.

Ethics Committee Approval: Not applicable.

Informed Consent: Not applicable.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authorship Contributions: Concept- Y.X., Y.D., L.H.; Design- Y.X., Y.D., L.H.; Supervision- Y.D., L.H.; Funding- Y.D.; Materials- H Y.X., J.S.; Data Collection or Processing- Y.X., J.S., Y.D.; Analysis and/or Interpretation- Y.X., J.S., Y.D.; Literature Review- Y.X., J.S., L.H.; Writing- Y.X.; Critical Review- Y.D., L.H.

Conflict of Interest: The authors declare that they have no conflict of interest.

Funding: This work was supported by Dalian Science and Technology Innovation Fund (2020JJ27SN084).

Supplementary: https://balkanmedicaljournal.org/img/files/2025.2025-10-205-suppl-r.pdf

REFERENCES

1. Hutton EK, Hofmeyr GJ, Dowswell T. External cephalic version for breech presentation before term. *Cochrane Database Syst Rev.* 2015;2015:CD000084. [CrossRef]
2. Rietberg CC, Elferink-Stinkens PM, Visser GH. the effect of the term breech trial on medical intervention behaviour and neonatal outcome in The Netherlands: an analysis of 35,453 term breech infants. *BJOG.* 2005;112:205-209. [CrossRef]
3. Sullivan EA, Moran K, Chapman M. Term breech singletons and caesarean section: a population study, Australia 1991-2005. *Aust N Z J Obstet Gynaecol.* 2009;49:456-460. [CrossRef]
4. Hannah ME, Hannah WJ, Hewson SA, Hodnett ED, Saigal S, Willan AR. Planned caesarean section versus planned vaginal birth for breech presentation at term: a randomised multicentre trial. Term Breech Trial Collaborative Group. *Lancet.* 2000;356:1375-1383. [CrossRef]
5. External cephalic version and reducing the incidence of term breech presentation: Green-top Guideline No. 20a. *BJOG.* 2017;124:e178-e192. [CrossRef]
6. Li HT, Luo S, Trasande L, et al. Geographic variations and temporal trends in cesarean delivery rates in China, 2008-2014. *JAMA.* 2017;317:69-76. [CrossRef]
7. Zhao Y, Zhang J, Hukkelhoven C, et al. Modest rise in caesarean section from 2000-2010: the dutch experience. *PLoS One.* 2016;11:e0155565. [CrossRef]
8. Melo P, Georgiou EX, Hedditch A, Ellaway P, Impey L. External cephalic version at term: a cohort study of 18 years' experience. *BJOG.* 2019;126:493-499. [CrossRef]
9. Cluver C, Gyte GM, Sinclair M, Dowswell T, Hofmeyr GJ. Interventions for helping to turn term breech babies to head first presentation when using external cephalic version. *Cochrane Database Syst Rev.* 2015;2015:CD000184. [CrossRef]
10. American College of Obstetricians and Gynecologists (College); Society for Maternal-Fetal Medicine; Caughey AB, Cahill AG, Guise JM, Rouse DJ. Safe prevention of the primary cesarean delivery. *Am J Obstet Gynecol.* 2014;210:179-193. [CrossRef]
11. Tsakiridis I, Mamopoulos A, Athanasiadis A, Dagklis T. Management of breech presentation: a comparison of four national evidence-based guidelines. *Am J Perinatol.* 2020;37:1102-1109. [CrossRef]

12. Tan JM, Macario A, Carvalho B, Druzin ML, El-Sayed YY. Cost-effectiveness of external cephalic version for term breech presentation. *BMC Pregnancy Childbirth.* 2010;10:3. [CrossRef]
13. Diguisto C, Winer N, Descriaud C, et al. Amnioinfusion for women with a singleton breech presentation and a previous failed external cephalic version: a randomized controlled trial. *J Matern Fetal Neonatal Med.* 2018;31:993-999. [CrossRef]
14. Wang ZH, Yang Y, Xu GP. Remifentanil analgesia during external cephalic version for breech presentation in nulliparous women at term: a randomized controlled trial. *Medicine (Baltimore).* 2017;96:e6256. [CrossRef]
15. Lim S, Lucero J. Obstetric and anesthetic approaches to external cephalic version. *Anesthesiol Clin.* 2017;35:81-94. [CrossRef]
16. Vaz de Macedo C, Clode N, Mendes da Graça L. Prediction of success in external cephalic version under tocolysis: still a challenge. *Acta Med Port.* 2015;28:554-558. [CrossRef]
17. Annapoorna V, Arulkumaran S, Anandakumar C, Chua S, Montan S, Ratnam SS. External cephalic version at term with tocolysis and vibroacoustic stimulation. *Int J Gynaecol Obstet.* 1997;59:13-18. [CrossRef]
18. External cephalic version: ACOG Practice Bulletin, Number 221. *Obstet Gynecol.* 2020;135:e203-e212. [CrossRef]
19. Couceiro Naveira E, López Ramón Y Cajal C. Atosiban versus ritodrine as tocolytics in external cephalic version. *J Matern Fetal Neonatal Med.* 2022;35:80-85. [CrossRef]
20. Velzel J, Vlemmix F, Opmeer BC, et al. Atosiban versus fenoterol as a uterine relaxant for external cephalic version: randomised controlled trial. *BMJ.* 2017;356:i6773. [CrossRef]
21. Hilton J, Allan B, Swaby C, et al. Intravenous nitroglycerin for external cephalic version: a randomized controlled trial. *Obstet Gynecol.* 2009;114:560-567. Erratum in: *Obstet Gynecol*. 2009;114:1148. [CrossRef]
22. Collaris R, Tan PC. Oral nifepidine versus subcutaneous terbutaline tocolysis for external cephalic version: a double-blind randomised trial. *BJOG.* 2009;116:74-80; discussion 80-1. [CrossRef]
23. Mohamed Ismail NA, Ibrahim M, Mohd Naim N, Mahdy ZA, Jamil MA, Mohd Razi ZR. Nifedipine versus terbutaline for tocolysis in external cephalic version. *Int J Gynaecol Obstet.* 2008;102:263-266. [CrossRef]
24. Kok M, Bais JM, van Lith JM, et al. Nifedipine as a uterine relaxant for external cephalic version: a randomized controlled trial. *Obstet Gynecol.* 2008;112:271-276. [CrossRef]
25. Nor Azlin MI, Haliza H, Mahdy ZA, Anson I, Fahya MN, Jamil MA. Tocolysis in term breech external cephalic version. *Int J Gynaecol Obstet.* 2005;88:5-8. [CrossRef]
26. Impey L, Pandit M. Tocolysis for repeat external cephalic version in breech presentation at term: a randomised, double-blinded, placebo-controlled trial. *BJOG.* 2005;112:627-631. [CrossRef]
27. El-Sayed YY, Pullen K, Riley ET, et al. Randomized comparison of intravenous nitroglycerin and subcutaneous terbutaline for external cephalic version under tocolysis. *Am J Obstet Gynecol.* 2004;191:2051-2055. [CrossRef]
28. Bujold E, Marquette GP, Ferreira E, Gauthier RJ, Boucher M. Sublingual nitroglycerin versus intravenous ritodrine as tocolytic for external cephalic version: a double-blinded randomized trial. *Am J Obstet Gynecol.* 2003;188:1454-1457; discussion 1457-9. [CrossRef]
29. Bujold E, Boucher M, Rinfret D, Berman S, Ferreira E, Marquette GP. Sublingual nitroglycerin versus placebo as a tocolytic for external cephalic version: a randomized controlled trial in parous women. *Am J Obstet Gynecol.* 2003;189:1070-1073. [CrossRef]
30. Fernandez CO, Bloom SL, Smulian JC, Ananth CV, Wendel GD Jr. A randomized placebo-controlled evaluation of terbutaline for external cephalic version. *Obstet Gynecol.* 1997;90:775-779. [CrossRef]
31. Marquette GP, Boucher M, Thériault D, Rinfret D. Does the use of a tocolytic agent affect the success rate of external cephalic version? *Am J Obstet Gynecol.* 1996;175:859-861. [CrossRef]
32. Chung T, Neale E, Lau TK, Rogers M. A randomized, double blind, controlled trial of tocolysis to assist external cephalic version in late pregnancy. *Acta Obstet Gynecol Scand.* 1996;75:720-724. [CrossRef]
33. Stock A, Chung T, Rogers M, Ming WW. Randomized, double blind, placebo controlled comparison of ritodrine and hexoprenaline for tocolysis prior to external cephalic version at term. *Aust N Z J Obstet Gynaecol.* 1993;33:265-268. [CrossRef]
34. Robertson AW, Kopelman JN, Read JA, Duff P, Magelssen DJ, Dashow EE. External cephalic version at term: is a tocolytic necessary? *Obstet Gynecol.* 1987;70:896-899. [CrossRef]
35. Vani S, Lau SY, Lim BK, Omar SZ, Tan PC. Intravenous salbutamol for external cephalic version. *Int J Gynaecol Obstet.* 2009;104:28-31. [CrossRef]
36. Tan GW, Jen SW, Tan SL, Salmon YM. A prospective randomised controlled trial of external cephalic version comparing two methods of uterine tocolysis with a non-tocolysis group. *Singapore Med J.* 1989;30:155-158. [CrossRef]
37. Stock A, Rogers M, Wong WM. External cephalic version–a cautionary tale. *Aust N Z J Obstet Gynaecol.* 1992;32:378-379. [CrossRef]
38. Kornman MT, Kimball KT, Reeves KO. Preterm external cephalic version in an outpatient environment. *Am J Obstet Gynecol.* 1995;172:1734-1738; discussion 1738-1741. [CrossRef]
39. Laros RK Jr, Flanagan TA, Kilpatrick SJ. Management of term breech presentation: a protocol of external cephalic version and selective trial of labor. Am J Obstet Gynecol. 1995;172:1916-1923. [CrossRef]
40. Teoh T. Outcome of external cephalic version: our experience. *J Obstet Gynaecol Res.* 1996;22:389-394. [CrossRef]
41. Lavie A, Reicher L, Avraham S, Ram M, Maslovitz S. Success rates of early versus late initiation of external cephalic version. *Int J Gynaecol Obstet.* 2019;145:116-121. [CrossRef]
42. Beuckens A, Rijnders M, Verburgt-Doeleman GH, Rijninks-van Driel GC, Thorpe J, Hutton EK. An observational study of the success and complications of 2546 external cephalic versions in low-risk pregnant women performed by trained midwives. *BJOG.* 2016;123:415-423. [CrossRef]
43. Yanny H, Johanson R, Balwin KJ, Lucking L, Fitzpatrick R, Jones P. Double-blind randomised controlled trial of glyceryl trinitrate spray for external cephalic version. *BJOG.* 2000;107:562-564. [CrossRef]
44. Vlemmix F, Kuitert M, Bais J, et al. Patient's willingness to opt for external cephalic version. *J Psychosom Obstet Gynaecol.* 2013;34:15-21. [CrossRef]
45. Kim MY, Park MY, Kim GJ. External cephalic version experiences in Korea. *Obstet Gynecol Sci.* 2016;59:85-90. [CrossRef]
46. Isakov O, Reicher L, Lavie A, Yogev Y, Maslovitz S. Prediction of success in external cephalic version for breech presentation at term. *Obstet Gynecol.* 2019;133:857-866. Erratum in: *Obstet Gynecol.* 2019;134:182. doi: [CrossRef]
47. Morgan ER, Hu AE, Brezak AMV, Rowley SS, Littman AJ, Hawes SE. Predictors of a successful external cephalic version: a population-based study of Washington state births. *Women Birth.* 2019;32:e421-e426. [CrossRef]
48. Kew N, DuPlessis J, La Paglia D, Williams K. Predictors of cephalic vaginal delivery following external cephalic version: an eight-year single-centre study of 447 cases. *Obstet Gynecol Int.* 2017;2017:3028398. [CrossRef]
49. Harendarczyk L, Riche VP, Arthuis C, et al. Management of external cephalic version in France: a national practice survey. *J Gynecol Obstet Hum Reprod.* 2022;51:102239. [CrossRef]
50. Devold Pay AS, Johansen K, Staff AC, Laine KH, Blix E, Økland I. Effects of external cephalic version for breech presentation at or near term in high-resource settings: a systematic review of randomized and non-randomized studies. *Eur J Midwifery.* 2020;4:44. [CrossRef]
51. Kohls F, Gebauer F, Flentje M, Brodowski L, von Kaisenberg CS, Jentschke M. Current approach for external cephalic version in Germany. *Geburtshilfe Frauenheilkd.* 2020;80:1041-1047. [CrossRef]